HONG KONG PHARMACEUTICAL JOURNAL

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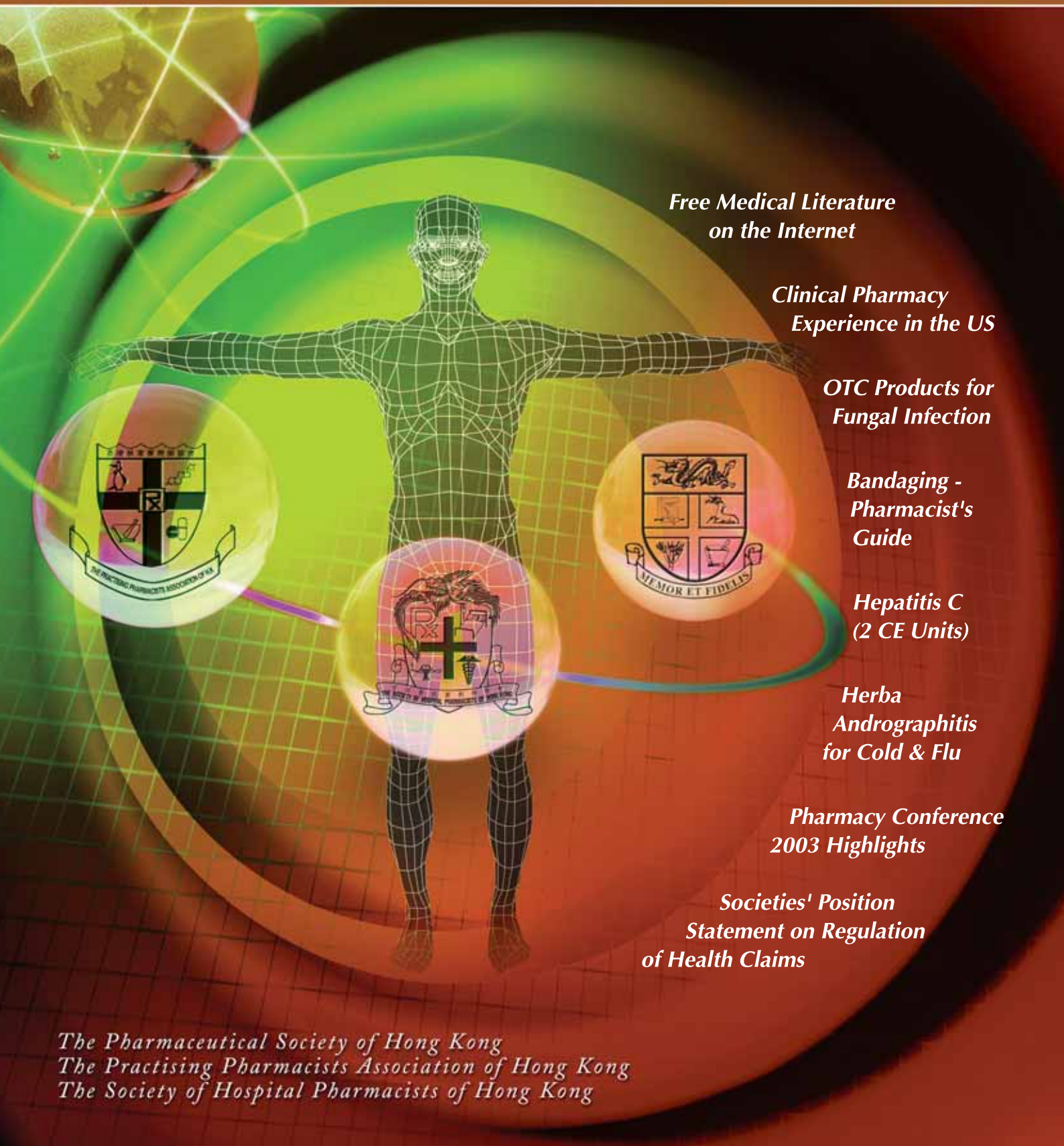

Free Medical Literature on the Internet

Clinical Pharmacy Experience in the US

OTC Products for Fungal Infection

Bandaging - Pharmacist's Guide

Hepatitis C (2 CE Units)

Herba Andrographitis for Cold & Flu

Pharmacy Conference 2003 Highlights

Societies' Position Statement on Regulation of Health Claims

The Pharmaceutical Society of Hong Kong
The Practising Pharmacists Association of Hong Kong
The Society of Hospital Pharmacists of Hong Kong

Targeted to increase survival in women with metastatic breast cancer

- A HER2-positive status is a predictor of poor prognosis[1]
- Identification of HER2 status is crucial to determining optimal treatment
- Herceptin significantly increases overall survival, time to disease progression, overall response rate, and duration of response, when used as first-line therapy[2, 3]
  - Overall survival increased by 25% compared to chemotherapy alone[4]
- Herceptin side effects are generally mild to moderate
  - Mostly infusion-related reactions occurring with the first dose
- When added to chemotherapy, Herceptin significantly improves quality of life[5, 6]

The first oncogene-targeted treatment for HER2-positive patients

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All communications and enquiries should be directed to the Secretary, Hong Kong Pharmaceutical Journal, G.P.O. Box 3274, General Post Office, Hong Kong.

For all enquiries regarding advertisement, please contact Ms Ivy Chan.
(Tel: 6082 6338; E-mail: pharmjadhk@hotmail.com)

INSTRUCTIONS FOR AUTHORS

The Hong Kong Pharmaceutical Journal is a journal of the pharmacists, for the pharmacists and by the pharmacists. Submissions are welcome for the following sections:

Pharmacy Practice	Drug & Therapeutics
OTC & Health	Pharmaceutical Technology
Medication Safety	Herbal Medicines & Nutraceuticals
Society Activities	New Products

Comments on any aspects of the profession are also welcome as Letters to the Editor.
There is no restriction on the length of the articles to be submitted. They can be written in English or Chinese. The Editorial Committee may make editorial changes to the articles but major amendments will be communicated with the authors prior to publishing.
It is preferable to have original articles submitted as an electronic file, in Microsoft Word, typed in Arial 9pt. Files can be sent to the following address:

e-mail: ***pharmjhk@yahoo.com***

address: ***G.P.O. Box No. 3274, General Post Office, Hong Kong***

For any queries on submission, please feel free to contact the Editorial Committee through mail or by the e-mail address.

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Editorial

2003 has been a difficult year. The year began with the Korean nuclear crisis which has been followed by the war in Iraq. Then, from quiet beginnings in China, Severe Acute Respiratory Syndrome (SARS) rapidly spread throughout world, claiming more than 700 lives. It probably is the worst disaster to many of the countries. In Hong Kong, residents were taking no chances but wearing masks as the outbreak worsened. And the terrorism continues to endanger people's lives with bomb attacks all around the world. These are yet to be resolved.

In Hong Kong, no one could have predicted such disasters still happening nowadays and that the damaging effects were so close to us, in terms of not only the collapsing economy of Hong Kong but also the threats of death around us. In July, 500,000 citizens joined the march to express their view on the legislation of Article 23 of the Basic Law and to call for speedy democratic reform. All in all, the implications of these events do not end there. Our integration with the Mainland China should not be neglected as we move into the new millennium, no matter in economy, in politics or in health issues.

While much focus has been put on to help boost the Hong Kong economy and to cut down government expenses, the public sector must find a way to sustain the healthcare services with the reduced resources. Cost-containment with controlling access to medications was one of the mainstream strategies since acquisition costs are easily identifiable. Foreign experience tells us no matter which approach to controlling drug costs has been used (formulary limitation, senior authorization, drug capitation, or fixed number of prescriptions per month), limiting physicians' prescribing choices of medications may be associated with increased overall pharmacologic and health care utilization. A much current concept was about providing optimal health services with lowest cost. That is through encouraging high-quality care to improve clinical outcome and, hence, to reduce subsequent utilization. One of the approaches to achieve a better clinical outcome is to improve drug compliance of patients through counseling and intervention. The public sector in Hong Kong must continue restructuring and reallocating its resources. Various initiatives related to the pharmacy profession have been piloted and implemented during the past twelve months, these include prescriptions of out-patient clinics being dispensed in the private community pharmacies; defining Patients Choice Items (PCI) to share drug costs with patients; establishing private pharmacies in public hospital settings; transferring the General Out-Patient Clinics from the Department of Health to the Hospital Authority to facilitate the integration of the primary and secondary care and etc. In private sector, both chained pharmacy stores and medical care organizations have also been expanding fast recently. These create huge opportunities for pharmacists to re-define the scope of services and, hence, to lead to the growth of our pharmacy profession. Our three mother societies have done lots of ground works and also have been playing an important role in the entire evolving process. Many of these key issues and initiatives have been discussed extensively in the Pharmacy Conference 2003 held in October. You may also keep up with these topics by reading the HKPJ!

Let's come back to the HKPJ. In 2003, we have a mixture of new and experienced members in the editorial committee. Selected colleagues also take up new assignments within the committee. I would like to grab this opportunity to show my sincere appreciation to their effort, being voluntarily but professionally. The editorial committee believes that the quality of our journal is largely dependent on the quality of articles being published. We were glad to have a variety of high quality submissions from all the authors in year 2003. I cannot list them all in here but I would like say thank you to them, especially on behalf of those HKPJ readers who have been beneficial from their articles. I am looking forward to receiving more contributions and submissions from different sectors of pharmacy profession in the coming year.

In this issue of the HKPJ, we have some sharing from Simon and Josephine on their trip to visit a hospital pharmacy in Chicago. Dr Poerschke introduces some free online resources of obtaining medical literature in the Pharmacy Practice section. To enrich your knowledge on hepatitis, you may go through the PCCC article on Hepatitis C in this issue as well as the one published in the previous issue regarding Chronic Hepatitis B. Are fungi friends or enemies to human beings? From different angles, you may understand more about the relationships between this creature and us, i.e. on how we tackle the topical fungal infections with OTC products as well as on how scientists identify fungal extracts to treat various complicated diseases.

During 2003, the government has finished public consultation on a total of 30 areas of government policy. Three of them are healthcare related, they include Consultation Paper of the Advisory Committee on the Promotion of the Fighting Spirit against SARS in July, Regulation of Medical Devices in September and on Regulation of Health Claims in November. In this issue, we gather the position statements from our three mother societies that you may be interested in. In the Society Activities section, Miss Chiang and Helen also give us very good summaries and pictures from the Pharmacy Conference 2003. Other than keeping the good memories from the event, let's do some actions to move forward into "partnership" and "success" with other pharmacy colleagues in Hong Kong.

Michael Leung
Managing Editor

The Pharmacists Guide to Free Medical Literature on the Internet

Gabriele Poerschke MD, MMedSc.

Abstract

Pharmacists are working with increasingly demanding and well-educated consumers in their environment. Pharmacists and other health professionals must develop a strategy to take the greatest advantage of information on the Internet.

Key words: Internet, website, online, medical information
Total word count: 1,089

I PHARMACISTS AND THE INTERNET

Pharmacists and other health professionals must develop a strategy to take the greatest advantage of information on the Internet. Pharmacists are working with increasingly demanding and well-educated consumers in their environment. It was estimated that in November 2000 more than 400 million people around the world accessed the Internet[1]. More than 70,000 websites disseminate health information[2]. The Internet provides people seeking for health information with access to a wealth of information and services whereby they can now access the same online information as health care providers. At present, there is almost no evidence regarding the effect of consumer Internet use on health outcomes. Internet based materials may provide consumers with necessary information and support to achieve positive health outcomes and thus the Internet may impact on the overall cost-effectiveness of health service provision and practices[2].

Increasingly, consumers and health-care providers use the Internet for communication and in the process make health decisions and shape their surrounding health care services[2]. Using the Internet to broaden the pharmacist's knowledge may solve the dilemma of the pharmacist's utility in the 21st century. The importance of the Internet is underscored by its ability to link healthcare professionals worldwide in unique collaborative efforts unmatched by any individual's output, regardless of his singular genius.

There are many useful resources online for pharmacists, for example government websites. In Hong Kong the Department of Health publishes public health and disease surveillance under http://www.info.gov.hk/dh/diseases/content.htm [3]. There are non-governmental organizations such as the World Health Organization http://www.who.int/wer/#WER;[4] and many sites are dedicated to a particular topic of general interest such as vaccines http://www.vaccinews.com[5] or to a professional research network http://www.ansorp.org/index_former.html [6]. A truly useful website deserving a bookmark is www.amedeo.com[9].

II WHAT IS AMEDEO?

AMEDEO is a free medical literature search service of PubMed [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi] [7] and MEDLINE[7] for over 80,000 subscribers around the world. Hong Kong alone has 120 subscribers[10]. All AMEDEO services are free of charge. This policy was made possible thanks to generous unrestricted educational grants provided by AMGEN, Berlex, Boehringer Ingelheim, Eisai, Novartis, Pfizer, Roche and Schering AG[8,9].

This website and affiliated sites operate under the concept that within the next few years, the most important medical journals will be available online, free and in full-text. The fast and convenient access to free scientific knowledge is thought to have a major impact on medical practice and attract Internet visitors to these journals. As a result, journals that restrict access to their publications will lose in popularity over time[8,9].

III HOW IT ALL BEGAN...

AMEDEO started of more than 10 years ago as an academic tool to speed up the international writing of a textbook about HIV and AIDS [http://hiv.net/2010/buch.htm.] [11]. Because the program worked well it was put on the Internet in 1997 as www.amedeo.com. Due to increasing international popularity it evolved further to cover other specialties.

IV HOW TO SUBSCRIBE?

To register, you select a topic of professional interest from a list of 24 fields [table 1]. After filling out a form you will receive the weekly AMEDEO literature newsletters with an overview of new articles published in your personal journal subset. In addition, you will receive a weekly update of your personal AMEDEO web page displaying the abstracts of your journal subset articles and archived updates. For each article cited, the e-mail gives a link to the MEDLINE abstract[8,9].

V OBTANING ARTICLES...AT NO CHARGE!

Those accessing PubMed or the subscriber to AMEDEO can obtain full-text versions of an article through MEDLINE's Loansome Doc Ordering System. Some articles are free, and some cost, depending on the journal[8].

Many health professionals in Asia working in pharmacies have limited access to institutional subscriptions, libraries and affordable specialty subscriptions. For these individuals who would like to keep abreast of medical literature and deepen their knowledge at a different location AMEDEO maintains an ever-growing list of direct links to

Table 1. Topic includes examples of sub-specialties in brackets. Complete list at www.amedeo.com

Topics in AMEDEO	Sub-specialties
Infectious Diseases	(Drug Resistance, Vaccines)
Disorders of the Cardiovascular System	(Arrhythmias, Venous Thrombosis)
Disorders of the Respiratory System	(Lung Cancer , Asthma)
Oncology	(Bladder Cancer, Prostrate Cancer)
Endocrinology and Metabolism	(Diabetes, Osteoporosis)
Neurologic Disorders	(Alzheimer's Disease, Parkinson's Disease)
Psychiatric Disorders	(Depression, Schizophrenia)
Women's Health	(Contraception)
Disorders of the Kidney	(Chronic Renal Failure)
Disorders of the Gastrointestinal System	(Pancreatitis, Liver Diseases)
Immunology	(Autoimmune Disorders)
Hematology	(Anemia, Leukemia)
Neonatology	
Men's Health	(Erectile Dysfunction)
Dermatology	(Malignant Melanoma)
Ophthalmology	
Otorhinolaryngology	
Surgery	(Fractures)
Dentistry	(Periodontology)
Intensive Care	(Pain Management, Poisoning)
Rehabilitation Medicine	
Diagnostic Procedures	(Nuclear Medicine)
Nutrition	(Anorexia, Obesity)
Substance Abuse	(Alcoholism)

biomedical publications that can be accessed online in full text for free: www.freemedicaljournals.com[12].

At present, more than 1010 international journals are listed. They are sorted by language and specialty. The majority of these journals are published in English, but other languages, such as Spanish, Portuguese, French, Bahasa Indonesia and Thai are represented. Journals include general medical publications such as Journal of the American Medical Association (JAMA) and British Medical Journal (BMJ) and the Journal of Korean Medical Science and specialty ones such as The AIDS Reader, Journal of Immunology and the Japanese Journal of Pharmacology[12].

In addition, another website www.FreeBooks4Doctors.com is dedicated to the promotion of free access to medical books over the Internet. It has more than 550 books sorted by specialties13.

Science is in continuous flow. The Internet provides the pharmacist, health professionals and consumers with an **unprecedented wealth of state-of-the-art medical information**. The ready availability of this information will have a tremendous impact on the role of the pharmacist in medical practice and the quality of life of patients in their care.

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3 Hong Kong Government Department of Health, http://www.info.gov.hk/dh/diseases/content.htm

4 World Health Organization, Weekly Epidemiological Report, http://www.who.int/wer/#WER

5 Asia-Pacific Vaccination Council: VacciNews© at http://www.vaccinews.com

6 Asian Network on Antimicrobial Resistance, http://www.ansorp.org/index_former.html

7 MEDLINE at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi

8 Anonymous. WebWatch. ACI International 2000;12/6:312-315

9 http://www.amedeo.com

10 Geographical distribution: http://AmedeoWorld.com

11 http://hiv.net/2010/buch.htm, in German

12 http://www.freemedical.journals.com

13 http://freebooks4doctors.com

Dr. Poerschke works as a medical consultant in the pharmaceutical industry.

My Clinical Pharmacy Experience in the United States - A Journey of Inspiration

Simon Leung, Pharmacist at Pamela Youde Nethersole Eastern Hospital, Chai Wan, HK

1. HOW THE JOURNEY STARTED

It was my honour to participate in the second year of the Overseas Clinical Attachment Program, co-organized by The Chief Pharmacist's Office of the Hospital Authority (HA) and the University of Illinois at Chicago (UIC). It was the program's objective to provide pharmacists of HA an opportunity to keep abreast with the new developments of Clinical Pharmacy in the United States. After learning the positive feedback from my colleagues who went through the program last year, I was eager to take up the challenge myself to enhance my clinical skills at this world-class training site. It was a not an easy decision to make at first, to leave my colleagues and family for 6 weeks to embark on a journey of intensive studying in a city that I know nothing before. This year, my HA "partner" was Josephine Yung, a pharmacist from TMH (Tuen Mun Hospital), who also happened to attend the UIC Training from February to March 2003. Months ahead of time, we joined forces to plan and make arrangements in transportation, accommodation and living chores together.

The Clinical Attachment Program was composed of a 6-week on-site clinical training within the Illinois Medical Centre at Chicago. Faculty members of the UIC College of Pharmacy served as our preceptors. I have chosen Internal Medicine as my area of interest. During the period, I worked alongside with the Clinical Pharmacists in both in-patient and out-patient settings. The work in the Internal Medicine Ward and Organ Transplant ICU was fascinating. My out-patient rotation includes the various ambulatory care clinics, such as the Transplant, Diabetes, Haemodialysis, and the Refill-10 clinics. The challenging experience of this overseas training in the cold winter weather was well worth it, which I had gained both academically and spiritually. With this article, I intend to share with you what I saw, and how it inspired me.

2. THE TRAINING SITE

Roughly 40 mintues of the CTA Subway ride from our downtown

Figure 1. The UIC Medical Centre in snow.

residence takes us to the site of action --- The Illinois Medical Centre. Ranked one of the nation's best teaching hospitals by *U.S. News*, the Illinois Medical Centre has over 30 academic and medical buildings and has the full complement of the six health science colleges. It's 454-bed tertiary care hospital performs all disciplines and surgical procedures, and provides an excellent training ground for approximately 800 medical and pharmacy residents. Next to the UIC Hospital is the Outpatient Care Centre (OCC), the famous glass building that you may see in the *E.R.* series in television. The OCC provides dozens of out-patient clinics for discharged patients to be followed-up by the respective ambulatory care multi-disciplinary team. A central pharmacy and two satellite pharmacies are located in the Hospital, and four Outpatient Pharmacies are scattered around the campus.

In line with its significance, the College of Pharmacy is conveniently located right next to the UIC Hospital. The third oldest in USA, the UIC College of Pharmacy is ranked one of the top colleges of pharmacy for excellence in curriculum, scholarship, and quality of faculty and students. It offers a basic 4-year Pharm.D. program as well as post-graduate Clinical Pharmacy Residency program for candidates from all nations. The College has about 100 professors who has different teaching and research responsibilities. Many of the teaching staff of the College also have a dual role in the Medical Center. These clinical pharmacists (or pharmacotherapists) provide clinical services to the patients at the UIC Hospital and the OCC. They also make use of real patient cases to teach their Pharm. D candidates and residents. Many of the clinical faculty members are renowned authors of pharmacy textbooks.

3. THE CLINICAL ROTATIONS

3.1 In-patient

Unlike the large wards in Hong Kong, the average wards in UIC are made up of many individual cubicle patient rooms, with the nursing station in the center. Furthermore, UIC uses a paperless patient record system with their computerized Patient Care System ("Gemini") taking care of all the admission & progress notes, lab results, medication ordering and administration records. There are some 10-15 stationed or mobile Gemini terminals in each ward, and all staff, including myself, has our own assess login and password to the system.

3.1.1 Internal Medicine (Ward "7 East")

Three patient management care team takes turn to admit patients overnight to the "7 East" Ward. The Team C that I belong has one Attending Physician, one Clinical Pharmacist (Dr. Karen Chin, my preceptor for this unit), one medical resident, 3 medical students, and 2 final year Pharm. D. students.

My first day at the "7 East" Ward represented a typical working day. The day started at 7am with the morning round. The whole team, except the Attending Physician, saw the patients together to assess the progress and discuss their treatment orders. I enjoyed seeing the pharmacist and physician members work closely to make clinical decisions. After the round, members would quickly run for a Gemini terminal (all with LCD monitors) to look up the latest lab results or enter the new medication orders that they have just decided.

Around 10a.m., the teaching round is held in the conference room, where members would present the cases to the attending physician who in turn poses challenging questions to them. The teaching atmosphere is intense. Karen, the clinical pharmacist, also makes lots of drug-related

interventions to the patients. I find Karen to be the true drug expert in the Team, and she is well respected by all of them.

Figure 2. Members in the teaching round listens carefully to the cases.

Figure 3. Medical residents and Pharmacy students often consults the Clinical Pharmacist in the Unit. All the patient's data are in the Gemini System.

The teaching round was too extensive that our Pharmacy gang could only grap a quick sandwich at the cafeteria before heading up to the Journal Club at 1:15p.m. A Clinical Pharmacy Resident led the discussion as a group of final year Pharm.D. students critically examine a primary literature on H.I.T. Held once or twice a week during the lunch hours, Journal Clubs provides excellent teaching sessions on various topics of Internal Medicine.

Around 3pm, Karen led the two Pharm.D students and myself into the afternoon case review session. We discussed the treatment approach and outcome measures for the patients in details and revised our S.O.A.P. Pharmaceutical Plans. We reviewed disease management and therapeutics in many common internal medicine disorders. After Karen left, the three of us have to catch up with medication history-taking for newly admitted patients, bedside discharge counseling, and Gemini documentations. It would be lucky if our day can end before 6:30p.m. Days at 7 East are long and exhausting, yet rewarding.

3.1.2 Organ Transplant ICU (Ward "7 West")

The Organ Transplant ICU provides care to recipients of kidney, pancreas, liver and small bowel transplants as well as their donors. There are twelve private rooms with state-of-the-art equipments. Tranplant surgeons, clinical pharmacists, specialist nurses, dietitians, respiratory therapists, social workers and psychologists make up the Transplant Team. I was told before the start of this rotation that the pharmacists working in this unit have a unique role, that I must not miss seeing them in action.

Figure 4. A Pharmacy student kneels down to the level of the patient to perform a thorough discharge counseling - what Pharmaceutical CARE is about.

Indeed, the transplant pharmacists here are highly specialized in this area. As the surgeons mostly took care of the surgical aspect of the transplantation, most of the prescribing privileges are left to the pharmacists here. When I arrived at the ward at 6:30a.m. the first day, the team has already started their morning rounds. The 12 of us talked through the rooms one by one, and discussed the progress. Whenever it comes to drug treatment, all the eyes would turn to the pharmacists, Kerri and Thuy, for recommendations. The surgeons trusted the pharmacists so much that often times, they would just say something like, "Kerri, go ahead and start a course of steroid for Mrs. L." or "Mr. T's B.P. seems a bit on the high side, hm... Thuy, why don't you increase his Anti-hypertensive doses a bit for me."

After the rounds, I saw Kerri and Thuy busy entering new drug orders in the Gemini system on behalf of the surgeons, and cc'ed the orders for them to co-sign.They would put down notes to remind themselves to monitor the progress later.

Figure 5. Pharmacist (second right) in a work round with the Transplant Team.

Besides putting in orders, writing notes, monitoring the patients, patient counseling, and being on-call 24/7, these specialized pharmacists also spends a lot of time teaching the Pharm.D. student and fellows (and visitors like me). They taught us how to do pre-transplant work-ups, HLA-matching, literature review, setting up drug protocols of prophylatic therapy as well as maintenance immunosuppressive therapy for different sub-groups of patients, TDM, etc. The pharmacists are very knowledgeable and are essential to the service. I am very impressed and proud of seeing how the pharmacists can contribute so much to patient care.

3.2 Out-patient

The Out-Patient Care Centre (OCC) houses a number of clinics where they provide ambulatory care to out-patients similar to the SOPD in Hong Kong. I had the opportunity to visit quite a number of the clinics, and learned some of their working routines. Pharmacists play a major role in ambulatory care setting in UIC.

Unlike our local setting, I find that a lot of emphasize is put into providing advanced pharmaceutical care in the Ambulatory Care settings in the OCC. There is at least one, or in some areas several, clinical pharmacists working in the individual clinics. These pharmacists received specialized training, and often see the patient alone or in conjunction with the attending physician. Many physicians would come over for drug-related consults for the pharmacists too.

I find several clinics to have similar work flow. Patients come to the clinic by prior appointments. After going through attendance and taking vital signs, patients would be arranged into a consultation room, where a pharmacist would walk in to greet them, take brief history, identify and evaluate signs and symptoms from the patient and the Gemini, and check drug compliance, etc. After gathering all the information, the pharmacist would leave the room to present the case to the attending physician, who runs around in the clinic. The pharmacist identifies any drug related problems (DRP) to the attending (physician), and suggests modifications in the drug therapy. The attending and pharmacist then sees the patient together, and discusses the treatment plans with the patient.

This unique way of screening patients by clinical pharmacists seems efficient in their setting, and saves the attending physician a lot of time. The pharmacists see themselves as "Clinicians" and manage the patient together with the doctor. I saw this "pre-doctor" assessment workflow at the Transplant Clinic, GI & Liver Clinic, Diabetes Clinic, Paediatric Clinic, and the Pulmonary Clinic.

Other clinics, like the Family Medicine Clinic, Haemodialysis Clinic, and Smoking Cessation Clinic, uses the Referral workflow. Patients are seen by doctors first, and whenever necessary, they would be referred to see the pharmacist for service right away. The pharmacist in the HD Clinic also plays an active role in the monthly lab rounds with the nephrologists, as she makes a lot of drug interventions to optimize their therapy.

The **Refill-10 Clinic** is a special ambulatory care clinic run by a pharmacist and several technicians. Dr. Mary Ann Kliethermes, the Clinic's chief pharmacist believes that good continuum of care in the Ambulatory Care setting is the key to success in patient's disease management in the long term. This clinic got its name as it serves problematic patients who are taking 10 or more drugs concurrently. Mary Ann sees her patients on a monthly basis at the clinic and tries to provide the best drug-disease monitoring to them. Assessing to all the clinical data from the Gemini, Mary Ann can monitor possible ADR and identify other DRPs. She could contact the prescribers for amendment of drug therapy when necessary. Otherwise , she would continue and refill the medications for the patients.

I witnessed Mary Ann spending about one hour per patient, solving all her problems, from drug-related issues, drug co-pay insurance problems, to arranging transportation to the next appointment. I am really inspired by Mary Ann's caring attitude towards her patients. She treated every patient as her family members, patted their hands as signs of comfort, and showed utmost care. The patients really appreciated her professional help.

For those patients with compliance problems, pharmacy technicians at the Refill-10 Clinic would help arrange their oral medications into specialized pillboxes for the patients to take home. This is very time-consuming, but it has greatly increased the compliance level of these patients. Since the start of this Refill-10 Clinic about 1 year ago, Mary Ann has accumulated about 40 or more patients in the files. It is the quality of care that counts, not the quantity. She has a thick file of notes for each of her individual patients.

Figure 6. The Outpatient Care Centre (left) is connected to the UIC Hospital (right)

Figure 7. Dr. Kerri Hood, pharmacist, assessing lab results while seeing her patient at the Transplant Clinic

Figure 8. Dr. Cheryl Gilmartin, pharmacist at Haemodialysis Clinic, caring for her patient by the HD Machine

Figure 9. Dr. Daphnie Smith, pharmacist at Diabetes Clinic, discussing with her DM patient.

Figure 10. Dr. Mary Ann Kliethermes, pharmacist at Refill-10 Clinic, checks with the computer during a follow-up assessment of a patient. She fills the pillboxes for this patient.

Figure 11. Mary Ann kneels down beside a patient to show him how to identify his tablets and capsules.

4. SIGHTSEEING IN CHICAGO - WHAT TO SEE AND WHERE TO DINE?

Exploring the city of Chicago, I must say, comes as a bonus to this clinical attachment. As one of the major cities of the States, Chicago stands as an important communication and trading centre. Located at the southern tip of the Lake Michigan, the city gets quite a bit of strong moist breeze. I can give a true testimonial to Chicago's name of "The Windy City" as the strong wind almost pushed me into the icy water one Sunday morning when I took a walk along the famous Navy Pier.

Chicago attracts me in many aspects. It has a modern downtown filled with skyscrapers. Dare yourself to go up the 110-storeyed Sears

Figure 12. The Michigan Avenue means shopping in midst of architecture.

Tower, the once tallest building in the world, and you will get a panoramic view of the city. Furthermore, just walking down the Michigan Avenue is like taking a course in architecture. The city also has relaxing lakeshores and beautiful suburbs. If you are as crazy in taking photos as I do, make sure you bring enough film or memory cards, as there are lots of subjects to point at. For those of you who like shopping, you can easily spend a day cruising down the Magnificent Mile at the Michigan Avenue where many famous brands and shopping malls are located. Take the CTA Subway south, and visit one of the nation's oldest Chinatown and get yourself a pound of barbecue pork. It would be nice break from the pizzas and instant noodles that you may have had all week long.

Figure 13. Sue, a real T. Rex fossil at the Field Museum

If you are a fan of arts and music, you will find joy in your stay. Be sure to go to the Arts Institute of Chicago to see a comprehensive display of modern and classic art works. Don't miss the miniature house models at the basement, as highly recommended by Prof. Lingtak Chan. Go on a Tuesday evening after work and you will get free admission too. There are several other museums in the city, but if you really have to choose one, I would go for the Field Museum. I was so happy to meet Sue, the world's most complete real fossil of a Tyrannosaurus Rex unearthed to date. If you like music, it is hard to choose between the grand classical performances in The Opera House and the sweet musical comedies in many local stages. You won't miss the Chicago Blues either.

Chicago is also a place for fine dinning. Prof. Alan Lau took Josephine and I to many fine restaurants around the city almost every weekend to try out the delicious cruisines. The all-you-can-eat Brazalian steak experience at Fogo de Chao was unique. Other restaurants like Cheesecake Factory, Joe's Stone Crab, Magianno's Little Italy, and even Edwardo's Pizza brought joyful memories to us all, after we get through the 1.5 hour wait. Just ask Prof. Lau where these famous restaurants are!

Sports fans might wonder why I haven't mentioned the Chicago "Bulls" yet. Sure, if you want to be part of a NBA Playoff, just visit the famous United Center several blocks away from the UIC Medical Centre. It will give you a night of palpitations, sore-throat, and a bleeding wallet.

Figure 14. Thanks to all the preceptors who had taught us so many things

5. CONCLUSION

"...We have always read about the advances in pharmaceutical care in USA, but being able to witness the work of clinical pharmacists right at this state-of-the-art institution is definitely breath-taking. Here, we see pharmacists making interventions in the ward rounds, and putting in medication orders for the physicians. In the Ambulatory Clinics, it is impressive to see how pharmacists assess and manage the patients together with the Attending Physicians, and make prospective interventions and give advice all along.

...In summary, this Clinical Attachment Program has broadened our view and has given us insight into many excellent clinical pharmacy services that one can offer, and we look forward to translating our knowledge and vision to benefiting the patients that we serve in Hong Kong."

The above is extracted from the "Thank You" letter written by Josephine and I to the UIC College of Pharmacy near the end of our Attachment Program. But is that all to it? So what is the take-home message? Can we really do it in Hong Kong?

It is impossible to become any specialist in 6 weeks' training. I think my UIC experience succeeded in one thing --- it has further strengthened my will to become a caring pharmacist to my patients. Yes, I have learned how brilliant pharmacists develop good pharmacy services at UIC. But most important of all, the UIC pharmacists had inspired me with the art of caring patients. From In-patient to Out-patient, I witnessed how the pharmacists think from their patient's side, how they lowered their bodies to talk to them, and pat their hands to show support. How many of us are doing this now? We often hear from our patients that many health care professionals are not really listening to them these days. Can we, the pharmacists, begin now to give our patients the personal touch that they want, show them empathy that they deserve, and provide the drug education or service that they really need?

In order to be able to provide better CARE for my patients, I need to be very knowledgable and competent in my chosen area. Care comes first, and then the knowledge and skill shall follow. Admit that we know very little, and continue to learn --- from your patients, from your colleagues, from your journals. Let us all be true Clinicians. Don't treat numbers, but treat your patient. Good lab values doesn't mean anything if your patient is suffering, or even dead, a professor once said to me.

May I end here with what Dr. Lingtak Chan, the MICU Pharmacist, has inspired me:

***Talk** to your patients, **Listen** to them.*
***Discuss** with your physicians, **Learn** from them.*
*Make your presence, Show that you **care.***
*Think as a **Clinician**, and You will be there!*

Figure 15. Beautiful scenery by the Northwestern University in the suburb.

6. ACKNOWLEDGEMENT

There are many parties I need to thank. Firstly, I appreciate Winham Lok and the Chief Pharmacist's Office for their initiative and support of this program. I thank Prof. Alan Lau, the Program's Coordinator, for all his hard work in squeezing me into seeing so many things in 6 weeks. Josephine and I truly appreciated the hospitality that Alan and his wife, Shirley, had given us in Chicago. We feel warmth in the snowy winter.

Needless to say, I am greatly indebted to the excellent clinical pharmacists for their time and eagerness in sharing their expertise with me. Especially to Lingtak and Mary Ann, who inspired me what a caring pharmacist is all about. I also appreciate the Pharmacy Administrators, Drs. Andy Donnelly, Glen Schumock, Jane Engle, for exchanging their experience and visions. Above all, may I extend my deepest thanks to Mr. S.L. Chan, DM(Pharmacy) of PYNEH, for his support and trust all along. Furthermore, I thank all my wonderful colleagues who shared my work during the study leave.

*The author, **Simon Leung**, can be contacted by email: RxSimon@hotmail.com*

Memories from the Windy City, Chicago

Josephine Yung, Pharmacist, Tuen Mun Hospital

Being a pharmacist trained locally, it had always been my dream to work in overseas setting and learn how clinical pharmacists practice there, especially in USA. **Why USA?** It was because clinical pharmacy services are well developed there and I hoped I could, by working with them, learn how to develop clinical pharmacy services and how to work as a clinical pharmacist. Therefore, after the attachment in University of Illinois at Chicago, UIC, I could contribute what I had learned to clinical pharmacy development in Hong Kong.

Figure 1. UIC Medical Centre

Beyond my expectation, during the attachment, not only had I learned about the development of clinical pharmacy and the role of clinical pharmacist in US, also I had learned about the art of care, experienced the joy of saving a life and gained the friendships of pharmacists, pharmacy students, nurses and medical doctors there. Actually, I had gained a few pounds too.

Be a Clinician-Treat the Patient, Not the Number

Whenever we tried to evaluate the conditions of the patients, we always put a lot of efforts evaluating the laboratory data, measurable data....anything that gave us a number. However, we might have ignored the fact that we should not solely rely on the number to tell us the conditions of our patients. Thanks to Lingtak and Simon for inspiring me and telling me the beauty of being a clinical pharmacist. Being a clinician, we should really treat our patient as a human holistically but not just treating the number.

Figure 2. Pharmacist at the Haemodialysis Clinic rounding her patients

Live to Learn-Know What You Don't Know

If I didn't have the experience of working with a clinical pharmacist, I would never know how much clinical skills I need to acquire before I can really work as a good clinical pharmacist. I should admit how much I don't know and don't be overly contented with what I know. Live to learn - that's why I carried an overweight luggage full of books and learning materials back to Hong Kong.

"Winning: We Cannot Direct the Wind but We Can Adjust the Sails"

That came from a poster hanged on the wall in the central pharmacy of UIC. The development of clinical pharmacy services in US was not without obstacles. In fact, clinical pharmacists in US have been facing a lot of problems during these few decades too. They could not change the macro-picture, like health care financing reforms, pharmacist shortage.... However, they adjusted themselves to fit in as if sailor adjusting the sails. That makes me re-think about the situation in Hong Kong. Should we be frightened by the obstacles we have? Should we let our heavy dispensing workload, shortage of pharmacists.....to hinder our steps? NO. It is high time for us to adjust ourselves. It is high time for us to review our everyday working process and practice. It is high time for use to look for opportunities. Sooner and later we will turn our threats into opportunities and finally **WIN WITH FLYING COLOURS**.

Figure 3. Prof. Alan Lau, Simon Leung and myself at the UIC College of Pharmacy

A Lot of Thanks

I should thank everyone who help to make my dream come true:
Dr. Alan Lau & the College of Pharmacy, the University of Illinois at Chicago, for his efforts to organize this marvelous clinical attachment program and for the care he and Shirley (Mrs. Lau) given to us. Simon and I were feeling very much at home in Chicago.

Mr. Winhom Lok & the Chief Pharmacist's Office, for his efforts to organize this marvelous clinical attachment program.

My wonderful boss, Ms Pauline Chu, who let me temporarily not to work for Tuen Mun Hospital for such a long time although I know that everybody, including her, missed me so much when I was out of town.

Dr. Lingtak Chan, Dr. Sinnari Khorana & all professors I met in UIC, for their patience and time in coaching me during the attachment period.

Figure 4. Michigan Avenue at sunset

Common OTC Products Used in Fungal Infection

Gloria Yung

I INTRODUCTION

Hong Kong is a city with sub-tropical climate. The weather is generally hot and humid especially from March to September. This subtropical climate, together with the close and crowded lifestyle of the Hong Kong people, are the contributing factors of superficial fungal skin infections and their frequent recurrence. Most of the commonly fungal infections in community pharmacy settings are not life threatening, but are troublesome as they affect patient health-related quality-of-life. However, they can usually be treated with proper drug use and complementary hygienic control. In this article, the treatment of three common superficial tinea infections (tinea pedis, nail infection, tinea versicolor), and vaginal candidiasis will be discussed.

II TINEA INFECTIONS

Tinea is a fungal infection. The causative dermatophytes include several species of *Microsporum* and *Trichophyton* and one species of *Epidermophyton*. They are fungi that are responsible for most superficial skin, nail and hair infections since they only survive on dead keratin, hair and nails. When the patient is not associated with other risk factors (e.g. multiple drug resistance, immunosuppression) and no secondary infection is suspected, empirical topical antifungal drug therapy can be initiated when presented with the clinical presentations of the tinea infections and after the medical history is assessed by the pharmacist because all dermatophytes respond to the same topical and oral agents. However, referral for culture sensitivity test is recommended when multi-drug resistance is suspected. Additionally, pharmacists can recommend patients to doctors for a fungal culture of the nail fungal infection before initiating a long course of oral treatment.

1) Tinea pedis (Athlete's foot)

Althlete's foot usually presents as blistering eruption with vesicles, pustules, fissures, and inflammation in the toe webs (especially the web between the fourth and fifth toes) or on the soles in acute form. Sometimes, typical ringworm pattern may occur. Excessive sweating of the feet may exacerbate the problem. Because itching is the most troublesome complaint of althele's foot, secondary infection of the lesions may result from intense scratching. A number of patients who have chronic athlete's foot, the hands may also be infected.

For tinea pedis management, topical treatment should be adjunctive to the hyperhidrosis control. Cure rates are higher and treatment courses are shorter with topical fungicidal allylamines than with fungistatic azoles. [1] Topical terbinafine 1% formulations are effective when applied once or twice daily for up to 2 weeks, achieving mycological cure in over 80% of patients with tinea pedis, cutaneous candidiasis and pityriasis versicolor. It is as effective as miconazole 2% cream and naftifine 1% gel in tinea pedis, and more effective than clotrimazole 1% cream. Mycological cure rates achieved with terbinafine generally improve after treatment cessation which is due to the fungicidal mechanism of action and its residual effect in tissue.[2] (Table 1)

In order to keep the feet and toewebs dry, sandals are preferred when it's possible. Personal belongings, which are in contact with infected skin such as shoes and socks should not be shared with others. In addition, powder (not necessary medicated) can be spread between the toe wesb and surfaces to absorb the moisture. In severe cases, aluminium chloride solution can be used adjunctly to control the hyperhidrosis.

2) Tinea versicolor

Tinea versicolor is a common superficial fungus infection which is caused by *Pityrosporon orbiculare*. "Versicolor" means "variation in colour". The lesion is characterized by brownish red or white patches over mainly the upper trunk or limbs. The lesions become more visible and noticeable after sunbathing as lesion areas fail to form pigment owing to the infection.

Topical antifungal treatment with econazole, miconazole, clotrimazole, ciclopirox, or terbinafine creams, ointments, and lotions is effective and can be tried initially when the infection is localized. Shampoo preparation for body washing may be an option when the infection is spread over the body trunk. Similar to the application of anti-dandruff shampoo for seborrheic dermatitis treatment, the shampoo applied should be in contact with the skin for least 5 minutes before rinsing. In addition, pharmacist should inform patients that

Table 1. Examples of topical preparations for tinea infections

Topical medications	Strength and form	Recommended dosage
Azoles		
Clotrimazole	1% cream, 1% lotion, spray	BID for 2-4 weeks
Miconazole	2% cream	BID for 2-4 weeks
Tolnaftate	1% spray liquid	BID for 2-4 weeks
Econazole	1% cream	QD for 2-4 weeks
Ketoconazole	2% cream	QD for 2-4 weeks
Tioconazole	1% cream	BID for 2-4 weeks (up to 6 weeks for tinea pedis)
Allylamines		
Naftifine	1% cream	QD for up to 4 weeks
Terbinafine	1% cream, 1% solution, 1% spray, 1% dermgel	QD - BID for 1 week

the colored patch would not resolve till re-exposing to UV light. The cure rate is usually high; however, recurrence is very common. (Table 2)

3) Nail infection

Nail fungal infection is the infection of either the toe or finger nails by dermatophytes *(tinea unguium)* or candida . According to a prospective epidemiological study on foot disease in Hong Kong, dermatophytes, in particular *Trichophyton rubrum*, are the most common pathogens in both skin and nail infections.[4] All nails may be infected, but the prevalence of toenail infection is higher than that of fingernails. The characteristics of infected nail plate includes discoloring, thickening with accumulation of debris. Vascular disease, diabetes mellitus and obesity were the three most prevalent predisposing factors in fungal nail disease in Hong Kong.[4] Traditional treatments include oral antifungal therapy or removal of nail plate by surgery. With the development of newer nail lacquers, despite the fact that data on the efficacy is still limited, topical treatment with antifungal agents has become a choice in the treatment of onychomycosis which has not settled under the nail in the nail bed. Topical treatment has a significantly lower potential for adverse drug reactions and drug-drug interaction. [3] In recent findings, a combination of oral and topical treatment could improve the outcome of onchomycosis treatment. [5] (Table 3)

III VAGINAL CANDIDIASIS

Candida albicans is the most common causative pathogen for 66-75% of fungal vulvovaginal infections. Candida-induced vaginitis is usually accompanied by a thick, curd-like, smelliness discharge.(Table 4) Pruritis and edema of the vulva are the usual associated symptoms. When secondary infection occurs, the vagina and vulva can become markedly edematous and tender. Sexual intercourse may be painful or impossible because of the swollen vagina. Women who are obese, diabetic, immunosuppressed, and who have had recent broad-spectrum antibiotics use (especially ampicillin, tetracyclines, clindamycin, and cephalosporins) and oral-contraceptive use (containing 75-150 micrograms of estrogen) are predisposed to candida vaginitis. [6] Similar to other superficial fungal infections, vulvovaginal candidiasis may be exacerbated by moisture, heat and friction.

Table 2. Shampoo preparations effective for treating tinea versicolor

Shampoo preparations	Direction of use
2% pyrithione zinc shampoo	Apply daily for 10 min; shower off; reapply to affected area; shower on rising. Repeat for 14 days
2.5% selenium sulphide shampoo	Apply daily for 10 min for 7 consecutive days
2% ketoconazole shampoo	Apply daily for 10 min for 5 consecutive days

Table 3. Topical preparations marketed for nail fungal infection

Drug name	Direction *
5% amorolfine nail lacquer (Loceryl nail lacquer 5%)	Once to twice weekly
8% ciclopirox olamine nail lacquer (Batrafen nail lacquer)	Apply QD
28% Tioconazole nail solution (Trosyd nail solution)	Apply BID

** Remarks: Prescribing information of individual products should be consulted.*

Since the symptoms of vaginal canadiasis resemble more serious infections, patient are advised to have at least one physician-diagnosed vaginal fungal infection before self-treating with OTC preparations. In addition, pregnant women should be referred to physicians once vaginitis symptoms develop.

Topical nonprescription antifungals are ideal first-line therapy for candidal vaginitis. [6] Adverse reactions are generally mild. Antifungal preparations for vaginal uses are available as pessary and cream. (Table 5) If the problem is mainly intravaginal, pessary is preferred. However, pessary together with antifungal cream should be recommended when both vulvar and intravaginal area are infected. Most of the intravaginal preparations are used once daily, preferably at bedtime to facilitate retention. Studies found that single-dose topical administration of clotrimazole was at least as effective as the multiple-dose regimen. [7] [8] [9]. However, from a practical point of view, multiple-dose regimen is preferred when patient is not familiar with the application of intravaginal products.

Patients should avoid wearing tight-fitting clothes (e.g. jeans) and cotton-type underwear should be encouraged. Frequent douching is not recommended as this disturbs the acid-base balance and the normal flora of the vaginal area. Pharmacists must also counsel sexually active patients; however, that the use of many vaginal products, such as antifungals, may damage certain barrier contraceptives, such as diaphragms and condoms. Complementary therapies such as oral *Lactobacillus acidophilus* preparations have also been promoted for vaginal infection prophylaxis and adjunct treatment, however high-quality evidence for their use is still lacking.[10]

IV PHARMACIST COUNSELLING

As superficial fungal infections are among the most common self-treated conditions, pharmacists are often consulted by patients for assistance and recommendations for treatment and prophylaxis. Proper recommendations can prevent patient from suffering unnecessary discomfort, delayed healing, and additional treatment cost. Pharmacists also play a very important role in providing the necessary information on possible adverse drug reactions and precautions of antifungal drugs to patients. (Table 6)

Table 4. Characteristics of vaginal discharge

Characteristics	Normal	Candidiasis	Trichomoniasis	Bacterial Vaginosis
Color	White or clear	White	Yellow-green	White to gray
Odor	Non-odorous	Non-odorous	Malodorous	Fishy smell
Consistency	Floccular	Floccular	Homogenous	Homogeneous
Viscosity	High	High	Low	Low
pH	≤ 4.5	4-4.5	5-6	> 4.5
Other characteristics	-	Thick, curd-like	Frothy	Thin

Ref: 45.4 Gynecological disorders. Women's Health. Handbook of applied therapeutics. Lippincott Williams & Wilkins

Table 5. Recommended Regimens for vulvovaginal candidiasis

Intravaginal agents	Strength	Direction of use
Clotrimazole	100 mg pessary	1 pessary for 7 d *
	100 mg pessary	2 pessaries for 3 d
	500 mg pessary	1 pessary at night in single dose
Miconazole	200 mg pessary	1 pessary for 3 d
	100 mg pessary	1 pessary for 7 d
	2% vaginal cream	5 g intravaginally for 7 d
Econazole	150 mg pessary	1 pessary at night in single dose
Nystatin	100 000 unit pessary	1 pessary for 14 d
Tioconazole	6.5% ointment	5 g intravaginally in a single application
	2% vaginal cream	1 applicatorful intravaginally Q HS for 3 d
	100 mg pessary	1 pessary for 3 d

Notes:

** Commercial packs of six 100mg clotrimazole vaginal tablets as a course of treatment are available in Hong Kong market*

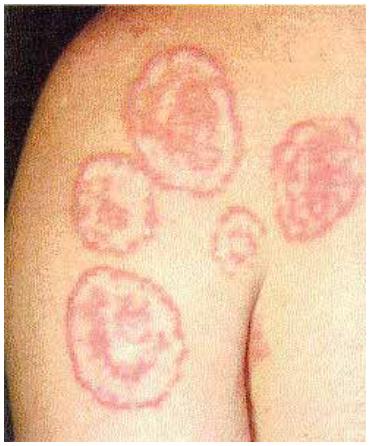
 # The Centers of Disease Control and Prevention states that the use of vaginally administered oil-based preparations may weaken latex products such as condoms and diaphragms.

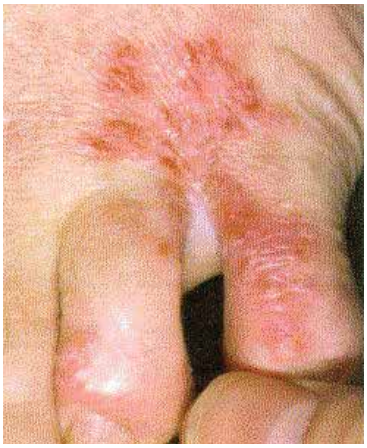
Ref: AAP 2000 Red Book: Report of the Committee on Infectious Diseases, 25th ed.

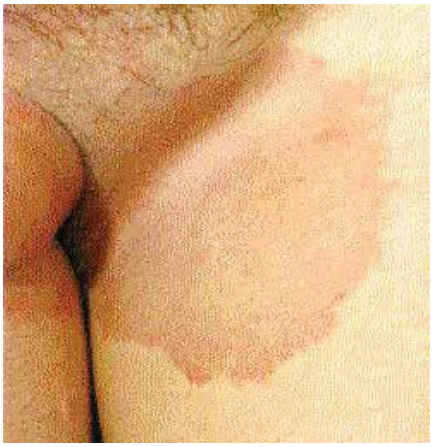
Table 6. Possible side effects and precautions of some oral antifungal drugs

Drug	Absorption	Monitor blood levels	Possible adverse drug reactions
Terbinafine *(Lamisil)*	Acid in stomach not necessary	Yes	Headache, gastrointestinal symptoms, rare taste disturbance, rare hepatitis, rare leukopenia
Itraconazole *(Sporanox)*	Acid in stomach is necessary	Yes	Nausea, vomiting, rare hepatitis, pruritus, edema
Fluconazole *(Diflucan)*	Acid in stomach not necessary	Yes	Nausea, vomiting, rash, pruritus, rare hepatitis, Stevens-Johnson syndrome
Ketoconazole *(Nizoral)*	Acid in stomach is necessary	Yes	Nausea, vomiting, pruritus, headache, adrenal insufficiency, decreased libido, gynecomastia

Ref: Chapter 522a. Skin diseases of general importance. Part II. Goldman: Cecil Textbook of Medicine, 21st ed







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Gloria Yung graduated from CUHK and is now working as a resident pharmacist in the Hong Kong Buddhist Hospital.

Basic Knowledge in Bandaging - *A Pharmacist's Guide*

Ann Chiang

The use of materials to bind a wound is as ancient as medicine itself. There has always been a strong need from the public to obtain the necessary knowledge from pharmacists on how to treat different types of wound. Therefore pharmacists should have the fundamental knowledge to differentiate and to apply the different types of bandages and dressings which are available on the market. Acquisition of such knowledge is essential for pharmacists to deliver quality pharmaceutical care.

I BANDAGES

When choosing and applying a bandage, it is important to differentiate between traditional and the ritual on one hand and what is best and most cost effective for the patient on the other hand. Bandages can be used for a number of purposes:

- Keeping a dressing in place
- Supporting an injured joint
- Assisting venous return in the lower leg, providing a pressure gradient to encourage the flow of blood back to the heart and reduce edema and swelling by compressions
- As a prophylactic in sports to prevent injury
- As a pressure bandage to help control bleeding
- Controlling post-surgical venous-oozing

Effectively, you can divide bandages into 3 types with reference to their functions:

1. Retention
2. Support
3. Compression

And each type is completely different in its composition and structure and its application in practice.

1. Retention bandages

The role of the retention bandages is to effectively hold a dressing in place. They are particularly useful when a patient has very friable skin, especially in the elderly, since such skin can be easily damaged where the dressing to be held in place with any type of adhesive tape. For many years, cotton crepe bandages have been used to hold dressings in place for this purpose. However, today there are a number of more effective and appropriate bandages that may be used. This includes a light weight crepe coated with a thin latex which sticks to itself and not to the skin, hair or clothing. You only require a very small length to hold the dressing in place compared with using a complete roll of a standard crepe bandage. Therefore it is cost effective as well. This type of bandage comes in widths that are appropriate for fingers, toes, limbs and for the head. Example of this type of bandage is Easifix™.

The other type of product is the elasticated tubular bandage available in light weight form that may be cut to the size required and be placed over the dressing, holding it in place. Example of this type is Tubifast™. Such products also come in different sizes to suit the appropriate body parts.

2. Support bandages

Support bandages are of a heavier construction and are made from both natural and synthetic fibres. Their main role is in the support of joints in strains and also in the management of muscular injuries. Strong support bandages can be used singularly or in combination to restrict movement, to help reduce some of the edema and act as a mean of support following soft tissue injuries. Example of this type of bandage includes heavy duty crepe bandages such as Elastocrepe™ and the heavier weight cohesive bandages such as Coban™.

Besides, a single layer of the heavier weight tubular bandage may also be used for this purpose e.g. Tubigrip™.

3. Compression bandages

Compression bandages are used as one of the main treatment modalities in the management of venous disease, especially when there is an association between venous ulcers and varicose veins. Their purpose is to aid the healing of the ulcer and ultimately in the management of the venous return, to help prevent reformation of a venous ulcer. Effective therapeutic compression starts with a sub-bandage pressure of 18mmHg at the ankle. Anything lower than this, whilst appropriate for support, is not appropriate for the treatment of venous leg ulcers or their prevention. The primary aim of compression is to reduce the pressure in the superficial veins to encourage venous return to the heart by increasing the velocity of flow in the deep veins. The aim is also to discourage edema by reducing the pressure difference between the capillaries and the tissue. The most effective method is to apply graduated compression from the toe to the knee. The highest pressure should be exerted at the ankle, gradually falling to about 50% at the knee. The action of compression bandages is to enclose the leg with pressure firm enough to compress the pathologically distended veins thus enabling valves to function more appropriately, increasing the velocity of the venous blood stream and normalizing the return of the flow of blood to the heart. The accumulated fluid and waste products are removed from the affected tissue by the accelerated circulation rate resulting from the application of the pressure bandage. Compression bandages are also used in the management of lymphoedema, a condition in which the intercellular spaces contain an abnormal amount of lymph due to obstruction in the lymph drainage.

a) Types of compression bandages

Compression bandages are available in two types:

i) High stretch compression bandages

These bandages have an extensibility ranging from 130 to 200%. They have high elasticity, high to medium resting pressure and high to medium working pressure. They exert their effects mainly superficially working in combination with the muscles and they are indicated for the treatment of venous edema and the management of venous ulcers. An example of high stretch compression bandage is Tensopress™.

ii) Short stretch bandages

These bandages have an extension ranging from 30 to 90%, low elasticity,

low to slight resting pressure but high to very high working pressure. They exert their effects mainly deep within the limb and they are indicated for both venous edema and lymphoedema. An example of short stretch bandage is Tensolan™.

b) Multi-layer bandages

A recent development in bandaging has been the introduction of a Charing-Cross four layered system. This combines a piece of orthopaedic wool, a crepe bandage, a light weight compression bandage and a cohesive bandage in multiple layers. This combination achieves 40mmHg at the ankle, graduating to 17mmHg at the knee. A number of published studies have shown good healing rates in 12 weeks using the system. An example of the four layered system is Profore™.

The other forms of compression garment include the straight tubular bandage. When used for this purpose it is usually applied in multiple layers commencing with a full bandage from toe to below knee, a second from toe to mid calf and a third from toe to ankle. This type of product is also available in shaped versions that provide the graduated compression. The application of a single layer of shaped tubular bandage will produce a pressure of 12-15mmHg and this may also be used in multiple layers.

c) Compression stockings

Compression can also be achieved through use of compression stockings. Stockings may form part of the treatment of venous leg ulcers, as an ongoing management modality of venous disease and for the prevention of venous stasis. They may be used alone or in conjunction with systemic medication. Compression stockings are usually worn by non-ambulatory patients pre and post surgery. In the case of venous leg ulcers, stockings overcome the difficulty of patients or family members having to reapply compression bandages over dressings.

Deep vein thrombosis and pulmonary embolism are potentially major health problems in terms of their immediate and long term effects. A number of chronic leg ulcers are due to post thrombic venous disease. Hence it is recommended to use anti-embolic stockings in low risk patients and in combination with heparin in moderate to high risk patients.

Many people who spend extended hours each day on their feet usually complain of tired, aching legs. This is due to the difficulty for venous blood to return to the heart against gravity, when one is not moving about. Such lack of return is known as venous stasis. Stockings are very supportive for venous stasis. Some patients should also wear such stocking when traveling long distances to minimize edema and thrombosis development.

d) Compression ratings

Compression stockings are available in a number of different compression ratings. There are two different classifications for compressions; a British classification and a European classification. (Tables 1 and 2)

e) Contraindications for the use of compression bandages/stocking

Great care must be taken before applying any pressure garment where there is an indication of arterial diseases. It is therefore important that before compression bandages or similar items are used on a patient, their peripheral arterial circulation should be checked to ensure that they may not be compromised by the application of compression bandages. Some simple observation will generally identify patients who are potentially at risk. (Table 3)

If a patient is observed to have some of the negative results (Table 3) they may need to be referred for a vascular assessment before compression is used. Some hazards regarding the use of compression include skin necrosis, direct trauma and ulceration from inappropriately applied compression bandaging and may eventually lead to amputation. It is essential when applying a compression bandage to a leg especially where there is unevenness of circumference that the area around the ankle in particular is padded out with cotton wool pads/gauze to ensure a even distribution of compression along the leg.

II PLASTERS AND TAPES

There are many types of plasters and tapes available in the pharmacy, and they are usually composed of simple cotton backing, cotton/synthetic mixtures and a number of synthetic fabrics. They are used both as a preventive measure in sports/exercise as well as an adjunct to wound management. The former applies to rigid strapping tapes with a zinc oxide backing to prevent injuries, whereas the latter is intended to be used as retention dressings over cuts, burns and grafts.

The major groups of plasters and tapes are:

- zinc oxide tapes
- rigid zinc oxide sports tapes
- elastic adhesive plasters (Elastoplast™, Leukoplast™)

Table 1. British Classification for compression stockings

Classification Group	Indications
Class 1 (14-17mmHg)	Superficial and early varices, varicosis during pregnancy.
Class 2 (18-24mmHg)	Medium varices, ulcer treatment and prevention of recurrence, varicosis during pregnancy, mild edema.
Class 3 (25-35mmHg)	Gross varices, post thrombotic venous insufficiency, gross edema, ulcer treatment and prevention.

Table 2. European Classification for compression stockings

Classification Group	Indications
Class 1 (18-22mmHg)	Tired aching legs, minor varicosis, varicosis during pregnancy.
Class 2 (25-32mmHg)	Mild chronic venous insufficiency, treatment of venous leg ulcers and prevention of recurrence, post vein surgery, edema reduction.
Class 3 (36-46mmHg)	Pronounced varices with edema, pronounced chronic venous insufficiency, mild lymphoedema.
Class 4 (>59mmHg)	Pronounced post thrombotic syndrome, severe lymphoedema.

Table 3. Signs of referral in patient using compression bandaging

Observation	Normal signs	Referral signs
Foot Temperature	Warm	Cold
Foot Colour	Pink	White
Toe Refill after Squeezing	Fast	Slow
Foot Pulses	Present	Absent

- polyacrylate tapes
- paper tapes (Micropore™, Albupore™)
- transparent tapes (Transpore™, Blenderm™)
- retention dressing tapes (Hypafix™)

1) Zinc oxide adhesive plasters

The characteristics of zinc oxide plasters are,
- strong adhesion
- good immediate strength
- high permanent adhesive power at skin temperature.

Zinc oxide adhesives are manufactured by adding a by-product of latex with natural resins to a zinc oxide base material. The latex by-product provides elasticity and also prevents excessive residue on the skin when the plaster is removed. Zinc oxide plasters are often used as rigid strapping in sporting injuries. An example is Strappal™.

2) Polyacrylate adhesive plasters

These are hypoallergenic, have good immediate bonding strength when pressed firmly into place, and have excellent permanent adhesive powers. Their unique mixtures of synthetic resins and backing materials provide a variety of hypoallergenic plasters that range from permeable to water-proof, rigid to elastic. The synthetic resins resist the impact of heat, ultra-violet light and other environmental factors. The more modern polyacrylate plasters has been used increasingly for dressing fixation, for use in island dressings and in general first aid.

Table 4. Adverse effects of taping and the possible causes

Adverse effects of taping	Causes
Tension	Caused by pulling or stretching the tape too tightly, resulting in blisters at each end of the tape.
Mechanical injury	Skin damage due to incorrect application or removal of tape which is too aggressive.
Maceration	Exposure of the skin to moisture by non vapour-permeable tapes.
Folliculitis	Inflammation of the hair follicles by blockage of the hair shaft.
Adhesive residue	Part of the adhesive remaining on the skin after tape removal.
Allergic reaction	Allergy to the adhesive compound.

3) The hazards of taping

Taping may be a simple process. However, it is possible that further damage or wound to the skin might occur through incorrect use of adhesive tape. Table 4 illustrates the few consequences that one should avoid when applying tapes.

Ann Chiang is a pharmacist from a local pharmacy chain. She has been actively involved in various health promotion campaigns, public forums and pharmacists training programs in both Singapore and Hong Kong.

Poisons List Plus
Helpers Wanted!!

藥物分類是否真的看得見但摸不清呢？你有否想像過一份中英文對照由A-Z整齊排列的毒藥表。除此之外，更具備附表1、附表2和附表3的表列毒藥。

POISONS LIST	藥名	S1	S2	S3
Abacavir; its salts	阿巴卡韋；其鹽類	√		√
Baclofen	巴氯芬	√		√
Cabergoline; its salts	卡麥角林；其鹽類	√		√
Dacarbazine	達卡巴嗪(氮烯唑胺)	√		√
Econazole; its salts	益康唑；其鹽類			
Famciclovir; its salts	泛昔洛韋；其鹽類	√		√
Gabapentin; its salts	加巴噴丁；其鹽類	√		√
Halofantrine; its salts	鹵泛群；其鹽類	√		√
Ibandronic acid; its salts	Ibandronic acid；其鹽類	√		√
Ketamine; its salts	氯胺酮；其鹽類	√		√
Labetalol; its salts	拉貝洛爾；其鹽類	√		√
Mangafodipir; its salts	Mangafodipir；其鹽類	√		√
Nabumetone	萘丁美酮	√		√
Octreotide; its salts	奧曲肽；其鹽類	√		√
Paclitaxel	紫杉醇	√		√
Quetiapine; its salts	富馬酸喹硫平；其鹽類	√		√
Rabeprazole; its salts	雷貝拉唑；其鹽類	√		√
Salbutamol; its salts	沙丁胺醇；其鹽類	except in aerosol		except in aerosol
Tacrine; its salts	他克林；其鹽類	√		√
Urapidil; its salts	烏拉地爾；其鹽類	√		√
Valaciclovir; its salts	伐昔洛韋；其鹽類	√		√
Warfarin salts	華法林鹽類	√		√
Xamoterol; its salts	扎莫特羅；其鹽類	√		√
Zoxazolamine; its salts	氯苯唑胺；其鹽類	√		√

一份類似以上毒藥表的藍圖已經由熟識藥物分類的專家完成編寫。為了讓藥劑師更方便地使用這份毒藥表，現誠邀有興趣的藥劑師參與完善這份毒藥表的工程。希望參與編寫和完善這份毒藥表的藥劑師請聯絡 **Hong Kong Pharmaceutical Journal (e-mail: pharmjhk@yahoo.com).**

Chance of a Cure in Hepatitis C

Christine Yip

2 CE Units

I VIRAL HEPATITIS

Hepatitis C is an inflammation of the liver, caused by an infection by the hepatitis C virus (HCV). It can result in cirrhosis, digestive haemorrhage, liver failure and liver cancer. [1]

HCV is not a single virus. It is a member of the Flaviviridae family of viruses. [2] A distinct characteristic of HCV is its genetic heterogeneity. Six major genotypes and over 100 subtypes have been described. [2] The most common genotypes are types 1, 2 and 3. Genotype 1 is the most common form of the virus in North America and Europe, and it is also the most difficult to treat. Genotypes 2 and 3 are commonly referred to as genotype "non-1" and are easier to treat. It has been well established that the responses to interferon therapy vary widely for patients carrying different HCV genotypes.

II HEPATITIS C: FACTS AND FIGURES

It has been estimated that the worldwide prevalence of chronic hepatitis C infection is over 170 million people (3% of the world's population). [1] There are 4 million infected people in the United States (US), 5 million in Western Europe and 2 million in Japan.

Situation in Hong Kong - The Hong Kong Red Cross Blood Transfusion Service (HKRCBTS) conducts regular screening and found that 0.2-0.3% of new blood donors had evidence of past infection of hepatitis C. [3] Genotypes 1b and 6a are the most common subtypes of the HCV virus found in Hong Kong. [4]

III SYMPTOMS

Symptoms of hepatitis C can vary widely from subclinical asymptomatic disease to fulminant hepatic failure. Initially the patient will have the following symptoms: malaise, weakness, nausea, vomiting, fever and abdominal pain. After 3 to 10 days, jaundice may become apparent. [5]

IV IMPACT ON HEALTH

It is widely accepted that HCV infection is a major cause of end-stage liver disease and hepatocellular carcinoma (HCC). [6]

Acute infection is typically mild and subclinical, yet there is a high rate of chronicity after infection. As many as 55-85% of individuals who have contracted HCV infection will develop chronic infection and hepatitis. [14] Continuous inflammation of the liver can cause cirrhosis. This condition occurs when extensive liver damage leads to formation of scar tissues. Cirrhosis is irreversible and can lead to liver failure. After approximately 30 years, one-third of infected patients will progress without treatment and one-third will progress in less than 20 years. The other one-third will probably never progress to cirrhosis. [1]

Hepatitis C is the major reason for liver transplantation, together with alcoholic cirrhosis in Europe and in the US. [1]

V EPIDEMIOLOGY

HCV is primarily transmitted in blood or blood products or by sexual contact. [5] Receiving contaminated blood or sharing contaminated drug injection equipment are two of the most common ways by which HCV is transmitted. [7, 8] Infection can also occur through the use of non-sterile needles in the case of, for example, piercing of ears or tattoo. [14]

High-Risk Populations - Individuals at greatest risk of infection include intravenous drug users, recipients of blood transfusions prior to 1991, patients with frequent exposure to blood products, and health care workers. High-risk sexual behaviour individuals are in the moderate-risk group. [1]

VI DISEASE MANAGEMENT

1. Goal of Treatment

Uncomplicated acute hepatitis is managed by symptomatic treatment. Interferon has been suggested to prevent the progression of acute hepatitis C to the chronic stage. [9]

There are three main goals for the treatment of hepatitis C: [14]

i. To eradicate the virus,
ii. To prolong the suppression of viral replication, and
iii. To reduce hepatic inflammation.

The ultimate goals are to prevent the development of cirrhosis and its complications and prevent transmission to other people (e.g. health care professionals).

2. Algorithm for treatment decision

Figure 1 shows the algorithm for the treatment decision.

Liver biopsy is performed before initiation of antiviral treatment as it allows identification of the causes of liver disease and evaluation of the extent of hepatic inflammation and fibrosis. Such information, particularly the presence or absence of cirrhosis, is essential in predicting a patient's long-term prognosis, and in establishing a management plan for monitoring of hepatic decompensation and development of hepatocellular carcinoma. [14]

PCR Amplification. Polymerase Chain Reaction (PCR) is the latest technique for detection of HCV RNA. It quantitatively assesses the HCV RNA levels via signal amplification. Different manufacturers have systems which can detect different levels of copies of RNA/ml. Sample dilution may be required if HCV RNA levels are too high. [14] HCV RNA level is the most specific test to diagnose the infection.

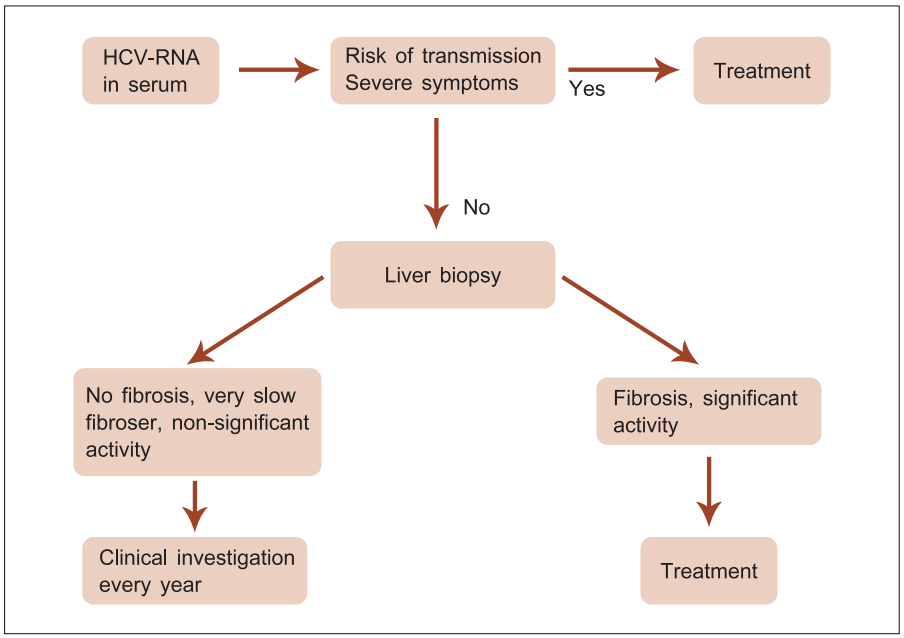

Figure 1. An algorithm for treatment decision

3. Therapeutic endpoints

There has been consensus at the 1997 National Institutes of Health Consensus Development Conference on the Management of Hepatitis C that sustained virological response (SVR) is the optimal surrogate endpoint for treatment of hepatitis C. [10]

a) Definition of virological response

In therapeutic clinical trials, virological response to HCV is defined by the absence of detectable HCV RNA in the serum by an assay with a sensitivity of at least 100 copies (50IU) per ml. Testing is regularly performed during treatment, at the end of treatment, and at 6 months after completion of treatment. [10]

b) Definition of sustained virological response (SVR)

Sustained virological response (SVR) is the most reliable endpoint for evaluation of treatment effect. It is defined by the absence of detectable HCV RNA in the serum using an assay with a sensitivity of at least 100 copies (50IU) per ml at the end of treatment and at 6 months after treatment has completed. [10]

SVR is associated with long-term beneficial clinical outcomes such as improvement in quality of life. Follow-up liver biopsy results showed that patients who achieved SVR had significantly lower extent of liver inflammation and fibrosis. [10]

4. Conventional therapy for chronic hepatitis C infection

a) Interferon alpha

Interferon alpha had been the only antiretroviral treatment option for patients with chronic hepatitis C infection for almost a decade. Treatment with interferon alpha is associated with SVR in less than 20% of treated patients. [2]

Interferon alpha is natural glycoproteins produced by cells in response to viral infections. Interferon alpha inhibits the replication of many viruses, including hepatitis viruses, through a variety of mechanisms. These include direct antiviral effects (inhibition of viral attachment and uncoating, induction of intracellular proteins and ribonucleases); and amplification of specific (cytotoxic T-lymphocyte [CTL]) and nonspecific (natural killer cell) immune responses. [11] The efficacy of interferon alpha in hepatitis C infection is probably attributed to its direct antiviral mechanisms.

Currently there are few indications for interferon monotherapy since the introduction of combination therapy with interferon alpha and ribavirin in 1998, and interferon alpha monotherapy should only be given to patients who are unable to tolerate ribavirin. The usual regimes are listed in the Table 1.

The main severe adverse events are depression, suicidal ideation, suicide, and sustained hypothyroidia and the most frequent adverse events are flu-like symptoms and alopecia. [1]

b) Ribavirin and combination therapy

Ribavirin is an orally active synthetic guanosine analogue. It has in-vitro activities against several DNA and RNA viruses, including the flaviviridae such as HCV [15, 16]. Its mechanisms of action in HCV infection, particularly the mechanisms that account for the increased efficacy of interferon when used in combination, are not clear. [17, 18] The most frequent adverse event with ribavirin is haemolytic anaemia. Ribavirin is contraindicated in pregnancy and in patients with child bearing potential as it is reported to be teratogenic in animals. [5]

The combination therapy significantly improves the rate of SVR to more than 40%. [12] However, monotherapy is still preferred if patients have anaemia, renal insufficiency [13], or develop hypersensitivity to ribavirin. If patients have pre-existing conditions such as significant cytopenia, severe depression or other psychiatric conditions, severe congestive or ischaemic heart disease, poorly-controlled diabetes, seizure disorders, inflammatory bowel disease, neuropathies, and autoimmune or potentially immune-mediated diseases (such as rheumatoid arthritis or systemic lupus erythematosis), interferon should be used with extreme caution or even avoided. [14]

5. New therapies

Table 1. Recommended regimes for interferon therapy with or without ribavirin for treatment of chronic Hepatitis C

Therapy	Dosage (by s.c. or i.m. injection)	Duration of treatment
Interferon alfa-2a		
Monotherapy	3 - 6 million units 3 times weekly Then 3 million units 3 times weekly Or 3 million units 3 times weekly	6 months 6 months 12 months
Combination therapy	3 - 4.5 million units 3 times weekly	6 months
Interferon alfa-2b		
Monotherapy	3 million units 3 times weekly	12 - 18 months or up to 24 months
Combination therapy	3 million units 3 times weekly	6 - 12 months

The natural history of HCV-related liver disease is variable among individuals, but without effective treatment strategies, the prevalence of hepatitis C-related morbidity and mortality is expected to increase nearly 3-fold by the year 2015. [19-22]

Recent clinical trials showed that the combination of pegylated interferon and ribavirin improves the rate of SVR to over 50% with an acceptable safety profile. [23] Peginterferon, in place of interferon, is considered to be the first-line treatment in combination with ribavirin for patients with chronic hepatitis C, according to the US National Institute of Diabetes and Digestive and Kidney Disease (NIDDK). [24]

a) Pegylation

Pegylated interferon (Peginterferon, PEG-INF) represents the most recent advance in the treatment of patients with chronic hepatitis C. Pegylation, which is the use of liposomal carriers and modification of therapeutic molecules through the attachment of poly(ethylene glycol) [PEG] moieties, is the commonest approach to enhance the delivery of parenteral agents. [25]

There are two peginterferons approved for sale in Hong Kong and in countries such as the US and European Union; namely PEG-INF alfa-2a [26] and PEG-INF alfa 2b [27], which differ in the structure of the PEG moieties. Peginterferons have a prolonged plasma half-life that allows once-weekly dosing. PEG-INF alfa-2a is predominantly metabolized in the liver, whereas PEG-INF alfa-2b is eliminated predominantly renally. [28]

The highest response rates for treatment of chronic hepatitis C have been achieved using the combination of peginterferon and ribavirin. Interestingly, the major determinant of treatment outcome is the HCV genotype where patients with genotype 1 achieve a higher rate of SVR. [10]

b) Peginterferon alfa 2a

Clinical trials showed that by week 12, 86% of patients treated with peginterferon alfa-2a plus ribavirin achieved a virological response, defined by a 2-log decrease from base-line HCV RNA levels or no detectable serum HCV RNA. Among the early responders, 65% subsequently had achieved SVR. [29] In patients with chronic HCV infection with or without cirrhosis, peginterferon alfa-2a resulted in higher rates of end-of-treatment and sustained virological response compared to standard interferon. [30-32]

Peginterferon alfa-2a is indicated for the treatment of histologically proven chronic hepatitis C in adult patients with elevated transaminases and who are positive for serum HCV-RNA, including patients with compensated cirrhosis. Combination therapy with ribavirin is indicated in previously untreated patients as well as in those who have previously responded to interferon alpha therapy but subsequently relapse after treatment was stopped. Monotherapy is indicated mainly in case of intolerance or contraindication to ribavirin. [33]

The recommended dose is 180mcg once weekly by subcutaneous administration, given in combination with oral ribavirin or as monotherapy. Dosage adjustment is required for patients who experience moderate to severe adverse reactions such as haematological toxicity and fluctuation in liver function tests. The dose of ribavirin is based on the patient's weight. The duration of combination therapy depends on the viral genotype; genotype 1 carriers should receive 48 weeks of therapy whereas patients with genotype non-1 may receive 24 weeks of therapy. The duration of peginterferon alfa-2a monotherapy is 48 weeks. [33]

Compared with standard interferon plus ribavirin therapy, combination therapy based on peginterferon alfa-2a is associated with less depression and fewer influenza-like symptoms. [24] The most commonly reported undesirable effects include fatigue, headache, pyrexia and myalgia, the frequency and severity of which are similar for peginterferon and interferon alfa-2a. These adverse events are mostly mild to moderate in severity and are manageable without dose reduction or discontinuation of therapy. [33]

c) Peginterferon alfa 2b

Peginterferon alfa-2b is indicated for use as monotherapy or in combination with ribavirin for the treatment of chronic hepatits C in patients with compensated liver disease who have not been previously treated with interferon alpha and are at least 18 years of age. [28]

The recommended dose of peginterferon alfa-2b monotherapy is 1mcg/kg/week. The duration of treatment is one year. For combination therapy with ribavirin, the recommended regime is peginterferon alfa-2b 1.5mcg/kg once weekly and ribavirin 800mg per day in 2 divided doses. Dosage reduction is required in patients who develop serious adverse reactions such as depression and haematological toxicity. [28]

In clinical studies of peginterferon alfa-2b/ribavirin combination, the most common adverse events were psychiatric symptoms which occurred in 77% of patients and included most commonly depression, irritability and insomnia. Suicidal behaviour occurred in 2% of all patients during treatment or during follow-up after treatment was stopped. [28] Other adverse events included fatigue or headache (~30%) and fever or rigors (~50%), the severity of which decreased as treatment continued. Up to 75% of patients had application site inflammation and reaction, double the frequency with standard interferon alfa-2b. The incidence of severe adverse events tends to be higher in the peginterferon than in the standard interferon groups. [28]

6. Management of Relapsers and Non-Responders

A relapser is a patient who has undetectable HCV RNA in the serum at the end of treatment, but the HCV RNA level becomes detectable after cessation of therapy.

If a patient has been treated with combination of interferon and ribavirin, the best strategy is to use peginterferon alpha/ribavirin combination therapy. If the patient relapses after cessation of this combination therapy, the strategy may be to administer treatment for a longer duration or to use a triple therapy that includes amantadine. [1]

The REPEAT study (Re-treatment with Pegasys in patients not responding to prior PEG-INF alfa-2b/ribavirin combination therapy) is underway to investigate the efficacy of PEG-INF alfa-2a in hepatitis C patients who do not respond to treatment with PEG-INF alfa-2b. It has been postulated that non-responders to PEG-INF alfa-2b may have a different pattern of viral clearance compared to patients who are able to achieve SVR. Although both are peginterferons, PEG-INF alfa-2a is a much larger molecule

than PEG-INF alfa-2b. Moreover, they have different pharmacological properties, which means that they may produce different clinical outcomes. [34]

7. Future treatment options

Although there has been significant advance in our understanding of the molecular virology of hepatitis C virus as well as the treatment modalities of chronic hepatitis C, current therapies are only effective in just over half of the patients. Moreover, the treatment is expensive, prolonged and may not be suitable for some patients due to contraindications. [28, 33]

A number of novel and potential usefully compounds are currently under development. Neutralizing antibodies or receptor inhibitors are being designed to neutralize the virus outside the hepatocytes [35], thereby preventing viral binding, uptake and uncoating. Intracellular HCV replication may be blocked in a variety of ways including inhibition of host or viral enzymes [36], and use of anti-sense oligonucleotides or ribozyme peptides [37]. By enhancing the host immune response to HCV by passive or adaptive immune transfer, the elimination of infected cells may also be facilitated. [38] Finally, agents such as interleukin-10 may be used to block the actions of proinflammatory cytokines, resulting in direct inhibition of hepatic inflammation. [39] These and other exciting strategies are currently in early development stage; it will take several years to determine their safety and efficacy in human before their approval by health authorities.

Christine Yip graduated in the UK and she is now working in a regulatory affairs department for an international pharmaceutical company.

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Questions for Pharmacy Central Continuing Education Committee Program

1. Which of the following statements about the Hepatitis C Virus (HCV) is false?

a. Genotype 1 is the predominant genotype of HCV in North America and Europe.
b. It belongs to the Flaviviridae family of viruses.
c. HCV of Genotypes 2 and 3 are more difficult to treat.
d. There are six major genotypes of HCV.
e. Patients infected with different genotypes of HCV may have different prognosis.

2. Which of the following statements about Hepatitis C is false?

a. Hepatitis C is a major cause of end-stage liver disease and hepatic carcinoma.
b. Hepatitis C is a leading cause of liver transplant.
c. The rate of development of chronic Hepatitis C following acute infection is over 50%.
d. Patients with Hepatitis C may present with malaise, fever, jaundice, nausea and vomiting.
e. Essentially, all patients infected with Hepatitis C will develop cirrhosis as the disease progresses.

3. Which of the following population groups are at highest risk of Hepatitis C infection?

a. People engaged in high-risk sexual behavior
b. Intravenous users
c. Health care workers
d. (a) and (b) only
e. (b) and (c) only

4. In major clinical trials of treatment for chronic Hepatitis C, sustained virological response (SVR) is commonly defined by:

a. Serum HCV RNA level <1,000 copies per ml at the end of treatment and at 6 months after treatment has completed.

2 CE Units

Chance of a Cure in Hepatitis C

b. Serum HCV RNA level <1,000 copies per ml at the end of treatment and at 12 months after treatment has completed.
c. Serum HCV RNA level <100 copies per ml at the end of treatment and at 6 months after treatment has completed.
d. Serum HCV RNA level <10 copies per ml at the end of treatment and at 6 months after treatment has completed.
e. Serum HCV RNA level <10 copies per ml at the end of treatment and at 12 months after treatment has completed.

5. Which of the following statements about interferon alpha in the treatment of chronic Hepatitis C is (are) true?

a. Sustained virological response is only achieved in 30% of patients treated with interferon alpha monotherapy.
b. Interferon alpha is natural glycoproteins.
c. The usual duration of monotherapy with interferon alpha-2a is 6 to 12 months.
d. (a) and (b)
e. (b) and (c)

6. Ribavirin:

a. Is an adenosine analogue.
b. Is associated with hemolytic anemia.
c. May be used in pregnant women.
d. Cannot be used concomitantly with interferon alpha.
e. Produced a rate of sustained virological response of over 80% when used as monotherapy.

7. statements about pegylated interferon is (are) true?

a. It involves the use of liposomal carriers to more effectively deliver the drug.
b. Combination therapy of pegylated interferon with ribavirin may be indicated in patients who have been previously treated with combination of interferon and ribavirin and who relapse.
c. It remains unknown whether patients who do not respond to peginterferon alfa-2b will respond better to peginterferon alfa-2a.
d. (b) and (c)
e. All of above

8. Which of the following statements about peginterferon alfa-2a is (are) true?

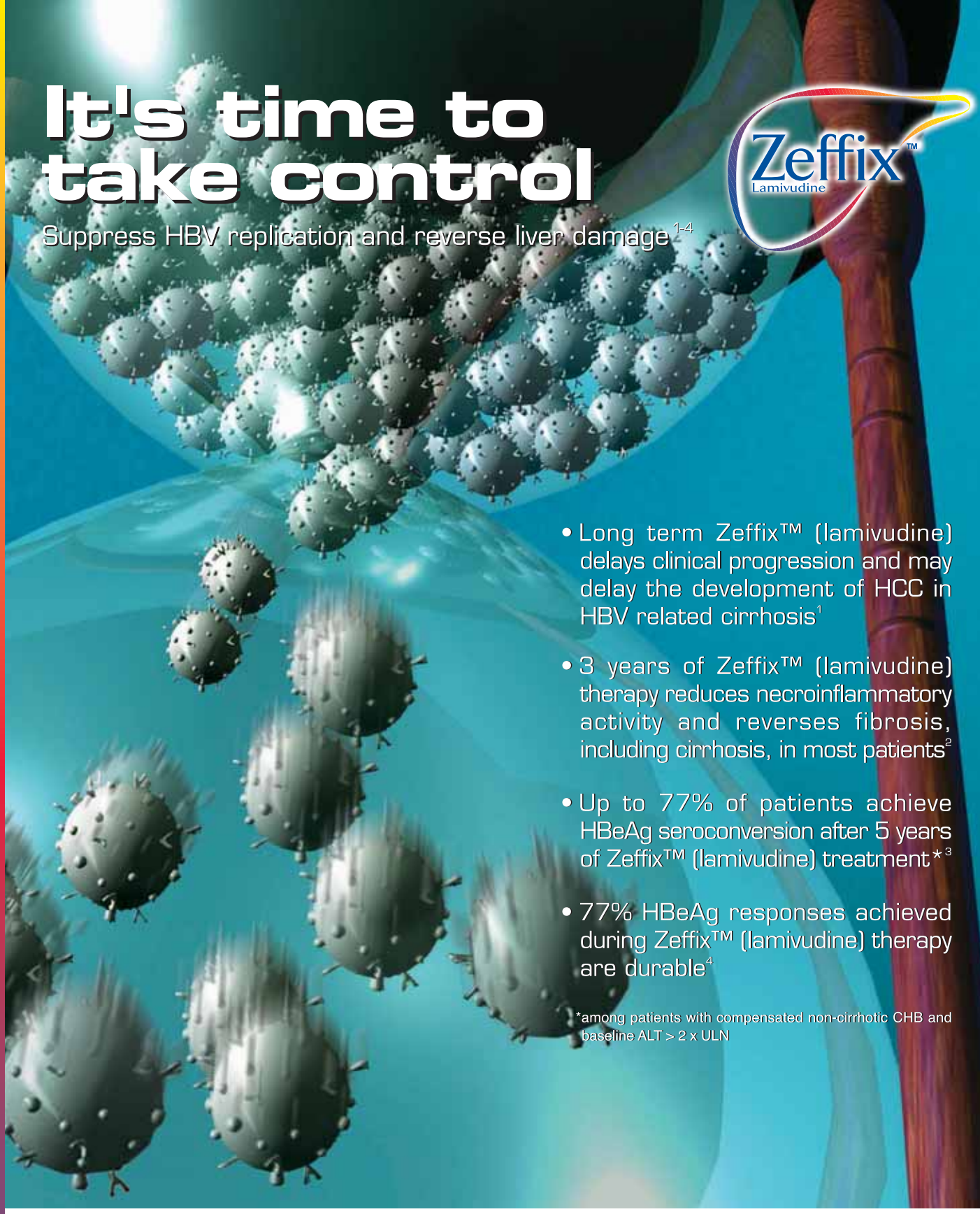
a. The route of administration is subcutaneous.
b. The recommended dose is 180mg once weekly.
c. The duration of therapy depends on the patient's HCV genotype.
d. (a) and (c)
e. All of above

9. Which of the following statements about peginterferon alfa-2b is (are) true?

a. Peginterferon alfa-2b may used for both monotherapy or combination therapy.
b. Irritability and insomnia are common adverse events with peginterferon alfa-2b treatment.
c. When used in combination with ribavirin, the recommended dosage for peginterferon alfa-2b is 1.5mcg/kg once weekly.
d. (a) and (c)
e. All of above

10. Treatment for chronic Hepatitis C is indicated in:

a. Patients who present with severe symptoms and have high risk of transmission
b. Patients who have demonstrated fibrosis on liver biopsy.
c. Patients once the diagnosis for chronic Hepatitis C is established despite the lack of symptoms and fibrosis.
d. (a) and (b)
e. All of above



It's time to take control

Suppress HBV replication and reverse liver damage[1-4]

Zeffix™ Lamivudine

- Long term Zeffix™ (lamivudine) delays clinical progression and may delay the development of HCC in HBV related cirrhosis[1]
- 3 years of Zeffix™ (lamivudine) therapy reduces necroinflammatory activity and reverses fibrosis, including cirrhosis, in most patients[2]
- Up to 77% of patients achieve HBeAg seroconversion after 5 years of Zeffix™ (lamivudine) treatment*[3]
- 77% HBeAg responses achieved during Zeffix™ (lamivudine) therapy are durable[4]

*among patients with compensated non-cirrhotic CHB and baseline ALT > 2 x ULN

References: 1. YF Liaw, JJY Sung, WC Chow et al. Lamivudine delays clinical progression and reduces incidence of liver cancer in patients with HBV related cirrhosis – results of a prospective placebo-controlled clinical trial *J of Gastroenterology and Hepatology* (2003) 18 (suppl) Sep 2003; Abst No.179 2. Dienstag JL, Goldin RD, Heathcote EJ, et al. Histological outcome during long-term lamivudine therapy. *Gastroenterology*. 2003;124(1):105-17. 3. Guan R, Lai CL, Liaw YF Lim SG, Lee CM. Efficacy and safety of 5 years lamivudine treatment of Chinese patients with chronic hepatitis B. *J Gastroenterol Hepatol*. 2001; 16(Suppl): A60 (abst 187). 4. Dienstag JL, Cianciara J, Karayalcin S, et al. Durability of serologic response after lamivudine treatment of chronic hepatitis B. *Hepatology*. 2003;37(4):748-55.

Abbreviated Prescribing Information

Product Name: Zeffix Active Ingredient: Lamivudine

Indications: treatment of patients with chronic hepatitis B and evidence of hepatitis B virus (HBV) replication.

Dosage & Administration: Adults and adolescents (≥ 12 years old): 100mg once daily. Children (2-11 years old): 3mg/kg once daily up to max. 100mg/day. Children (<2 years old): insufficient data to propose specific dosage recommendation in this age group. Renal impairment: lamivudine serum concentrations (AUC) are increased in patients with moderate to severe renal impairment due to decreased renal clearance. The dosage should therefore be reduced for patients with a creatinine clearance of <50ml/min (see Tables 1).

Table 1: Dosing Recommendation in Patients with Renal Impairment

Creatinine clearance (ml/min)	Adults and Adolescents (≥12 years old)		Children (2 – 11 years old)	
	First dose of Zeffix	Maintenance Dose Once Daily	First dose of Zeffix	Maintenance Dose Once Daily
30 to <50	100 mg	50 mg	3 mg/kg	1,50 mg/kg
15 to <30	100 mg	25 mg	3 mg/kg	0,75 mg/kg
5 to <15	35 mg	15 mg	1 mg/kg	0,45 mg/kg
<5	35 mg	10 mg	1 mg/kg	0,30 mg/kg

Contra-indication: patients with known hypersensitivity to lamivudine or to any ingredient of the preparation

Warnings and Precautions: During treatment patients should be monitored regularly by a physician experienced in the management of chronic hepatitis B. If Zeffix is discontinued or there is a loss of efficacy, some patients may experience clinical or laboratory evidence of recurrent hepatitis. If Zeffix is discontinued, patients should be periodically monitored both clinically and by assessment of serum liver function tests (ALT and bilirubin levels), for at least four months for evidence of recurrent hepatitis; patients should then be followed as clinically indicated. In patients with moderate to severe renal impairment, serum lamivudine concentrations (AUC) are increased due to decreased renal clearance, therefore the dose should be reduced for patients with a creatinine clearance of <50 ml/min. Transplantation recipients and patients with advanced liver disease are at greater risk from active viral replication. Hepatitis reactivation at discontinuation of lamivudine or loss of efficacy during treatment may induce severe and even fatal decompensation. It is recommended that these patients are monitored for parameters associated with hepatitis B, for liver and renal function, and for antiviral response during treatment. If treatment is discontinued for any reason, it is recommended that these patients are monitored for at least 6 months post cessation of treatment. Patients experiencing signs of hepatic insufficiency during or post-treatment should be monitored frequently, as appropriate. For the treatment of patients who are coinfected with HIV and are currently receiving or are planning to receive an anti-retroviral treatment regimen including lamivudine, the dose of lamivudine usually prescribed for HIV infection should be maintained.

Interaction: The possibility of interactions with other drugs administered concurrently should be considered, particularly when their main route of elimination is active renal secretion via the organic cationic transport system e.g. trimethoprim. Other drugs (e.g. ranitidine, cimetidine) are eliminated only in part by this mechanism and were shown not to interact with lamivudine. Administration of trimethoprim/sulphamethoxazole 160 mg/800 mg increased lamivudine exposure by about 40%. Lamivudine had no effect on the pharmacokinetics of trimethoprim or sulphamethoxazole. Zidovudine had no effect on the pharmacokinetics of lamivudine. Lamivudine may inhibit the intracellular phosphorylation of zalcitabine when the two medicinal products are used concurrently. Zeffix is therefore not recommended to be used in combination with zalcitabine.

Pregnancy: Use in pregnancy should be considered only if the benefit outweighs the risk. Zeffix administration is not recommended during the first three months of pregnancy.

Lactation: Following oral administration of lamivudine was excreted in human breast milk at similar concentrations to those found in serum (range 1 – 8 μg/ml).

Undesirable effects: In clinical studies of patients with chronic hepatitis B, Zeffix was well tolerated. The incidence of adverse events was similar between placebo and Zeffix treated patients. The incidence of laboratory abnormalities in chronic hepatitis B patients were similar in the Zeffix and placebo treated groups, with the exception of ALT elevations which were more common post-treatment in patients treated with Zeffix. In patients with HIV infection, cases of pancreatitis and peripheral neuropathy (or paresthesia) have been reported, although no relationship to treatment with lamivudine has been clearly established. Cases of lactic acidosis, usually associated with severe hepatomegaly and hepatic steatosis, have been reported with the use of combination nucleoside analogue therapy in patients with HIV. There have been occasional reports of these adverse events in hepatitis B patients with decompensated liver disease, however there is no evidence that these events were related to treatment with Zeffix

Overdose: If overdose occurs the patient should be monitored, and standard supportive treatment applied as required. Since lamivudine is dialyzable, continuous haemodialysis could be used in the treatment of overdose, although this has not been studied.

Storage condition: Store below 30°C.

Please read the full prescribing information prior to administration.

Abbreviated Prescribing Information Version 6 prepared in October 2003.

gsk GlaxoSmithKline

Further information is available on request from GlaxoSmithKline Limited
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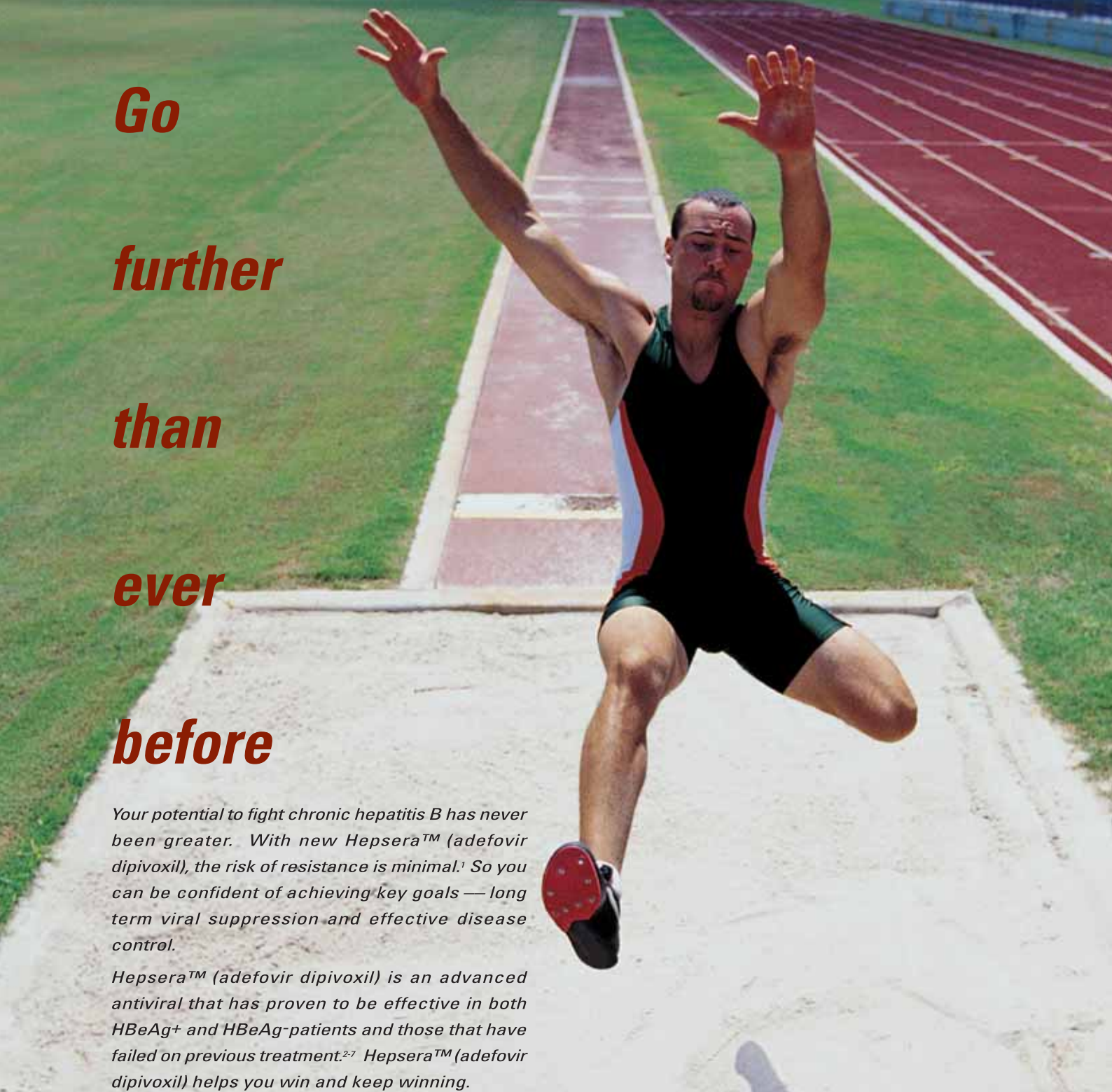

Go further than ever before

Your potential to fight chronic hepatitis B has never been greater. With new Hepsera™ (adefovir dipivoxil), the risk of resistance is minimal.[1] So you can be confident of achieving key goals — long term viral suppression and effective disease control.

Hepsera™ (adefovir dipivoxil) is an advanced antiviral that has proven to be effective in both HBeAg+ and HBeAg-patients and those that have failed on previous treatment.[2-7] Hepsera™ (adefovir dipivoxil) helps you win and keep winning.

Hepsera is a registered trademark of the GlaxoSmithKline group of companies.

References : (1) Westland CE, Yang H, Delaney WE, et al. Week 48 resistance surveillance in two phase 3 clinical studies of adefovir dipivoxil for chronic hepatitis B. *Hepatology* 2003;38:96-103 (2) Marcellin P, Chang TT, Lim SG, et al. Adefovir dipivoxil for the treatment of hepatitis B e antigen-positive chronic hepatitis B. *NEJM* 2003; 348:808-816 (3) Hadziyannis S, Tassopoulos NC, Heathcote EJ, et al. Adefovir dipivoxil for the treatment of hepatitis B e antigen-negative chronic hepatitis B. *NEJM* 2003; 348:800-807 (4) Hadziyannis S, Tassopoulos NC, Heathcote EJ, et al. Two year results from a double-blind, randomized, placebo-controlled study of adefovir dipivoxil for presumed precore mutant chronic hepatitis B (0-96 weeks). *J Hepatol* 2003;38(suppl 2):143 (5) Schiff E, Willems B, Leung N, et al. Safety and efficacy of adding adefovir dipivoxil to lamivudine therapy in compensated chronic hepatitis B patients with YMDD variant HBV and a reduced response to lamivudine- 52 week results. *Hepatology* 2002;36(N0.4 Pt 2 of 2):636A (6) Mutimer D, Hann H, Buti M, et al. Significant clinical improvement following the addition of adefovir dipivoxil to lamivudine in decompensated patients with YMDD variant HBV and a reduced response to lamivudine - 1 year results. *Hepatology* 2002;36(N0.4 Pt 2 of 2):625A (7) Peters M, Hann HW, Partin P, et al. Adefovir dipivoxil alone and in combination with lamivudine suppresses YMDD mutant hepatitis B virus replication: 48 week preliminary analysis. *Hepatology* 2002;36(N0.4 Pt 2 of 2):374A

Abbreviated Prescribing Information

Product Name: Hepsera **Active ingredient:** Adefovir dipivoxil **Indications:** treatment of chronic hepatitis B in adults with evidence of active hepatitis B viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease. **Contra-indication:** patients with previously demonstrated hypersensitivity to any components of the product. **Warnings and Precautions:** Doses higher than those recommended must not be administered. Patients with advanced liver disease or cirrhosis should be monitored closely during initiation of therapy. Exacerbations of Hepatitis after Discontinuation of Treatment: Severe acute exacerbation of hepatitis has been reported in patients who have discontinued anti-hepatitis B therapy, including therapy with Hepsera. Patients who discontinue Hepsera should be monitored at repeated intervals over a period of time for hepatic function. If appropriate, resumption of therapy may be warranted. Nephrotoxicity: Chronic administration of Hepsera (10mg/day) may result in nephrotoxicity. The overall risk of nephrotoxicity in patient with adequate renal function is low. However, this is of special importance in patients at risk of or having underlying renal dysfunction and patients taking concomitant nephrotoxic agents. It is important to monitor renal function for all patients during treatment with Hepsera, particularly for those with pre-existing or other risks for renal impairment. Patients with renal insufficiency at baseline or during treatment may require dose adjustment. The risks and benefits of Hepsera treatment should be carefully evaluated prior to discontinuing Hepsera in a patient with treatment-emergent nephrotoxicity. HIV Resistance: Treatment with anti-hepatitis B therapies that have activity against HIV in a chronic hepatitis B patient with unrecognized or untreated HIV infection may result in emergence of HIV resistance. Hepsera has not been shown to suppress HIV RNA in patients; however, there are limited data on the use of Hepsera to treat patients with chronic hepatitis B co-infected with HIV. **Interaction:** Since adefovir is eliminated by the kidney, co-administration of Hepsera with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of either adefovir and/or these co-administered drugs. Ibuprofen 800mg three times daily increased adefovir exposure by approximately 23%. The clinical significance of this increase in adefovir exposure is unknown. While adefovir does not inhibit common CYP450 enzymes, the potential for adefovir to induce CYP450 enzymes is not known. The effect of adefovir on cyclosporine and tacrolimus concentrations is not known. **Pregnancy:** There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, Hepsera should be used during pregnancy only if clearly needed and after careful consideration of the risks and benefits. Women of child-bearing potential must use effective contraception. **Lactation:** It is not known whether adefovir is excreted in human milk. Mothers should not breastfeed if they are taking adefovir dipivoxil. **Undesirable effects:** posttreatment elevations in ALT were observed at a higher incidence in patients who had received 10 mg adefovir dipivoxil than in patients who had received placebo. **Dosage & Administration:** *Adults (18-65 years):* 10 mg once daily taken orally with or without food. *Children and adolescents (< 18 years) or Elderly (> 65 years):* Safety and efficacy have not been established. **Renal impairment:** The dosing interval of Hepsera should be adjusted in patients with baseline creatinine clearance, < 50mL/min using the following suggested guidelines (Table 1). Clinical response to treatment and renal function should be closely monitored in these patients. The pharmacokinetics of adefovir have not been evaluated in non-hemodialysis patients with creatinine clearance <10mL/min; therefore, no dosing recommendation is available for these patients.

Table 1: Dosing recommendations in patients with renal impairment

	Creatinine Clearance (mL/min)*			
	> 50	20 - 49	10 - 19	Haemodialysis Patient
Recommended Dose and Dosing Interval	10mg every 24 hours	10mg every 48 hours	10mg every 72 hours	10mg every 7 days following dialysis

* Creatinine clearance caculated by Cockcroft-ault method using lean or ideal body weight.

Overdose: Doses of adefovir dipivoxil 500mg daily for 2 weeks and 250mg for 12 weeks have been associated with gastrointestinal side effects. If overdose occurs, the patient must be monitored for evidence of toxicity, and standard supportive treatment applied as necessary.

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Extends your power to fight Hepatitis B

N03HE006/11-2003

Isolation and Identification of Triptonide and Its Analogous Compounds from a Fungal Culture of *Pestalotiopsis leucothës*

D.S.S. Kumar[a]; Hon-Yeung Cheung[b*]; Guo-Yuan Zhu[c]; D. Yang[d]; Wang-Fun Fong[b,c]; K.D. Hyde[a]

[a] *Centre for Fungal Diversity Research, Department of Ecology & Biodiversity, The University of Hong Kong, Hong Kong SAR, China*
[b] *Department of Biology & Chemisty, City University of Hong Kong, Hong Kong SAR, China*
[c] *City University of Hong Kong, Biotechnology & Health Centre, Virtue University Park, Shenzhen, China 518057.*
[d] *Department of Chemistry, The University of Hong Kong, Hong Kong SAR, China*

Pestalotiopsis leucothës, an endophytic fungus isolated from the underlayer of root of Tripterygium wilfordii (Lei Gong Teng), was found to produce immunosuppressive substances in mycelial culture. The bioactive materials were extracted from the ethyl acetate - methylene chloride fraction. Individual compound was successfully isolated and purified by two solvent systems and chromatographic techniques. Structures of the compounds were subsequently identified as triptonide and its analogous compounds by LC/UV/MS.

Keywords: endophytes; triptonide; Tripterygium wilfordii; immunomodulatory activity; LC/UV/MS

I INTRODUCTION

Medicinal plants have been used virtually in all societies as therapeutic substances. Seventy five percent of today's world population still relies on traditional herbal medicines from plants for curing diseases[5]. There are about 250,000-300,000 species of plants used as sources of drugs[6]. Despite their effectiveness, the increasing use of medicinal plants is being threatened by complacent concern for their conservation. Therefore, alternative approaches for obtaining the pharmaceutical compounds through large scale biotechnology are needed.

Endophytic fungi are special biotopes that live asymptomatically inside tissues of living plants[11]. Each plant species can harbor between 10 and 100 different fungal species. Therefore, the endophytic fungi alone could account for 1.3×10^6 fungal species[4]. These endophytes may account for some of the biological activities in their hosts[20]. Diverse bioactive metabolites, that may have potential for therapeutic purposes and could be used as research tools, have been found in some endophytic fungi isolated from medicinal plants[23,24].

Pestalotiopsis spp are ubiquitous in many tropical plants and are frequently isolated as endophytic fungi from rain forest plants[19]. They are commonly found in tropical plants and considered as "*Escherichia coli* of the rain forest"[22]. These fungi have been frequently reported to express highly specialized natural products, such as taxol, an anticancer drug produced by *Pestalotiopsis* spp. that live inside *Taxus brevifolia* (Yew trees) as well as by the tree itself[22]. Another *Pestalotiopsis* sp. isolated from Yew tree has been shown to produce immunosuppressive pestalotiopsins A and B in liquid culture[17]. It appears that the *Pestalotiopsis* sp. from the yew tree is a potential producer of bioactive compounds.

Sometimes fungi may have symbiotic relationships with their host. They produce phytohormone like substances. For instance, pestalotin, a gibberellin synergist was isolated from the culture broth of *Pestalotia cryptomeriaecola*, which was isolated from *Cryptomeria japonica* (Japanese cedar)[9]. *Pestalotiopsis microspora,* an endophyte commonly found in rain forest plants is known to be a "microbial factory of bioactive secondary metabolites" because it has been shown to produce various bioactive compounds such as ambuic acid, an antifungal agent, torreyanic acid, a cyototoxic agent against human cancer cell lines, phytotoxic peastaloside and pestalopyrone[22]. Jesterone and hydroxyl-jesterone, are antioomycete agents from *Pestalotiopsis jesteri*, which is an endohytic fungus of *Fragraea bodenii*[14].

Previous studies have revealed that fungi are potential sources of immunosuppressive agents such as Cyclosporine A, FK506 and ripamycin. These fungal metabolites, however, have been found to exhibit some undesirable side effects such as nephrotoxicity and hepatotoxicity[28]. New immunosuppressive agents which lack these side effects, therefore, are required. Recently Kumar *et al.*, 2003 isolated an array of endophytic fungi from *Tripterygium wilfordii*. Extracted products of these fungi showed antiproliferative activity against peripheral blood monocular cells (PBMC) with no cytotoxicity. Among them, partially purified extracts of *Pestalotiopsis* sp. showed significant inhibition on proliferation of PBMC, leading to a lower T cell subpopulation and immunoglobulin (IgG and IgM) production[10]. This report describes exploration of differential purification procedures leading to the discovery and identification of some bioactive principles responsible for the immunomodulatory activities in the crude ethyl acetate extract of *Pestalotiopsis* sp.

II MATERIALS AND METHODS

a) Media and Chemicals

Two types of media; namely potato

* Corresponding author. Tel:+852-2788 7746; Fax:+852-2788 7406; E-mail: bhhonyun@cityu.edu.hk

dextrose agar (PDA) and potato dextrose broth purchased from Oxoid and Difco, respectively, were used. All solvents used were analytical grade from Labscan (Thailand). Chemicals used for preparing staining agents and for other purpose were also analytical grade from Merck.

b) Cultivation and preparation of crude extracts of Pestalotiopsis sp.

Pestalotiopsis sp. (HKUCC RA4) was maintained at -196°C in liquid nitrogen. The culture was thawed at 37°C immediately before making the subsequent culture. The fungus subcultured on potato dextrose agar (PDA) at 25°C for 5 days was used to inoculate 200 ml potato dextrose (PD) liquid medium in a 1000 ml flask. After 3 days of incubation at 25°C on an orbital shaker at 120 rpm, 20 ml of the broth culture was inoculated as starter culture into each of a total of ten 5 L flasks containing 2 L of PD medium. Cultivation was set at a 12 hr light/dark cycle at 22°C for 21 days. After fermentation, the entire culture was filtered using a cheese cloth to separate mycelium from the broth. Spent medium (50 L) was extracted three times with one-fifth a volume of methylene chloride followed by the same quantity of ethyl acetate. The organic phase was dried over Na_2SO_4 for 10 min and filtered using the silicon coated Whatmann filter paper. Freeze dried mycelia was extracted in the same solvent sequence (1 g in 10 ml) and concentrated *in vacuo* at 35°C. All crude extracts obtained were stored at -20°C for further assay.

c) Purification of the crude extracts

Crude extracts of fungal mycelium in EtOAc were eluted with different solvent systems by flash chromatography on silica gel 60 (size: 230-400 mesh, from Merck). The solvent systems used were either, (a) hexane and EtOAc (4:1) or (b) benzene and chloroform (4:1). Compounds present in each fraction were detected by thin layer chromatography (TLC) on silica plates (Merck Silica F_{254} plates, 20x20 cm). Different developing solvents such as (1) hexane and EtOAc (1:1) or (2) henzene and acetone (4:1) were used as the mobile phase. Chromatograms were visualized under UV at 254 and 365 nm and then discolored by spraying with staining reagents. The staining reagents for identifying triterpenes and steroids were phosphomolybdic acid (PMA), 2, 4, dinitro- phenylhydrazine (2, 4-DNP), p-anisaldyde, or Liebermann-Burchard reagent. For unsaturated lactone ring containing compounds, such as triptolide, triptonide and triptophenolide, Kedde reagent was used[25].

d) Liquid chromatography -UV-Electro spray Ionization- Mass spectroscopy (LC/UV/ESI-MS)

LC/UV/MS was performed for purifed samples BS, GS and YS using a LC/MS (Surveyor HPLC and LCQ Advantage, USA, Finnigan, San Jose, CA). The Surveyor HPLC system consists of a pump, controller, autosampler and photodiode-array detector. UV spectra were taken in the range of 200-800 nm. An InertsilODS3 C18 reverse phase column (size 2.1x150 mm, particle size 5 μm, 100 A° pore size) (GL Sciences Inc.) was used for separation and the column temperature was set at 40°C. In order to ascertain the purity of the samples in the column, the following parameters were used for each sample. Gradient system of Solvent A (methanol) and B (water) was used for the mobile phase and the suitable ratio of the mobile phase was separately indicated for each sample. The samples were dissolved in MeOH (1:10 dilution) and 5 μl of MeOH solution was injected for analysis. Elution condition for BS - mobile phase, A:B(90:10) (v/v) for 30 min, flow rate: 200 μl/min and UV detection at 270 nm. Elution condition for GS - mobile phase, A:B(70:30) (v/v) for 45 min, flow rate at 200 μl/min and UV detection at 254 nm. Elution condition for YS- mobile phase, A:B(67:33), flow rate at 200 μl/min and UV detection at 430 nm. The purity was also confirmed with MS detection. The ion trap mass spectrometer was equipped with an ESI interface as an ionization source of MS. ESI was carried out in positive ionization mode to produce protonated and adduct molecular ions. MS spectra were scanned as centroid date from m/z 100 to 500. Data were collected and analyzed with Xcaliber software.

e) Preparation of extract for bioassays

All extracts were dissolved in absolute ethanol and sterilized by filtration in Nalgene filters (0.22 μm pore size). A stock solution of the extracts was prepared by adding an appropriate volume of RPMI1640 medium to the filtrate. Concentration of ethanol in the final solution was always less than 0.1% (v/v) which had no measurable effect on growth of test culture. 200 μl of drug solution was added to each well of a 96-well titer micro-plate. Two fold dilutions were then made across the plate in each column in order to produce various concentrations of drugs from 0.1-50 μg/ml.

f) Preparation of peripheral blood mononucluear cells (PBMC)

PBMC were isolated from buffy coats by gradient centrifugation with Ficoll-hypaque in accordance with the procedure of Böyum[1]. Buffy coats from healthy individuals were obtained from the Hong Kong Red Cross Society, Hong Kong. PBMC were adjusted to $1x10^6$ cells per ml.

g) Effects on lymphocyte proliferation study

PBMC were cultured at a density of $1x10^6$ cells/ml in 50 μl of RPMI-1640 complete medium on 96 well flat-bottomed microplates with or without various concentrations of fraction extracts from 0.1-50 μg/ml. Five μg/ml of PHA (phytohemagglutinin) in 50 μl of RPMI-1640 was added to induce the proliferation of lymphocyte and the plates were incubated at 37°C in a humidified atmosphere containing 5% CO_2 for 3 days. Four hours before the end of the incubation, 0.5 μCi [^{3}H]-thymidine in 20 μl of RPMI-1640 was added to each well. The cells were harvested onto glass fiber filter papers with an automated Matrix96™ cell harvester (Packard). Incorporation of [^{3}H]-thymidine by PBMC measured as count per minute (CPM) was monitored by a liquid scintillation counter.

h) Viability assay

PBMC viability was determined by the standard tryphan blue exclusion test[27]. Approximately, $1x10^6$ cells/ml of PBMC with PHA-M were treated with two-fold diluted concentration from 0.1 to 50 μg /ml of fungal extracts and controls with 0.1% of ethanol for 3 days at 37°C in a humidified atmosphere containing 5% CO_2. The total number of viable and non-viable cells was counted under a microscope with a hemocytometer following staining by tryphan blue (0.4% in 0.9% NaCl) (Pharmengin™).

III RESULTS AND DISCUSSION

a) Fermentation products

Pestalotiopsis sp. is relatively easy to grow in suspension and on solid agar plates. About 100 g of mycelial mat was obtained per fifty liters of *Pestalotiopsis* sp. culture in PD broth. The combined yield of brown crude extract for each fraction was 7 and 5 g, respectively.

b) Bioassay directed purification of bioactive substances from Pestalotiopsis sp. culture

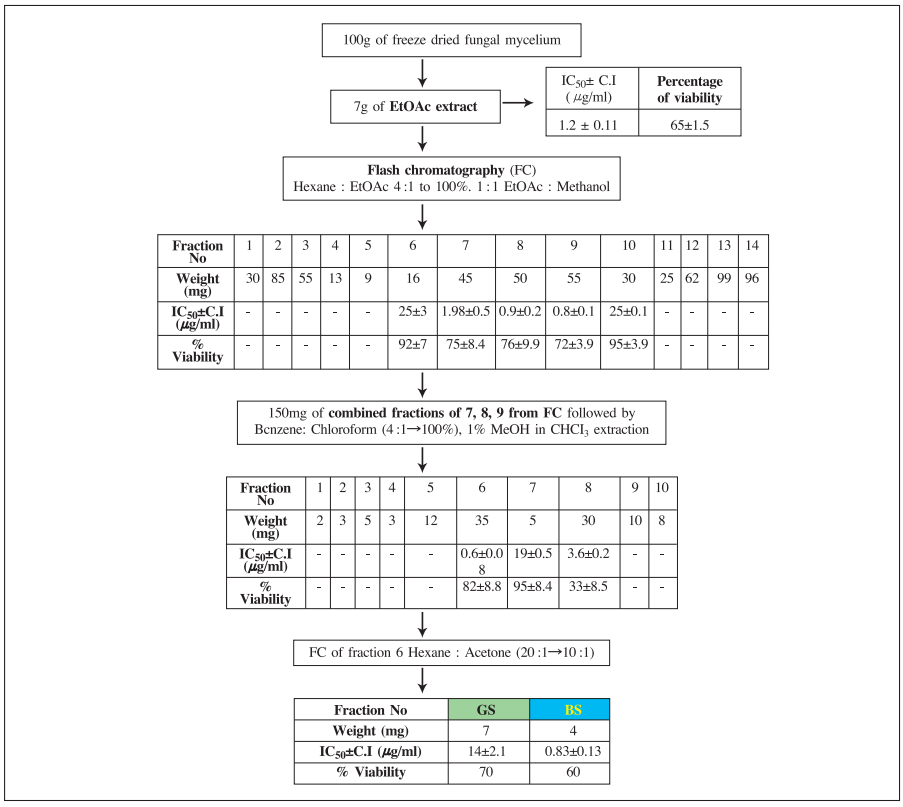
Partially purified fractions of *Pestalotiopsis* sp. have previously been shown inhibitory on various activities of human PBMC (proliferation, immunoglobulins, and surface markers)[10]. In this study, the flash column chromatography was applied to

purify the mycelial extract (ME) and broth extract (BE) of *Pestalotiopsis* sp. to further fractionate the bioactive principles of the fungal extracts. Proliferation and viability assay of PBMC are the common experiments in search for immunomodulatory compounds.

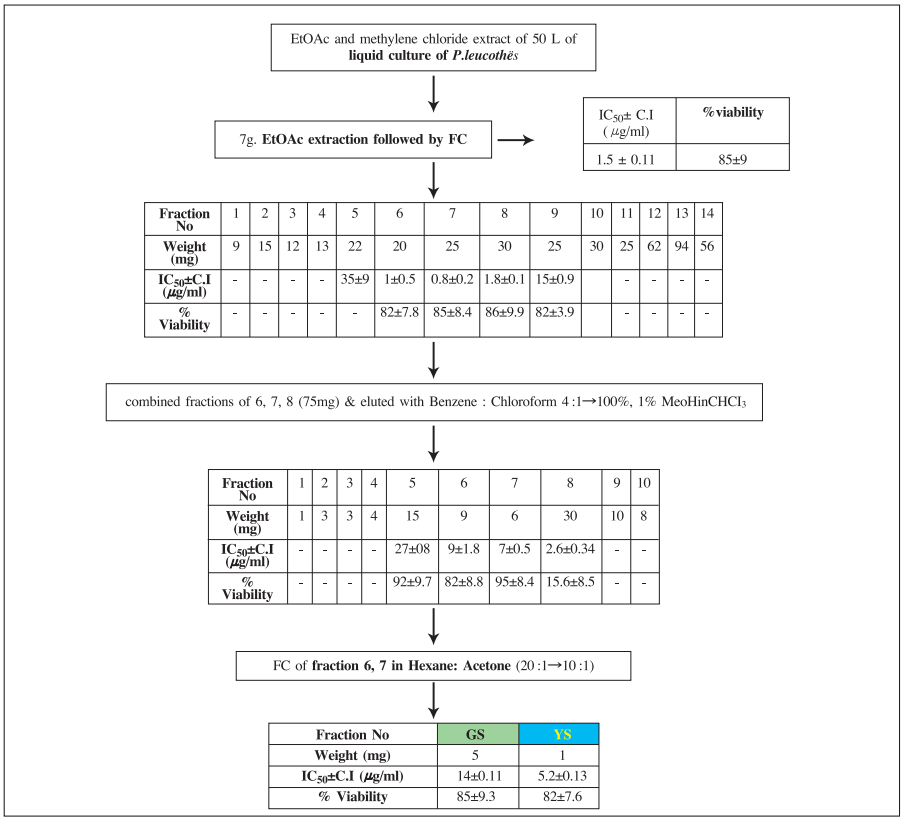
c) Fractionation of mycelial extract (ME)

The human PBMC proliferation and viability assay *in vitro* guided the fractionation of ME. Scheme 1 shows that ME was potent in inhibiting PBMC proliferation (IC_{50} = 1.5 μg/ml) with 65 ± 1.5% viability at 50 μg/ml. The decrease in viability may be due to the synergetic effect of compounds in crude extract. The flash chromatography of ME gave 14 fractions by linear gradient elution using the solvent system A. During chromatography, most of the starting material in the fractions 1, 2 and 3 consisted of lipophilic inactive materials. Among the 14 fractions, 7, 8, 9 fractions only showed profound antiproliferation and less cytotoxicity of PBMC (IC_{50} = 0 .8-1.98 μg/ml, 75-82% viability) and fractions 6 and 10 showed much less activity (IC_{50} = 25 μ g/ml). The active fractions (7, 8, and 9) were combined after monitoring TLC profiles to obtain 150 mg of extract, which is about 2% yield from the total extract. This extract was again chromatographed in solvent system B to obtain 10 sub-fractions. Among the subfractions, fraction 6 showed three fold more inhibition than crude extract (IC_{50} = 0.6 μg/ml, 75-82% viability). Subfraction 8 also showed significant inhibition in PBMC proliferation, however, it had impact on the percentage viability (IC_{50} = 3.6 μg/ml, 33.5% viability). Subfraction 8 weighed 35 mg, which is 0.5% of the yield from the total extract. This subfraction was further fractionated in solvent system C and two pure compounds were obtained and designated as BS and GS (Scheme 1 & 2) because these compounds showed single green and blue spots respectively in TLC when anisaldehyde was used as staining agent (Fig. 1). The R_f values for BS and GS were 0.49 and 0.53 respectively in TLC in hexane: ethyl acetate (1:1). BS compound had significant inhibition on PBMC proliferation (IC_{50} = 0.83 μg/ml) than GS (IC_{50} = 14 μg/ml). The antiproliferation effect of PBMC by BS and GS was not due to cytotoxicity which was revealed by their percentage viability values 60 and 70, respectively (Scheme 1). Finally BS (4 mg) and GS (7 mg) were isolated as purified and major compounds from 7 g of mycelial extract, which represents 0.06% and 0.1% yield, respectively.

d) Fractionation of broth extract (BE)



Scheme 1. **Isolation of compounds GS and BS from the ethylacetate extract of the mycelial of *P. leucothës culture***



Scheme 2. **Isolation of compounds GS and YS from the ethylacetate extract of broth culture of *P. leucothës***

Five grams of BE was obtained from 50 L of broth culture of *Pestalotiopsis* sp. BE showed tremendous antiproliferation and no cytotoxicty for lymphocytes (IC_{50} =1.5 and 85% viability). The percentage viability of BE was 10 times more than ME, but the IC_{50} of ME was similar. Therefore, BE was subjected for fractionation to localize the active compounds as performed for ME. Flash chromatography of BE in a linear gradient of solvent system A yielded 14 fractions. Among the 14

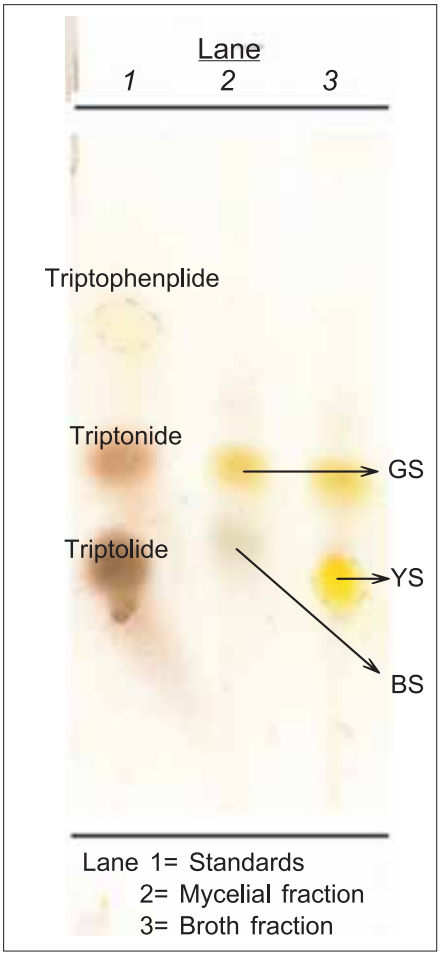


Figure 1. Thin layer chromatographic profile of bioactive compounds in different extracts of fungal culture.

fractions, 6, 7 and 8 showed significant inhibition of proliferation of PBMC (IC_{50} = 0 .95-1.8 μg/ml, 82-85% viability. These fractions were combined according to their TLC profiles to yield 75 mg of extract, which is 1.5% of the weight of initial extract. Ten sub fractions were obtained from further separation of the combined active extract by chromatography in solvent system B. Among the 10 sub-fractions, 6 and 7 showed considerable activity and weighed 9 (0.2%) and 6 mg (0.12%), respectively. However, fraction 6 showed significantly less activity than 7 which was revealed from the IC_{50} value of subfraction 6 (Scheme 2). Therefore, these sub fractions were fractionated separately in solvent system C. GS (5 mg) and YS (1 mg) compounds were isolated respectively from fraction 6 and 7, respectively. The yield of GS and YS compounds were 0.1% and 0.02%, respectively. The YS compound did not react with any of the staining agents and produced yellow color spots on the TLC plate. YS showed 9 times more antiproliferative activity than GS without affecting the cell viability (Scheme 2).

e) *Thin layer chromatography (TLC) analysis*

Table 1. Comparison of R_f values of various fungal and host substances on TLC plate

Samples	R_f value (Solvent I)	R_f value (Solvent II)	2,4, DNP	Liebermann -Burchard	Anisaldehyde	Kedde
BS	0.47	0.25	brown	blue	blue	-
GS	0.51	0.35	Pale brown	-	green	-
YS	0.44	0.3	brown	-	yellow	-
Triptolide	0.45	0.18	brown	grayish blue	brown	pink
Triptonide	0.50	0.31	brown	blue	light brown	pink
Triptophenolide	0.72	0.52	-	-	pale yellow	pink

Bioassay directed purification of *Pestalotiopsis* sp. yielded three active compounds BS, GS and YS. These compounds produced a single spot on the TLC plate in each solvent system I and II and their R_f values are displayed in Table 1. Different staining reagents were used to observe the composition of fungal metabolites. BS, GS and YS produced blue, green and yellow spots, respectively, when anisaldehyde was used as a staining agent (Fig. 1). These compounds were compared with active principles of T. *wilfordii* (host plant). Special attention was given to the host compounds such as triptolide, triptonide and triptophenolide, which might be present in the fungal compounds. Although the fungal compounds showed similar R_f values only in Solvent System I, they did not produce the specific pink color when Kedde reagent was used which is specific to the host compounds. Therefore, the purified compounds of *Pestalotiopsis* sp. were not similar to triptolide, triptonide and triptophenolide. BS produced a typical blue colour in the presence of Liebermann-Burchard reagent indicating the presence of steroid in BS. GS and YS failed to produce the characteristic colour when stained with this reagent. All fungal and host compounds produced a brown color when stained with 2, 4, DNP (Table 1.).

f) *LC/UV/ESI-MS analysis of fungal metabolites*

Fungal antiproliferative metabolites such as BS, GS, and YS isolated by flash chromatography were ascertained for purity by the LC/UV/ESI-MS method. LC and UV detection was mainly used to separate the compounds and impurities in the isolated active fractions such as BS, GS and YS. LC-ESI-MS was used to eliminate misidentification of coeluting compounds or impurities with similar UV spectra. An HPLC-UV analysis of fungal highly active metabolite BS exhibited typical UV spectra in the range from 250 to 300 nm with a main absorption peak displaying UV maxima (λ_{max}) at 270 nm (Fig. 2). The identification of peaks of BS compound was performed by LC-MS. Simultaneous LC-UV and total ion

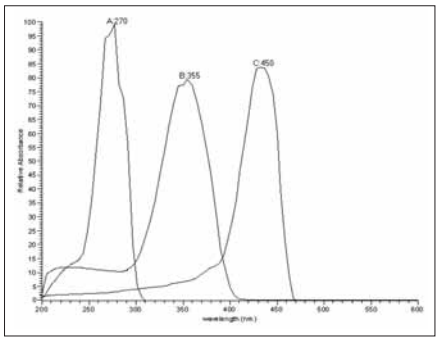


Figure 2. UV spectra of purified samples of BS (Spectrum A), GS (Spectrum B) and YS (Spectrum C).

chromatogram of BS showed a single peak at retention time (t_R) of 6.61 and 6.69 min, respectively, by UV detection at 250 nm (Fig. 3). LC-ESI-MS at 7.20 t_R indicated two protonated molecules $[M+H]^+$at m/z 353.6 and $[M+H]^+$ at m/z 355.6 and its moderately intense adduct ions $[M+Na]^+$ at m/z 375.4 and $[M+Na]^+$ at m/z 377.3, respectively (Fig. 3). This kind of spectrum may be due to the BS compound being isomeric in structure. However, the BS mass spectrum had a lot of noise peaks due to the presence of impurities in the BS extract. The additional ionization peaks detected in the ESI spectra cannot be assigned to specific fragments as their intensity in comparison to the molecular ion varied during several experiments, and they may therefore be due to impurities still remaining in the sample after chromatographic separations. Therefore, the strongest protonated molecular ions such as at 353.6 and 355.6 of the BS mass spectrum indicate that probable molecular weight of BS would be 352.6 or 354.6 (Fig. 3).

GS exhibited a typical chromophore with λ_{max} at 355 nm (Fig. 2). Both the LC-UV and HPLC-reconstructed total ion current chromatogram showed a characteristic single peak at t_R of 13.20 and 12.69 min, respectively, at 280 nm (Fig. 4). LC-ESI^+MS of GS at t_R 12.69 min revealed a very intense protonated ion at $[M+H]^+$ at m/z 347 and less intense adduct ions at $[M+Na]^+$ at m/z 375 (Fig. 4). Furthermore, the mass spectrum of GS was clear without any contaminating peaks indicating that GS was well separated by flash chromatography. The molecular mass of GS is 346.

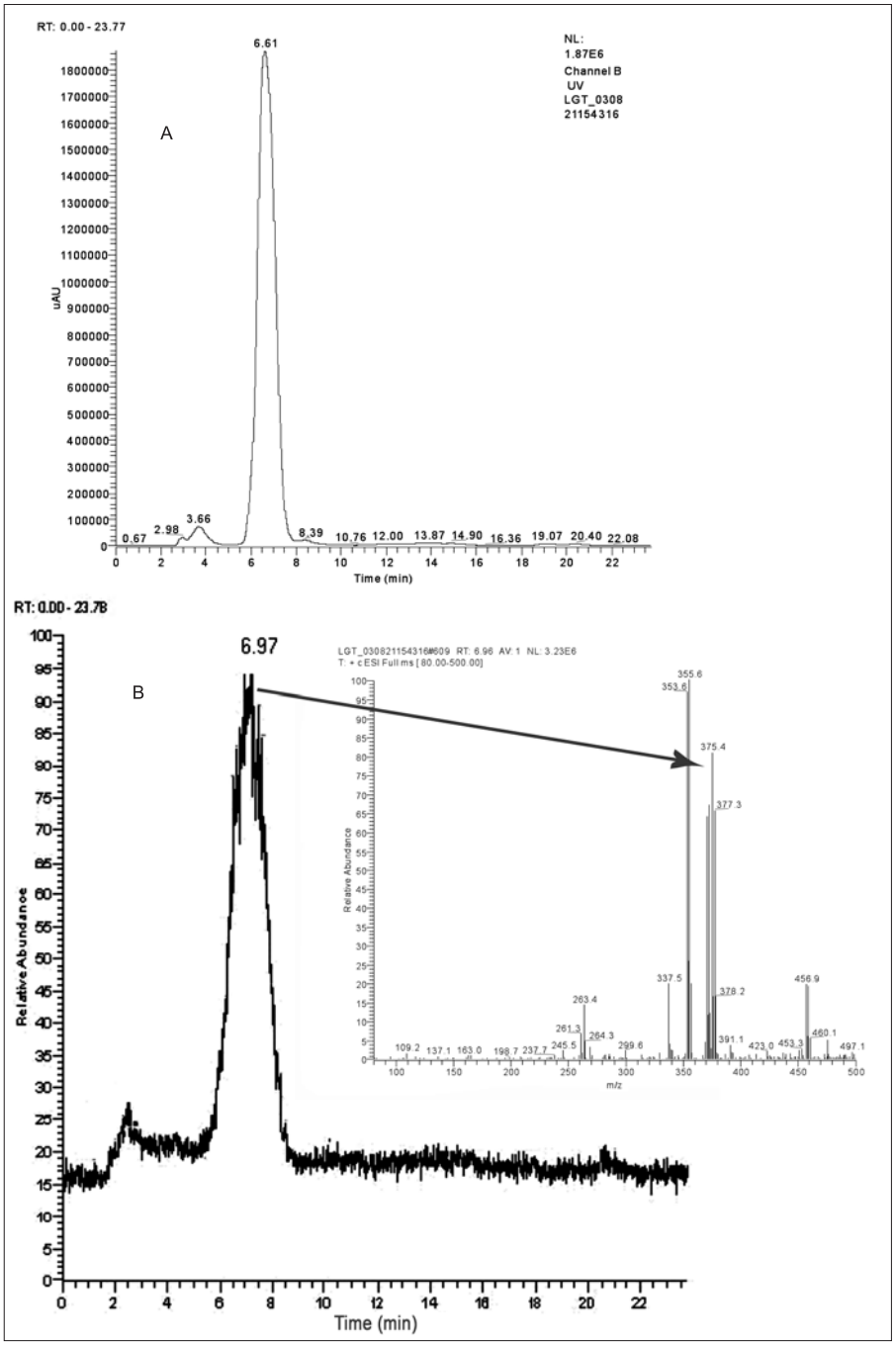


Figure 3. HPLC-UV (250 nm) chromatogram (Panel A) and HPLC-Total Ion Current (TIC) chromatogram along with MS spectrum (insert) of BS compound eluted at t_R 6.97 min (Panel B).

YS showed an UV spectrum with λ_{max} at 450 nm (Fig. 2). Simultaneous analysis of LC/UV/ESI$^+$MS of YS revealed relatively small peaks in TIC at t_R of 9.41 but were large in the LC-UV chromatogram at t_R of 9.41 at 430 nm. LC-ESI$^+$MS of YS at t_R 9.41 min exhibited an intense protonated ion at $[M+H]^+$ at m/z 387 and less intense adduct ions at $[M+Na]^+$ at m/z 409 (Fig. 5). These two peaks attributed to the YS indicates a molecular mass of 386. The MS spectrum also showed two extra peaks which do not match with fragments of the protonated ion and are due to impurities present in the sample.

Detection of LC-UV chromatogram of BS, GS and YS was also performed in PDA from 200-600 nm and the chromatogram of these metabolites are similar to the LC-UV chromatogram specifically detected at 270, 300 and 430 nm, respectively (results not shown). The differences in the retention time (t_R) between LC- MS and LC-UV chromatograms of fungal metabolites may be due to the differences in instrumentation (tubing, dead volume) and/or the gradient.

Ultimately three compounds, BS, GS, and YS were isolated from the *Pestalotiopsis* sp. culture crude extract by using flash column chromatography (Scheme 1, 2). The antiproliferative and viability assays of human PBMC were taken as tools for preliminary screening for immunomodulatory compounds. There were also other fractions which showed significant antiproliferation activity with the same degree of cytotoxicity (Scheme 1, 2). These fractions showed synergistic because no significant quantities of compounds with immunomodulatory activity were identified by bioassay guided separation using flash column chromagraphy. This kind of situation is common in many bioassay guided purifications[7,18]. However, it is understood that since lymphocyte proliferation inhibition was the only assay used to define the immunomodulatory activity of the purified fractions, it remains possible that the use of another screening assay might have identified additional immunomodulatory compounds.

TLC analysis of fungal metabolites with various staining agents especially Kedde reagent showed absence of triptolide and their derivatives (Fig. 1, Table 1). This study cannot prove the assumption and possibility of obtaining host compounds from endophytic fungi such as *Pestalotiopsis* spp[22]. Endophytic fungal species of *Taxus brevifolia* such as *Taxomyces andreanae* and *Pestalotiopsis microspora* produced taxol only up to concentrations of 50 and 113 ng/L, respectively[13]. Identification of taxol in the culture broth of these fungi was not accomplished by UV and Mass spectroscopy because these instruments can detect the compound only in microgram quantities. The approach is similar to a taxol immunoassay kit which could identify the production of taxol in the nanogram scale (1 ng/ml)[13,21]. In this study, *Pestalotiopsis* sp. may have produced triptolide and its derivatives in nanogram quantities in the culture. However, there are no immunoassay kits for triptolide and its derivatives to identify them in *Pestalotiopsis* sp. culture. Because triptolide and its derivatives are immunosuppressants (inhibit the production of immunoglobulin)[27], therefore it is not possible to develop mono or polyclonal antibodies.

Further analysis with Libermann-burchard reagent showed the presence of a steroid group in BS compound. Ergosterols and ergosterol peroxide are reported to appear in the lipid bilayer of cell membranes of all fungal species[2,12]. Ergols have been isolated from the purified fractions of *Cordyceps sinensis, C. cicadae* and *Inonotus radiatus*. These fractions have been known to inhibit the PHA induced proliferation of PBMC with moderate IC_{50} values of 21.7, 32.5 and 26 μg/ml, respectively[8,12]. In this study

BS showed only 25-40 fold more activity than ergols producing fungi which was indicated from low IC_{50} value of BS (IC_{50} = 0.75-0.82 μg/ml). Moreover, GS and YS also showed 2 and 6 times more activity by having IC_{50} values of 14 and 5 (μg/ml), respectively.

Automated, data-dependent LC-MS^n is a screening experiment that is generic in its application[26]. It has recently been applied to identify and localize mixtures of unknowns from the known in natural product discovery, in metabolite identification, drug impurity analysis and formulation degradant studies[16]. Characterization of purified BS, GS and YS metabolites using the LC-ESI^+-MS proved to be a sensitive and convenient approach. The capacity for acquiring data using automated, data-dependent analyses allowed a board range of data, including molecular weight and retention time to be collected from a single run of LC-MS. The LC/UV/ESI^+-MS method verified that BS, GS and YS fractions were attained at 90, 99 and 95% purity, respectively. The proposed molecular weight of BS was determined as either 352 or 354. GS and YS compounds showed unambiguous molecular weights of 346 and 386, respectively. The MS and UV spectra obtained in this study were compared with a database of spectra earlier detected for 400 fungal secondary metabolites to aid detection and identification when standards are not available. The data analyzed for MS spectra were taken in positive ESI^+MS along with common fragments and adduct ions along with suggestions on whether UV or ESI^+MS should be used[15]. Valuable structure information can be obtained from the parent ion peaks for further MS^n experiments. The MS^n experiments were also performed for the reference peaks for BS, GS and YS (data not shown). However, further MS^n can only give information about the fragmentation pattern of the molecules and the side chain derivates, NMR analyses were required to prove the exact structure information. Currently, the usefulness of MS information is limited by the lack of a large and more complete database.

Although, the positive result in Libermann-Burchard reagent and R_f of BS is similar to ergosterol (UV=272 and R_f =0.47)[2], BS has a quite different MW from the MW of protonated and adduct ions fragments of ergosterol (MW=396) which was revealed from the database. The fragmentation spectrum, including impurities of BS did not match with fragment patterns of ergosterol and all compounds (BS, GS and YS) with correlated molecular weights and UV spectra could not be found in the database of secondary metabolites of fungi. The spectra were matched with spectra in the handbook of Secondary Fungal Metabolites prepared by Cole *et al*[3]. This handbook is comprised of three volumes of up-to-date information on secondary fungal metabolites. Again, no exact match was found for the spectra of BS, GS and YS. It is quite possible that BS may be structurally similar to ergosterol. Therefore, further high resolution spectral details such 2D NMR and X-ray crystallography analysis are needed to confirm the structural information of BS, GS and YS.

IV CONCLUSION

In the course of our investigation of immunomodulatory substances from endophytic fungi of *Tripterygium wilfordii*, we focused on *Pestalotiopsis* sp. because this taxon has already been reported to have profound immunodulatory activity among the screened endophytic fungi in various immunological assays [10]. This present study focuses on the isolation of bioactive compounds of *Pestalotiopsis* sp by bioassay directed fractionation. Bioassay guided fractionation is essential for bioactive metabolite isolation. Without this method it would be a difficult task to isolate active compounds from a crude extract. In order to have any assurance of isolating the active compounds it would be necessary to isolate every component of an extract or at least all of major components [18].

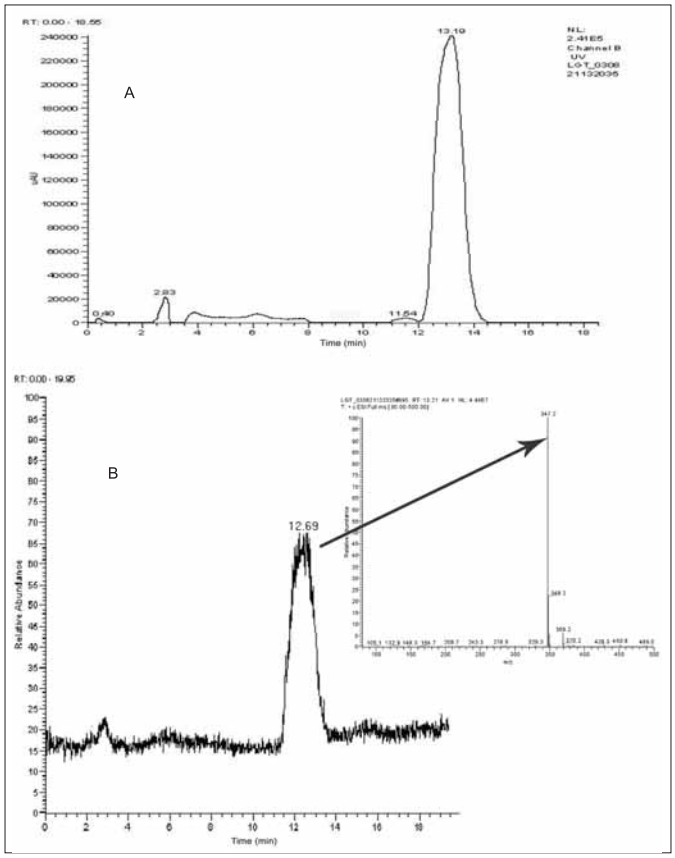


Figure 4. HPLC-UV (280 nm) chromatogram (Panel A) and HPLC-Total Ion Current (TIC) chromatogram along with MS spectrum (inserted) of GS compound eluted at t_R 12.69 min (Panel B)

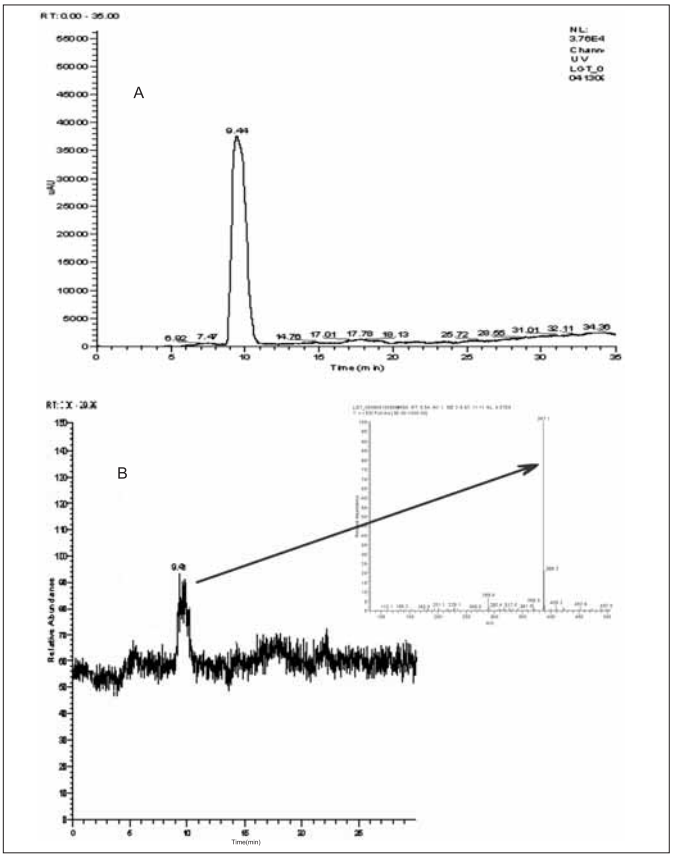


Figure 5. HPLC-UV (450 nm) chromatogram (Panel A) and HPLC-Total Ion Current (TIC) chromatogram along with MS spectrum (inserted) of YS compound eluted at t_R 9.41 min (Panel B)

Bioassay directed purification serves as the only viable method to identify the bioactive constituents in the crude extract. The LC/UV/MS method is useful for getting preliminary information about the content and nature of components of crude and purified fungal extracts. Establishment of LC/UV/MS for BS, GS and YS compounds will be useful when a large number of fungal isolates have to be processed since unnecessary isolation of known compounds is avoided. It is proposed that BS, GS and YS are the major antiproliferative components of crude extract of *Pestalotiopsis* sp. However, a number of partially purified fractions showed high cytotoxicty which may have various biologic activities after further purifications. The anti-proliferative activity of BS, GS and YS may not be sufficient to fully account for the immunomodulatory activity of the fungal medium. Further studies such as the effects of these compounds on the production of cytokines, i.e. IL-2, TNF-α, IFN-γ, immunoglobulins and direct effect on T cell subpopulation and/or macrophages are needed.

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Great News ....

Continuing Education Units (CEUs) for Authors of Articles in the HKPJ. At the most recent meeting of the Pharmacy Central Continuing-education Committee (PCCC), it was decided that CEU would be awarded to authors of articles published in the HKPJ. For each issue, the Editorial Committee, led by the Managing Editor, will choose an article from all the published articles in that issue, for PCCC to use for CE purposes. The author(s) is(are) responsible for setting questions for the approved CE article. Primary authors are entitled to receive 6 CEUs and other co-authors of the same CE article are entitled for 4 CEUs granted by PCCC. For details on how to get CEU, please refer to the article named "PCCC Continuing Education Units (CEU) Accrediting System" [HKPJ 2002;11(2):79-80].

Great news to boost the professional standard and recognition of the contributions to the HKPJ!

Herba *Andrographitis* (穿心蓮) and Its Extracts as Xenobiotics for Treatment of Fever, Sore Throat and Viral Infections as well as Prevention of Common Colds

Jie-liang Li[a]; Hon-Yeung Cheung[a, b]; Wai-Ping Lai[b]; Chui-Shan Cheung[b]
[a]*Department of Biology & Chemistry, City University of Hong Kong, 83 Tat Chee Ave., Kowloon, Hong Kong*
[b]*Pharmaceutical & Chemical Technology Center Ltd., City University of Hong Kong, 83 Tat Chee Ave., Kowloon, Hong Kong*

Botanical Name: *Andrographis paniculata* (Burm.f.) Nees (穿心蓮)
Plant Family: Acanthaceae
Pharmacopoeia Name: Herba Andrographis
Other Names: Chuanxinlian, Lanhelian, Yijianxi, Kemlegh, Chirreta, The Creat, King of Bitters
Brand Names: 穿心蓮片, KangYan Tablets®, Chuanxilian Tablets®, Yamdepieng®, Chuan Xin Lian Antiphologistic Pill®, Chuanxinlian Ruangas®

I ABSTRACT

Andrographis, also known as "King of Bitters" is a shrub widely distributed in India and other Southeast Asian countries. It is a well-known herbal medicine used for centuries to treat gastrointestinal tract and upper respiratory infections, fever, herpes, sore throat and a variety of other chronic and infectious diseases; such as influenza. Research conducted in the 80's and 90's has demonstrated that *A. paniculata*, properly administered, has a surprisingly broad range of pharmacological effects. Some of them are extremely beneficial. This review attempts to conglomerate the available information related to its use for promoting health.

II DESCRIPTION AND BACKGROUND

Andrographis paniculata Nees (Family Acanthaceae) is an annual plant grown in tropical areas. It grows abundantly in Southeast Asia because of its well-known curing effects and it is also cultivated extensively in China, Thailand, and the East and West Indies [1]. It is a branched, erect herb with height running from 1/2 to 1 meter. The stem of *A. paniculata* is square in shape with large knobs at intervals along the stem. Leaves are usually 4-8 cm long, needle shaped and with parallel veins [2-3]. It is one of the prominent ingredients in at least 26 Ayurvedic formulas listed in *Indian Pharmacopoeia*. This herb is described as bitter and cold in nature in traditional Chinese medicines and is commonly used to remove body heat as in fever and to dispel toxins from the body.

III BIOACTIVE CONSTITUENTS

A. paniculata is collected in early autumn when the stem and leaves are growing exuberantly. Although the whole plant of *A. paniculata* is frequently used for medicinal purpose, different bioactive ingredients are found in different parts of the herb [4, 5]. It has been reported that the leaves contain the highest amount of andrographolide (2.39%), the most medicinal active phytochemical in the plant, while the seeds contain the lowest [6]. But both growing region and season play an important role on concentration of the components. *A. paniculata* grows best

Figure 1. Photo of Andrographis paniculata

Contraindications
May cause abortion during pregnancy and should be avoided during pregnancy.

Undesirable Effects
Andrographis has not been associated with any side effects in human studies, although animal studies have raised concerns about its effects on fertility.

Interaction with Conventional drugs
No interaction with conventional drugs has been reported.

in tropical and subtropical areas of China and Southeast Asia. The highest concentration of the active components is found just before the plant blooms, making early autumn the best time to harvest. Bioactive constituents found in *A. paniculata* include diterpene lactones, diterpenoids, flavonoids, alkanes and many other types of components. Figure 2 is the chemical structure of some isolated constituents reported in the literature.

1. Diterpene lactones and Diterpenoids

Andrographolide, neoandrograpolide and deoxyandrographolide are the major representative substances under this category (Fig 2). Andrographolide (Fig. 2A) is colorless, crystalline in appearance and has a very bitter taste. A γ-lactone ring is connected to a decalin ring system via an unsaturated C_2 moiety. Hydrolysis of andrographolide in alkali can cleave the lactone ring to yield salts of andrographolic acid which can be reconverted by acidification [7, 8, 9, 10].

Neoandrographolide (Fig. 2C) is a diterpene glucoside and deoxyndrographolide (Fig. 2B)is structurally closely related to andrographolide [11, 12, 13].

Beside the three main diterpene constituents, many other diterpenoids have been isolated from *A. paniculata* and their structures elucidated. These include dideoxyandrographolide, 14-deoxy-11, 12-didehydroandrographolide (Fig. 2D), panicolide, homoandrographolide and andrographoside [10, 14-17].

2. Flavones and Flavonoids

Two flavones were isolated from the leaves of *A. paniculata* that were named oroxylin A and wogonin (Fig. 2F) by Zhu[18]. Flavonoids including andrographin, andrographidine A-F and flavone glucosides are the main components in the root [19].

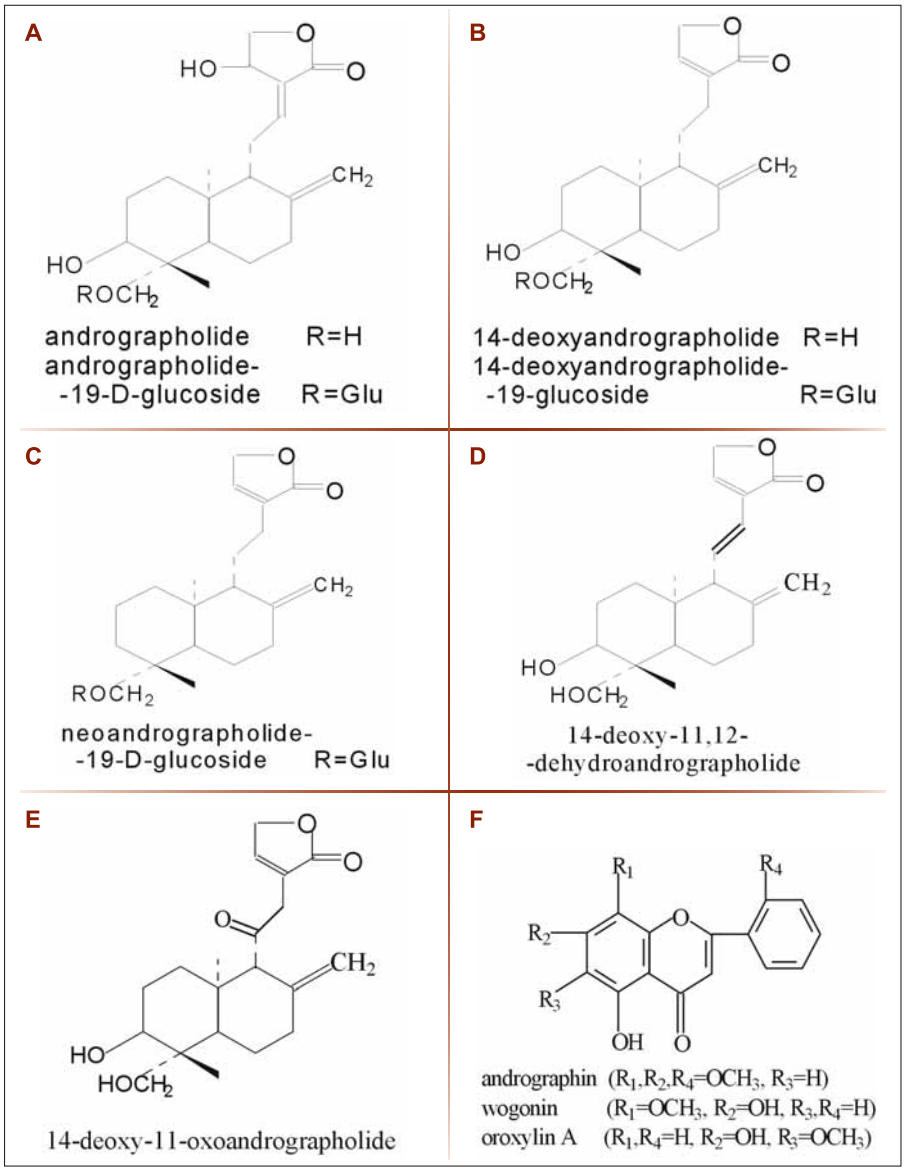

Figure 2. Chemical structure of some constituents in Andrographis paniculata

3. Other Constituents

Alkanes, ketones, organic acids and sterin have also been found in *A. paniculata*. These include andrographan, andrographon, caffeic acid, chlorogenic acid and andrographosterin.

IV CONTEMPORARY USES

A. paniculata has been widely used to treat GI tract and upper respiratory infections, influenza, fever, herpes, bronchitis, diabetes and a variety of other chronic and infectious diseases. It is the prominent ingredient in many Indian and traditional Chinese formulas for treatment of liver disorders. The herb also exerts cardiovascular benefits and is used to treat patients with destroyed heart muscle resulting from acute myocardial infarction. *A. paniculata* has also been used for tonsillitis, tuberculosis, leptospirosis, acute pyelonephritis, tumor, leprosy and pelvic infection.

V MODE OF ACTION

1. Antibacterial and anti-inflammatory effects

Many reports in China claim that the decoction of *A. paniculata inhibited Staphylococcus aureus, Pseudomonas aeruginosa, Proteus vulgaris, Shigella dysenteriae, and Escherichia coli* [20, 21]. The same results were found by Gupta *et al* [22]. Furthermore, the water-soluble fraction of the herb was found to have a strong inhibitory action against *Shigella dysenteriae* [23]. The significant antimicrobial activity of aqueous extract of *A. paniculata* might be due to the combined effect of arabinogalactan proteins and andrographolides [24].

It was reported that after treatment with *A. paniculata* extract and andrographolides, inflammation caused by histamine, dimethyl benzene, croton oil and acute pneumocytsis was reduced or relieved [25]. However, the anti-inflammatory effect of this herb disappeared whenever bilateral adrenal glands were removed. High dosage of andrographolide lactones also caused thymic atrophy in young mice and markedly decreased vitamin C content in the body. These observations suggest that the anti-inflammatory effect worked by a mechanism that involved the adrenal gland. The active components of *A. paniculata* are capable of activating the pituitary gland, promoting the synthesis of adrenocorticotrophic hormone (ACTH), and consequently enhancing the

adrenocortical function [26, 27, 28].

A study conducted by Chiou *et al* confirmed the anti-inflammatory effect of andrographolide. It was found that andrographolide inhibited nitrite synthesis by suppression of inducible nitric oxide synthase (iNOS) expression in RAW264.7 cells [29]. Shen *et al* reported that andrographolide pretreatment could prevent reactive oxygen species (ROS) production and neutrophil adhesion in rat neutraophils [30].

2. Immunostimulant function

From clinical experiments, pretreatment with *A. paniculata* can significantly decrease the incidence of cold as compared to the placebo group [31]. The symptoms such as tiredness, shivering, sore throat and muscular aches of the patients diminished significantly on the fourth day of treatment with Kan Tang, a medicine made from *A. paniculata*. Anju Puri *et al* reported that ethanol extract and purified diterpene andrographolides of *A. paniculata* induced significant stimulation of antibody and delayed type hypersensitivity (DTH) response to sheep red blood cells (SRBC) in mice. The plant preparations also stimulated nonspecific immune response by the animals in terms of macrophage migration index (MMI) phagocytosis of ^{14}C-leucine labeled *E. coli* and proliferation of splenic lymphocytes. The decoction of *A. paniculata* can increase leukocytic phagocytosis of *S. aureus in vitro* [32].

Recent research has indicated that extracts of *A. paniculata* may have great promise for interfering with the viability of HIV. In an *in vitro* test system of human HIV-I, anhydrographide was able to decrease the expression of a cell division controlling enzyme, p34cdc2 kinase. This enzyme in association with cyclin B is the serine/threonine kinase subunit of M phase-promoting factor involving in the G1/S transition and initiation of mitosis. Holt and Comac reported that andrographolide could prevent transmission of the virus to other cells and stop the progress of the disease by modifying cellular signal transduction [33]. Researchers in the National Institute of Health (USA) in 1995 reported that T-cells infected with HIV accumulated high levels of overphosphorylated CDK-1. It was found that agents which can protect the phosphorylation of p34cdc kinase can lessen the severity of AIDS and andrographolide is such an agent (Fig. 3).

Cooperative research at the National Cancer Institute (USA) has shown that andrographolide could also

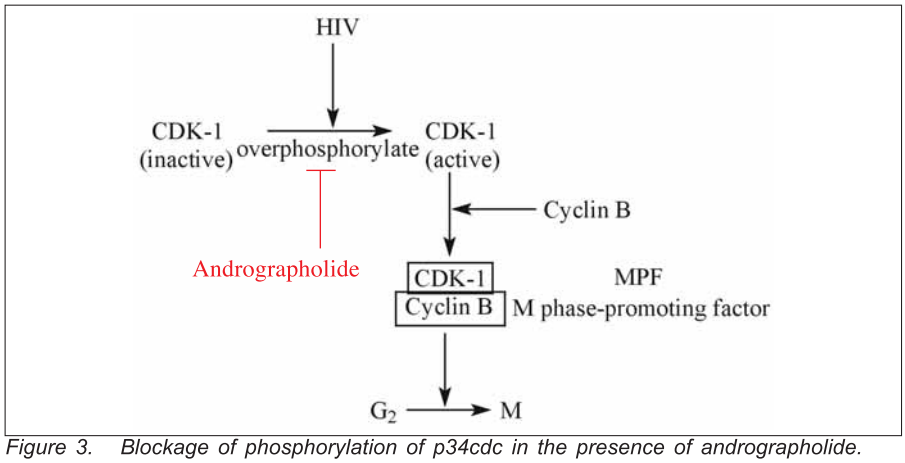

Figure 3. Blockage of phosphorylation of p34cdc in the presence of andrographolide. Red line indicates inhibitory effect (after Barish, J.G.)[50].

inhibit HIV's toxic effect on cells by inhibiting c-mos, a genetic component involved in HIV propagation and T-cell death (Fig. 4). Testing of *A. paniculata* done at the Frederick Research Center demonstrated that extracts of *A. paniculata* could increase AZT's ability to inhibit replication of HIV and that could lower the doses of AZT, thereby minimizing the side effects (Fig. 5).

3. Anti-cancer activity

The study by Matsuda *et al* has demonstrated that *A. paniculata* has potent cell differentiation-inducing activity on leukemia cells [34]. Talukdar and Banerjee found that in addition to causing cancer cell maturity or differentiation, extract of *A. paniculata* leaves had cancer cell-killing abilities [35]. *A. paniculata* stopped stomach cancer cells from multiplying and inhibition of the growth of human breast cancer cell was demonstrated to be similar to the drug tamoxifen (from laboratory tests conducted in Buffalo, New York). The extract safely and effectively blocked growth of prostate and breast cancer as well as non-Hodgkin's lymphomas. Cancer studies at Roswell Park Cancer Institute in Buffalo, New York, showed that the extract from *A. paniculata* has an anti-prostate cancer action comparable to that of the widely used and highly toxic agent, cisplatin, without the toxicity.

Li *et al* tested the anticancer activity of *A. paniculata* extract on different kinds of cancer cells and found that at a concentration of 500 µg/ml, it potently inhibited the proliferation of HepG2 cells (>97%) and to SW620, LS180, HT29, the inhibition rates were 40%, 34%, and 48%, respectively [36].

Many researchers believe that *A.*

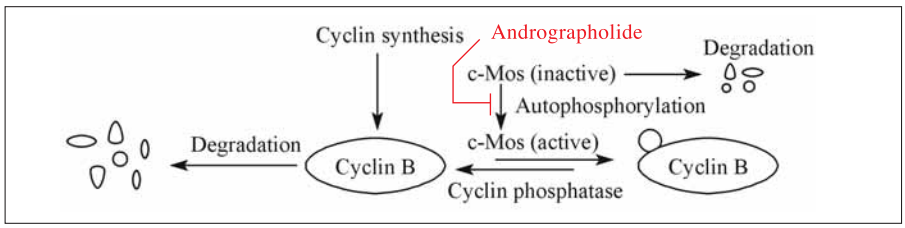

Figure 4. Involvement of andrographolide on cyclin B phosphorylation by Mos. Red line indicates inhibitory effect.

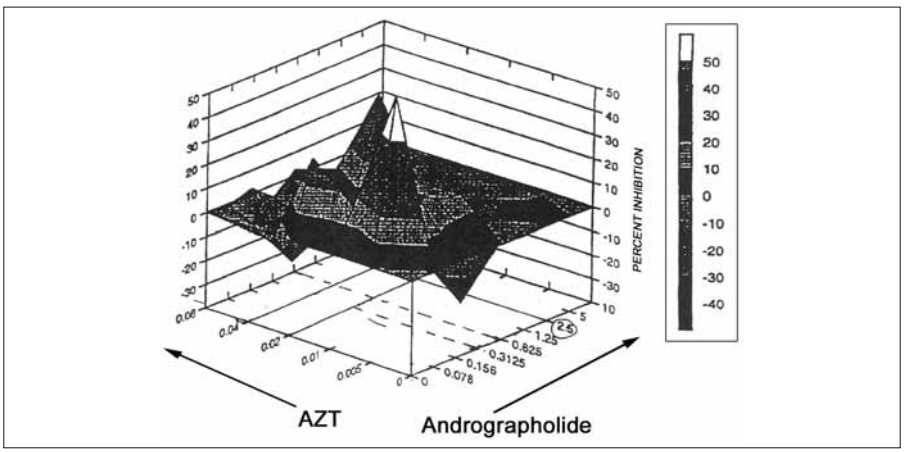

Figure 5. Anti-HIV-1$_{WEJO}$ of Andrographolide and AZT in PBMC (after Barish, J.G.)[50].

paniculata inhibits synthesis of cancer cell DNA. Recently, more and more reports suggest that the activity of anticancer herbs work by inducing apoptosis of tumor cells. But this has not yet been reported about the antitumor effect of *A. paniculata*.

4. Cardiovascular benefits

Serial studies conducted by Tongji Medical University in China have demonstrated that *A. paniculata* has potential to treat patients with destroyed heart muscle resulting from an acute myocardial infarction (heart attack). Zhang *et al*. found that extract of *A. paniculata* inhibited the 1 min and 5 min platelet aggregation induced by ADP, and serotonin (5-HT) release from platelet decreased but plasma 5-HT level remained unchanged. Ultrastructural observations showed that *A. paniculata* slows down the release of dense and aggranules from platelet and dilating canalicula system [37]. The study done by Wang *et al* has shown that the effects of *A. paniculata* extract could significantly alleviate antherosclerotic iliac stenosis induced by deendothelialization and high-cholesterol diet in rabbits [38]. Guo *et al* demonstrated that *A. paniculata* extract could prevent the intramyocardial increase of Na^+, Ca^{2+} and the loss of K^+, Mg^{2+} which may explain the basic mechanism in decreasing the reperfusion arrhythmia [39]. *A. paniculata* isolates -0134 (API_{0134}) can markedly inhibit aggregation of platelet, increasing the cellular cAMP level. The activity of phosphodiesterase-I (PDE-I) stimulated by Ca^{2+}/calmodulin (CaM) was apparently inhibited by API_{0134}. API_{0134} can intensively suppress expression of PDGF-B, c-sis mRNA and c-myc RNA which may contribute to the explanation of one molecular mechanism of anti-smooth muscle cell proliferation and anti-atherosclerosis [40, 41]. Zhang and Tan reported that crude water extract of *A. paniculata* produced a significant fall in mean arterial blood pressure (MAP) which may work via α-adrenoceptors, autonomic ganglion and histaminergic receptors, because the hypotensive effect was negated or attenuated in the presence of phentolmine, hexamethonium as well as pyrilamine and cimetidine [42].

5. Liver & Gallbladder protection

Four *A. paniculata* related medicinal compounds were tested for a protective effect against liver toxicity produced in mice by giving them carbon tetrachloride, alcohol or other chemicals. These chemicals damage the liver by causing lipid peroxidation due to free radicals produced by the chemical attack and destroy cellular membranes that surround liver cells. When *A. paniculata* compounds were given orally to animals three days before the toxic chemicals, there was a significant protective effect in the liver [43].

Handa and Sharma identified the hepatoprotective activity of andrographolide in detail and their results suggested that andrographolid might be the major anti-hepatotoxic ingredient present in *A. paniculata* [44]. Comparison of the anti-hepatotoxic activity of andrographolide with other lactones, andrographiside and neoandrographolide, resulted in andrographolide being found to exhibit a lower protective potential than the other two which were as effective as silymarin (a standard hepatoprotective agent).

A. paniculata extract could markedly decrease the level of alkaline phosphatase (ALP), GOT, GPT and increase the level of SOD which is a well-known anti-oxidant agent [45].

Andrographolide was shown to produce a significant increase in bile flow. After treatment with andrographolide, the usual decrease in bile induced by paracetamol was prevented. Andrographolide produced a dose dependent choleretic effect, as evidenced by the increase in bile flow, bile salt and bile acids in conscious rats and anaesthetized guinea pigs. This increase is beneficial and results in enhanced gallbladder function. Use of *A. paniculata* might, therefore, decrease the probability of gallstone formation and might also aid fat digestion [46].

VI CONTRAINDICAIONS

Women during pregnancy and lactation period should avoid taking the herbal extract and the andrographolides chemical components. The sodium salt of andragrapholide hemisuccinate was deleterious to the placental chorionic trophoblastic cells [47].

VII UNDESIRABLE EFFECTS

Large oral doses of *A. paniculata* may cause gastric discomfort and loss of appetite. Emesis may be caused by the bitter andrographolide. Some people may have allergic reactions ranging from minor skin rashes to more serious anaphylaxis, which is a potential problem at high doses [48].

VIII INTERACTIONS WITH CONVENTIONAL DRUGS

Because *A. paniculata* has a potent anti-viral effect on HIV, a combined *A. paniculata* and AZT medicinal treatment may be more effective and beneficial because it can lower the doses of AZT used, thereby minimizing the side effects of AZT.

The combination of andrographolide plus rifampin results in a 2.6-fold decrease in fatality rate [49].

IX MODE OF ADMINISTRATION

The entire plant or parts of the plant such as leaves, stems, root etc., can be employed therapeutically. *A. paniculata* can be taken orally or through injection.

X DOSAGE

The recommended dosage for injection of total andrographolides is 200~300 mg per day and for oral administration of andrographolide is 0.03~0.06 g per dose.

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"A Ray of Hope" and a Sharing of My Humble Thoughts

Ms S C Chiang, B Pharm(Hons), MRPS, MHA

Dear fellow pharmacists,

More than a month has elapsed since the Hong Kong Pharmacy Conference 2003. I was waiting to see if anybody would attempt to put down on record the opinion and thoughts gathered from the participants after their attendance at the 16th annual event for the pharmacy profession. But my patience wore me out and do allow me to share my humble thoughts with you.

I had always been a faithful supporter of the Annual Conference, being an attendant as well as a part of the organizing team each year in the past many, many years. Every time, right after the conference, a small group of us in the organizing team would sigh with relief wondering how we had made it yet another year and each time we would say - no more please next year! But then, the uncontrollable thoughts about what we didn't do so well and what we should have done better would soon creep into our minds and before long we would start talking about how we can do this and do that for the next year's conference!

This year, however, it was more than these usual feelings. It was some how different. First of all, we had Mrs Mary Cheng from the Department of Health to be the Chair lady. She was totally new to the organizing committee yet she assumed the roles and functions of the chairlady so perfectly well, that a majority of the credits must go to her for the successful delivery of this year's conference. And because of this, I was able to step back and watch the conference delivery process more clearly.

I observed several phenomenons that are new to the conference. There was an obvious influx of new blood - a group of supreme quality pharmacists, from the government sector - the Department of Health, who showed their colors and gave in their best. Hence, many of the tedious, behind the scene tasks were thoughtfully and meticulously taken care of, sparing the rest of the organizing team the time and resource on other things. This would not have been possible if the Department of Health was not involved and engaged as one of the official organizers. Then, there were the pharmacy students from the Chinese University. They were the unsung heroes who helped to attend to all the seemingly tiny, yet important, laborious details at the registration desk, the conference sessions and the dinner. Without the participation of the Chinese University, these tasks would be shouldered by the usual thinkers in the organizing committee who inescapably had to be the doers too in the past years. Then, there was the unfailing support from some of the pharmaceutical industry which mobilized their bank of intelligent pharmacists who helped tremendously following up some of the more time consuming tasks and ironing out other teething problems for the conference. All these together added to the smooth running of the ever growing conference with near to four hundred participants this year.

But more importantly, there was a definite and significant increase in pharmacists' participation from the community as well as the industrial sectors. We saw many old and familiar friends, from the community, who after so many years still showed a genuine concern and care about the pharmacy profession. Despite our brief conversation, here and there, I could still sense the raw passion within them for the pharmacy profession. Most of them showed eagerness to want to do something together with us, not just the conference but any activities that would truly help to restore the roles and functions of the pharmacists to regain our professional confidence. As I moved in and out, I could sense the surging abundance of 'lets come together and do something' feeling. I was almost certain, surprisingly, for the first time, of the presence of *a ray of hope* in our profession.

Scanning the conference attendees, I saw many new and old faces, young and experienced pharmacists, even some retired senior pharmacist members were with us. I hope they all had a good time - they should be - good venue, good conference, good companion, good food and there was so much to take away - the gimmicks, the goodies, the prizes, and the conference bag, not to mention the good fun and the pleasant memories!

But scanning, yet again, I saw the immense importance and the significance in these participants. All these highly trained professional pharmacists work in different areas of the pharmacy practice and are indeed the fundamental members of the health care delivery system in Hong Kong. The Conference has brought them together for a common event. But if only we could bring them together for a common course and a common vision, i.e. to develop a strategic plan for the future development of the pharmacy; to deliberate on the time table for the actions required; to recapitulate and find ways to live up to our different roles and functions in our areas of influence; or simply how can we rekindle the fire from within? Perhaps, because of the synergistic effects and because of the concerted partnering efforts, we could have more than *a ray of hope* in the pharmacy profession.

Scanning the environment leads me to believe that the opportunity is here. And many of us are tired of the time wasted so far. My humble thoughts are each of us should think big and start small. We should not wait for others to

lead us, but to take lead ourselves. We must not count on others to make the difference. We should make the difference ourselves. Starting from our small circle of influence, we should aim to expand the circle. Be both the mentors and the mentees. Make plans now to cast your steps in the history of pharmacy making and let your steps be shown and remembered.

To kick off, you would be pleased to know that the discussion meetings on the Public Private Partnership Program for Pharmacy Service have already been initiated. The details of the plan are being formulated with the active and useful involvement of pharmacists from both the community and the public hospitals. So far, there have been definite interests, understanding and support from both sides of the practice sectors despite the fact that there is a lot of additional work involved and there would be a lot of potential changes to the medication management process of our patients.

I see this partnership program as a direct means of communication, a convenient forum for exchange of experience and an innovative method for utilizing available resources to enable better quality of patient care. This is certainly a big step forward as an improvement of our pharmacists' contribution to the society at large and a boost of our professional image. More details of the program will be announced in the appropriate timing and no matter where you are working, make sure you are not left out in this important issue.

Simultaneously, there have been other discussions amongst the various professional groups e.g. within the three professional societies and the societies with the Pharmacy School, or with the Department of Health or the Hospital Authority or with the Hong Kong Government. All in all, new relationship building and creative thinking are in momentum. The Conference is just a vivid example of our successful collaboration and it is expected that many other programs of equal significance and no less meaningful would take heed.

Finally, let me quote again the remarks that I made at the conference closing speech in the 1998 Pharmacy Conference:

"Life is like a field of fallen snow; where I choose to walk, every step will show."

My dear fellow pharmacists, I am saying in all things we do, we must strive not to be respected but to be respectable. At the end of the day, it does not matter how people judge you because the important applause comes from within. It is the faster heartbeat, the pride and the satisfaction of accomplishment that will see us through. See you around.

Yours truly,

S C Chiang
A pharmacist still with a passion for the pharmacy profession

Hong Kong Pharmacy Conference 2003 - *Partnering for Success*

Helen Wong

Following the success from last year, the Hong Kong Pharmacy Conference 2003 was again jointly organized by six organizations, namely the Chinese University of Hong Kong (CUHK), Hospital Authority (HA), Department of Health (DH), Pharmacists Association (PA) and Society of Hospital Pharmacists (SHPHK), under Mrs Mary Cheng's leadership. It was held at the Kowloon Shangri-la Hotel on Oct 11-12, 2003. In connection to the theme "Partnering for Success", the Conference programs included a variety of topics, aiming to provide sufficient knowledge and background to fellow pharmacists to facilitate partnership within the profession and with the others organizations.

It was the first time "Good Regulatory Practice" was so much emphasized in this yearly event. It was certainly a need for doing so, seeing the establishment of mandatory requirement of Good Manufacturing Practice at the end of 2002 and the commencement of regulatory control of Chinese medicines at the end of 2003. Experts in the development of Chinese

Figure 1. Opening ceremony. [from left to right] Mr Kim Ng (SHP), Mr Benjamin Kwong (PSHK), Dr Wing-Man Ko (HA), Dr PY Lam (DH), Ms Mary Cheng (Chairlady), Prof Moses Chow (CUHK), Mr Billy Chung (PPA).

Figure 2. One of the guest speaker, Prof Godwin Wong, University of California, Berkeley, USA.

Figure 3. "We play attention to the talks!!!"

medicines, local pharmaceutical manufacturers and regulators from the Department of Health were invited to present the progress of development in this aspect and share their experiences.

Public Private Partnership (PPP) was another major topic of the Conference. The existing partnership programs between public and private sectors were evaluated and possible future development was discussed substantially. With the enormous fiscal deficit of Hong Kong, ways must be found to transfer patients out from public sector to private sector, including pharmaceutical service. That was solidly stated by Dr Ko Wing-Man, Director (Professional Service & Public Affairs) of Hospital Authority, in his theme speech on Day 1 of the Conference. At the same time, the Severe Acute Respiratory Syndrome (SARS) outbreak earlier this year reveals there is a deficiency in public health education among the general public. This is high time the roles of pharmacists in Hong Kong can be extended and redefined.

Figure 5. "We enjoy the dinner so much!"

Same as the past years, the popular and practical topic, Clinical Practices, was one of the focuses of the Conference. This year's programs emphasized on ischaemic heart disease, hyperlipidemia, hypertension, herbal medicines, pharmacoeconomic analysis of atypical antipsychotic agents, as well as pharmacokinetic monitoring of aminoglycosides.

All pharmacists need to demonstrate some kinds of leadership skills at the workplace. Indeed, "Organizational Leadership" has great impact on the success and failure of an institution or a working group. Therefore Professor Godwin Wong, who had been an international consultant for various organizations on leadership training, was invited as a guest speaker from the University of California, Berkeley, USA. He gave two very inspiring and interesting speeches on organizational leadership during the conference.

The SARS outbreak was not only a crisis to the Hong Kong society, but also a warning to the existing public health policy and model. A sharing session was held before the end of Day 2 of Conference. A multi-media slide show was presented by Mr Michael Ling. Mr. William Chui also shared his personal feelings with the attendants.

With all these rich and exciting programs, it was not surprising there were close to 400 participants in this Conference, from different areas including regulatory agency, hospitals, community pharmacies, pharmaceutical manufacturers, business enterprises and research institutions. Last, but not the least, the chairlady of Pharmacy Conference 2004 has already been announced and she is Dr. Vivian Lee from the Department of Pharmacy, Chinese University of Hong Kong.

Figure 4. The vice chairpersons of the Conference 2003, Ms Andrea Chang and Mr Jack Wong.

Figure 6. Dr Mohamed H Farah, the programme leader. Traditional Medicine at WHO collaborating Centre for International Drug Monitoring, Sweden [left two], with Mr Michael Ling [left one], Mr Clive Chan [left three] & Dr Susan Ho [right one].

Figure 7. Dance performance, by fellow pharmacists, at the conference dinner.

Figure 8. The chairladies of the Conference 2003, Ms Mary Cheng, is leadingher successor, Dr Vivian Lee, for next year conference.

The PSHK Response to Consultation Document Sep 2003 - Proposed Regulation of Health Claims in Hong Kong

Benjamin Kwong

Secretariat
Consultation on Regulation of Health Claims
3/F Public Health Laboratory Centre
382 Nam Cheong Street
Kowloon

30th October 2003

Proposed Regulation of Health Claims - Response to Consultation Document

The Pharmaceutical Society of Hong Kong (PSHK) would like to take this opportunity to express the views of our General Council with regard to the consultation document of the captioned matter. The views expressed below were shared at a face to face consultation meeting between representatives of the Department of Health and members of our profession on 8th October, 2003. This letter serves as a written documentation of those views expressed at that meeting.

As rightly pointed out in the introduction of this consultation document, an increasing number of food products claiming specific beneficial health effects have been found in the Hong Kong market in recent years. The PSHK feels that the current proposed amendments to the existing Undesirable Medical Advertisement Ordinance (UMAO) as a response to complaints from consumers against misleading / exaggerated claims as well as calls from the public and Legislative Council is well overdue while the extent of control is inadequate.

Specifically, the PSHK pinpointed the following areas for further consideration:

1. Definition of 'advertisement'
We feel that the current definition of 'advertisement' is too narrow to cover the many different diverse modes of promotion employed nowadays. Promotion often can be disguised as health talks, seminars, direct selling by agents or even by word of mouth. Package circular of products are also not included under the control of the UMAO. We propose that the control of health claims should take into account the 'spirit' of the advertisements. Once an advertisement (of any nature) purports the public to try a specific product in believe of that health/medical claim, it should fall into the premise of the control of the UMAO.

2. Enforcement and dealing with false claims
Under the Pharmacy & Poisons Ordinance, western medicines are well controlled in terms of each product's efficacy (i.e. indications or claims), safety and quality. The Chinese Medicine Ordinance which we understand to be introduced by the end of 2003 will also control products which are composed of Chinese medicines. Hopefully with good enforcement of these ordinances, much of the problem of false claims would be under control. There still remains products which are defined as 'food items' that may not be effectively controlled, especially when the health claims are not explicitly printed black and white. The PSHK urges the Government to tighten up control and surveillance on health food by enforcing the existing ordinances, as well as setting up new control measures for items that do not fall under the control of the existing ordinances. Ideally an evaluation system for pre-marketing registration would be the best. But understanding the difficulty of doing so due to a lack of worldwide agreement on the definition and control of health food, the PSHK propose a listing procedure as a first step to provide a platform for enforcement of control on health foods and their proposed claims. In this way, the distributor or responsible person for the distribution of these products can be traced and held liable. At the meeting, compulsory labelling of all ingredients on the packaging material has been mentioned as a means to tackle the problem of false claims.

Currently, the execution of the UMAO is by the DoH together with the Police Force. This current system is inefficient and unsatisfactory. We agree that the DoH should be empowered to enforce the UMAO on its own to improve efficiency and to reduce duplication of manpower from different Government departments.

3. Penalty
While the proposed additional control on nine groups of claims that should be prohibited is welcome by the PSHK, we feel that with the current level of penalty, the UMAO can hardly serve its objective of curbing improper and even false claims of health food and related products. As evidenced by the business in various community outlets (including community pharmacies) and the level of public promotion, it is obvious that health food business enjoys a tremendous growth. The current penalty laid out in the UMAO is out of proportion to the business return and thus even good enforcement of the ordinance would unlikely bring about any deterring effect to false claims of such products. We urge the Government to revisit the level of penalty as this is impacting on human health and life.

Apart from the above points which we specifically expressed, we also echoed on the following raised at the meeting. Firstly, like other professional bodies, we thought that the four claims that were deemed unnecessary to be included in the prohibited list should be considered as well as they ARE areas of concern. At the same time, proposed health claims prohibition should apply to dosage forms other than oral as well for good overall control. One other point discussed was that the power of the Director of DoH to add extra control to the list should be spelled out clearly. For example, under what circumstances and by what mechanism can the Director exercise this statutory power? We feel at least there should be consultation with professional bodies before new items are being added to the control list.

Regarding the nine specific categories of claims recommended to be prohibited, we believe the Expert Committee has already provided input from different views points. In general the PSHK endorse this recommendation. The PSHK strongly believe that the general public should be empowered and educated to take a higher level of care for their personal health. At the same time, the Government should provide a legal framework such that the general public is also protected from substandard products and/ or false claims and that may be detrimental to their health. With this framework, the pharmacy profession, especially the community pharmacy sector, will be able to work closely with other health care professionals to uplift the overall health standard of the Hong Kong population.

Yours sincerely,

Benjamin Kwong
President
The Pharmaceutical Society of Hong Kong

The SHP / PPA Response to Consultation Document Sep 2003 - Proposed Regulation of Health Claims in Hong Kong

NG Kim Wah; Billy Chung

The Secretary
Consultation on Regulation of Health Claims
3/F Public Health Laboratory Centre
382 Nam Cheong Street, Kowloon

13 November 2003

Dear Sir / Madam,

Regulation of Health Claims in Hong Kong
(Consultation Document Sept 2003)

We would like to submit the consolidated views of the Pharmacists from the Society of Hospital Pharmacists of Hong Kong and the Practising Pharmacists Association of Hong Kong regarding the Consultation Document on Regulation of Health Claims published in September 2003.

First and foremost, we are in support of the initiative taken by the Department of Health to address the problems experienced by the community over the past years due to the flooding emergence of health foods/ health products with exaggerated/ unfounded or unsubstantiated health claims.

However, we are concerned on the proposed enforcement method i.e. to include a list of prohibited claims as a new schedule in the Undesirable Medical Advertisements Ordinance (UMAO). Our concerns are focused in several areas in the proposed Regulation (see table 1).

Table 1. Areas of concern viewed by SHP and PPA in the proposed Regulation of Health Claims

Areas of concern	Our Comments
Chapter 4 : The Proposed Regulation	
4.2 "The Director of Health would have the power to amend the new schedule and to extend its coverage to other products and services as and when necessary having regarding to latest developments and for the protection of public health."	• The public would need to know how would the Director of Health decide and based on what criteria and rationale would the Director of Health regulate "products and services" of any kind in future.
4.2 "The Director of Health would have the power to authorize public officers to be inspectors to enforce the relevant provisions of the UMAO"	• It would be acceptable to assume under the above proposal that the inspectors could inspect the community pharmacies for orally consumed products with misleading and exaggerated health claims, and that such an investigation could lead to prosecution of the Pharmacist under the UMAO (Cap. 231) for displaying and keeping such a product for sale as he /she is the person in charge of the store. However, the fact is that the Pharmacist may not be the owner of the community pharmacies and he /she has no say for the inventory keeping of such a product. Despite this, he /she could be convicted to a fine of HK 10,000 for the first time and upon a second or subsequent conviction to a fine of HK 25,000 and imprisonment for one year. • This would be a very disturbing thought to our pharmacists practicing in the community pharmacies.
4.3 "An Expert Committee consisting of representatives from the Consumer Council, Chinese medicine practitioners, medical practitioners, pharmacists and a nutritionist was set up at the end of 2002 to study and recommend a list of health claims..."	• Please clarify the future role of the Expert Committee. Would they still play an advisory role to the Director of Health for future amendments and products /services inclusion in the UMAO?
4.4 "Claims with less risk may be excluded from the list"	• There are 4 categories enlisted in Appendix 4 which have been suggested to exempt from control, for their relative lack of risk when taken by human. The Government should not knowingly endorse false claims of any commercial products, risk or no risk. • To avoid the likely abuse of this exemption, these 4 categories of items should also come under the overall umbrella of control in line with the control of health claims for the 9 proposed categories. • The proposed control seems to be intended only for orally consumed products. As pharmacists, we know that injectable and topical products could equally cause harm. Furthermore, harmful effects do not come only from the product itself, but also from the reliance on the ineffective product leading to delay in medical attention. Hence, oral, injectable and topical products should be subjected to the same proposed controls.

4.6 "Claims not to be included in the Prohibited List"	• Should consider to include the Appendix 4 into Appendix 3
Chapter 5: The Way Forward	
5.4 "The Schedule can also be amended in future by the Director of Health to include other products and services"...	• Please clarify and explain if any appeal mechanism is available?
Appendix 2 : Undesirable Medical Advertisement Ordinance (Cap.231)	
Section: 2 Heading: Interpretation Version Date 30/6/1997 "advertisement" includes any notice, poster, circular, label, wrapper or document, and any announcement made orally or by any means of producing or transmitting light or sound;	• When a community pharmacist is doing his /her professional services such as the patient counseling, talking about the disease symptoms and product information, it is not uncommon for the pharmacists to refer to the "advertisement". • How can the pharmacist be sure that what he /she has said or quoted is not considered as a violation of law?
Section: 7 Heading: Power to amend Schedules Version Date: 30/06/1997 The Director of Health may, by order published in the Gazette, amend the Schedules	• For any future and subsequent amendments on the schedules, the Director of Health should actively seek public opinions on the proposed amendment before publishing in the Gazette.

Finally, although the change in law is a commendable first step in protecting the health of the public, we have some doubts as to the effectiveness of such move alone. We worry that prohibiting verbal claims is difficult to enforce in reality. While the law may be able to prohibit recordable formats of advertisements or claims, it is difficult to secure evidence against verbal claims. If the loophole is not mended, your efforts will be futile.

We strongly feel that the ultimate solution would be to implement a product registration system for all health products. The gist of the matter should not be what type of claims people make, but whether the claims are not supported by scientific evidence, or would be misleading to the public at large due to exaggeration. The control should be on the products and not just on the claims. For that matter, many claims you proposed to prohibit could actually be reasonably made if there is good evidence to support them. It would be unfair for those genuinely effective products not to be able to make such claims.

It is our mission to help promote the health of the people of Hong Kong. We feel that controlling health claims would only be an intermediate measure. Both the promotion (claims) and the sale of any products which would affect the health of the public should come under professional control within a legal framework.

Yours sincerely,

NG Kim Wah
President,
The Society of Hospital Pharmacists of Hong Kong

Mr Billy Chung
President,
The Practising Pharmacists Association of Hong Kong

NEW PRODUCTS

AVANDAMET (GlaxoSmithKline)

Active ingredient:
Rosiglitazone and metformin

Presentation:
Each film-coated tablet contains 500mg metformin hydrochloride and 1mg, 2mg or 4mg rosiglitazone as the maleate.

Pharmacological Properties:
AVANDAMET combines two antidiabetic agents with different mechanisms of action to improve glycemic control in patients with type 2 diabetes: Rosiglitazone maleate, a member of the thiazolidinedione class and metformin hydrochloride, a member of the biguanide class. Thiazolidinediones are insulin sensitizing agents that act primarily by enhancing peripheral glucose utilization, whereas biguanides act primarily by decreasing endogenous hepatic glucose production.

Indications:
As an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus who are already treated with combination rosiglitazone and metformin or who are not adequately controlled on metformin alone.

Dosage and Administration:
The selection of the dose of AVANDAMET should be based on the patient's current doses of rosiglitazone and/or metformin. The safety and efficacy of AVANDAMET as initial therapy for patients with type 2 diabetes mellitus have not been established.

For patients inadequately controlled on metformin monotherapy: the usual starting dose of AVANDAMET is 4 mg rosiglitazone (total daily dose) plus the dose of metformin already being taken.

For patients inadequately controlled on rosiglitazone monotherapy: the usual starting dose of AVANDAMET is 1000 mg metformin (total daily dose) plus the dose of rosiglitazone already being taken.

Contraindications:
Rosiglitazone maleate and metformin hydrochloride tablets are contraindicated in patients with renal disease or renal dysfunction, congestive heart failure requiring pharmacological treatment, known hypersensitivity to rosiglitazone maleate and metformin hydrochloride, acute or chronic metabolic acidosis, including diabetic ketoacidosis

Precautions:
Rosiglitazone-metformin is effective only in the presence of insulin and should not be used in type 1 diabetes mellitus.

Rosiglitazone-metformin treatment in premenopausal anovulatory patients with insulin resistance may result in resumption of ovulation. These patients may be at risk of pregnancy.

Lactic acidosis is a rare, but serious metabolic complication that can occur due to metformin accumulation.

Rosiglitazone-metformin is not recommended in patients with hepatic impairment.

Thiazolidinediones can cause fluid retention, which can exacerbate congestive heart failure.

Side effects:
Rosiglitazone: oedema, anaemia and hypercholesterolaemia are reported. An increased incidence of heart failure has been observed when rosiglitazone is used in combination with insulin compared to insulin alone. Dose-related weight gain was seen with rosiglitazone alone and in combination with other hypoglycaemic agents. Post marketing reports of Cardiovascular Heart Failure, pulmonary oedema and hepatic dysfunction have been received rarely.

Metformin: gastrointestinal symptoms nausea, vomiting, diarrhoea, abdominal pain and loss of appetite, metallic taste, mild erythema, lactic acidosis

Drug Interactions:
In vitro studies demonstrate that rosiglitazone is predominantly metabolised by CYP 2C8, with CYP 2C9 as only a minor pathway. There is an increased risk of lactic acidosis in acute alcohol when concomitant use with Metformin.

Forensic classifications:
P1S1S3

HEPSERA (GlaxoSmithKline)

Active ingredient:
Adefovir dipivoxil

Presentation:
Available in 10mg tablet

Pharmacological Properties:
Adefovir is an acyclic nucleotide analog of adenosine monophosphate. After phosphorylation, adefovir diphosphate inhibits HBV DNA polymerase (reverse transcriptase) by competing with the natural substrate deoxyadenosine triphosphate and by causing DNA chain termination after its incorporation into viral DNA.

Indications:
Treatment of chronic hepatitis B in adults with evidence of active hepatitis B viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease.

Dosage & Administration:
Adults (18-65 years): 10 mg once daily taken orally with or without food.
Renal impairment: The dosing interval of HEPSERA should be adjusted in patients with baseline creatinine clearance, < 50mL/min.

Contraindication:
Patients with previously demonstrated hypersensitivity to any components of the product.

Precautions:
Doses higher than those recommended must not be administered.

Severe acute exacerbation of hepatitis has been reported in patients who have discontinued anti-hepatitis B therapy, including therapy with HEPSERA. Patients who discontinue HEPSERA should be monitored at repeated intervals over a period of time for hepatic function. If appropriate, resumption of therapy may be warranted.

Chronic administration of HEPSERA (10mg/day) may result in nephrotoxicity. This is of special importance in patients at risk of or having underlying renal dysfunction and patients taking concomitant nephrotoxic agents.

Treatment with anti-hepatitis B therapies that have activity against HIV in a chronic hepatitis B patient with unrecognized or untreated HIV infection may result in emergence of HIV resistance.

Drug Interactions:
Since adefovir is eliminated by the kidney, co-administration of HEPSERA with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of either adefovir and/or these co-administered drugs.

Ibuprofen 800mg three times daily increased adefovir exposure by approximately 23%. The clinical significance of this increase in adefovir exposure is unknown. While adefovir does not inhibit common CYP450 enzymes, the potential for adefovir to induce CYP450 enzymes is not known.

Side effects:
Post-treatment elevations in ALT were observed at a higher incidence in patients who had received 10 mg adefovir dipivoxil than in patients who had received placebo.

Forensic classifications:
P1S1S3

HERCEPTIN (Roche)

Active ingredient:
Trastuzumab.

Presentation:
1 single dose vial contains 150mg of trastuzumab of powder for concentrate for solution for infusion. 1 multidose vial contains 440 mg of trastuzumab of powder for concentrate for solution for infusion.

Pharmacological Properties:
Trastuzumab is a recombinant DNA-derived humanised monoclonal antibody that selectively targets the

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Requirements:

- ❖Degree holder in Pharmacy with Hong Kong Pharmacist Practising Certificate
- ❖Pro-active and customer orientated
- ❖Proficiency in English and Cantonese
- ❖Pre-registration Pharmacists awaiting for the result of " Registration Examination for Pharmacist " will be considered as Dispensers

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extracellular domain of the human epidermal growth factor receptor 2 protein (HER2). Trastuzumab has been shown, both in *in-vitro* assays and in animals, to inhibit the proliferation of human tumour cells that overexpress HER2. *In vitro*, trastuzumab-mediated antibody-dependent cell-mediated cytotoxicity (ADCC) has been shown to be preferentially exerted on HER2 overexpressing cancer cells compared with cancer cells that do not overexpress HER2.

Indications:
HERCEPTIN is indicated for the treatment of patients with metastatic breast cancer who have tumours that overexpress HER2:
a) as monotherapy for the treatment of those patients who have received one or more chemotherapy regimens for their metastatic disease.
b) in combination with paclitaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease.

Dosage and Administration:
HER2 testing is mandatory prior to initiation of HERCEPTIN therapy.

Standard dosage for adult and over 18 years of age:
Loading dose:
The recommended initial loading dose is 4 mg/kg body weight HERCEPTIN administered as a 90-minute intravenous infusion.
Subsequent doses:
The recommended weekly dose of HERCEPTIN is 2 mg/kg body weight. If the prior dose was well tolerated, the dose can be administered as a 30-minute infusion.

Contraindications:
HERCEPTIN is contraindicated in patients with known hypersensitivity to trastuzumab or to any other component of the product.

Precautions:
HERCEPTIN administration can result in the development of ventricular dysfunction and congestive heart failure. Discontinuation of HERCEPTIN treatment should be strongly considered in patients who develop a clinically significant decrease in left ventricular function. The incidence and severity of cardiac dysfunction was particularly high in patient who receive HERCEPTIN in combination with anthracyclines and cyclophosphamide.

Signs and symptoms of cardiac dysfunction, such as dyspnea, increased cough, paroxymal nocturnal dyspnea, peripheral edema, S_3 gallop, or reduced ejection fraction, have been observed in patient treated with HERCEPTIN. Extreme caution should be exercised in treating patients with pre-existing cardiac dysfunction.

Severe pulmonary events leading to death have been reported rarely with the use of HERCEPTIN in the post marketing setting. Signs, symptoms, and clinical findings include dyspnea, pulmonary infiltrates, pneumonia, pneumonitis, pleural effusions, non-cardiogenic pulmonary edema, pulmonary insufficiency and hypoxia, and acute respiratory distress syndrome. These events may or may not occur as sequelae of infusion reactions. Patients with symptomatic intrinsic lung disease or with extensive tumor involvement of the lungs, resulting in dyspnea at rest, may be at greater risk of severe reactions.

Side effects:
Cardiac Failure/Dysfunction, anaemia and leukopenia and diarrhoea were reported.

Infection, primarily mild upper respiratory infections of minor clinical significance or catheter infections, was observed in patients receiving HERCEPTIN in combination with chemotherapy.

Infusion Reactions: During the first infusion with HERCEPTIN, a symptom complex most commonly consisting of chills and/or fever was observed in about 40% of patients.

Severe hypersensitivity reactions (including anaphylaxis), infusion reactions, and pulmonary adverse events have been reported. These events include anaphylaxis, angiodema, bronchospasm, hypotension, hypoxia, dyspnea, pulmonary infiltrates, pleural effusions, non-cardiogenic pulmonary edema, and acute respiratory distress syndrome.

Drug Interactions:
There have been no formal drug interaction studies performed with HERCEPTIN in humans. Clinically significant interactions with the concomitant medication used in clinical trials have not been observed.

Forensic classifications:
P1S1S3

LANTUS (Adventis)

Active ingredient:
Insulin glargine

Presentation:
One pack of 5 cartridges, each containing 3 ml (300 IU)

Pharmacological Properties:
Insulin glargine is a human insulin analogue designed to have a low solubility at neutral pH. At pH 4, insulin glargine injection solution is completely soluble. After injection into the subcutaneous tissue, the acidic solution is neutralised, leading to the formation of micro-precipitates from which small amounts of insulin glargine are released continuously, yielding a smooth, peakless, predictable concentration/time profile with a prolonged duration of action.

Indications:
For the treatment of adults, adolescents and children of 6 years or above with diabetes mellitus, where treatment with insulin is required.

Dosage and Administration:
Given its prolonged duration of action, LANTUS may be administered once daily at any time of the day, however, at the same time every day. The physician will adjust the dosage individually, and will also give guidance on where to inject LANTUS, when blood sugar measurements are to be performed and whether urine tests are necessary.

LANTUS in a cartridge is intended for use in the OptiPen injection device. It is given by subcutaneous injection.

Contraindications:
Hypersensitivity to insulin glargine or to any of the excipients

Precautions:
In the event of insufficient blood sugar control or a tendency to hypo- or hyperglycaemic episodes, possible underlying factors (such as patient compliance, choice of injection site and proper technique, handling of the pen) must be excluded prior to considering prescription of a dose adjustment.

Due to limited experience the efficacy and safety of LANTUS could not be assessed in children < 6 years old, in patients with impaired liver function or in patients with moderate to severe renal impairment.
In patients with renal impairment, insulin requirements may be diminished due to reduced insulin metabolism. In the elderly, progressive deterioration of renal function may lead to a steady decrease in insulin requirements.

In patients with severe liver impairment, insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism.

Side effects:
Hypoglycaemia; a marked change in blood sugar level may cause temporary visual impairment; fatty tissue under the skin may shrink or swell (lipoatrophy or lipohypertrophy) at the injection site and delay insulin absorption and its effect.

Drug Interactions:
Certain medicines affect glucose metabolism and require insulin dose adjustment and particularly close monitoring.

Agents that might increase blood-sugar-lowering effect e.g., oral antidiabetics, ACE inhibitors, disopyramide, fibrates, fluoxetine, MAO inhibitors, pentoxifylline, propoxyphene, salicylates, or sulfonamide antibiotics.

Agents that might decrease in the blood-sugar-lowering effect e.g. corticosteroids, danazol, diazoxide, diuretics, glucagon, isoniazid, oestrogens and progestogens (e.g. in oral contraceptives), phenothiazine derivatives, somatropin, sympathomimetic agents such as [epinephrine, (adrenaline), salbutamol, terbutaline], or thyroid hormones.

Beta-blockers, clonidine, lithium salts or alcohol may either potentiate or weaken the blood-sugar-lowering effect of insulin.

Pentamidine may cause hypoglycaemia, sometimes followed by hyperglycaemia.

Forensic classifications:
P1

NEW

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When Patients on Metformin Do Not Reach Goal,

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- **DISTINCT ACTION:** Complementary mechanisms that target core defects, resulting in improvements in insulin sensitivity and estimates of beta-cell function[1]
- **DEPENDABLE THERAPY:** Low incidence of hypoglycemia[1]
- **ADDITIONAL CONTROL:** Combination of rosiglitazone and metformin provides additional glycemic control than metformin alone[2]

Further information is available upon request.
Avandia, Avandamet are registered trademarks of the GlaxoSmithKline group of companies.

References: 1. Avandamet (package insert). Research Triangle Park NC: GlaxoSmithKline; October 2002 2. T. A. Jones, M. Sautter, L. F. Van Gaal and N.P. Jones. Addition of rosiglitazone to metformin is most effective in obese, insulin-resistant patients with type 2 diabetes Diabetes, Obesity and Metabolism, 2003; 5 : 163-170

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rosiglitazone maleate/metformin HCl

DURABLE POWER OF TWO

ABBREVIATED PRESCRIBING INFORMATION **Presentation** Each Avandamet™ film-coated tablet contains 500mg metformin hydrochloride and 1mg, 2mg or 4mg rosiglitazone as the maleate. **CLINICAL INFORMATION Indications** AVANDAMET is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus who are already treated with combination rosiglitazone and metformin or who are not adequately controlled on metformin alone. Management of type 2 diabetes mellitus should include diet control, Caloric restriction, weight loss, and exercise are essential for the proper treatment of the diabetic patient because they help improve insulin sensitivity. This is important not only in the primary treatment of type 2 diabetes, but also in maintaining the efficacy of drug therapy. Prior to initiation or escalation of oral antidiabetic therapy in patients with type 2 diabetes mellitus, secondary causes of poor glycemic control, e.g., infection, should be investigated and treated. The safety and efficacy of AVANDAMET as initial pharmacologic therapy for patients with type 2 diabetes mellitus after a trial of caloric restriction, weight loss, and exercise has not been established. **DOSAGE AND ADMINISTRATION General** The selection of the dose of AVANDAMET should be based on the patient's current doses of rosiglitazone and/or metformin. The safety and efficacy of AVANDAMET as initial therapy for patients with type 2 diabetes mellitus have not been established. The following recommendations regarding the use of AVANDAMET in patients inadequately controlled on rosiglitazone and metformin monotherapies are based on clinical practice experience with rosiglitazone and metformin combination therapy. • The dosage of antidiabetic therapy with AVANDAMET should be individualized on the basis of effectiveness and tolerability while not exceeding the maximum recommended daily dose of 8 mg/2000 mg. • AVANDAMET should be given in divided doses with meals, with gradual dose escalation. This reduces GI side effects (largely due to metformin) and permits determination of the minimum effective dose for the individual patient. • Sufficient time should be given to assess adequacy of therapeutic response. Fasting plasma glucose (FPG) should be used to determine the therapeutic response to AVANDAMET. After an increase in metformin dosage, dose titration is recommended if patients are not adequately controlled after 1-2 weeks. After an increase in rosiglitazone dosage, dose titration is recommended if patients are not adequately controlled after 8-12 weeks. **Dosage Recommendations For patients inadequately controlled on metformin monotherapy:** the usual starting dose of AVANDAMET is 4 mg rosiglitazone (total daily dose) plus the dose of metformin already being taken (see Table 5). **For patients inadequately controlled on rosiglitazone monotherapy:** the usual starting dose of AVANDAMET is 1000 mg metformin (total daily dose) plus the dose of rosiglitazone already being taken (see Table 5).

Table 5. AVANDAMET Starting Dose

PRIOR THERAPY	Usual AVANDAMET Starting Dose	
Total daily dose	Tablet strength	Number of tablets
Metformin HCl*		
1000 mg/day	2 mg/500 mg	1 tablet b.i.d.
2000 mg/day	1 mg/500 mg	2 tablets b.i.d.
Rosiglitazone		
4 mg/day	2 mg/500 mg	1 tablet b.i.d.
8 mg/day	4 mg/500 mg	1 tablet b.i.d.

*For patients on doses of metformin HCl between 1000 and 2000 mg/day, initiation of AVANDAMET requires individualization of therapy.

When switching from combination therapy of rosiglitazone plus metformin as separate tablets: the usual starting dose of AVANDAMET is the dose of rosiglitazone and metformin already being taken. **If additional glycemic control is needed:** the daily dose of AVANDAMET may be increased by increments of 4 mg rosiglitazone and/or 500 mg metformin, up to the maximum recommended total daily dose of 8 mg/2000 mg. No studies have been performed specifically examining the safety and efficacy of AVANDAMET in patients previously treated with other oral hypoglycemic agents and switched to AVANDAMET. Any change in therapy of type 2 diabetes should be undertaken with care and appropriate monitoring as changes in glycemic control can occur. **Specific Patient Populations** AVANDAMET is not recommended for use in pregnancy or for use in pediatric patients. The initial and maintenance dosing of AVANDAMET should be conservative in patients with advanced age, due to the potential for decreased renal function in this population. Any dosage adjustment should be based on a careful assessment of renal function. Generally, elderly, debilitated, and malnourished patients should not be titrated to the maximum dose of AVANDAMET. Monitoring of renal function is necessary to aid in prevention of metformin-associated lactic acidosis, particularly in the elderly (see WARNINGS). Therapy with AVANDAMET should not be initiated if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels (ALT >2.5X upper limit of normal at start of therapy) (see PRECAUTIONS, Hepatic effects and CLINICAL PHARMACOLOGY, Hepatic Impairment). Liver enzyme monitoring is recommended in all patients prior to initiation of therapy with AVANDAMET and periodically thereafter (see PRECAUTIONS, Hepatic effects). **Contraindications** Rosiglitazone maleate and metformin hydrochloride tablets are contraindicated in patients with:- Renal disease or renal dysfunction - Congestive heart failure requiring pharmacological treatment - Known hypersensitivity to rosiglitazone maleate and metformin hydrochloride - Acute or chronic metabolic acidosis, including diabetic ketoacidosis **Warnings and Precautions • Type I diabetes mellitus** Rosiglitazone-metformin is effective only in the presence of insulin and should not be used in type 1 diabetes mellitus. • **Premenopausal anovulatory women** Rosiglitazone-metformin treatment in premenopausal anovulatory patients with insulin resistance may result in resumption of ovulation, These patients may be at risk of pregnancy. • **Lactic Acidosis** Lactic acidosis is a rare, but serious metabolic complication that can occur due to metformin accumulation. Associated risk factors of lactic acidosis, should be assessed prior to initiation of metformin, and therefore rosiglitazone-metformin, therapy. If lactic acidosis is suspected, rosiglitazone-metformin should be discontinued and the patient should be hospitalised immediately. • **Renal impairment** Serum creatinine levels should be determined before initiating treatment with rosiglitazone-metformin and regularly thereafter, Special caution should be exercised in patients likely to have renal impairment, or in situations where renal function may become impaired. • **Hepatic impairment** Rosiglitazone-metformin is not recommended in patients with hepatic impairment. • **Cardiovascular** Thiazolidinediones can cause fluid retention, which can exacerbate congestive heart failure. The fluid retention may very rarely present as rapid and excessive weight gain. Patients at risk for heart failure (particularly those on insulin) should be monitored for signs and symptoms of heart failure. Rosiglitazone-metformin is not recommended in patients with acute or severe cardiac failure unless the potential benefit is believed to outweigh the potential risk. • **Iodinated contrast agent** Rosiglitazone-metformin should be discontinued prior to, or at the time of the test and not reinstituted until renal function has been confirmed as normal. **Interactions ≻ Rosiglitazone** In vitro studies demonstrate that rosiglitazone is predominantly metabolised by CYP 2C8, with CYP 2C9 as only a minor pathway. ≻ **Metformin** There is an increased risk of lactic acidosis in acute alcohol. **Pregnancy and Lactation Fertility** Rosiglitazone-metformin treatment in premenopausal anovulatory patients with insulin resistance may result in resumption of ovulation. These patients may be at risk of pregnancy. **Pregnancy** Adequate data are not available for rosiglitazone-metformin during pregnancy in humans. **Lactation** Adequate data are not available for rosiglitazone-metformin during lactation in humans. **Adverse Reactions ≻ Rosiglitazone** Adverse experiences with rosiglitazone were generally not dose related, were mostly mild and transient in nature. In a small number of patients treated with rosiglitazone adverse experiences of oedema (dose-related), anaemia (decreased haemoglobin) and hypercholesterolaemia were reported in double blind studies. In clinical trials, an increased incidence of heart failure has been observed when rosiglitazone is used in combination with insulin compared to insulin alone. Patients who experienced heart failure were on average older, had a longer duration of diabetes, and were mostly on the higher 8 mg daily dose of rosiglitazone. Dose-related weight gain was seen with rosiglitazone alone and in combination with other hypoglycaemic agents. The mechanism of weight gain is unclear but probably involves a combination of fluid retention and fat accumulation. Patients receiving rosiglitazone in combination with insulin or oral hypoglycaemic agents may be at risk for hypoglycaemia, and a reduction in the dose of the concomitant agent may be necessary. Post marketing reports of CHF and pulmonary oedema have been received rarely. Post marketing reports of hepatic dysfunction, primarily evidenced by elevated hepatic enzymes have been received rarely, although a causal relationship to rosiglitazone has not been established. ≻ **Metformin** Gastrointestinal symptoms nausea, vomiting, diarrhoea, abdominal pain and loss of appetite Metallic taste Mild erythema Lactic acidosis

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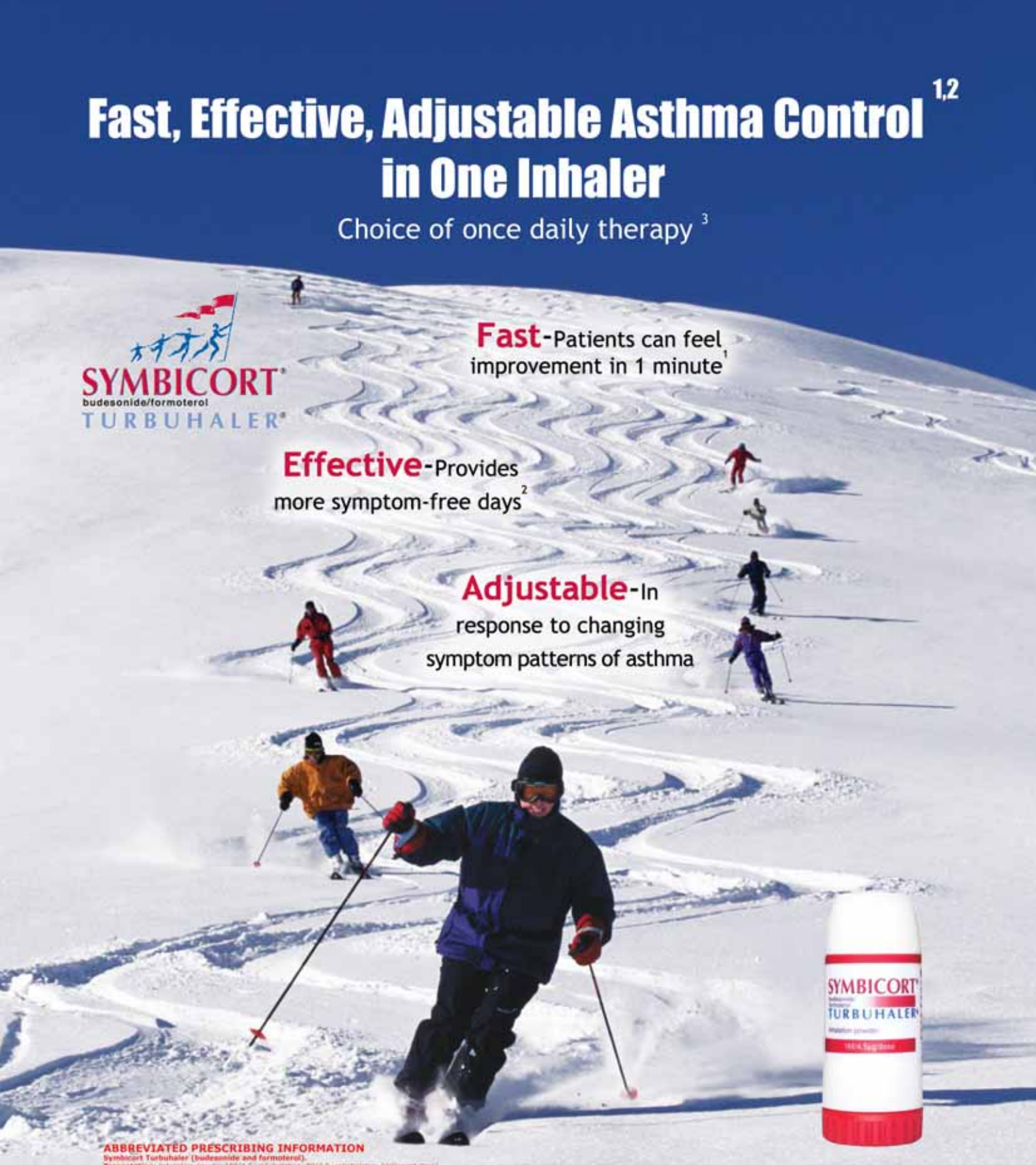

ABBREVIATED PRESCRIBING INFORMATION

Symbicort Turbuhaler (budesonide and formoterol).

Presentation: Inhalation powder: 160/4.5 µg/inhalation, 80/4.5 µg/inhalation (delivered dose).

Properties: Symbicort Turbuhaler is an inhaled combination medicinal product. It contains budesonide and formoterol, which show additive effects in terms of reduction of asthma exacerbations. Budesonide is a glucocorticosteroid with local anti-inflammatory effect. Formoterol is a selective β_2-adrenergic agonist that produces relaxation of bronchial smooth muscle. The bronchodilating effect sets in rapidly, within 1-3 minutes after inhalation and has a duration of 12 hours after a single dose. **Indications: Asthma** Regular treatment of asthma where use of a combination (inhaled corticosteroid and long acting beta-agonist) is appropriate. **COPD** Symptomatic treatment of patients with severe COPD (FEV_1 < 50% predicted normal) and a history of exacerbations, despite regular therapy with long-acting bronchodilators. **Dosage:** Dosage is individual according to disease severity. If an individual patient should require dosages outside the recommended regimen, appropriate doses of beta-agonist and/or corticosteroids should be prescribed. **Asthma** *Adults and adolescents (12 years and above):* 1-2 inhalations twice daily. *Children (6 years and older):* 2 inhalations of low dose Symbicort (80/4.5 µg /inhalation) twice daily. **COPD** Adults: 2 inhalations of Symbicort (160/4.5 µg /inhalation) twice daily. The dose should be titrated to the lowest dose at which effective control of symptoms is maintained. When control of symptoms is maintained with the lowest recommended dosage, then the next step could include a test of inhaled corticosteroid alone. In usual practice when control of symptoms is achieved with the twice daily regimen, titration to the lowest effective dose could include Symbicort Turbuhaler given once daily, when in the opinion of the prescriber, a long acting bronchodilator would be required to maintain control. **Note:** To minimise oropharyngeal thrush, rinse the mouth out with water after each dosing occasion. *Children under 6 years:* Symbicort Turbuhaler is not recommended for children under 6 years. **Contraindications:** Hypersensitivity to budesonide, formoterol or inhaled lactose. **Warnings and Precautions:** It is recommended that the dose is tapered when the treatment is discontinued. The patient should seek medical advice if a previously effective dosage regimen no longer gives the same relief. There are no data available on the use of Symbicort Turbuhaler in the treatment of an acute asthma attack. Particular care is needed for patients who have transferred from systemic to inhaled glucocorticosteroids. Excessive doses of, or long term treatment with glucocorticoids may lead to signs or symptoms of hypercorticism, suppression of HPA function and/or suppression of growth in children and adolescents. The long-term effects of glucocorticosteroids in children and adolescents are not fully known. The growth of children and adolescents taking glucocorticosteroids in long term treatment by any route should be monitored. Symbicort Turbuhaler should be administered with caution in patients with severe cardiovascular disorders, diabetes mellitus, phaeochromocytoma, untreated hypokalemia or thyrotoxicosis. **Pregnancy and lactation:** As with other drugs administered during pregnancy, the benefits for the mother should be weighed against the risks for the foetus. It is not known whether budesonide or formoterol passes into human milk. **Undesirable effects:** Common: Headache, palpitations, tremor, candida infection in the oropharynx, mild throat irritation, coughing, hoarseness. Uncommon: Tachycardia, muscle cramps, agitation, restlessness, nervousness, nausea, dizziness, sleep disturbances. Rare: Exanthema, urticaria, pruritus, skin bruising, bronchospasm. Other rare or very rare: (budesonide) Psychiatric symptoms such as depression, behavioural disturbances, signs or symptoms of systemic glucocorticosteroid effects, immediate and delayed hypersensitivity reactions (including dermatitis and angioedema), bruising. (formoterol) angina pectoris, hyperglycaemia, taste disturbances, variations in blood pressure, cardiac arrhythmias. **Interactions:** Beta-adrenergic blockers (including eye drops) can weaken or inhibit the effect of Symbicort Turbuhaler. Ketoconazole may increase systemic exposure to budesonide. This should be taken into consideration during long term treatment with ketoconazole. Other interactions are documented in the full prescribing information. "Symbicort" is a registered trademark owned by the AstraZeneca group of companies. Date of preparation of this abbreviated prescribing information: July 2003. Based on PLT 68 012 92.97 and 68 010 58.97 **References:** 1. van der Woude HJ et al. Am J Respir Crit Care Med 2002; 165 (8)(Suppl): A567. 2. Zetterström O et al. Eur Respir J 2001; 18: 262-268. 3. Buhl R et al. Am J Respir Crit Care Med 2001; 163 (Suppl 5): A864 + poster.

AstraZeneca

Further information is available on request
AstraZeneca Hong Kong Limited
2301 Cosco Tower, Grand Millennium Plaza,
183 Queen's Road Central, Hong Kong
Tel : 2420 7388 Fax : 2422 6788

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