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Patients Referral Scheme on Drug Compliance & Counselling Services

Critical Appraisal of Clinical Articles

Common Over-the-Counter Herbal Supplements

Japanese Encephalitis (2 CE Units)

Anti-microbials for Peritonitis in CAPD Patients

Engineering of Rituximab - a Drug Targeting Technology

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

Recently, there have been several major changes in the leadership of the public health related organization. These changes suggest that health care policies and implementation are stepping into a new era. We shall have a look at some of these changes and see they provide a clue to the future.

First, in early October, Dr York Chow was approved as the new Secretary for Health, Welfare & Food . Dr Chow, as many of us already know, was the Hospital Authority's Hong Kong West Cluster Chief Executive. Quoting Chief Executive Tung Chee Hwa, "Dr Chow is a medical specialist with extensive experience and knowledge in policy making and management, and has long been participating in social welfare." Taking up the post at his moment will not be an easy task given the current issues including health care financing, risk management of health related disasters, and an aging population. According to Dr Chow, his top priorities are to address the provision of effective services to the elderly, the disabled, the chronically-ill and families disadvantaged by poverty, and the early detection and control of infectious disease. Whether or not the speech was intended to comfort those who were affected by the reduction of government subsidy not long ago, his message tells us that he cares about these important social welfare issues.

Mr Anthony Wu has been appointed Hospital Authority (HA) Chairman as a succession to Dr CH Leong. Mr Wu, first appointed as an authority member in 1999, has been the authority's Finance Committee and Main Tender Board chairman since 2000. He was also a member of the Pamela Youde Nethersole Eastern Hospital Governing Committee from 1997 to 2001. Rather than being a physician, Mr Wu is an accountant and has solid business and finance experience. He also played a key role in the authority's administrative control process and its internal and external audit functions. His appointment demonstrates how desperate the organization is on spending their cash wisely. The challenges for this new chairman are how the HA organization should be re-structured and how to strike for balance between maintaining quality and limiting expenditure.

We are also excited to see new faces appearing in the Legislative Council (Legco). In the 2004 election, Dr Kwok Ka Ki and Mr Lee Kok Long beat the prior LegCo members to represent Medical and Health Services Functional Constituency, respectively. It is our hope and expectation that the new representatives can work more closely together with the Government for the overall benefit of the community.

Last, let's also give thanks to Dr EK Yeoh, Dr CH Leong, Dr WL Lo and Mr KF Mak for their years of services in the Government, Hospital Authority and Legislative Council, respectively. Their contribution to the society is too significant and deserves high regards from us.

Coming back to this issue of HKPJ, we have included articles about a series of events carried out by the pharmacy professionals. These include the Pharmacy Exhibition organized by the students from the School of Pharmacy to promote pharmaceutical care to the general public and the PharmAssist Program helping community pharmacists to improve communication skills. In another article, Miss Chiang walks through how the Patient Referral Scheme on Drug Compliance and Counselling Service (DCCS) was developed. From pharmacy practice research, we have heard a lot about patients' need for counseling services for quite some time. However, prior to this program, it was rare to hear of a formal partnership between the public and private pharmaceutical sector in order to fulfill this need. The establishment of the DCCS Program is likely to become a landmark in the history of Hong Kong pharmacy profession.

We have gained much knowledge about various herbs from the Herbal Medicines & Nutraceuticals section during the past 3 years. In this issue, Lai and colleagues introduce a very common Chinese medicine, *Eucommia ulmoides* Oliver, to us. It is well known that *Eucommia ulmoides* can be good for general health maintenance, especially for bone and muscle health. Lai *et al* provide a comprehensive review on this plant. You will find some useful information about its pharmacological effects and potential interaction with western medicine relevant to your daily practice. Then, if you turn to the Over-the-Counter section, you can find a brief summary from Cammie Lai describing several different Chinese Herbs that can easily be purchased from drug outlets.

As a pharmacist, we read journal and clinical papers almost everyday in order to maintain our drug consultancy role. We have thousands of clinical reports being published in big and small journals every day. Scientific reports about pharmaceutical products often reach different conclusions. Lack of competence on interpreting the data may lead to an inappropriate clinical decision. I believe that an article in the HKPJ that help guide us to critically appraise data from clinical trials would be great! Thanks to our Editorial members, Prof O'Toole and Dr Cheung, who have written an article in the Pharmacy Practice section for this purpose.

This issue also contains some more hot topics like the new technology on monoclonal antibody therapy, anti-microbials for renal patients with peritonitis, and the CE article on Japan Encephalitis. They are all written in an easy-to-read manner by the authors and you will enjoy reading them.

Michael Leung
Managing Editor

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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.

All Things Made Possible Through the 1st Public Private Partnership Program - the Patients Referral Scheme on Drug Compliance and Counselling Service (DCCS)

Chiang, SC, BPharm (Hons), MRPS. MHA

Think Outside the Box

The Director, *Dr. Timothy William Mazzaro*, for the Centre for Entrepreneurial Management and Innovation, Graduate School of Management, University of Western Australia, in his book "Leading Innovation within Public Organisations" pointed out that the government and non-profit sectors are faced with increasing pressures to adopt commercial orientations and competitive market responses. He suggested that managers within such organisations must lead innovation in the creation of new products, services and processes in order to survive. He further acknowledged that, innovation is the offspring of creative, entrepreneurial minds with the willingness to take risks and commit to sustained persistent efforts; and that, managers within government and non-profit organizations are frequently challenged in achieving such innovation by structural impediments and 'sticky' organisational cultures.

As a very experienced (just about two and a half decades !), senior staff member working in a very large public organization, dealing with the health care delivery processes for such a majority of the population, I would say I agree completely with Dr Mazzaro. To me, all things are possible, but just you think outside the box.

The truth and nothing but the truth

Lets look at some facts and figures, in the fiscal year 2003/04, the pharmacies in the public hospitals dispensed a total of 3.5 millions of prescriptions (the SARS effect during the March to May period brought the monthly prescriptions number down by a third) involving 10.5 millions prescription items for a total of 5.67 millions attendances at all the Specialist Out-Patient Clinics (SOPC)s in the Hospital Authority. Our pharmacists working at these SOPCs are battling daily to cope with the dispensing workload so that the patients' waiting time can be maintained within reasonable limits. Understandably, their encounters with the patients at the dispensing window would be very brief, providing only the very basic core information on drug administration instructions. Attempts for our pharmacists to check their patients' understanding of their medicines at the dispensing window may be a luxury and were mostly confined to the Medication Compliance Clinics operated at a no more than a dozen of the SOPCs. Also, given the busy and congested environment setting at most of the SOPCs, patients may not feel comfortable to ask our pharmacists questions for a combination of reasons including fear or embarrassment about asking, lack of awareness of which questions they should or could ask, they felt that the pharmacists are too busy, or may be even our patients are too busy, and they may not want to bother the pharmacists.

The service gap

So, apparently, an enormous gap existed in the needs of the patients and our ability to meet that need. This has always been a frustration to our pharmacists as we are fully aware that there is mounting research evidence to suggest that when patients become more confident in their knowledge of medicines, this will lead to improved outcomes, including enhanced treatment adherence and patients' satisfaction. However, despite this, given the traditional service delivery model in the Hospital Authority, we are very limited in what we can do to fulfill that pharmacists' role. But on second thoughts, is this really so?

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Critical Appraisal of Clinical Report of Evidence-based Medicine

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The contemporary practice of selling an evidence-based medicine requires some forms of clinical studies. Clinical trials, however, are not necessarily carried out in the same way and reports of the trials may not be of equal value. Being able to understand them and having their results at your fingertips will impress your clients as well as your colleagues and other healthcare professionals. This article aims to assist pharmacists to discern good and poor quality information from reports of clinical trials.

I INTRODUCTION

Evidence-based medicine is regarded as a new paradigm, replacing the traditional medical paradigm which is based on authority. It depends on the use of randomized controlled trials (Table 1), as well as systematic reviews and meta-analysis, although it is not restricted to these. There is also an emphasis on the dissemination of information, as well as its collection, so that the evidence can reach clinical practice.

The premier standard for the investigation of medical interventions and clinical treatments is the large double blind randomized controlled trial. For the pharmacist the trials of interest are those where a placebo and the target drug are compared or two different drugs are compared.

Now imagine a regular client/patient who comes in to fill a prescription for a new drug that the Doctor has prescribed. In many cases patients can be wary of a new drug as they are familiar with the old drug they were taking and they may think the new drug too expensive. If the Pharmacist is familiar with the relevant trials done with the new drug he/she can assure or more fully inform the patient, from an independent point of view, on the efficacy of the new drug recommended by the Doctor. In addition, these days it is easy for a patient to obtain general information about a drug from the Internet with which he can challenge the Pharmacist. If the Pharmacist can access the actual trial reports and can understand them he can give an informed opinion about the new drug.

Table 1. Randomization methods used in clinical trials

Three types of randomization methods commonly adopted in clinical trials:
• Permuted block randomization
• Stratification randomization
o e.g. by hospital or by prognostic factor (usually no more than 3 factors involved)
• Centralized randomization

II EVALUATE DATA FROM A RANDOMIZED CONTROLLED TRIAL

Although different types of randomization methods are available (Table 2), the double blind randomized controlled trial is the most favorable choice. In large double blind randomized controlled trials, participants are allocated on a random basis to different groups with each group receiving a different treatment. The groups have to be identical, as far as possible, so that the groups are matched with regard to various important parameters, e.g., age, sex, physical and other characteristics, etc, so that results obtained are attributed to the treatment used in the experiment alone. Being able to critically read these reports and understand them will enable Pharmacists to give better advice to those who come seeking it from them.

Table 2. Major Principles in clinical trials

Four major principles of a good clinical trial:
• Minimize bias
• Maximize precision
• Identify possible sources of bias in the discussion section
• How results of the trial being relative to the bias should be well discussed.

i) General question to ask

When the results of a large randomized controlled and double blind trial are published they are arranged in a set format, namely abstract, introduction, methods, results, discussion and conclusions. To fully understand the reports it is helpful to have a checklist of questions and points to consider when appraising the report. However, two basic questions have to be answered first. They are:

Where have the trial results been published?

The ideal publication place for these trials is in a peer-reviewed Journal, that is, one of those Journals that send out papers for external and anonymous refereeing before being accepted for publication. Examples are the *New England Journal of Medicine, Antimicrobial Agents and Chemotherapy, Clinical Infectious Diseases,* the *British Medical Journal* or *The Lancet*. These Journals, and others like them, are considered the premier Journals with regard to reliable information. Papers published in less well-known Journals or Journals that do not peer-review papers may be far less reliable.

Has the trial been sponsored by a Company?

This can show up in various parts of the report while the affiliations of the Authors(s) can also reveal connections to companies that might be interested in a favorable outcome from the research. The report of the outcome of the research may be slightly biased in favor of a positive outcome. So how the results are presented might be distorted by such a relationship, or by such sponsorship.

ii) Evaluate "methods"

The methods used can bias the results obtained so a careful reading is necessary to detect such bias that can affect the interpretation of results (Table 3). A careful reading of the methods will tell one whether or not the results are likely to be reliable or the method is seriously flawed. This is one possible reason why the trial may not be published in a high quality Journal. Then other questions need answers:

Is the aim of the study given precisely?

Table 3. Types of control study and blinding in clinical trials

Control arm	
	1. Placebo control
	2. Active control
	3. Dose comparison control
	4. Observation control
Blinding	
	1. Triple Blind
	2. Double Blind

The aim, also called "primary outcome" of a trial, should be clearly stated and if so one can then check with the results to see if that aim was achieved. Does the study achieve the end?

Are all the details of the steps taken to avoid bias, presented in the section?

The points needing attention include:

1. How subjects from the population of patients to be studied were selected to ensure it was in a random fashion, and what method was used to ensure their random allocation to a treatment.
2. In a double blind trial both patient and investigator must not know what treatment is being administered to each patient. Are the procedures adopted able to achieve that end, and if the treatment is one in which it is impossible to achieve that end, is it possible that the method adopted could compromise the results?
3. The participants in the trial should be matched so that identical, as far as possible, groups are compared. Consequently the base line characteristics of the groups must be carefully scrutinized to see if that was the case.
4. Patients must also be treated equally with regard to other drugs they may be taking, the advice given, as well as the monitoring methods used.

When choosing the patients from the population, criteria for inclusion or exclusion from the treatment groups are needed.

These criteria should be checked. In this step the eventual population included in the trial may not resemble the group for which the treatment is intended. An example of this is the inclusion of healthy 25 year-old males in a trial designed to test a treatment more likely to be used for elderly patients. Any pharmacokinetic data would be of doubtful value for the real world treatment group.

Were sufficient numbers of patients used in the groups and was the trial conducted over sufficient length of time for the study?

The number of participants must be sufficient to detect either beneficial effects or adverse effects. A cohort too small may preclude detection of the full range of responses. Also the length of time must be commensurate with the medical condition being treated or examined. An example is the effect of some teenage activity amongst females on their menopausal condition. Clearly a long time would be needed to assess such an outcome.

Is the new drug being compared with the drug of first choice at the time of the trial?

A comparison with some obscure drug would be of little value.

Are the doses of the drugs being compared realistic?

If, for example, the relative effectiveness of ranitidine at 150 mg *on* and omeprazole 40 mg *od* were being compared you may be wary of the results obtained.

What about the variable selected to measure the efficacy of the treatment?

Sometimes the real variable cannot be measured economically so a surrogate marker is used instead. Or alternately there may be no variable available. The surrogate marker, however, must be treated with caution, particularly in drug trials, and particularly if the marker is a poor predictor of the "hard clinical endpoint". An example is the choice of bone mineral density measurements as a predictor of potential changes in bone fracture rates. Because other factors also impact on fracture rates it may not be an ideal marker.

iii) Evaluate "results"

The results of a clinical trial also need careful scrutiny. The following questions should be asked in order to evaluate their accountability and reliability.

What Statistical tests were used?

The results may be due to pure chance because of the innate variation in the participants. Properly performed and suitable statistical tests can help decide if we can have confidence that the results are a real reflection of the effects of the treatment. The results of statistical tests are given as a P value, or probability value, and a value equal to or less than 0.05 is taken to be significant.

What are the confidence intervals?

When a trial is carried out based on a random sample of patients a repeat of the trail would result in a different set of data. This variation is due to the inherent variability of the subjects under test. In the results this variability is expressed as confidence intervals. In other words, the mean result alone is insufficient as the true value is actually within a band and this band is the confidence interval. By convention this confidence interval is set at 95%, that means that you can be 95% sure that the true value lies within the range or band. The narrower the bands the more reliable

are the results and if the bands for each treatment overlap then there is no significant difference between the two results.

In what way are the results expressed?

The results can be expressed in either absolute terms or in terms relative to some other measure, but they may not be relevant to clinical practice or experience. To make the results more understandable terms such as the "number needed to treat" (NNT) are used. "The NNT is the number of people who need to be treated to produce one additional successful outcome."

What happened to all the patients?

The results should be carefully scrutinized to see that all patients completed and did not pull out of the trial before its end. Some participants may drop out due to side effects so they cannot be ignored. They should be included in any analysis of the results otherwise their exclusion could skew the results in favor of the treatment.

Is the surrogate marker a true indicator of effectiveness when compared with the "hard clinical endpoint"?

The result may be significant according to the statistical tests on the surrogate marker results but it may bear no relationship to the actual clinical outcome desired. For example, the bone mineral density result may be good (the surrogate marker) but it may not reflect the reality in the clinical situation.

It is statistically significant but is it clinically significant?

Although the test results are good, one has to step back from the trial and take a broad view of the results and ask oneself, "Does it really matter in the real clinical world?" For example, if the result from a comparison of two antihypertensive drugs resulted in a significant difference of 1-2 mm Hg, would it really matter in the real clinical situation?

iv) Evaluate "discussion", "conclusion" and "abstract"

These sections should be the last that you read so you are not persuaded by any author bias. Ideally the discussion section should review the report of the results, integrate them with previous work and lead logically to the conclusion of the work. The conclusion should not be what the Authors of the study wanted to find but what the actual results indicate. It should also cover any inconsistencies or shortcomings in the trial, especially those you have noted.

What you read in the discussion and abstract may not be in accord with what you read and the conclusion you came to on reading the trial. In the work the primary outcome of the work may have not been confirmed so the author(s) may ignore this and focus on some secondary outcomes for which the trial was not designed. Consequently the results of such a trial should be approached with caution as the trial would have been designed to find the primary outcome, not the secondary outcomes.

v) Evaluate "conclusion"

You may or may not find the results of the trial acceptable and of value to assess the drug or treatment. However, the trial only answers one question and in the clinical situation a number of other factors must be borne in mind before a reliable opinion can be formed from the results. These factors can be remembered using the acronym STEP [1]:

"**Safety**: bear in mind that many trials, especially those on new drugs, may not give information about long term or serious side effects
Tolerability: what are the withdrawal rates from the trial compared to those from trials on a similar drug?
Efficacy: how does the drug compare with its most popular equivalent?
Price: is this drug affordable? Financial information does not normally appear in trials. Has a cost-benefit analysis been performed?"

In the situation of a particular client seeking help or advice, the client's particular medication regime or other factors likely to influence the efficacy of a drug, should also be taken into account.

III ACTIONS FOR THE FUTURE

i) Get formal training and practice the skills.

There are sources of advice and training available to develop critical appraisal skills. One source is the National Health Service (NHS) Critical Appraisal Skills Programmed in the UK whose website is: www.phru.org.uk/~casp/index.htm. It will help give the basics but practice enhances the skill so critically appraising one report a week and sharing the experience with peers will sharpen the skill.

ii) Use independent reviews from good sources.

It is likely that a number of papers may have been published about a particular drug. Ideally the report from one trial should be supplemented with the reports from other trials. A good source of information is a published systematic review of all the trials as a good review will be invaluable in brining out the details concerning the value of the work on the drug. For a review of sources of evaluated information on clinical results refer to MeReC [2].

A good website source is that maintained by CASP at: http://libsuni.jr2.ox.ac.uk/caspfew/soircess.html. This website has links to Journals, sources of review, books, guidelines from, e.g. the National Institute for Clinical Excellence, and databases.

Finally, do not forget your local network. Maintain contact with your peers and fellow practitioners who may have access to information, or may have produced reports of value and may be able to point you in directions to obtain information you may find useful for providing a top quality service to your clients.

ACKNOWLEDGEMENT

This article is heavily indebted to Claire Jones. It was written based on her work published in the Pharmaceutical Journal [3].

Suggestions for Further Reading

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Common Herbal Supplements - What We Should Know?

Lai, Cammie PW

It wasn't long ago that names like Echinacea or St. John's Wort are unknown to people in Hong Kong. But times have changed. Now these and many other herbal products and supplements are widely available on drugstore and supermarket shelves, not only as pills and liquids, but also in teas and throat lozenges. Herbal supplements are usually promoted as all-natural, alternative medicines. Consumers tend to think of them more as vitamins than as actual drugs. Basically, herbal remedies are claimed to be able to: alleviate disease, detoxify the body system, maintain a state of balance, prevent disease from recurring, and support the immune system. Easy access to herbal remedies gives rise to concerns about their uses, safety, efficacy, drug interaction with conventional medicine and potential side effects for long term administration. Consumers might very often ask questions about how herbs and supplements work, whether they are safe and effective, and if they do what the label promises? Healthcare professionals, as frontline health information providers, should advise customers on herbal products like other medicinal products.

I HISTORY OF HERBAL SUPPLEMENT USE

Herbal supplements have been widely used in western countries for thousands of years. In the ancient world, herbs and plants were essential part of medicine. People believed that herbal remedies were able to restore an individual's physical, emotional and mental health. They offer a natural approach to maintaining the overall well being of the body. Today, herbal supplement has become a major industry. In many developed countries, the herbal remedies business gives a sales growth which is comparable to that of the cosmetic and pharmaceutical industries. In this article, we are going to discuss some of the most commonly used herbal remedies.

II MOST COMMON HERBAL REMEDIES

i) Ginkgo *(Ginko biloba)*

Ginkgo fruits and seeds (Figure 1) have been used in traditional Chinese medicine for ages (mostly to treat asthma and chilblains). It belongs to ginkgolides and heterosides in terms of its chemical constituents. Ginkgo leaves are used for preparing those pharmaceutical preparations.

Figure 1. Ginkgo biloba

Actions and uses: Ginkgo is used mostly for memory impairment, dementia, tinnitus, and intermittent claudication. In some European countries, ginkgo is registered for these indications. It improves brain functioning by increasing cerebral and peripheral blood flow, circulation and oxygenation. It is also used by some for depression, headaches and leg cramps. It is also good for asthma. Patients are recommended to take the herb for at least 2 weeks for best results.

Safety precautions: Adverse effects of ginkgo are usually mild, transient and reversible. Potentially serious adverse effects are bleeding (including intraocular bleeding and subcutaneous bleeding) and seizures, which were seen in children after excessive ingestion of seeds. Because gingko has antiplatelet activity, it may interact with anticoagulants which is important for patients taking warfarin.

ii) Ginseng *(Panax ginseng)*

There are a lot of ginseng species, among which Siberian ginseng (Figure 2), Russian ginseng, American ginseng and Asian ginseng (Chinese, Japanese or Korean ginseng) are the most popular species available. Its chemical and nutrient content includes arabinose, calcium, camphor, gineosides, iron, mucilage, panaxosides and vitamins A, B, B_{12} and E. Ginseng roots are used as raw material.

Actions and uses: Ginseng has been used for its sedative, hypnotic, demulcent, antidepressant and diuretic activity. It is often recommended to improve stamina, concentration, vigilance and well-being. The pharmacological activities of *P. ginseng* range from stimulation of central nervous system to modulation of immune system and anabolic effects. It enhances immune function, promotes lung functions and stimulates appetite. Some athletes might take ginseng for overall body strengthening.

Safety precautions: P. ginseng has several relatively serious adverse effects, ranging from insomnia, diarrhea, vaginal bleeding, severe headache and schizophrenia. It should not be used by people with hypoglycaemia, high blood pressure or heart disorders.

Figure 2. Panax Ginseng

iii) Echinacea *(Echinacea species)*

Commercially available herbal medicines are produced from *Echinacea angustifolia* (Figure 3), *E. pallida and E. purpurea*. Different products use different parts of the plants, mostly roots. Echinacea preparations contain many potentially active ingredients such as polysaccharides, glycoproteins, alkamides and flavonoids.

Figure 3. Echinacea angustifolia

Actions and uses: With the outbreak of SARS in Hong Kong last year, Echinacea has become a popular herbal supplement for the prevention of common cold and upper respiratory tract infections. In fact there are studies showing that Echinacea increases white blood cells production. It also has anti-inflammatory and antiviral properties. It is available in oral form as extract, liquid, tea, capsules and in topical form for various conditions like burns, wound healing and eczema.

Safety precautions: Adverse effects of Echinacea preparations seem rare and consist mainly of people who are allergic to plants in the sunflower family. Rash, nausea, dizziness with swollen tongue are its possible adverse reactions.

iv) Saw Palmetto *(Serenoa repens)*

The ripe berries of the American dwarf palm *(Serenoa repens* or *Sabal serrulata)* have been traditionally used in genitourinary problems. The saw palmetto (Figure 4) berries contain saturated and unsaturated fatty acids and sterols.

Figure 4. Saw palmetto

Actions and uses: The American Indians used saw palmetto berries in the treatment of genitourinary tract disturbances. It was administered to men to increase the function of the testicles and to women with disorders of the mammary glands. Today, saw palmetto is mostly used for benign prostatic hyperplasia. In France and Germany, saw palmetto berry extracts have been approved for treatment of this purpose. It acts as a diuretic and urinary antiseptic.

Safety precautions: Adverse effects of saw palmetto are rare and usually mild. But it should be used with special caution to avoid false-negative results in prostate-specific antigen test. Patients should be excluded from prostate cancer before taking saw palmetto as alternative supplement.

v) St. John's Wort *(Hypericum perforatum)*

St. John's Wort *(Hypericum perforatum)* (Figure 5) is a shrubby plant with numerous bright yellow flowers. Flowers, leaves and stems are used for production of pharmaceutical preparations. The major constituents of St. John's Wort include essentials oils, glycosides, flavonoids and tannins.

Figure 5. St John's Wort

Actions and uses: St. John's Wort has a long history of folk use. St. John's wort, applied topically or systemically, has been used to treat bronchitis, burns, insomnia and haemorrhoids. Today, it is used almost exclusively as a herbal antidepressant. Its mechanism of action is thought to be most likely through serotonin uptake inhibition. It also has anti-viral property.

Safety precautions: The most serious potential adverse effect of St. John's wort is photosensitization which is rare and only occurs when taken internally in large amounts. Therefore, it should be avoided in patients taking other prescribed medications such as anticoagulants, oral contraceptives and antiviral agents.

vi) Milk thistle *(Silybum marianum)*

Milk thistle (Figure 6) is also known as Mary thistle or wild artichoke. It is a stout, annual or biennial plant, found in dry rocky soils in Europe. Its useful parts include fruits, leaves and seeds. Milk thistle contains silymarin which is a mixture of flavonoids with unique antioxidating property.

Actions and uses: Milk thistle extracts are currently used for hepatic disorders. Silymarin is one of the most potent liver-protecting substances. The protective effect of silymarin against liver damage has been demonstrated in a number of experimental and clinical studies. Milk thistle, with its powerful antioxidative property, is used as a supplement for preventing liver damage by free radicals. It also stimulates the production of new liver cells and prevents formation of damaging leukotrienes. It therefore has beneficial effects on the immune system. It can be used to support detoxification reactions. Other studies have shown that milk thistle has therapeutic effect for psoriasis which is probably due to its inhibition on leukotriene synthesis.

Figure 6. Milk thistle

Safety precautions: Silymarin preparations are widely used remedies. However, it should not be used in the treatment of hepatitis as delayed diagnosis of symptoms of hepatic diseases can be fatal. It should only be administered as a preventive agent but not drugs for liver disorders.

vii) Kava *(Piper methysticum)*

Kava (Figure 7) is made from dried rhizomes and roots of the kava plant. It is traditionally used in the south pacific as a recreational drink. The rootstock is used for medicinal purposes. Chemical composition of kava includes starch, water, protein, sugar, minerals and kavalactones.

Figure 7. Kava

Actions and uses: Kava is helpful for physical and mental relaxation. However, its anxiolytic effect is still controversial. It also acts as diuretic and genitourinary antiseptic.

Safety precautions: Kava can cause drowsiness. If this occurs, use should be discontinued. There are reported cases that the effects of kava may be potentiated when kava is taken concomitantly with alcohol or with medications that act on the central nervous system. Kava self-medication has also been associated with toxic liver damages.

III CONCLUSIONS

Improper use of herbal remedies can bring unwanted and sometimes dangerous results. Some remedies are toxic when taken in high doses, or taken by pregnant women or children. Herbal remedies should never be substituted in cases of severe or acute illness. Patients should be advised to avoid using a wide variety of herbs concomitantly because herb-herb interactions are poorly understood. Dose should be initiated at the lowest level at which the desired effects occur. Long-term use should be discouraged because long-term effects are unknown. At present, there is still a lack of quality control and standardization of herbal medicinal products. Traditional knowledge and 'test of time' are poor guides for establishing the efficacy or safety of herbal supplements. In the long run, more reliable research, vigorous clinical studies are essential for both consumers and healthcare professionals to decide which brands of herbal remedies to buy or recommend.

Generally speaking, trials of herbal medicinal products have been too few, too small, and too short. The lack of long-term studies is especially unfortunate simply because there is a lack of regulatory control over the sales of these products. It is often claimed that the herbal industry cannot sustain the high costs of long-term studies. Incentives for research investments are low because herbal medicinal products cannot usually be patented. The important point is that herbal remedies should not be assumed to be safe simply because they are natural. Herbal remedies contain substances that can have powerful effects upon the body. People should be cautious if they are pregnant or attempting to become pregnant. Herbal remedies should not be used concomitantly with other medications unless doctor is consulted. As a general rule, these products should be avoided in infants or children. It is recommended to buy only preparations that identify plants on the label and states contraindications for use from reputable outlets.

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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!

Japanese Encephalitis and Vaccines

2 CE Units

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Graphics adapted from the HKSAR Food & Environmental Hygiene Department website

I DISEASE BURDEN

Japanese encephalitis (JE) is a mosquito-borne arbovirus infection and principally a disease of rural areas in which vector mosquitoes breed in close association with birds and pigs and lead to high levels of seroconversion in exposed animals and humans. Humans and horses are accidental hosts and may become sick after exposure.[1] JE is endemic in parts of China, India, Korea, Japan, South East Russian Federation, Islands in the Torres strait Australia, Nepal, Thailand, Vietnam, Cambodia, Lao PDR, the Philippines, Taiwan, Indonesia, Malaysia, and Sri Lanka. The Japanese encephalitis virus (JEV) belongs to the Flaviviridae family. JE is the leading cause of viral encephalitis and neurological infection in Asia. Although severely under-reported, 50,000 cases are annually reported throughout Asia, with 15,000 deaths annually (WHO , 5-35% case fatality rate) and a 75% JE-related disability rate (767,000 DALYs**, WHO, 2002). An annual incidence ranging from 10 to 100 cases per 100,000 inhabitants has been reported in heavily endemic areas. It is estimated that on average 1 in 300 infections results in symptomatic illness.[2] In rural villages, all elements of the enzootic transmission cycle (mosquito - birds/pigs - human/horses - birds/pigs - mosquito) are found close to human residence and activities. Consequently, exposure and infection occur at an early age.[1] The majority of people living in JE-endemic areas are infected with the virus before the age of 15.[2]

II JEV IN HONG KONG

In Hong Kong in the last ten years, the majority of the cases were imported and only three local cases were reported in 1996, 2003 and 2004 involving a 15-year-old boy, a 38-year-old lady and a 29 year-old Indonesian domestic helper, respectively. Of the eight imported cases from 1967 to 2003, four were from Singapore, two from the Mainland, one from Nepal and one unknown (Figure 1).[3, 4]

Most of the 44 cases suffered from fever, drowsiness, headache and vomiting. These symptoms were consistent with those described in the literature. There were a total of three deaths due to JE since 1967, corresponding to a case-fatality rate of 7% (excludes the most recent case in 2004).[3]

III CLINICAL SYMPTOMS AND TREATMENT

Mild infections occur without apparent symptoms other than fever with headache. More severe infection is marked by quick onset, headache, high fever, neck stiffness, stupor, disorientation, coma, tremors, occasional convulsions (especially in infants) and spastic (but rarely flaccid) paralysis. The incubation period is typically 5 - 15 days. Case fatality rates range from 0.3% to 60%. About 50% of survivors have severe neurological sequelae, including motor weakness, intellectual impairment, and seizure disorders. Magnetic Resonance Imaging (MRI) shows a characteristic pattern of mixed intensity or hypodense lesions, especially in the thalamus, but also in basal ganglia and midbrain. Diagnosis is facilitated

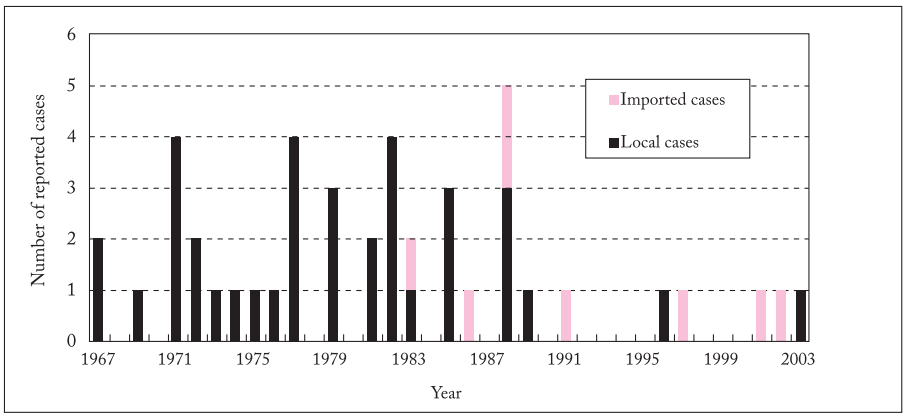

Figure 1. Number of Reported Cases of Japanese Encephalitis in Hong Kong, 1967 - 2003 Adapted From: H Chung and R Lam. Epidemiology of Japanese Encephalitis in Hong Kong, 1967-2003. Public Health and Epidemiology Bulletin 2004;13(2):17-23

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* Oral Granules Study Design: A double-blind, placebo-controlled study of montelukast 4 mg oral granules, administered once daily in the evening to patients aged 6-24 months with asthma. Montelukast 4 mg oral granules was generally well tolerated over 6 weeks of treatment. The safety and tolerability profile was consistent with that in children aged 2-14 years and adults.

Phenylketonuric patients should be informed that the 4 mg and 5 mg chewable tablets contain phenylalanine (a component of aspartame).

References : 1. Hong Kong Physician Circular (Singulair, MSD) 2. Data on file (MSD, Hong Kong)

10-2005-SGA-2004-HK-4019-J-(HK)

by detection of IgM (Immunoglobulin M) in cerebro-spinal fluid (CSF). There is no specific therapy. Intensive supportive therapy is indicated.[5, 6]

IV COST-EFFECTIVENESS OF VACCINATION

A recent study of cost-effectiveness of routine immunization to control JE in Shanghai, China showed that compared with no immunization, a programme using the inactivated JE vaccine would prevent 451 JE cases, 113 JE deaths, and the loss of 6,888 DALYs per 100,000 persons. A live-attenuated JE vaccine could prevent 461 cases, 115 deaths, and the loss of 7,035 DALYs. Both immunizations are cost saving, but the live-attenuated vaccine strategy resulted in more than a 40% greater savings (US$ 579,210) compared with the inactivated vaccine strategy (US$ 408,272).[2]

Definition of DALY

Disability Adjusted Life Year (DALY) measures the state of health of a population and, together with the concept of cost-effectiveness, to judge which interventions to improve health deserve the highest priority for action. The Disability Adjusted Life Year is the only quantitative indicator of burden of disease that reflects the total amount of healthy life lost, to all causes, whether from premature mortality or from some degree of disability during a period of time.

i) Vaccines

There is no JE-specific therapy other than supportive care. JE control programmes include mosquito control (spraying, impregnated bed nets), pig control (segregation, slaughtering, and vaccination) and human vaccination. Several vaccines are now available and others under development. A formalin-inactivated JE vaccine propagated in mouse brain tissue has been used successfully to reduce the incidence of JE in Japan, Taiwan, Korea, Thailand, and Vietnam. The vaccine is available internationally, but remains expensive. Since 1988 it is included in the expanded immunization schedule (EPI) programme in Thailand.[2]

A live-attenuated vaccine (SA 14-14-2) has been developed and tested in China. The vaccine is produced on primary hamster kidney cells. This attenuated vaccine appears to be safe and effective in annual Chinese immunization programmes involving millions of children, but it was not yet pre-qualified by WHO for international use. Vero cell-derived inactivated JE vaccines have been developed in China, where the vaccine is now licensed and 2 million doses are produced annually.[3]

JE vaccine is not recommended for all people traveling or residing in Asia. In Hong Kong, a JE vaccine (Biken, HK45744) is sold on an individual basis. In the decision to vaccinate, the risk of exposure to the virus and the risk of developing illness, the availability and acceptability of mosquito repellents and other alternative protective measures, and the adverse effects of the vaccine need to be taken into consideration. Although the JE vaccine is reactogenic, rates of serious allergic reactions (eg. generalized urticaria, angioedema) are low (1 to 104/10,000).[5]

ii) Dosage and Duration of Protection

In the United States, JE-VAX (Biken, distributed by Aventis Pasteur) is used.[4] The Center for Disease Control (CDC) recommends the following schedule: The recommended primary immunization series is three doses of 1.0 mL each, administered subcutaneously on days 0, 7, and 30. An abbreviated schedule of days 0, 7, and 14 can be used when the longer schedule is impractical or inconvenient because of time constraints. However, this schedule should be used only under unusual circumstances, such as travel or military deployment to hyperendemic areas, and is not routinely recommended. The vaccine is contraindicated in those who have a history of allergic disorder, hypersensitivity to proteins of rodents and neural origin and previous adverse reaction after receiving JE vaccine. The last dose should be administered at least 10 days before the commencement of travel to ensure an adequate immune response and access to medical care in the event of delayed adverse reactions.

The immunization schedule for children 1-3 years of age is identical to that for adults except that the manufacturer recommends 0.5 mL administered subcutaneously. No data are available on vaccine safety and efficacy in infants less than 1 year of age.

Protective levels of neutralizing antibody persist for at least 2 years in vaccinees who have completed a three-dose primary series. The full duration of protection is unknown, therefore, definitive recommendations cannot be given on the timing of booster doses. Booster doses of 1.0 mL (0.5 mL for children less than 3 years of age) may be administered after 2 years.[8]

In conclusion, JE is a zoonotic disease with natural viral reservoirs and cannot be eliminated. Transmission can be modulated trough prevention strategies (e.g. spraying, removal of stagnant water etc.). The decision to use universal vaccination has been successful in some countries, but unresolved issues for the approved vaccines limit the acceptability for region-wide control of this disease.[1]

Glossary

CDC	Center for Disease Control, Atlanta, USA
CSF	Cerebro-Spinal Fluid
EPI	Expanded Schedule of Immunization
DALY	Disability Adjusted Life Year
IgM	Immunoglobulin M
JE	Japanese Encephalitis
MRI	Magnetic Resonance Imaging
WHO	World Health Organziation

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Questions for Pharmacy Central Continuing Education Committee Program

2 CE Units

Japanese Encephalitis and Vaccines

1. ***Which of the following is the major vector for transmission of Japanese encephalitis virus (JEV)?***

A. Mosquito
B. Human
C. Pig
D. Horse

2. ***Which family of virus does JEV virus belong to?***

A. Picornavirus
B. Hepadnavirus
C. Flavivirus
D. Satellite virus

3. ***JP experiences symptoms suggestive of Japanese encephalitis (JE) since he returned from a trip to Thailand 10 days ago. Which of the following tests are required to confirm such diagnosis?***

A. Ultrasound imaging of brain and test for JEV RNA in blood
B. Magnetic resonance imaging of brain and test for Anti-JEV IgM in blood
C. Ultrasound imaging of brain and test for Anti-JEV IgG in blood
D. Magnetic resonance imaging of brain and test for Anti-JEV IgM in cerebrospinal fluid

4. ***JP is confirmed to have JE; which of the following treatment regimes would you recommend?***

A. Acyclovir 500mg q8h ivi x 10days + supportive therapy
B. Lamivudine 100mg daily x 6 months + supportive therapy
C. Prednisolone 30 mg daily x 1month, then taper + supportive therapy
D. Supportive therapy alone

5. ***Which of the following type(s) of JE vaccine is/are available?***

(I) Inactivated JE vaccine
(II) Live-attenuated JE vaccine
(III) detoxified exotoxins produced by JEV

A. I only
B. II only
C. I and II only
D. I, II and III

6. ***The following are symptoms of severe JE infection except:***

A. Respiratory depression
B. Spastic paralysis
C. Neck stiffness
D. Tremors

7. ***Which of the following measure(s) reduce the risk of contraction of JE?***

(I) Use of insect repellents when going outdoors
(II) Keeping all drains free from blockage
(III) Avoidance of contact with patients with active JE

A. I only
B. II only
C. I and II only
D. I, II and III

8. ***The factors to consider before JE vaccine may be administered in an individual include:***

A. Risk of exposure to the virus
B. Availability of mosquito repellents
C. Pros and cons of alternative protective measures
D. All of the above.

9. ***AP is a 65-year old lady who will travel to the Caribbeans on cruise in four weeks' time with her husband. She has not received any previous vaccination against JE and visited her family doctor for vaccination. What vaccination schedule is most suitable for AP if JE-VAX is used?***

A. Days 0, 7, 30
B. Days 0, 7, 21
C. Days 0, 7, 14
D. Single dose on day 0

10. ***AP's husband, who is 62, also needs to get vaccinated, but he has already been vaccinated according to the recommended schedule when he traveled to Vietnam 3 years ago. What vaccination schedule of JE-VAX may be most suitable for AP's husband?***

A. Days 0, 7, 30
B. Days 0, 7, 14
C. Days 0 and 14
D. Single dose on day 0

Answers will be released in the next issue of HKPJ.

Answers for the past issues in 2004

Vol 13 No 1 - Anti-fungal Agents Old and New: Revisited
1)D 2)A 3)A 4)B 5)B 6)C 7)A 8)B 9)C 10)D

Vol 13 No 2 - Insights into Hormone Replacement Therapy (HRT)
1)E 2)D 3)E 4)C 5)E 6)B 7)A 8)B 9)C 10)E

A Review on Use of Anti-microbials in the Treatment of Continuous Ambulatory Peritoneal Dialysis (CAPD) Associated Peritonitis

Ho, Josephine YY

I INTRODUCTION

Peritonitis remains one of the major causes of technique failure and hospitalization in patients requiring Continuous Ambulatory Peritoneal Dialysis (CAPD) since the latter was first introduced and widely used. The median peritonitis-free survival in patients requiring peritoneal dialysis was about 18.5 months for Australian and 11.6 months in New Zealand according to the ANZDATA registry 2001 report. The percentage of patients completely free of peritonitis in three years was 31% and 21%, respectively.[1] According to data from the National Renal Registry in Malaysia in 2001, peritonitis accounted for 15% of deaths of patients on CAPD and was also the major cause of transfer to haemodialysis (35%).[2] Peritonitis thus became a matter of concern. Comprehensive guidelines exist to recommend the antibiotic therapy for the treatment and prevention of this complication. Comments based on researches and clinical experience were continuously given to existing guidelines and they were also reviewed and updated at intervals.

II DOSING GUIDELINES

The Travenol Peritonitis Management Advisory Committee published its first international guideline on the management of peritonitis in 1987. The guideline was updated later in the year 1989, 1993, 1996 and the most current one was published in the year 2000.[3-7] The name of the committee was also changed to the Ad Hoc Advisory Committee on Peritonitis Management of the International Society for Peritonitis Management (ISPD) later.

Over the past 15 years or so, the choices and dosing strategy of anti-microbials used in the treatment of CAPD peritonitis have been changing. The reasons for changes are primarily concerns for emergence of antibiotic resistance as more clinical experiences are obtained about certain antibiotics. The trend in the choices and dosage of anti-microbials used is reviewed in the following based on the ISPD guideline 2000 recommended by the Ad Hoc Advisory Committee.

III EMPIRIC TREATMENT FOR BACTERIAL PERITONITIS

Prompt initiation of empiric antibiotic therapy is important in patients diagnosed of peritonitis while awaiting culture results. Vancomycin, cefazolin and aminoglycosides had been included in the first-line empiric therapy until 1996. Since then routine use of vancomycin in the empiric treatment was no longer recommended. Table 1 summarized the empiric antibiotic regimen recommended for CAPD peritonitis from 1987 to 2000.

Intravenous route of antibiotic administration, for instance, IV vancomycin, was also tried and was successful. However, no therapeutic advantage over the intra-peritoneal (IP) route was found. Since the IP route was considered more convenient, it became the preferred route. The intermittent dosing approach for vancomycin was introduced in 1989 as broad clinical experience was obtained. The dose changed from a loading dose of 500 mg/L exchange and maintenance dose of 15 mg/L exchange to 1-2 g/2L every 5-7 days depending on residual renal function of

Table 1. Summary of first-line empiric antibiotic therapy recommended for treatment of CAPD peritonitis by the Ad Hoc advisory Committee on Peritonitis Management guideline from 1987 to 2000

	Gram +ve organism	*Gram -ve or not known*
1987	Vancomycin (LD 500 mg/L IP, MD 15 mg/L IP); OR Cefazolin (LD 500 mg/L IP, MD 125 mg/L IP)	Aminoglycosides (LD 1.5 - 2 mg/kg IP, MD 4 - 8 mg/L IP) [a] + cefazolin (LD 500 mg/L IP, MD 125 mg/L IP); OR Aminoglycosides (LD 1.5 - 2 mg/kg IP, MD 4 - 8 mg/L IP) [a] + vancomycin (LD 500 mg/L IP, MD 15 mg/L IP)
1989	Vancomycin alone (2g IP Q 7 days x 2 doses); OR Cefazolin (LD 500 mg/L, MD 125 mg/L) + aminoglycosides (LD 1.5 - 2 mg/kg IP, MD 4 - 6 mg/L)	Aminoglycosides (LD 1.5 - 2 mg/kg IP, MD 6 - 8 mg/L) [a] + cefazolin (LD 500 mg/L, MD 125 mg/L); OR Aminoglycosides (LD 1.5 - 2 mg/kg IP, MD 6 - 8mg/L) [a] + vancomycin (2 g IP x 1 doses)
1993	Vancomycin (2 g IP every 7 days x 2 doses)	Vancomycin (2 gram IP x 1 doses) + Ceftazidime (LD 500 mg/L IP, MD 125 mg/L IP); OR Vancomycin (2 gram IP x 1 doses) + aminoglycosides once daily [b]
1996	Cefazolin/ cephalothin (500 mg/L LD, then 125 mg/L in each exchange MD) + aminoglycosides once daily[c]	
2000	Cefazolin/ cephalothin (1 g/bag QD or 15 mg/kg/bag QD) + ceftazidime (1 g/bag QD)	

Note:
BW - body weight; IP - intra-peritoneal into exchange;
LD - loading dose; MD - maintenance dose;
QD - once daily; IP route is used unless otherwise specified

[a] *Dosage range of aminoglycosides refer to gentamicin, netilmicin and tobramycin only*
[b] *gentamicin/ tobramycin/ netilmicin 20 mg/L in one exchange daily; amikacin 60 mg/L in one exchange daily*
[c] *0.6 mg/kg BW in one exchange per day for gentamicin, tobramycin, netilmicin; 2 mg/kg BW in one exchange per day for amikacin*
[d] *Original guidelines should be consulted for exact dosage of different agents*

the patient into one 6-hour exchange.

In 1993, intermittent dosing of aminoglycosides was also introduced. A lot of studies had been done to compare the efficacy and toxicity of once daily dosing of aminoglycosides in other severe infections. In a meta-analysis involving over 3,000 patients with bacterial infections, once daily dosing of aminoglycosides was found to be as efficacious and caused a lower risk of nephrotoxicity and no greater risk of ototoxicity compared to multiple daily dosing in patients without pre-existing renal impairment.[8] The once daily IP dose of aminoglycosides was aimed to produce a drug concentration of at least ten times higher than the minimum inhibitory concentration (MIC) of susceptible bacteria.[7] The dose was 20 mg/L for gentamicin, tobramycin and netilmicin and 60 mg/L for amikacin in one exchange daily. A loading dose was no longer recommended by the committee. While aiming at filling the body compartments other than the peritoneal cavity and its surrounding membrane, the loading dose contributed little to the anti-microbial effect at the infection site. It, however, led to sustained serum levels that were toxic. In 1996, the dose of aminoglycosides was further modified to base on body weight. A dose of 0.6 mg/kg/day for gentamicin, netilmicin and tobramycin and 2 mg/kg/day for amikacin was recommended.

As vancomycin-resistant strains of microorganism emerged and became a concern, routine use of vancomycin for empiric treatment and prophylaxis was discouraged worldwide. In 1996, the guideline withdrew vancomycin from the empiric antibiotic therapy and reserved it for use in true methicillin-resistant *S. aureus* (MRSA) infection or infection due to other beta-lactam-resistant organisms or for patients allergic to other antibiotics.

In the latest guideline published in 2000, the routine use of aminoglycosides as empiric therapy is also discouraged. This change was due to the concern to preserve the residual renal function which was considered an independent predictor of patient survival. The use of aminoglycosides as an alternative in empiric therapy and in treatment of gram negative infections is now restricted to patients without residual renal function, i.e. residual urine output < 100 ml/day.

The criteria for use of an antibiotic in empiric treatment as stated in the guideline include good antibacterial efficacy for coagulase-negative staphylococcus, *S. aureus* and gram-negative *Enterobacteriaceae*, and reasonable efficacy for pseudomonas. With vancomycin and aminoglycosides withheld from the first-line empiric therapy, cefazolin is now used to cover susceptible strains of Staphylococci, Streptococci and some *Enterobacteriaceae*. Ceftazidime is added to broaden the gram negative and pseudomonas coverage. Another criterion for selection of an antibiotic is that the drug should have a reasonable half-life for once-per-day therapy and this dosing strategy has to have clinically proven efficacy. The intermittent dosing approach of intraperitoneal vancomycin and aminoglycosides was proved successful and was recommended in the treatment of CAPD peritonitis in 1989 and 1993, respectively. However, cefazolin, with shorter half-life and no post-antibiotic effect, has to be dosed continuously under the recommendation for peritonitis treatment until the year 2000. Two studies in 1997, one retrospective and one prospective, suggested that once daily dosing of cefazolin was also successful in the treatment of CAPD peritonitis.[9,10] Despite the promising results of these two studies, the concerns for the efficacy of intermittent dosing of cephalosporins remained. As an antibiotic without a post-antibiotic effect, the intermittent dosing approach would require the body to act as a drug reservoir to deliver an adequate amount of drug to the infection site throughout the period between the doses. Moreover, high serum concentrations of cefazolin would also be required for organisms with low sensitivity to cefazolin.[11] Later in 1999, in a study investigating the pharmacokinetics of intermittent dosing of cefazolin, it was found that a single daily dose of 15 mg/kg/day cefazolin could achieve dialysate concentration levels greater than the MIC for sensitive organisms over 24 hours.[12] Based on this evidence, once daily dosing of cefazolin and ceftazidime was introduced in the current ISPD guideline.

Antibiotic regimen should be changed according to culture and sensitivity results. The choice of antibiotics depends on the type of organisms isolated and the sensitivity towards the antibiotics. Table 2 shows the first-line and alternative antibiotics suitable for the treatment of peritonitis caused by different organisms.

IV FUNGAL PERITONITIS

Previously, fungal peritonitis had been treated with amphotericin B at a dose of 2 - 8 mg/L intra-peritoneally or if given intravenously, 1 mg as a test dose followed by 10 mg on day 1

Table 2. Antibiotics regimen based on different types of microorganism isolated recommended by current ISPD guideline

Organism	*First-line therapy*	*Alternatives*	*Duration*
Enterococcus	Ampicillin 125 mg/L in each exchange +/- aminoglycosides (depending on sensitivity)	Vancomycin (if ampicillin-resistant)	14 days
Staphylococcus aureus	Cefazolin / cephalothin +/- rifampin 300 mg BD po	Clindamycin (LD 300 mg/L, 150 mg/L IP) / vancomycin + rifampin 300 mg BD po (if methicillin-resistant)	21 days
Other gram positive (e.g. *Staphylococcus epidermidis)*	Cefazolin / cephalothin alone	Vancomycin / clindamycin (LD 300 mg/L, 150 mg/L IP) (if resistant strain)	14 days
Gram negative (e.g. Klebsiella, Proteus or *E.coli*)	Amioglycosides	Ceftazidime (if urine output > 100 ml/day)	14 days
Pseudomonas aeruginosa	Ceftazidime + (piperacillin 4 g Q12H IV or ciprofloxacin 500 mg po bid or aztreonam LD 1 g/L, MD 250 mg/L continuously IP or Sulfamethazole-trimethoprim 1-2 DS/day po)	Ceftazidime + aminoglycosides	21 days
Anaerobic	Metronidazole 500 mg Q8H po or IV + ceftazidime	Metronidazole 500 mg Q8H po or IV + aminoglycosides	21 days
Tuberculous	Isoniazid 300 mg po QD + rifampicin 600 mg po QD + pyrazinamide 1.5 g po QD + pyridoxine 100 mg po QD#	---	12 months

Notes:
BD - twice daily; IV - intravenously;
IP - intra-peritoneally; po - orally;
LD - loading dose; MD - maintenance dose;
QD - once daily;

Aminoglycosides, vancomycin, cefazolin and ceftazidime are dosed according to the latest recommendation introduced above.
Aminoglycosides are only used if residual urine output < 100 ml / day
 # Discrepancy in the dosing frequency of anti-tuberculous drug was found between the text and the table in the ISPD guidelines 2000.

and 30 mg on day 2 - 9 until 1993. The recommended treatment regimen in 1993 was changed to flucytosine (LD 2g orally; MD 1 g QD orally) together with fluconazole (200 mg po or IP daily) for 4 to 6 weeks. The combination was shown to be as efficacious as amphotericin B.[7]

V CONCLUSIONS

Antibiotic regimens employed for treatment of CAPD associated peritonitis have been changing over the last decade. The aim of empiric regimen is to provide a wide range of coverage over usual organisms seen in CAPD peritonitis, and to reduce the emergence of resistant strains of bacteria as well as preservation of residual renal function in patients. Like treatment of any other types of infections, antibiotic regimen should be modified according to organisms isolated and sensitivity results. Local treatment protocol for CAPD associated peritonitis can be drawn up based on current ISPD recommendation, local epidemiology and drug availability.

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Rituximab: An Engineered Antibody-based Therapeutic Agents for the Treatment of Lymphoma

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Rituximab or Rituxan® is a monoclonal antibody with human IgG1 constant regions that bind specifically to the CD20 antigen expressed on the surface of malignant and normal B-cells of the immune system. It is the first approved antibody-based therapeutic agent for the treatment of non-Hodgkin's lymphoma. This article reviews how it was cloned and structurally engineered to increase its binding activity to receptor-bearing cells, leading to lyses of the targeted cell. A number of advantages of this engineered antibody are also discussed.

I INTRODUCTION

The immune system of the human body plays an important role in the fight against infectious pathogens. The lymphocytes (B cells) of both humans and mice have the ability to express antibodies able to (1) virtually recognize by binding to the antigenic determinant (epitope), and (2) to discriminate between even similar epitopes [1, 2]. Not only does this provide the basis for protection against invading organisms by the expressed antibodies, but it makes them attractive candidates to target other types of molecules found in the body, such as receptors or other proteins present on the surface of normal cells, and molecules present uniquely on the surface of cancer cells [3, 4].

The potential use of antibodies in medicine has a long history. As far back as 1895, Hericourt and Ricket described the first attempt in which cancer cells were injected into animals to raise an antiserum for treating patients with advanced cancer. The results seemed promising, with many patients showing a significant improvement, although none were cured. During the early 1900s many researchers repeated their experiments but the results were inconsistent and contradictory. It was later discovered that this was due to the fact that antiserum contains many different antibodies (Figure 1a); some of which recognize antigens on the cancer cells but these antigens are also present on normal healthy cells. What was needed was a method to isolate or produce one type of antibody that specifically recognized one antigen [5]. Kohler and Milstein achieved this in 1975 with the invention of the hybridoma technique for the production of monoclonal antibodies (mAB), for which they won a Nobel Prize.

II HYBRIDOMA TECHNIQUE FOR THE PRODUCTION OF mABs

Kohler and Milstein's technique involved isolating a single antibody secreting B cell so that they could produce a homogenous preparation of antibodies. One problem they faced, however, was the limited lifespan of B cells in culture. To overcome this, B cells were fused with cells derived from an 'immortal' tumor cell line. This resulted in hybrid cells, which had the ability to produce antibodies and to multiply indefinitely in culture. The procedure for producing monoclonal antibodies involves immunizing a mouse or rat with a target antigen, isolating the relevant B cells and fusing them with the immortal cell lines to create antibody producing hybridoma cells [6]. Typically for each antigen a number of mice are immunized over a period of 2-6 months, followed by a further 1-2 months of laboratory work to produce the hybridoma cells (Figure 1b). These hybridoma cells were capable of producing large quantities of a single antibody. Each mAB has a precise definable specificity and affinity, and is of one Ig class.

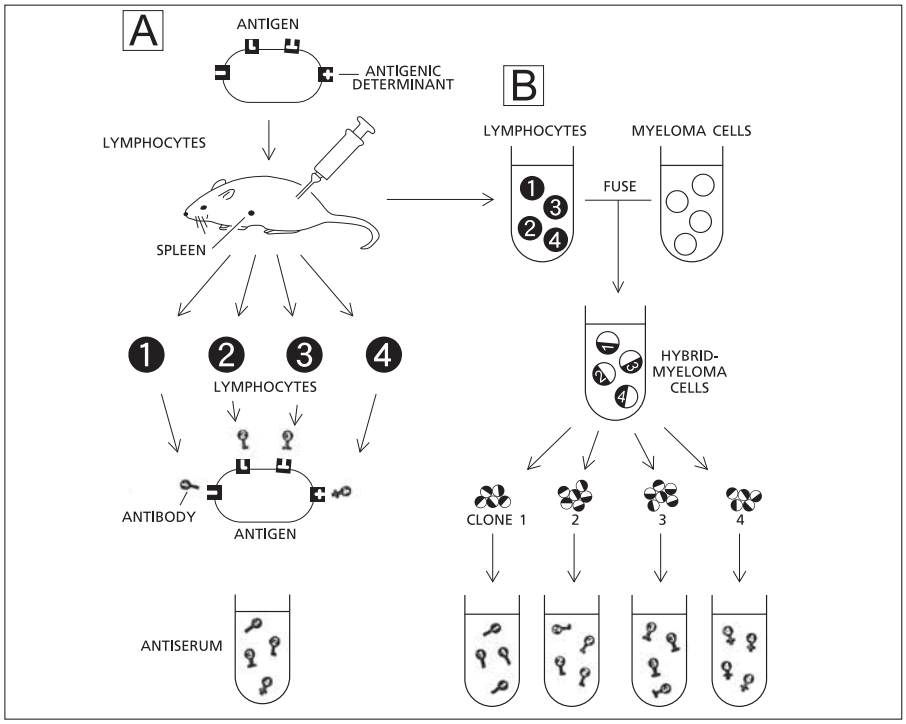

Figure 1. Production of antibodies. (a) antiserum contains polyclonal antibodies; (b) mass cultivation of selected hybridoma clone allows the production of monoclonal antibodies.

III USES OF MONOCLONAL ANTIBODIES

The remarkable specificity of mABs makes them promising agents for various purposes. Since its invention, mABs have been widely used as diagnostic, purification and research reagents [7]. Their application in human therapy, however, was only a matter of recent development [8, 9,10].

As a research tool mABs have been used to isolate or track target proteins. Once an antibody is produced against a target protein it can be used as a specific probe to track down and isolate the protein that induced its formation thus allowing researchers to determine where the protein is made, stored and where it ends up, which molecules it interacts with, its structure and function etc. This technique can also be used to determine the role of a protein in disease states. These techniques have since been used successfully in many areas of research and diagnosis.

In the clinic, mABs offer a basis for human therapeutic products. They are highly specific and target particular molecules and therefore offer the potential for the so-called 'Magic Bullet' approach of drug design. An antibody that binds only to one kind of cancer cell in a patient can be made and by coupling a cytotoxic agent (e.g. a strong radioactive isotope) to that antibody and then giving the complex to the patient, it can seek out and destroy the cancer cells (and no normal cells). Thus, mAbs can deliver a toxic agent directly a target, such as a tumor, while minimizing the damage to healthy cells. Besides, mABs can also be used as effective antagonists at specific receptor sites.

In some *in vivo* applications, mAB itself is sufficient. Once bound to its target, it triggers the normal effector mechanism of the body. But in other cases, the mAB is coupled to another molecule; for example a fluorescent molecule to aid in imaging the target or a strongly-radioactive atom to aid in killing the target.

IV CLINICAL APPLICATIONS OF RITUXIMAB

The use of antibodies as "magic bullets" to deliver destructive payloads to targeted cells for treatment of disease can be exemplified by the successful introduction of Rituximab in recent year [10, 11]. Rituximab binds specifically to antigen CD20 which is a transmembrane molecule located on pre-B and mature B lymphocytes. The antigen is a non-glycosylated phosphoprotein found on most (>95%) mature B-cells. It is also found on all non-Hodgkin's lymphoma (NHL), but not on haematopoietic stem cells, pro-B cells, normal plasma cells or other normal tissues (Figure 2). This receptor is an excellent target antigen for monoclonal antibody therapy of this disease. Rituximab or *Rituxan*® is a chimeric anti-CD20 mAb. It is the first antibody-based therapeutic agent approved by the FDA for treating non-Hodgkin's lymphoma (NHL) and a milestone in drug development based on hybridoma biotechnology.

i) What is non-Hodgkin's lymphoma (NHL)

Lymphomas are cancers evolving from the lymphatic system; the network of glands and vessels that circulate lymph throughout the body. Lymph is a clear, colorless, watery fluid that contains the white blood cells that form the basis of the immune system. Tumors may form on lymph nodes, small, bean-shaped organs found throughout the lymph system, specifically around the neck, under the arms, in the groin and abdomen.

NHL occurs when B-cells, the cells that produce antibodies, begin to grow abnormally. The B-cells (or more rarely, T-cells) divide too rapidly and grow out of control. Tumors result when too much tissue is formed. Because the lymphatic system is distributed throughout the body, the cancer cells may spread to other organs including the liver, spleen or the bone marrow.

Non-Hodgkin's lymphoma, also called B-cell lymphoma, is the most common type of lymphoma. It is the sixth most common type of cancer in the US. Each year, some 54,000 new cases are diagnosed and more than 24,000 die from the disease. The overall incidence of NHL has increased more than 80% since the 1970s, a fact that is attributed to the AIDS epidemic and the aging population. One-half of NHL patients have low-grade or follicular lymphoma. A portion of these patients develop multiple relapses and their disease has been successfully controlled by *Rituxan*® therapy [10, 12].

ii) Design and structure of Rituximab

The new compound, called Rituximab or *Rituxan*®, is a genetically-engineered IgG1 immunoglobulin that targets a receptor called CD20 found on B-cells. It is a specific type of drug known as a chimeric monoclonal antibody. Chimeric antibodies take their name from the chimera, a mythical beast with the head of a lion, the body of a goat and the tail of a dragon. It is a human IgG1 kappa immunoglobulin with mouse variable regions isolated from a murine anti-CD20 monoclonal antibody. As illustrated in Figure 3A, it has variable region (Fab) of a murine anti-CD20 antibody and human IgG1 and K constant regions. It is a small glycosylated protein composed of 1328 amino acids and has a molecular weight of 144 kD. This chimeric antibody was developed by scientists of IDEC Pharmaceuticals Corporation in California through immunization of BALB/c mice with the CD20+ human lymphoblastoid cell line SB.

The production of chimeric human-mouse antibodies represented a substantial advance over the use of unmodified murine antibodies since the human Fc domains interacted more effectively with human complement and effector cells, mediated apoptosis more efficiently, and were less immunogenic [13]. The Rituxan antibody binds with high affinity (approximately 8.0 nM) to cells expressing the CD20 antigen found on

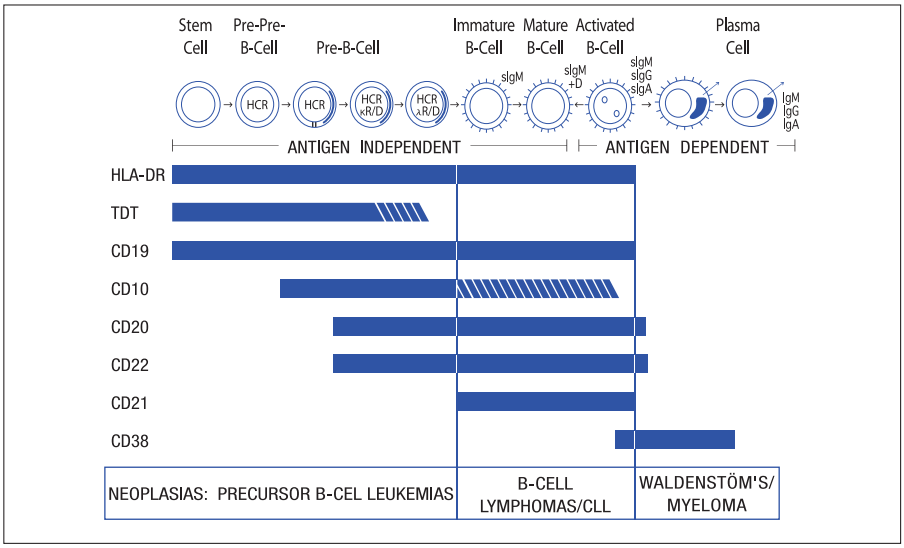

Figure 2. Pattern of expression of CD20 and other surface antigens on cells of the human B-lymphocyte lineage.

the surface of malignant and normal B cells, but not on other normal tissues. It marks the B-cells for destruction after which new B-cells are generated by stem cells. Stem-cells and B-cells bearing antibodies are spared by *Rituxan*®, since they lack the CD20 antigen. The problem of the development of human antimouse antibodies (HAMA) is also overcome in this engineered monoclonal antibody.

iii) Structural modification for improvement of activities

In vitro studies of the mechanism of action demonstrate that the antibody binds human complement and lyses lymphoid B-cell lines (CDC), lyses human target cells through antibody-dependent cellular cytotoxicity (ADCC) [13], induces apoptosis in human lymphoma cell lines [14, 15], induces tyrosine phosphorylation [15], and inhibits cell proliferation [15]. Since recruitment of human complement is the key step to initiate the cell-killing function of Abs, the type of residues affecting the binding of C1q, a constituent of the functional unit of complement, to the C_H2 domain of Igs, IgG and IgM, which are in complex with the Ag, have been studied [16, 17]. Cell-killing by Rituximab was dramatically increased after amino acid substitutions at certain sites on the molecule (Figure 3B). Idusogie and his associates reported that the C1q and CDC binding activity of Rituximab was increased or rescued when amino acids on two sites in human IgG, K326 and E333, were substituted with alanine while substitution with tryptophan and serine, respectively, conferred biological activity in the complement-dependent cytotoxicity assay in comparison to the wild-type antibody (Figure 4) [18, 19]. Figure 4 shows C1q binding and CDC activity of the single and double Rituximab-IgG2 mutants. The binding affinity of a variant of double mutation in IgG2, K326W/E333S, was higher for C1q than Rituximab (Figure 4A). Although complement at a high concentration is able to rescue the activity of low affinity C1q binding mutants [18], the CDC assay for the IgG2 mutants at a concentration of complement approaching physiological levels give a better picture of the cytotoxic effect of each variant. Consistent with the C1q binding data, the K326W/E333S mutation in IgG2 also increased CDC activity significantly (Figure 4B). The results also indicate that IgG1 and IgG2 have different amino acid requirements for C1q interaction. These reveal that different isotypes show different effects on C1q binding and CDC activity when point mutations at K326 and E333 are constructed. Thus, by amino acid substitutions at these two residues, the ability of Rituximab to recruit complement could be augmented, which in turn, affected the lytic activity of Rituximab.

iv) Advantages of engineered antibody for clinical applications

The development of Rituximab described above illustrates how biotechnology can be applied to construct hybrids composed of human antibody and regions linked with a murine or primate backbone. Through this approach it overcomes some inherent problems that arise in the first generation of monoclonal antibodies.

The clinical use of a chimeric antibody rather than a murine monoclonal

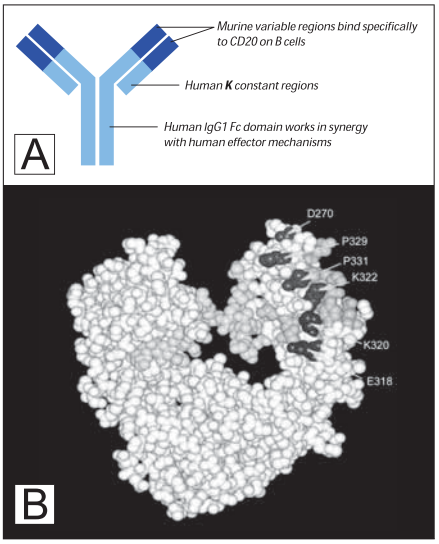

Figure 3. The design and three-dimensional structure of the Rituximab. Diagram A illustrates how the murine variable regions are designed to bind specifically to CD20 on B cells. Diagram B shows the importance of four residues (D270, K322, P329 and P331) that form the binding epicenter of C1q region [18, 19].

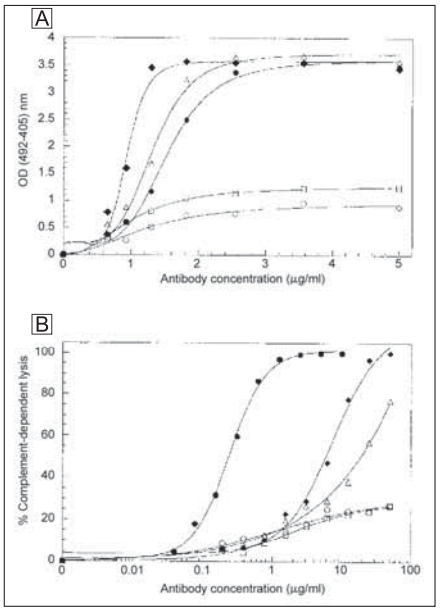

*Figure 4. Ability of rituximab and its variants to bind C1q and confer complement-dependent lysis. Diagram **A** shows C1q binding and diagram **B** shows CDC activity using a 1/3 dilution of human complement as a probe. Legends: wild-type Ab (●), rituximab-IgG2 (○), IgG2 E333S (△), IgG2 K326W (□) and IgG2 K326W/E333S (◆) [19].*

antibody has three advantages. First, reduced immuno-genicity permits repeated administration [20, 21]. Second, a chimeric antibody has a longer half-life that produces a prolonged effect, even after low doses compared with a murine antibody [20, 22]. Finally, a chimeric antibody, because of its human constant regions, induces human effector functions including CDC or ADCC pathways [12]. ADCC is mediated by interaction of the Fc regions of IgGs with the Fcγ receptor expressed on a wide variety of cells. The Fc receptor-bearing cells are activated upon binding to Ab-Ag complexes, resulting in lysis of the targeted cell [23]. In a recent clinical study, it was found that patients with central nervous system (CNS) lymphomas developed no toxicity after receiving rituximab. When five of these patients with primary or metastatic CNS lymphoma were given an immunochemotherapy regimen consisting of rituximab and temozolomide, good tolerance and efficacy were reported while the control group was not [24]. These observations suggest that the side effect of chemotherapy can be bypassed by giving patients immunoche-motherapeutic treatments.

V OTHER mABs DEVELOPED AS HUMAN MEDICINE [25]

Significant advances have now been made in the use of mABs for the treatment of carcinomas. Table 1 summarizes some recently developed and investigated mABs used for immunotherapy. Other mABs that have been developed as human medicines are described below:

- **OKT3.** A mAB binds to a molecule on the surface of T cells. It is used to prevent acute rejection of organ transplants, e.g., kidney.
- **LymphoCide.** A mAB binds to CD22, a molecule found on some B-cell leukemias.
- **Lym-1** (trade name = Oncolym). A mAB binds to the HLA-DR-encoded histocompatibility antigen that can be expressed at high levels on lymphoma cells.
- **Daclizumab** (trade name = Zenopax). A mAB binds to part of the IL-2 receptor produced at the surface of activated T cells. It is used to prevent acute rejection of transplanted kidneys.
- **Infliximab.** A mAB binds to tumor necrosis factor-alpha (TNF-alpha). It shows promise against some inflammatory diseases such as rheumatoid arthritis.
- **Herceptin.** A mAB binds HER-2/neu, a growth factor receptor found on some

Table 1. Examples of some recently developed and investigational monoclonal antibodies used for immunotherapy [25]

Antibody	Brand name	Specificity (antigen)	Target cell/ disease	Type (chimerized, etc)
Edrecolomab	Panorex®	17-1A Ag	Colon/rectal cancen	Murine IgG2a
Trastuzumab	Herceptin®	HER2 oncoprotein	Mammary cancer	Humanized murine IgG1
Anti-idiotype antibodies	_____	Individual patients' B-cell tumor Ag	B-cell lymphoma	Customized human mAB
CAMPATH-1	_____	CD52 Ag	CLL	Humanized IgG1
Rituximab	Rituxan®	CD20 Ag	NHL	Chimeric human/murine IgG1
Anti-B1	Tositumomab	B1 Ag	NHL	Mouse
LYM-1	_____	HLA-Dr Ag	NHL	Murine IgG2a
LL2 (Tositumomab)[a]	_____	CD22 Ag	NHL	Murine IgG2a
Anti-CD33 (Hu-M195)	_____	CD-33 Ag	Acute/chronic myelogenous leukemia	Humanized murine mABb
Ibritumomab Tiuxetan[b,c]	(Zevalin™, IDEC-Y2B8)	CD20 Ag	NHL	Chimeric human/murine IgG1

Note:
[a] ^{131}I-conjugated. [b] ^{90}Y-conjugated. [c] ^{111}In-conjugated.
Ag: antigen; mAB: monoclonal antibody; CLL: chronic lymphocytic leukemia; NHL: non-Hodgkin's lymphoma

tumor cells (some breast cancers, lymphomas). The only monoclonal so far that seems to be effective against solid tumors.

- **CMA-676.** It is a conjugate of a monoclonal antibody that binds **CD33**; a cell-surface molecule expressed by the cancerous cells in **acute myelogenous leukemia (AML)** but not found on the normal stem cells needed to repopulate the bone marrow, and **calicheamicin**; an oligosaccharide that blocks the binding of transcription factors (proteins) to DNA and thus inhibits transcription. CMA-676 is the first **immunotoxin** that shows promise in the fight against cancer.

- **Vitaxin.** A mAB binds to a **vascular integrin (anb3)** found on the blood vessels of tumors but not on the blood vessels supplying normal tissues. Vitaxin is still in its Phase II clinical trials, but it has shown some promise in shrinking solid tumors without harmful side effects.

- **Abciximab** (trade name = Reopro). This Mab inhibits the clumping of platelets by binding the receptors on their surface that normally are linked by fibrinogen. It is helpful in preventing reclotting of the coronary arteries in patients who have undergone angioplasty.

VI PROBLEMS WITH MONOCLONAL ANTIBODY THERAPY

Why are there so few mABs being used in human therapy since its invention a quarter of century ago? The main difficulty is that mouse antibodies are "seen" by the human immune system as foreign, and the human patient mounts an immune response against them, producing **HAMA** ("human anti-mouse antibodies"). These not only cause the therapeutic antibodies to be quickly eliminated from the host, but also form immune complexes that cause damage to the kidneys. Monoclonal antibodies raised in humans, of course, would lessen the problem but few people would like to be immunized in an attempt to raise the antibodies and most of the attempts that have been made have been unsuccessful.

Nevertheless, two approaches have been made in an attempt to eliminate the problem of HAMA:

- **Chimeric antibodies.** The antigen-binding part (variable regions) of the mouse antibody is fused to the effector part (constant region) of a human antibody using genetic engineering. **Infliximab** is one of these.
- **"Humanized" antibodies.** The amino acids responsible for making the antigen binding site (the hypervariable regions) are inserted into a human antibody molecule replacing its own hypervariable regions. **Daclizumab, Vitaxin,** and **herceptin** are examples.

In both cases, the new gene is expressed in mammalian cells grown in tissue culture (*E. coli* cannot add the sugars that are a necessary part of these glycoproteins).

VII THE FUTURE

Although still in the experimental stage, other ways of solving the problem of HAMA are being studied. One of these is to exploit transgenic technology to make transgenic mice that have human antibody gene loci inserted into their bodies (using the embryonic stem cell method) and that have their own genes for making antibodies "knocked out". The result is a mouse that can be immunized with the desired antigen; that produces human, not mouse, antibodies against the antigen and that can yield cells to be fused with myeloma cells to manufacture all-human monoclonal antibodies.

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Extracts of Bark and Leaf of *Eucommia ulmoides* Oliv. (杜仲) Enforce Biological Functions of Internal Organs and Defer Aging in Adults

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Botanical Name: *Eucommia ulmoides* Oliv. (杜仲)
Plant Family: Eucommiaceae
Other Names: Du-Zhong, Tochu, Tochu-cha
Pharmacopoeia Name: Cortex Eucommiae
Brand Names: 杜仲降壓片, Qing'e Wa

I ABSTRACT

Bark of *Eucommia ulmoides* has been used to enforce the functions of internal organs, tendons and bones for a long time. Recently, it was demonstrated that leaves of this herb offered similar beneficial effects to human beings. Aqueous extracts of bark and leaves were anti-hypertensive, hypolipidemic and anti-oxidative. The last effect is due to the polyphenolic compounds. Both bark and leaves of this herb have been shown to stimulate the formation of collagen and granuloma; which indirectly strengthen biological functions of internal organs and defer aging in adult. The bioactive compounds responsible for these beneficial effects have been identified. They are iridoids, geniposide and aucubin.

II DESCRIPTION AND BACKGROUND

Eucommia ulmoides Oliver (Family Eucommiaceae) is a large deciduous tree which can grow to 70 ft (20 m). It is a monospermous, dioecious tree with trunk growing to 50 cm in diameter. The trunk normally is covered with scabrid to scabrous bark. This tree is widely distributed in Sichuan, Shanxi, Hubei, Henan, Guizhou and Yunnan in mild and wet but sunny regions at altitudes of 300=2,500 meters above sea level. In the bark of trunk, branches and roots, as well as in the leaves, there are rubber-like substances. Lateral veins and veinlets of the leaf are prominently depressed above but raised beneath (Figure 1).

Traditionally, cortex of the tree officially named Cortex Eucommiae (杜仲, Du-Zhong) (Figure 1, insert) is used as crude medicine. The bark of the tree is normally peeled off between April and June. After scraping off excessive cork, it is dried under the sun. Du-Zhong is one of the oldest tonic herbs amongst traditional Chinese medicines and is also officially listed in the Chinese Pharmacopoeia. The herb has been used to strengthen the biological functions of internal organs, muscles, tendons and bones[1]. It has been recently claimed that the herb is suitable for the treatment of hypertension and lumbago and for the prevention of miscarriage[2,3].

Figure 1. Bark (left) and leaves (right) of E. ulmoides [adapted from http://ou99.myrice.com/jjekeezr/wlxx/yd/pi/pi10.html]

Contraindications
At the moment of this publication, no contraindication has been reported.

Undesirable Effects
E. ulmoides has not been associated with any side effects in human studies.

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

Because of its effectiveness, demand for the herb is huge. The supply of bark of *Eucommia ulmoides* oliver tree, however, is very limited. Each year a lot of Du-Zhong trees are killed. Because regeneration of the cortex of the tree takes a long time, the tree has become less and less

and is listed as a second-class protection plant in China. In order to minimize consumption of the tree trunk, interests has recently focused on the leaves of *Eucommia ulmoides*. The leaves have recently become a popular folk drink and are regarded as a functional herb.

III BIOACTIVE CONSTITUENTS

Iridoids and lignans are the main constituents found in the bark of Du-Zhong[2,4]. Recent research has shown that leaves contain chemical constituents similar to the bark[5].

i) Iridoids

Iridoid glycodsies, such as aucubin, harpagide, acetate, ajugoside, reptoside and eucommiol, are all monoterpene cyclic ethers with a basic skeleton of hexahydrodimethylcyclo-penta[c]pyran. Amongst these glycosides, aucubin is the major constituent in the stem (0.1-4.0%) and in the leaves (1.6-1.7%). Eucommioside I, geniposidic acid and geniposide, all of which are diglycosides have also been found in the stem, bark and leaves of Du-Zhong (Figure 2)[5,7,8]

ii) Lignans

Lignans are natural products of low molecular weight molecules that arise primarily from the oxidative coupling of p-hydroxyphenylpropene or a variant of the same chemical skeleton in which the two units are linked by an oxygen bridge. In the bark of *E. ulmoides*, most lignans are derivatives of bisbenzyl-perhydrofuro[3,4-c]furan. Different lignan glycosides (Figure 3) have been isolated from the bark of *E. ulmoides*; for example, syringaresino O-β-D-glycopyranoside, cycloolivil and olivil di-O-β-D-glucopyranoside. Pinoresino di-O-β-D-glucopyranoside is the major bioactive components of *E. ulmoides*. It is mainly found in the phloem of bark and its content ranges from 0.30 to 0.55% (w/w) in various samples[4].

iii) Phenolic Compound and Flavonoids

Low-molecular weight phenolic compounds found in Du-Zhong are simple phenolic derivatives and flavonoids (Figure 4 and 5). The basic structure of flavonoids is comprised of diphenylpropane (C6-C3-C6) and two aromatic rings that are linked through three carbons which usually form an oxygenated heterocycle[9]. Flavonoid glycosides present in Du-Zhong include quercetin[10,11] and rutin[12] while chlorogenic acid[11,12,13], ferulic acid, caffeic acid[12], protocatechuic acid[11,12,13], pyrogallol and p-trans-coumaric acid[11] are phenolic compounds.

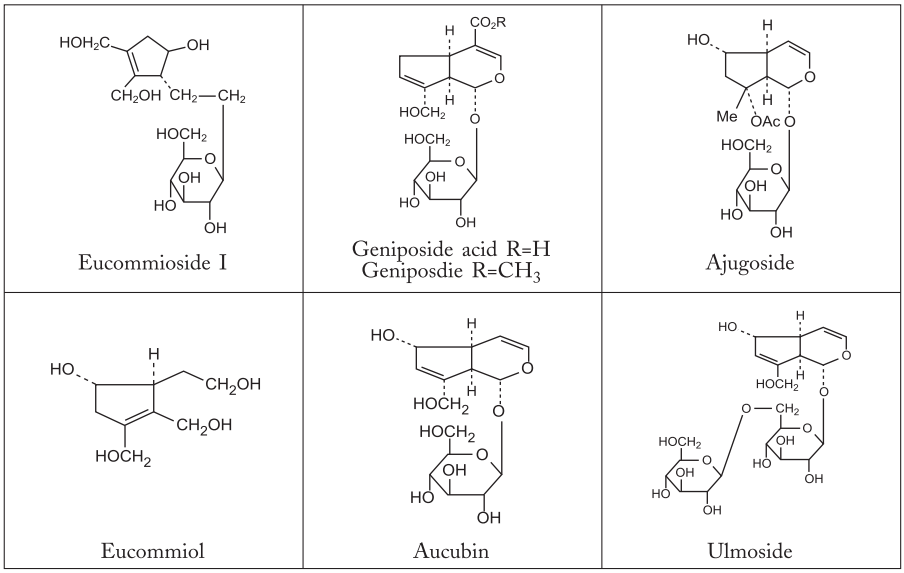

Figure 2. Chemical structure of iridoids in Eucommia ulmoides.

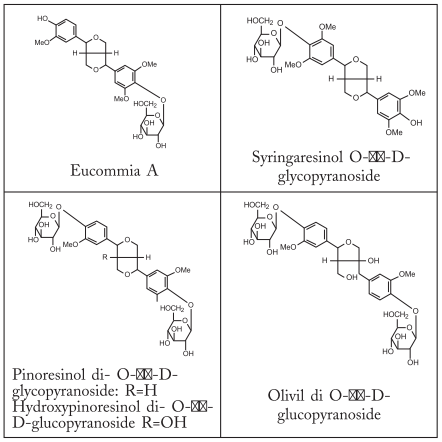

Figure 3. Chemical structure of some lignans in E. ulmoides.

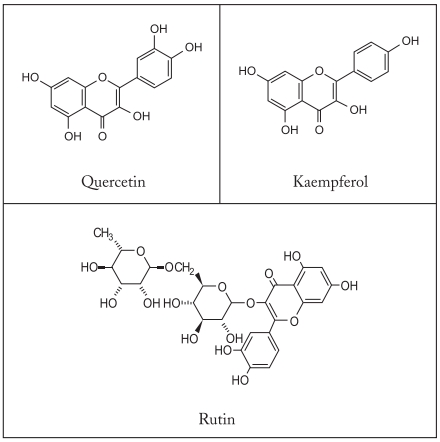

Figure 4. Chemical structures of flavonoids in E. ulmoides.

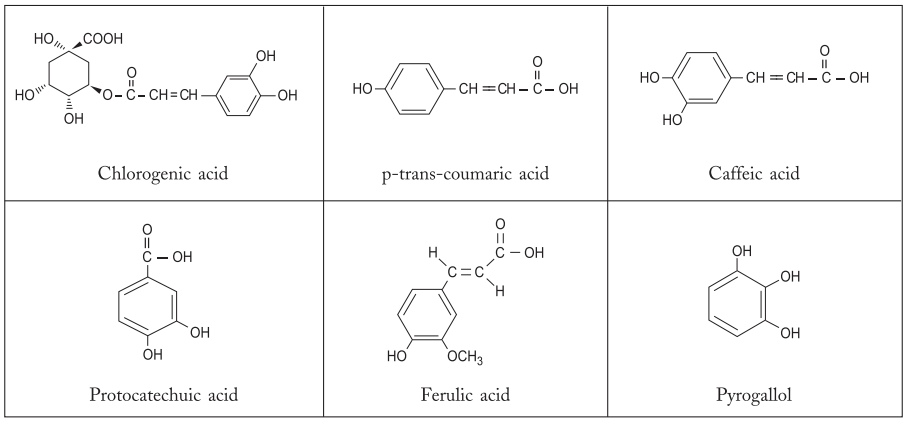

Figure 5. Chemical structures of phenolic compounds in E. ulmoides.

IV CONTEMPORARY USES

E. ulmoides is traditionally used for remediation of liver and kidney, reinforcing bones and tendons, prevention of miscarriage, treatment of deficiency conditions of the kidney indicated with lumbago and lack of strength. It has sedative, anti-hypertensive and anti-inflammatory effects. More recently, the decoction of Du-Zhong leaves is taken as beverage or functional drink and has become a popular nutraceuticals.

V MODE OF ACTION

1. Lowering of blood pressure

Both leaf and bark extracts of *E. ulmoides* were demonstrated to have a hypertensive effect. Chien showed that water extract of bark of *E. ulmoides*

lowered blood pressure and dilated the ear vein of rabbits[14]. Blood pressure of rats was lowered after receiving an oral administration of aqueous extract of bark of *E. ulmoides*[15]. Another study showed that after oral administration of an aqueous extract of the leaves of *E. ulmoides* for four weeks, blood pressure of a hypertensive dog dropped and heart rate slowed down[16]. A clinical study carried out by Uezono *et al* revealed that drinking leaf extract of *E. ulmoides* mildly lowered blood pressure throughout 24 hr in people who have relatively high blood pressure[17]. Kwan *et al* also reported that bark extract of *E. ulmoides* had the vasodilating effect on both large elastic arteries and small muscular arteries in rats. The bark extract induced endothelium-dependent relaxation in smaller arteries. This was found to be mediated by both endothelium-derived hyperpolarizing factors (EDHF) and NO. Leaves of *E. ulmoides* also had a similar physiological effect[18]. A bioactive component, pinoresino di-O-β-D-glucopyranoside was found to responsible for the antihypertensive effects. It could act directly on the vascular smooth muscle and cause peripheral vasodilation. Consequently, system arterial anti-hyptension resulted[19].

2. Antimutagenic activity

A study performed by the Sasaki group reported that leaf extracts of *E. ulmoides* could lower mutagenic effect of urine in people after eating raw fish and cooked beef which contented high amount heterocyclic amines and other mutagens[20]. The mutagenicity of the urine from a group of people drank leaf extracts was lower than the control. Thus, exposure of dietary mutagens could be reduced by administration of leaf extracts of Du-zhong. This effect is probably attributed to the flavonoid components, such as quercetin, kaempferol and phenols - pyrogallol, protocatechuic acid, p-trans-coumaric acid and chlorogenic acid. Another study done by the same group reported that crude extract of *E. ulmoides* leaves possessed an anti-clastogenic effect. Crude extract of *E. ulmoides* tea suppressed chromosome aberrations in CHO cells and mice induced by mitomycin C (MMC) clastogenesis treatment. Iridoids (geniposidic acid, geniposide, asperulosidic acid, deacetyl asperulosidic acid and asperuloside) and phenol (pyrogallol, protocatechuic acid and p-trans-coumaric acid) in extracts of *E. ulmoides* leaves were found anti-clastogenic. The α-unsaturated carbonyl group on iridoid compounds was assumed to react with SH-group on enzymes causing higher-order structural changes which are responsible for bio-antimutagenicity. Besides, oral administration of leaf extracts to mice 6 hr before intrapereitoneal injection of MMC decreased frequency of micronuclei[21].

3. Antioxidative activity

Several studies conducted by the National Chung Hsing University in Taiwan demonstrated that Du-Zhong extract possessed antioxidant activities in biomoleucles. Deoxyribose, DNA and 2'-deoxyguanosine (Figure 6) were protected from oxidation induced by the Fenton reaction when incubated with Du-Zhong leaves, roasted cortex and raw cortex extract[22]. Besides, the extracts were found to inhibit damages of DNA by H_2O_2 in human lymphocytes. The leaf extracts of Du-Zhong were proved significantly inhibitory compared to other two herbal extracts. Mechanism of the protective effect may be due to the scavenging ability of leaf extract on H_2O_2[23].

Further studies carried out by the same research group demonstrated that aqueous water extract from barks of *E. ulmoides* had a significant scavenging effect on Reactive Oxygen Species (ROS). Oxidative stress caused by ROS and free radicals can lead to damage of biological macromolecules which is correlated to mutagenesis and carcinogensis. The extract of leaves had the highest scavenging activity compared with extract of raw cortex and roasted cortex. (Figure 7) Protocatechuic acid (PCA) was found as an active component responsible for the scavenging activity in a dose dependent manner. The content of protocatechuic acid in leaves, roasted coasted cortex and raw cortex was 17.17 mg/g, 2.99 mg/g and 1.16 mg/g, respectively. Du-Zhong could be used as a prophylactic agent for the prevention of free radical-related diseases[13].

It has also been reported that water extract of leaves, raw cortex and roasted cortex of Du-Zhong had an antioxidative effect on different lipid peroxidation models including peroxidation of linoleic acid, microsomal peroxidation (Figure 8) and peroxidation of liposome. The antioxidant ability of Du-Zhong extract was shown to correlate to their polyphenol content. The total polyphenol contents of leaves, roasted and raw cortex is shown in Figure 9. Extracts of Du-Zhong thus could be used to prevent membrane lipid peroxidation and free radical-linked disease [24].

Aqueous extract of Du-zhong was also demonstrated to have inhibitory effects against the oxidative modification of low-density lipids (LDL). *E. ulmoides* extract suppressed LDL oxidative modification induced by copper (II) ions. The major antioxidant component was identified as a phenolic compound, protocatechuic acid (PCA). The mechanism of the antioxidant could be due to the presence of phenolic compound to chelate with metal ions to form complexes which can scavenge free radicals[25].

Du-Zhong extract was found to

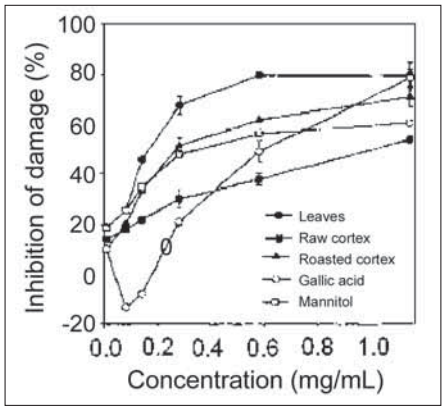

Figure 6. Effect of water extracts of Du-zhong on the Fe^{3+}-EDTA/H_2O_2/Asc induced oxidative damage of deoxyribose. *Ability of the extracts to inhibit oxidative damage in deoxyribose was evaluated according to the Fenton reaction model system by mixing the tested sample (0-1.14 mg/ml), deoxyribose (3 mM), H_2O_2 (1 ml), potassium phosphate buffer (20 mM, pH7.4), $FeCl_3$ (50 μM), and EDTA (100 μM) followed by incubating at 37°C for 1 hr with the addition ascorbic acid (100 μM). The extent of degradation of deoxyribose was measured using TBARS method. One millilitre of 1% TBA and 1 ml of 2.8% TCA were added to the mixture, which was then heated in a water bath at 100°C for 20 min. The absorbance of the resulting solution was measured spectrophotometrically at 532 nm. Each value represents mean ± standard deviation [22].*

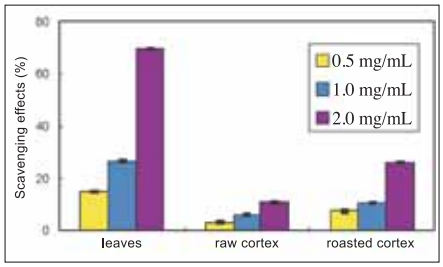

Figure 7. Hydrogen peroxide scavenging effect of water extract from E. ulmoides. *Scavenging effect % (capacity to scavenging the superoxide anion) = [(absorbance of control at 610 nm) - (absorbance of sample at 610 nm) / (absorbance of control at 610 nm)] × 100 Each value is the mean ± standard deviation of three replicate analyses and is significantly different ($P < 0.05$) [13].*

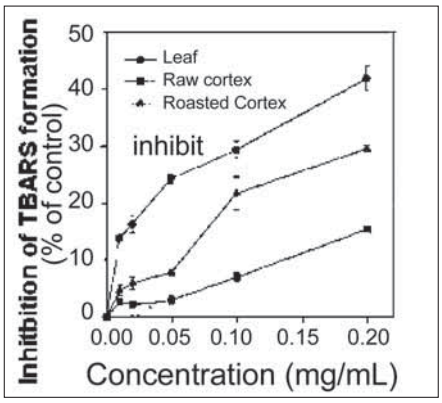

Figure 8. Effect of water extracts from Du-zhong on the lipid peroxidation of mitochondria induced by Fe^{2+}/H_2O_2. *Mitochondria were isolated from rat and oxidation of mitochondria was induced by Fe^{2+} and H_2O_2. The extent of oxidation of mitochondria was determined by the thiobarbituric acid reactive substances (TBARS) measurement. One millliter each of 1% TBA and 10% HCl was added to the reaction, and then it was heated in a water bath at 100°C for 30 min. After the mixture had cooled in an ice bath for 15 min, 5 ml of chloroform was added to the mixture, and the mixture was centrifuged at 1600g for 20 min. The absorbance of the supernatant was measured spectrophotometrically at 532 nm. Inhibition of TBARS formation (percent of control) indicates the capacity to inhibit the TBARS formation in mitochondria. Each value represents mean ± standard deviation of three independent experiments[24].*

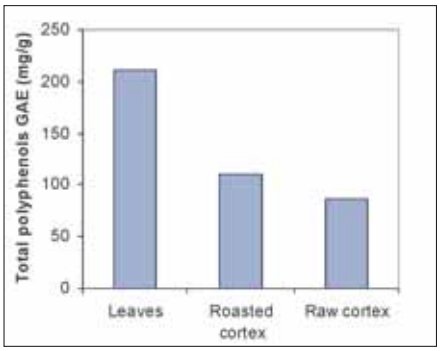

Figure 9. Polyphenol content of water extracts from E. ulmoides. *The herbs powder (0.1 g) was dissolved in 5 ml of 0.3ml HCl in methanol/water (60:40 v/v). The resulting solution (100 µl) was added to 2 ml of Na_2CO_3. After 2 min, 50% Folin-Ciocalteu reagent (100 µl) was added to the mixture, which was th en left for 30 min. Absorbance was measured at 750nm using a spectrophotometer. Total polyphenols are expressed as mg/g of gallic acid equivalents (GAE). Average values ± standard deviations are significantly different ($P < 0.05$)[24].*

increase the activity of superoxide dismutase (SOD), glutathione peroxidase (GSH-Px) and NOS; all of which are well-known anti-oxidative agents of aging induced by a D-galactose in mice[26].

4. Collagen synthesis

Traditionally Du-Zhong has been used to strengthen tendons and bones and to counteract the effects of aging. These pharmaceutical effects are highly related to protein metabolism especially collagen synthesis. It was reported that methanol extracts of *E. ulmoides* cortex stimulated collagen synthesis in false aged rat model. Eucommiol was identified as the active component[27]. Geniposidic acid and aucubin in the methanol extract of Du-Zhong leaves and fresh cortex were also demonstrated to have similar effects as eucommiol. However, these two active components in dried cortex were in low concentration as most of them were destroyed by enzymes in the cortex during the drying process and storage[28]. Besides, geniposidic acid and aucubin in the *E. ulmoides* leaf extracts were found as a key component to increase the turnover rate of stratum corneum of false aged rats, which is associated with the prevention of aging[29].

5. Granuloma formation

Wound healing involves granulation and collagen deposition in granuloma. Maturation of granuloma and deposition of collagen were reported to increase significantly after oral administration of aqueous extract of Du-Zhong leaves by rats at a dose of 1.8 g/kg of body weight per day for 3 weeks. Therefore, Du-Zhong tea could probably be used to speed up the wound healing process[30].

6. Hypolipidemic effect

Du-Zhong leaf extract inhibited a significant increase of total serum cholesterol, triacylglycerol and hepatic triacylglycerol in Wistar rats after being fed a high-fat diet supplemented with animal fat, cholesterol and cholate. Very-low density lipoprotein and low density lipoprotein were also suppressed without affecting high density lipoprotein cholesterol. These result suggested the leaf extract may be useful for the regulation of hyperlipidemia[31].

7. Activation of osteogenesis and inhabitation of osteolysis

It is reported that the methanol extract of *Eucommia* cortex was able to induce rat pituitary cells to release grow hormone and had a potential for proliferation of osteoblast. Besides, geniposidic acid, geniposide and aucubin in the aqueous fraction of the methanol extract enhanced proliferation of osteoblastic cells as well as inhibiting the significant proliferation of oseoclast, from co-culture of mouse bone marrow cells and ST-2 cells,. Thus, *Eucommia* cortex may activate osteoblast cells for osteogensis and inhibit osteoclast activity to suppress osteolysis[32].

8. Sedative and analgesic effect

It has been reported that intraperitoneal administration of decoction of the Du-Zhong bark at 10 g/kg reduced spontaneous activity of mice and prolonged their pentabarital-sleeping time[33]. Pinoresinol, a lignan found in *E. ulmoides* suppressed acetic acid-induced writhing in mice dose-dependently[34].

9. Diuretic effect

Extract of bark of Du-Zhong was illustrated to posse a diuretic effect on anesthetized dogs. The diuretic effect could also be observed in dogs which had developed an acute tolerance to the hypotensive action of the herbs[33].

10. Effect on uterus

Several studies showed that the ethanol decoction of bark of Du-Zhong had an antagonistic effect on the contraction induced by pituitrin and acetylcholine on the isolated uteri from normal and pregnant rats and rabbits. Normal development of organs, however was not affected[33].

11. Anti-cancer activity

E. ulmoides was found to have an inductive effect on apoptosis in HL-60 cells. The reduction of mitochondrial transmembrane potential of HL-60 cells and the enhancement of caspase-3 activity by the extract showed that the apoptosis induction was through the mitochondrial rout and apoptosis-conducting mechanism acted through a cascade involving caspase-3[35].

12. Immunological activity

Egg white induced paw edema in rats could be suppressed by the decoction and ethanol extract of *E. ulmoides* cortex. After administration of the decoction of Du-Zhong extract, the blood eosinophilic granulocytes of rats decreased significantly. Oral or injection administration of the decoction of Du-Zhong extract to young mice induced thymic atrophy which implies the anti-inflammatory mechanisms involving enhancement of the adrenocortical function[33]. Okada *et al* demonstrated that loliolide isolated from the leaves of *E. ulmoides* had immunosuppressive activity on T-lymphocytes in a dose dependent manner[36].

VI CONTRAINDICATIONS

At the moment of this publication, no contraindications have been reported.

VII UNDESIRABLE EFFECTS AND TOXICITY

There was no mortality in mice after oral administration of the decoction of Du-Zhong cortex at a dose of 15-25 g/kg within five days. No alternation or abnormality was found in the liver, spleen and heart of the dogs after receiving intraperitoneal dose of 10 ml of the 35% decoction of Du-Zhong bark for 42 days, except some mild degenerative changes in renal tubule epithelial cells[33].

VIII INTERACTIONS WITH CONVENTIONAL DRUGS

A report showed that combining leaves of *E. ulmoides* and roots of *Panax ginseng* in a ratio of 1:3 can provide a most effective synergistic effect of stimulation of collagen synthesis and prevention of decreased protein metabolism in aging[37].

IX MODE OF ADMINSTRATION

Aqueous or ethanol extracts of Leaves or bark of the plant can be employed therapeutically. Extracts of *E. ulmoides* are normally taken orally.

X DOSAGE

The recommended dose for oral administration of *E. ulmoides* cortex is 6-9 g.

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「藥到=病除？ 服藥對錯話你知」藥劑展覽

人生中，生病是少不免的，我們或多或少也會使用到藥物。服藥的最終目的當然是希望藥到病除，但是我們是否真的了解如何使用藥物呢？

香港中文大學藥劑學院院會「藥浪」與香港華都獅子會於二零零四二月二十及二十一日假葵芳新都會廣場天晶館合辦舉行一個名為「**藥到=病除？** 服藥對錯話你知」的藥劑展覽，展覽目的在於增廣普羅大眾的藥物知識。展覽的節目十分豐富，除了展板展示一般市民用藥過程中常犯的錯誤外，還會有註冊藥劑師介紹多種藥物劑型及解答市民對藥物資料的查詢，當中更設有攤位遊戲，讓各位朋友輕鬆地得到藥物常識。

開幕典禮

我們誠邀醫院管理局總監(專業事務及人力資源)高永文醫生、衛生署副署長梁挺雄醫生 JP、國際獅子會總監譚榮根博士、香港華都獅子會會長譚國翹獅兄及香港中文大學藥劑學院院長周樫森教授擔任這次藥劑展覽開幕典禮的嘉賓，主持簡單而隆重的開幕儀式。「藥劑健康大使」陳鍵鋒先生更親臨會場推廣正確的藥劑保健訊息，吸引了一大批電視台、電台及報館記者到場採訪，場面非常壯觀。

用藥知識展覽

這次藥劑展覽名為「**藥到=病除？** 服藥對錯話你知」，顧名思義，展板內容會以服藥的正確知識為中心，包括了自行停藥、自行服藥的弊病、忘記服藥的處理方法、正確運用藥物標籤及服藥方法，從而使市民知道藥到未必等於病除，要正確使用藥物才是藥到病除的不二法門。此外，藥劑師的角色在大眾的心目中是極其模糊的，亦藉著這個機會透過展板形式說明藥劑師的工作性質，令市民加深對藥劑師的了解。

「知多一點點」的展板講述病人使用藥物的權益和責任，亦介紹了維他命、抗生素和皮質類固醇的用途及其過量服食的反效果。

健康講座

展覽期間一共舉行了三場健康講座，而講者均為註冊藥劑師。講座題目簡單介紹如下：

(1) 「敏感」
調查顯示，哮喘病患者約香港人口百分之四點五；若只計算十三至十四歲學童，該百分比則高達一成。另外，每年因哮喘而須入院接受治療的人數亦超過一萬二千人。從這些數據看來，敏感問題絕對不容忽視。講者陳天佑藥劑師為大家分析敏感的成因及治療方法。

(2) 「問問社區藥劑師」
社區藥房遍佈港九，非常便利，部分社區藥房為方便市民，更營業至晚上十、 十一時，而且毋須預約，並由備有專業知識的藥劑師提供免費藥物諮詢服務。是次講座由劉敏儀藥劑師講解社區藥劑師的工作範疇，從而加深市民對社區藥劑師的了解。

(3) 「減肥有理？」
近來，越來越多的減肥瘦身廣告，聲稱「瘦」就是健康和美麗的象徵，掀起連串減肥浪潮。但是，什麼是「肥」？什麼時候才需要減肥？怎樣才能減肥健康？陳碧琪藥劑師為大家詳細分析減肥的理由和各項減肥方法的利與弊，讓大眾能作出明智選擇。

三場講座皆反應熱烈，座無虛席。市民細心聆聽，踴躍發問，獲益良多。

藥物資料查詢服務

藥劑師親身為市民解答糖尿病、高血壓、高血脂、肥胖症、敏感等藥物資料的查詢。有部分市民更拿出自己所服食的藥物詢問藥劑師其用途、及一些副作用。

藥物劑型介紹

展覽會場展出不同藥物劑型，並由註冊藥劑師親身講解其效用及使用方法，藉以灌輸市民正確的藥物知識。

攤位遊戲

「快快落藥」遊戲吸引了大批市民參加，以輕鬆的方法學習不同服藥的途徑。

總結

舉行是次展覽，我們的宗旨是增加大眾對藥劑師專業的認識與藥物的知識，在傳遞正確的藥物知識之餘，亦向市民介紹藥劑師的重要性。最後，用以下八句作為總結：

藥物標籤要識得，亂服藥物你損失；
儲存藥物你要識，控制飲食有得益；
咖啡酒類減療效，自行停藥損療程；
藥劑與你齊關心，藥到病除擢滿分。

PharmAssist Programme in Hong Kong

Chan, Charmaine[a]; Chiu, Sandra[b]

[a] *32nd GC Member, Practising Pharmacists Association of Hong Kong*
[b] *Medical Marketing Manager, Consumer Healthcare, GlaxoSmithKline*

Primary care, a focus of the Hong Kong public health policy, has become more and more important in the local society. This is particularly true after the Severe Acute Respiratory Syndrome (SARS) outbreak in last year. In view of this, the Practising Pharmacists Association (PPA) of Hong Kong collaborated with GlaxoSmithKline (GSK) planned a series of training workshops consisting of both academic and soft skills topics. Some of these workshops have now been conducted. The workshops were supported under the PharmAssist Programme by GSK. PharmAssist Programme is a worldwide programme initiated by GSK to sharpen the knowledge and communication skills of community pharmacists (CPs) in providing better service in primary care to the general public.

The workshops conducted covered the topics of "Effective Consultation Skills" and "Empathy and Caring to Your Patients". They were held on the 2nd and the 16th of June respectively. Apart from attracting over 100 fellow pharmacists to participate both workshops, academic scholar, Prof Kenneth Lee of the Chinese University of Hong Kong, attended the 16th workshop, while senior pharmacists, such as Ms Sau-Chu Chiang of Hospital Authority, and Mr Kim-Wah Ng of Society of Hospital Pharmacists of Hong Kong (SHPHK) attended both of the meetings. Many positive feedbacks on these workshops were provided by the attendants.

I EFFECTIVE CONSULTATION SKILLS

Date: *June 2*
Speaker: *William Chau, Executive Director, Tiptop's Consultants Ltd*

1) New Definition of Service Excellence

As the level of education and health awareness of the general public has risen nowadays, people tend to expect more from the services they receive. In face of keen market competition, pharmacy services need to take a step further. In this case, the CPs play a key role and certainly will make a difference by contributing not only with professional advice but also in a customer-oriented way. One of the main responsibilities of a pharmacist is to counsel patients to ensure drug compliance. This not only helps to make certain that patients benefit from the optimal therapeutic effect of their drug treatments, but also helps to reduce the unnecessary wastes of medical and financial resources. In drug counselling, communication gaps between patients and pharmacists can be lessened with empathy and care. Besides, getting to know the personality types of patients is beneficial, which can be categorized into 4 main groups: (1) "promoting"; (2) "socializing", (3) "controlling" and (4) "analyzing".

Anna Chin, Head of Sales (OTC) of GSK presented a souvenir to Charmaine Chan, 32nd GC Member.

2) Be Concise and Prompt for Action

There are several aspects about drug products which need to be addressed. They include features, characteristics, advantages and benefits. In reality, it is typical behaviour for consumers to look for only the subjective benefits. Given that consultation time is usually short, a pharmacist must give concise recommendations. Therefore, it is important to mention the "Unique Treatment Points" (UTPs). On the other hand, during the consultative process, you should observe the psychological and cognitive developments of the individual. When you notice that one has already passed through different stages such as the "attention", "interest", "desire to buy" and "product information memory" stages, it is the right time to prompt him to act.

Sandra Chiu, Medical Marketing Manager, Consumer Healthcare, GSK, presented a souvenir to William Chau.

II EMPATHY AND CARING TO YOUR PATIENTS

Date: *June16*
Speaker: *William Chau, Executive Director, Tiptop's Consultants Ltd*

Empathy is a very critical element in communication. Failure to observe its importance brings negative impacts on your relationships with patients and coworkers. The definition of service excellence for the medical profession does not equate with the conventional belief in the retail business world that "customers / patients are always right". Rather, it should be stressed that professional health advice is better heeded and complied with if empathy and care are shown from the health caregiver. We can summarize that there are 6 tips for acquiring empathy skills. They consist of (1) "Sharpening Observations",(2) Enriching Senses", (3) "Widening Perspectives", (4) "Removing Hang-Ups", (5) "Drilling Responses" and (6) "Strengthening Confidence". Practice makes perfect is an immortal truth.

(From left to right) Billy Chung (President of PPA), Dave Yuen (33rd GC member), Alex Cheung, Estella Wang (33rd GC member), SC Chiang (Senior Pharmacist (Pharmacy Practice Management), CPO, HA), William Chau (speaker), Kim Ng (Kowloon Central Cluster, Cluster Manager, Pharmacy / QEH DM Pharm), Sandra Chiu (Medical Marketing Manager, GSK), Iris Chang (33rd GC member), Charmaine Chan (32nd GC member), Catherine Yeung (Vice President of PPA) and Wong Or (33rd GC member).

III TESTIMONIALS OF PHARMACISTS

"This is a good opportunity for us to meet and share with our peers." - Ms. SC Chiang

"The workshop contains many practical tips for achieving service excellence. It inspires me to view life situations with different perspectives." - Ms. Wanda SY Kwan

"GSK has done a very good job in organizing this meeting. I feel welcomed and I enjoy it very much. It is truly a pleasant experience to learn and have fun at the same time." - Mr. Lui Shek Man.

The General Committee Members of Practising Pharmacists Association of HK 2004/2005

President:	Mr. Billy Chung	**General Committee:**	Ms. Estella Wang
Vice Presidents:	Ms. Catherine Yeung		Ms. Yvonne Fung
	Ms. Dorothy Chin		Ms. Tina Yap
Hon. Secretary:	Mr. Nelson Lam		Mr. Wong Or
Hon. Treasurer:	Mr. Jack Wong		Ms. Sylvia Chan
			Ms. Iris Jacqueline Chang
			Mr. Dave Yuen
			Mr. Matthew Sin
			Mr. Cheung Chiu Hang
			Ms. Phyllis Kwong

Day 1 Saturday, 9 October 2004

Time	Program	Speaker
1:30 - 2:30 p.m.	Registration	
2:30 - 2:50 p.m.	Opening Ceremony	
2:50 - 3:00 p.m.	Welcome Address by Conference Chairperson	*Professor Vivian Lee*
3:00 - 3:30 p.m.	A Changing Paradigm in Health Care System: How Can We Do Better?	*Professor Joseph Sung*
3:30 - 4:15 p.m.	Clinical Pharmacy in the United States: Progress and Challenges & How This Service has Benefited Our Patients	*Dr. Jerry Bauman*
4:15 - 4:45 p.m.	Tea Break, Exhibition & Poster Display	
4:45 - 5:15 p.m.	Sustainable Development - What is This and Why are We Doing This?	*Mr. Jonathan McKinley*
5:15 - 6:00 p.m.	Technology as the Enabler in Patient Care & Patient Management	*Mr. Steve Freeborn*
6:00 - 7:00 p.m.	Cocktail, Exhibition & Poster Display	
7:00 - 11:00 p.m.	Conference Dinner	

Day 2 Sunday, 10 October 2004

Time	Program		
8:00 - 9:00 a.m.	Registration & Breakfast		
	Early Clinical Case Presentations		
8:00 - 8:30 a.m.	Case Presentation in Nutrition Support, Focusing on TPN *Dr. Lingtak Chan*		
8:30 - 9:00 a.m.	Cases in Therapeutic Monitoring of Erythropoietin Therapy *Dr. Alan Lau*		
	Concurrent Session I: Clinical Practice	**Concurrent Session II: Safe Medication Practice**	**Concurrent Session III: Technology in Practice**
9:00 - 9:05 a.m.	Welcome & Introduction	Welcome & Introduction	Welcome & Introduction
9:05 - 10:00 a.m.	*IA.* Drug-Induced Torsade de Pointes: How Does It Affect Clinical Practice? *Dr. Jerry Bauman*	*IIA.* Reporting Systems on Medication Safety - Information Sharing from the DH & HA. How Pharmacists Can Contribute to the Reporting Systems in Reducing the Risk of Medication Related Adverse Events *Mr. Clive Chan & Miss Anna Lee*	*IIIA.* Safety and Efficiency Gains in the Medication Supply Chain Using RFID and its Related Information *Dr. Michael Chua*
10:00 - 10:55 a.m.	*IB.* Practical Methods for Renal Function Assessment *Dr. Alan Lau*	*IIB.* Medication Safety - Tricks or Threats ..... How Pharmacists Can Use Human Behavior Concepts to Prevent Medication Errors in Hospitals *Mr. Michael Ling*	*IIIB..* Enhancing Patient Safety in the Prescribing Process - What are the Technical Solutions? *Mr. Steve Freeborn*
10:55 - 11:25 a.m.	Morning Tea Break, Exhibition and Poster Display		
11:25 - 12:30 p.m.	*IC.* What is Pharmacogenomics? It's All About the Genes, Silly!! *Dr. Lingtak Chan*	*IIC.* Who Will Keep the Public Healthy? *Mr. William Chui*	*IIIC.* Communicating with Our Patients - the Body Language Skills and the Human Skills *Mr. William Chau*
12:30 - 2:00 p.m.	Lunch		
	Theme Speech Session		
2:00 - 2:30 p.m.	The Pains and Gains of the First Public Private Partnership Program in Pharmacy Service - The Patients Referral Scheme on Drug Compliance and Counselling Service *Miss S C Chiang*		
	Special Plenary Session		
2:30 - 3:30 pm.	Pharmacists and Patients Getting Together - An Interview Show Panel Moderator: *Miss Scarlett Pong* Panel Members: Representatives of Public and Private Hospital Pharmacists, Community Pharmacists, Consumer Council, Patient Interest Group and Insurance Company		
3:30 - 3:50 p.m.	Patients & Pharmacists: In Sickness and In Health - Coming Together to Say "I Do!" - The Multimedia Show		
3:50 - 4:00 p.m.	Closing Remarks by Conference Vice-Chairperson - *Miss Barbara Fung*		

NEW PRODUCTS

EBIXA
(Lundbeck)

Active ingredient:
Memantine Hydrochloride

Presentation:
Available in 10 mg film-coated tablet

Pharmacological Properties:
Memantine is a voltage-dependent, moderate-affinity uncompetitive N-methyl-D-aspartate-receptor antagonist. It blocks the effects of pathologically elevated tonic levels of glutamate that may lead to neuronal dysfunction.

Indications:
Treatment of the symptoms of moderately severe to severe Alzheimer's disease.

Dosage and Administration:
Adults - The maximum daily dose is 20 mg per day. To reduce the risk of side effects the maintenance dose is achieved by upward titration 5 mg per week over the first 3 weeks as follows: Treatment should be started with 5 mg daily (half a tablet in the morning) during the 1st week. In the 2nd week 10 mg per day (half a tablet twice a day) and in the 3rd week 15 mg per day is recommended (one tablet in the morning and half a tablet in the afternoon). From the 4th week on, treatment can be continued with the recommended maintenance dose of 20 mg per day (one tablet twice a day).

Elderly - On the basis of the clinical studies the recommended dose for patients over the age of 65 years is 20 mg per day (10 mg twice a day) as described above.

Contraindication:
Hypersensitivity to the active substance or to any of the excipients.

Precautions:
As no data are available for patients with severe renal impairment (creatinine clearance less than 9 ml/min/1.73 m^2) therapy is not recommended.

Based on pharmacological considerations and single case reports, caution is recommended with patients suffering from epilepsy.

Concomitant use of N-methyl-D-aspartate(NMDA)-antagonists such as amantadine, ketamine or dextromethorphan should be avoided. These compounds act at the same receptor system as memantine, and therefore adverse drug reactions (mainly CNS-related) may be more frequent or more pronounced.

Drug Interactions:
The mode of action suggests that the effects of L-dopa, dopaminergic agonists, and anticholinergics may be enhanced by concomitant treatment with NMDA-antagonists such as memantine. The effects of barbiturates and neuroleptics may be reduced. Concomitant administration of memantine with the antispasmodic agents, dantrolene or baclofen, can modify their effects and a dosage adjustment may be necessary.

Concomitant use of memantine and amantadine should be avoided, owing to the risk of pharmacotoxic psychosis. Both compounds are chemically related NMDA-antagonists.

Side Effects:
Common adverse reactions (1 - 10% and more frequent than with placebo) for memantine and placebo patients respectively were: hallucinations (2.0 vs. 0.7%), confusion (1.3 vs. 0.3%), dizziness (1.7 vs. 1.0%), headache (1.7 vs. 1.4%) and tiredness (1.0 vs. 0.3%).

Uncommon adverse reactions (0.1 - 1% and more frequent than with placebo) were anxiety, hypertonia (increased muscle tone), vomiting, cystitis and increased libido.

Forensic Classification:
P1S1S3

HUMIRA
(Abbott)

Active Ingredient:
Adalimumab

Presentation:
40mg solution for injection in pre-filled syringe

Pharmacological Properties:
HUMIRA (adalimumab) is a recombinant human immunoglobulin (IgG1) monoclonal antibody containing only human peptide sequences.

Adalimumab binds specifically to TNF and neutralizes the biological function of TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors. TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Elevated levels of TNF are found in the synovial fluid of rheumatoid arthritis (RA) patients and play an important role in both the pathologic inflammation and the joint destruction that are hallmarks of RA.

Adalimumab also modulates biological responses that are induced or regulated by TNF, including changes in the levels of adhesion molecules responsible for leukocyte migration.

Indications:
HUMIRA is indicated for reducing signs and symptoms and inhibiting the progression of structural damage in adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more DMARDs.

HUMIRA can be used alone or in combination with methotrexate or other DMARDs.

Dosage and Administration:
The recommended dose of HUMIRA for adult patients with rheumatoid arthritis is 40 mg administered every other week as a single dose via subcutaneous injection. Methotrexate, glucocorticoids, salicylates, nonsteroidal anti-inflammatory drugs, analgesics or other DMARDs may be continued during treatment with HUMIRA.

Some patients not taking concomitant METHOTREXATE may derive additional benefit from increasing the dosing frequency of HUMIRA to 40 mg every week. (optional)

Contraindications:
HUMIRA should not be administered to patients with known hypersensitivity to HUMIRA or any of its excipients.

Precautions:
Infections - Serious infections, and sepsis, including fatalities, have been reported with the use of TNF antagonists. Treatment with HUMIRA should not be initiated in patients with active infections including chronic or localized infections until infections are controlled.

Patients who develop a new infection while undergoing treatment with HUMIRA should be monitored closely. Administration of HUMIRA should be discontinued if a patient develops a new serious infection until infections are controlled.

Neurologic Events - TNF antagonists, including HUMIRA, have been associated in rare cases with exacerbation of clinical symptoms and/or radiographic evidence of demyelinating disease.

Tuberculosis - As observed with other TNF-antagonists, tuberculosis associated with administration of HUMIRA in clinical trials has been reported. Before initiation of therapy with HUMIRA, all patients should be evaluated for both active or inactive (latent) tuberculosis infection. This evaluation should include a detailed medical history with possible previous exposure to patients with active tuberculosis and previous and/or current immunosuppressive therapy. Appropriate screening tests (e.g., chest x-ray or tuberculin test) should be performed in accordance with local recommendations. If active tuberculosis is diagnosed, HUMIRA therapy must not be initiated. If latent tuberculosis is diagnosed, appropriate anti-tuberculosis prophylaxis in accordance with local recommendations should be initiated before starting treatment with HUMIRA.

Patients should be instructed to seek medical advice if signs/symptoms (e.g., persistent cough, wasting/weight loss, low grade fever) suggestive of a tuberculosis infection occur.

Concurrent vaccination - Since no data are available, concurrent administration of live vaccines and HUMIRA is not recommended.

Drug Interactions:
HUMIRA has been studied in RA patients taking concomitant methotrexate. The data do not suggest the need for dose adjustment of either HUMIRA or methotrexate.

Interactions between HUMIRA and drugs other than methotrexate have not been evaluated in formal pharmacokinetic studies. In clinical trials, no interactions have been observed when HUMIRA was administered with commonly used DMARDs (sulfasalazine, hydrochloroquine, leflunomide and parenteral gold), glucocorticoids, salicylates, nonsteroidal anti-inflammatory drugs or analgesics.

Side Effects:
Infections - In placebo-controlled trials, the rate of infection was 1 per patient year in the HUMIRA treated patients and 0.9 per patient year in the placebo-treated patients. The incidence of serious infections was 0.04 per patient year in HUMIRA treated patients and 0.02 per patient year in placebo-treated patients. The infections consisted primarily of upper respiratory tract infections, bronchitis and urinary tract infections. Most patients continued on HUMIRA after the infection resolved.

Autoantibodies - Patients had serum samples tested for autoantibodies at multiple time points. In the adequate and well-controlled trials, 12.6% of patients treated with HUMIRA and 7.3% of placebo-treated patients that had negative baseline anti-nuclear antibody titers reported positive titers at week 24. One patient out of 2334 treated with HUMIRA developed clinical signs suggestive of new-onset lupus-like syndrome. The patient improved following discontinuation of therapy. No patients developed lupus nephritis or central nervous system symptoms. The impact of long-term treatment with HUMIRA on the development of autoimmune diseases is unknown.

Other adverse events -
Body as a whole: asthenia, clinical flare reaction, flu syndrome, abdominal pain
Hemic and Lymphatic system: decreased hemoglobin
Metabolic and Nutritional Disorders: hyperlipidemia
Nervous System: headache, dizziness
Respiratory System: upper respiratory infection, rhinitis, sinusitis, bronchitis, cough increased, pneumonia
Digestive System: nausea, diarrhea, sore throat
Skin and Appendages: rash, pruritis, herpes simplex, skin disorder, herpes zoster
Urogenital System: urinary tract infection
Injection Site Reaction: injection site pain, injection site reaction, injection site hemorrhage, injection site eruption

Forensic Classification:
P1S1S3

REMICADE
(Janssen)

Active ingredient:
Infliximab

Presentation:
100 mg infliximab available in a 20mL single-use vial

Pharmacological Properties:
Elevated concentrations of TNF α have been found in trheumatoid arthritis and Crohn's disease patients and correlate with elevated disease activity. Infliximab neutralizes the biological activity of TNF(by binding with high affinity to the soluble and transmembrane forms of TNFα and inhibits binding of TNFα with its receptors.

Infliximab inhibits the functional activity of TNFα in a wide variety of *in vitro* bioassays utilizing human fibroblasts, endothelial cells, neutrophils, B and T lymphocytes and epithelial cells. Anti-TNFα antibodies reduce disease activity in the cotton-top tamarin colitis model, and decrease synovitis and joint erosions in a murine model of collagen-induced arthritis.

Indications:

Rheumatoid Arthritis - REMICADE, in combination with methotrexate, is indicated for reducing signs and symptoms, inhibiting the progression of structural damage and improving physical function in patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to methotrexate.

Crohn's Disease - REMICADE is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy.

REMICADE is indicated for the reduction in the number of draining enterocutaneous fistulas in patients with fistulizing Crohn's disease.

Ankylosing spondylitis - Remicade is indicated for treatment of ankylosing spondylitis, in patients who have severe axial symptoms, elevated serological markers of inflammatory activity and who have responded inadequately to conventional therapy.

Dosage and Administration:
Rheumatoid Arthritis - The recommended dose of REMICADE is 3 mg/kg given as an intravenous infusion followed with additional similar doses at 2 and 6 weeks after the first infusion then every 8 weeks thereafter. REMICADE should be given in combination with methotrexate. For patients who have an incomplete response, consideration may be given to adjusting the dose up to 10 mg/kg or treating as often as every 4 weeks.

Crohn's Disease - The recommended dose of REMICADE is 5 mg/kg given as an induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter for the treatment of moderately to severely active Crohn's disease. For patients who respond and then lose their response, consideration may be given to treatment with 10 mg/kg. Patients who do not respond by week 14 are unlikely to respond with continued dosing and consideration should be given to discontinue REMICADE in these patients.

In patients with fistulizing disease, an initial 5 mg/kg dose should be followed by additional 5 mg/kg doses at 2 and 6 weeks after the first infusion.

Ankylosing spondylitis - The recommended dose of REMICADE is 5 mg/kg given as an intravenous infusion over a 2-hour period followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 6 to 8 weeks. If a patient does not respond by 6 weeks (i.e. after 2 doses), no additional treatment with infliximab should be provided.

Contraindications:
REMICADE is contraindicated in patients with moderate or severe (NYHA Class III/IV) congestive heart failure.

REMICADE should not be administered to patients with known hypersensitivity to any murine proteins or other component of the product.

Precautions:
Tuberculosis (frequently disseminated or extrapulmonary at clinical presentation), invasive fungal infections, and other opportunistic infections, have been observed in patients receiving REMICADE.

Patients should be evaluated for latent tuberculosis infection with a tuberculin skin test. Treatment of latent tuberculosis infection should be initiated prior to therapy with REMICADE.

REMICADE should not be given to patients with a clinically important, active infection.

Doses greater than 5 mg/kg should not be administered to patients with congestive heart failure. Patients should be closely monitored, and REMICADE must not be continued in patients who develop new or worsening symptoms of heart failure.

The safety and efficacy of therapy for fistulizing Crohn's disease continued beyond 3 doses have not been established.

Since no data are available on the response to vaccination, it is recommended that live vaccines not be given concurrently.

Drug Interactions:
Specific drug interaction studies, including interactions with methotrexate, have not been conducted. The majority of patients in rheumatoid arthritis or Crohn's disease clinical studies received one or more concomitant medications. In rheumatoid arthritis, concomitant medications besides methotrexate were nonsteroidal anti-inflammatory agents, folic acid, corticosteroids and/or narcotics. Concomitant Crohn's disease medications were antibiotics, antivirals, corticosteroids, 6-MP/AZA and aminosalicylates. Patients with Crohn's disease who received immunosuppressants tended to experience fewer infusion reactions compared to patients on no immunosuppressants.

Serum infliximab concentrations appeared to be unaffected by baseline use of medications for the treatment of Crohn's disease including corticosteroids, antibiotics (metronidazole or ciprofloxacin) and aminosalicylates.

Side Effects:
Acute infusion reactions - Approximately 20% of REMICADE-treated patients in all clinical studies experienced an infusion reaction compared to approximately 10% of placebo-treated patients.

Infections - In REMICADE clinical studies, treated infections were reported in 35% of REMICADE-treated patients and in 26% of placebo-treated patients. When longer observation of patients on REMICADE was accounted for, the event rate was similar for both groups.

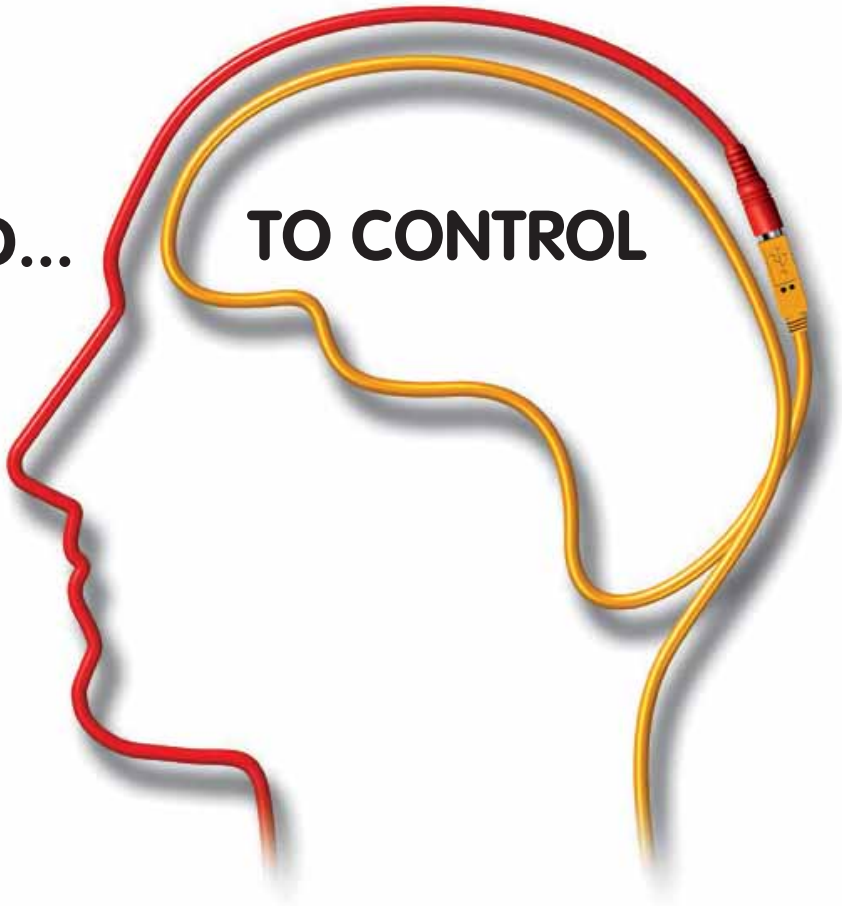
Autoantibodies/Lupus-like Syndrome - Approximately 52% of 1261 infliximab-treated patients in clinical trials who were antinuclear antibody (ANA) negative at baseline developed a positive ANA during the trial compared with approximately 19% of 129 placebo-treated patients.

Other adverse events (occurring in 5% or more of patients receiving 4 or more infusions for rheumatoid arthritis) -
Body as a whole: fatigue
Respiratory: upper respiratory tract infection, pharyngitis, sinusitis
Skin and appendage disorders: rash, pruritis
Resistance mechanism disorders: fever, abscess, moniliasis
Central and peripheral nervious system disorders: headache
Musculoskeletal system disorders: arthralgia, back pain
Psychiatric disorders: insomnia, depression
Cardiovascular disorders: hypertension

Forensic Classification:
P1S1S3

NEW ADJUNCTIVE THERAPY FOR PARTIAL SEIZURES IN ADULTS

FROM UNCONTROLLED...



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- Highly effective: up to 4 out of 10 refractory patients had 50% partial seizure reduction
- Remarkably well tolerated with mild side effects
- No known drug/drug interactions; an effective initial dosage (500 mg bid)

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SIMPLIFYING SEIZURE CONTROL

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