Message from President

This is the 3rd issue of the Society's Newsletter. I would like to thank all writers who have contributed to the Newsletter, in particular, Dr. Jak-Yiu Lai, Dr. Ming-Leung Szeto and Dr. Yiu-Wing Luk. Dr. Lai and Dr. Szeto have shared with us the Treatment on Chronic Hepatitis B and Dr. Luk Scientific Highlights at UEGW.

The Annual Scientific Meeting has been scheduled to be held on September 2, 2000. The Meeting was jointly organised by the Hong Kong Society of Digestive Endoscopy and the Hong Kong Society for Coloproctology. The Society has received favourable responses for last year's meeting. I would like to hereby congratulate the Organising Committee on the organisation of the meeting last year. This time the Society has Dr. Francis K.L. Chan to be the co-ordinator. Dr. Chan is working hard on it and I believe this coming meeting will bring new ideas to our members. I hope that our members will give their support to this meeting again.

Our research project on "Colorectal Screening" is underway and a curriculum in gastroenterology update is organised by Dr. Francis Chan. I would like to hereby extend my gratitude to Dr. Chan. I hope that the curriculum will be in harmony with the theme of continuing education in the Specialty of Gastroenterology and Hepatology of Hong Kong College of Physicians.

REPORT AND SCIENTIFIC HIGHLIGHTS AT THE 7TH UNITED EUROPEAN GASTROENTEROLOGY WEEK (UEGW)

Rome, Italy, 13-17 November 1999

Dr. Yiu-Wing Luk
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Being the last gastroenterology congress to the millennium, the meeting provided a lot of opportunities to gain current perspectives on priorities and advances in various fields of gastroenterology. With rapid development in the field of media technology, extensive use of the electronic media becomes the hallmark of all conferences held at the turn of the century. In fact, the scientific proceedings of this year's UEGW is now on-line, one can visit the official website at www.uegw.org/uegw99/ to have a glance through all the presentations and poster abstracts.

Colorectal Cancer Screening

Colorectal cancer (CRC) screening is a hot topic in last few years and certainly be one of the major components in health care policy making for the developed countries in the next millennium. It will continue to be a "must" topic in all near-future gastroenterology congresses.
Flexible sigmoidoscopy

This year in Rome, the preliminary result of the first prospective randomised controlled trial of flexible sigmoidoscopy in CRC screening, collaborated by the UK and Italy was presented. The baseline results of the UK randomised trial of ‘once-only’ flexible sigmoidoscopy screening were presented by the MRC Flexi-Scope Trial Investigators Group. The recruitment and screening have been completed. Flexible sigmoidoscopy (FS) alone was used as CRC screening strategy in the ‘average-risk’ individuals - asymptomatic men and women aged 55-64 years. Over 190,000 (55%) of the mailed individuals showed an interest in having a FS screen. A fairly satisfactory proportion (71%) of the invited subjects attended the screening. A total of 40,520 sigmoidoscopies were done in 14 centres and complete examination to the distal descending colon was achieved in 85%. The prevalence of adenomas and cancers were respectively 12% and 0.3%. ‘High risk’ adenomas ≥3 in number, size ≥1cm, villous histology or severe dysplasia) were detected in 2089 (5%), all of whom were referred for a total colonic examination with colonoscopy. With 1966 colonoscopies performed so far, proximal adenomas were found in 19% and proximal cancers in 0.3% (6 cases). Six perforations were noted, 1 in 40,520 FS (0.003%) and 5 in 1966 colonoscopies (0.25%). There were 4 procedure-related deaths, all following surgery. As a collaborative study with the Italian, the recruitment in Italy was complete, however, the screening has not been finished. Similar screening flexible sigmoidoscopy trial was undertaken in Norway - Telermark Polyp Study no.1 (TPS-1) with a high subject compliance rate also. These results suggested that FS alone in CRC screening for average-risk individuals is logistically feasible, acceptable to the population and relatively safe in the studied countries and settings. Follow-up reports of these studies with respect to the effectiveness, safety and cost, are necessary to show FS alone in CRC screening for average-risk population as a cost-effective mean of reducing CRC incidence and CRC-related mortality.

Obstacles for implementing CRC screening

In countries with high CRC prevalence, lack of physician participation was noted to be one major obstacle to CRC screening program even in areas with adequate supporting endoscopy services. One recent survey in the Eastern Switzerland with respect to the general practitioners’ compliance to the WHO CRC screening guideline for the average-risk population found that only 0.9% adhered strictly to the guideline. Twenty-two percent of the general practitioners did faecal occult blood tests (FOBT) occasionally to their regular patients with age above 50. Similarly, a report from Israel also indicated that the lack of physician’s support to refer subjects with family history of CRC for screening. Undoubtedly, updating the primary care doctor’s knowledge and with their support is crucial for the successful implementation of CRC screening program in the community.

Post-polypectomy surveillance

Concerning the issue of post-polypectomy surveillance intervals, the long term data of the US National Polyp Study (NPS) was presented. Surveillance colonoscopy were done either at 1, 3 and 6 years or (3 and 6 years) after the complete removal of the newly-diagnosed polyp(s). Adenomas with advanced pathology (AAP) - adenoma ≥1cm, high-grade dysplasia, or invasive cancer, were the colonoscopic end-point. Of more than 900 patients with 1 or more surveillance colonoscopies, 8% had AAP detected by 6 years followed. The high risk subgroups ≥3 adenomas at initial examination or diagnosed at age>60 and with a parent with CRC) were 6 times more likely to have an AAP detected than those without these risk factors. The study panel led by Professor Sidney Winawer recommended that these high risk adenoma patients should have follow-up surveillance colonoscopy at 3-year intervals whereas patients without these characteristics (70% of sporadic adenoma cases in their study) could have surveillance colonoscopy deferred for at least 6 years.

Digestive Endoscopy

Further development of gastrointestinal endoscopy at the dawn of the new millennium should be based on upgrading the endoscopic technology, preventing or minimising complications and focusing on outcome research.

Optical coherence tomography

The group from Harvard Medical School reported the early experience of an evolving endoscopic technology - optical coherence tomography (OCT) in gastrointestinal diseases, which is a new optical technique which obtains cross-sectional images with the highest tissue resolution (10μm) currently achieved (penetration depth: 2mm). OCT operates in a manner analogous to ultrasound imaging but uses light waves instead of sound. It has been tried for in vivo tissue imaging in the gastrointestinal tract and enabled visualisation of tissue structures at a resolution approaching that of the conventional histopathology (i.e., tissue diagnosis). Its potential uses include the surveillance for dysplasia, for example, Barrett’s oesophagus. The beauty of this technique is that the device functions via the working channel of conventional gastrointestinal endoscopes. The prototype device costs about US$100,000 at the start. Further studies are needed in validating the applicability as well as the cost-effectiveness in various gastrointestinal diseases before its clinical implementation can be ascertained.

Prevention of ERCP-related pancreatitis

With respect to ways preventing endoscopy-related complications, Deviere, et al. from Belgium reported the result of a prospective double blind randomised trial of prophylactic administration of intravenous interleukin 10 (IL-10) for the prevention of ERCP-related pancreatitis. A single bolus injection of IL-10 was given half an hour before the procedure. More than 40 patients were recruited in each group. The results showed a significant reduction in the occurrence of clinical post-ERCP pancreatitis in the treated groups. Further studies are necessary to confirm this single centre experience before this prophylactic treatment can be recommended for clinical use.

Biotherapeutic Agents

Probiotics are live microbial products which can be used to replenish suppressed bacteria and inhibit pathogenic bacterial growth. Besides its potential uses in paediatric gastroenterology, there were studies aiming at expanding its indications in adult gastroenterology. There were two reports from Italy, one from Bologna, in which anti-inflammatory cytokine tissue levels were found to be increased with a corresponding decrease in the pro-inflammatory cytokine tissue levels during probiotic treatment as maintenance therapy in pouchitis. This sounds as an immunopathological explanation for the usefulness of this treatment in pouchitis. Another study from Rome found that Lactobacillus GG administration did decrease the antibiotic-associated gastrointestinal side effects especially in reducing episodes of belching and diarrhoea during Helicobacter pylori eradication regimen. Nevertheless, before recommending biotherapeutics in clinical practice, additional studies on their bioactive properties and safety are definitely mandatory.
Update on Treatment of Chronic Hepatitis B

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Introduction
Current therapy of chronic hepatitis B (CHB) is based on the understanding of the natural history of CHB, the viral replication cycle of hepatitis B virus (HBV) and the viral dynamics of HBV infection. The available therapies include immunomodulators, viral suppressors and their potential combinations.

Natural history of chronic hepatitis B
HBV infection acquired early in life results in active viral replication with minimal liver damage, a phase of immune tolerance. Immune elimination of HBV generally occurs spontaneously in the second to fourth decade of life. It is produced by a cell-mediated immune response to HBV epitopes, particularly core proteins such as HBeAg. It results in cytolysis of infected hepatocytes. This immune clearance phase is associated with decreasing viral load, elevation of serum alanine aminotransferase (ALT) and necroinflammatory disease in the liver. The majority of patients eventually clear HBeAg from the serum and enter the chronic carrier state or quiescent phase with persistent HBsAg in serum, cessation of viral replication and normal serum ALT. This spontaneous HBeAg seroconversion occurs in 10 - 15% of patients under observation for various treatment trials and must be considered in assessing the efficacy of any therapy claimed to be useful.

A subgroup of patients in immune clearance phase has more overt episodes of serum ALT elevations associated with clinical symptoms. When prolonged, they have increased risk of cirrhosis, liver failure and hepatocellular carcinoma. Another subset of patients has a point mutation in the precore region of HBV genome which prevents synthesis of HBeAg. This precore mutant form of HBV is usually associated with continued viral replication, elevated serum ALT despite HBeAg negativity, more rapid progression to cirrhosis and adverse clinical outcomes.

Replication cycle of HBV
The replication of HBV in hepatocytes has a reverse transcription process (RNA to DNA instead of DNA to RNA) similar to that of retroviruses. The HBV DNA polymerase serves as a reverse transcriptase in the synthesis of viral DNA from a pre-genomic DNA template. Following infection of a hepatocyte, the HBV genome enters the nucleus and is converted to covalently closed circular DNA (ccc DNA). Transcription of ccc DNA yields an RNA intermediate which moves to the cytoplasm where the viral DNA polymerase acting as a reverse transcriptase, catalyses the synthesis of a new relaxed circular DNA.

Viral dynamics model
Once HBV infects a hepatocyte, some viral DNA is retained in the nucleus as ccc DNA and becomes associated with nucleosomes. Reverse transcriptase inhibitors have no activity against ccc DNA. ccc DNA can gradually be lost through natural hepatocyte division and cell death. ccc DNA does not appear to transmit into new hepatocytes. Mathematical modelling\(^1\) has demonstrated that the half life of the HBV in peripheral blood is less than 24 hours, but the half life of HBV infected cell ranges from 10 to 100 days depending on the inflammatory activity in the liver. Protracted half life of the virus infected cell suggests that even when viral suppressive therapy is 100% effective in inhibition of viral replication, eradication can take between one and ten years. When viral suppressive therapy is less than 100% effective, such protracted periods of treatment with single inhibitor often result in the emergence of resistant variants.

Aim of therapy
The main aim is to suppress HBV replication before there is significant irreversible liver disease. It is generally believed that sustained resolution of necroinflammatory activity will reduce the risk of developing cirrhosis and hepatocellular carcinoma. Response in most therapies is defined serologically as sustained clearance of HBeAg (for wild type HBV) and serum HBV-DNA by hybridization assay, and clinically as improvement in liver disease evidenced by normalization of serum ALT and reduction of necroinflammation in liver biopsies.

Immunomodulatory therapy
Interferon
Interferons (IFN) are proteins secreted by cells in response to viral and other stimuli. They have anti-proliferative and immunomodulatory effects. Interferon is the first approved treatment for chronic hepatitis B.

A meta-analysis of 15 randomized, controlled trials involving 837 patients has confirmed the efficacy of IFN\(^2\). IFN at doses of 5 - 10 MU 3 times weekly for 3 to 6 months was associated with significantly greater loss of HBV-DNA (37% vs 17%, \(p = 0.0001\)), loss of HBeAg (33% vs 12%, \(p = 0.0001\)) and loss of HBsAg (7.8% vs 1.8%, \(p = 0.001\)) in treated patients compared with controls. Long term follow up of patients suggests that remission is maintained in the majority of patients initially responsive to IFN treatment. Long term beneficial effects in terms of reduction of hepatocellular carcinoma and prolonging survival have been reported\(^3\).

Treatment with IFN is recommended for patients with persistent elevations in serum ALT, positive serum HBeAg (wild-type HBV), positive HBV-DNA by hybridization, chronic hepatitis on liver biopsy, and compensated liver disease. Because exacerbation of liver disease may occur with IFN, treatment of marginally compensated patients should be undertaken with caution.

The recommended regimen is 5 MU daily or 10 MU 3 times a week subcutaneously for 4 to 6 months. Predictive factors of favourable response include low pre-therapy HBV-DNA levels (< 200 pg/ml), high pre-therapy ALT levels (> 100 IU/ml), short duration of infection, acquisition of disease in adulthood, active histologic profile, and absence of immunosuppression or human immunodeficiency virus (HIV) infection.

The commonest side effect of IFN is flu-like symptoms especially on initiation of therapy. Other side effects include fatigue, anorexia, weight loss, bone marrow suppression, hair loss, emotional liability and depression, thyroid dysfunction, induction of auto-antibodies and enhancement of autoimmune disease.

Thymosin,
Thymosin, (T\(\alpha\)), a 28 amino acid thymic peptide, is an immune modifier that has been shown to trigger maturational events in lymphocytes, to augment T cell function, and to promote reconstitution of immune defects. It is currently registered for the treatment of chronic hepatitis B in many Asian countries, Italy, but not Hong Kong and North America.

In a phase III, multi-centre, randomized, placebo-controlled, double-blind study in the United States involving 99 patients, T\(\alpha\), at the dose
of 1.6 mg subcutaneously 2 times a week for 6 months was compared with placebo. Results have suggested a trend in favour of Tα, but have not reached statistical significance.

Subsequently in a randomized, placebo-controlled trial conducted in Taiwan involving 98 patients, complete virological response was significantly higher in Tα group than placebo group (41% vs 9%, p = 0.004) 18 months after entry, although complete response rates were similar at the end of treatment.

The recommended regimen of Tα is 1.6 mg subcutaneously twice a week for 6 months. The available data suggest a delayed response to Tα, therapy and therapy is free from side effects. While the immunostimulatory effect was comparable to IFNα, Tα is free from side effects in contrast to IFNα. Further small studies in China showed that Tα is safe even in patients with decompensated liver function.

**Corticosteroid withdrawal**

The withdrawal of corticosteroid in patients with CHB frequently results in an acute hepatitis-like elevation of serum ALT levels and a transient decline in HBV-DNA levels, representing an immunologic rebound directed at HBV infected hepatocytes. Corticosteroid withdrawal has no role as a primary therapy. There are several randomized controlled trials of prednisolone or prednisolone withdrawal followed by IFN. The results suggest that corticosteroid priming tends to increase the efficacy of IFN therapy in patients with low abnormal ALT levels. However, it may induce a severe or even fatal reactivation of the hepatic process in patients with cirrhosis. A recent case report of dramatic response to lamivudine therapy following corticosteroid priming in CHB may rekindle interest in this immunomodulatory therapy.

**Viral suppressive therapy**

Four agents in this group were found to have activity against HBV in vitro and in vivo. They include nucleoside analogues lamivudine, famciclovir, lobucavir and nucleoside analogue adeovir dipivoxil. They inhibit the reverse transcription process by incorporating into the growing DNA chain and virus replication is thus terminated.

**Lamivudine**

Lamivudine is the (-)-enantiomer of 3-thiacytidine. It is well absorbed orally and side effects are uncommon. Lamivudine is the first nucleoside analogue approved for treatment of CHB.

In the Asian multi-centre randomized controlled trial of prolonged lamivudine therapy for CHB, 358 Chinese patients with HBeAg positive CHB were randomized to 100 mg daily, 25 mg daily or placebo for one year. Lamivudine 100 mg daily was associated with substantial improvement in necroinflammatory activity, reduced progression to fibrosis, the highest rate of HBeAg seroconversion (16%), the greatest suppression of HBV-DNA (98%) and the highest rate of sustained normalization of ALT level (72%). Further analysis of the same study has shown that patients with a pre-therapy ALT level of more than 5 times upper limit of normal (ULN) have a much higher HBeAg seroconversion rate compared with patients with a pre-therapy ALT level of less than 2 times ULN (64% vs 5%, p < 0.001) 11.

In a multi-centre placebo-controlled, double-blind study of 124 patients from Mediterranean Europe with pre-core mutant variant CHB, the response to lamivudine 100 mg daily in HBeAg-negative patients is similar to the response reported in studies on HBeAg positive patients.

Lamivudine is strongly recommended before and after liver transplantation for CHB. It is advisable as pre-emptive therapy in CHB patients before immunosuppression for other illness, to treat flare-up of CHB in the immunocompromised. It is also advisable for CHB with multiple flare-ups, with progressive deterioration in liver function tests or with early cirrhosis and significant hepatic activity. Indication is uncertain for patients with mildly abnormal ALT, patients with cirrhosis without hepatic activity or patients with advanced cirrhosis. Lamivudine is not indicated for CHB patients with normal ALT 13.

Lamivudine may have to be given on a long term basis until HBeAg seroconversion is sustained for over 2 months. More recent data show that HBeAg seroconversion rate at 2 years increases to 27%, and at 3 years increases to 40%. Those who do not seroconvert tend to relapse when therapy is discontinued. In those who seroconvert, the seroconversion appears to be durable.

The main concern with prolonged treatment is the development of drug resistance. The resistance is associated with specific mutation in the YMDD (tyrosine-methionine-aspartate-aspartate) motif in the DNA polymerase gene. Mutation of the methionine to either valine (YMDD) or isoleucine (YIDD) will result in reduction in the action of lamivudine. The YMDD mutants begin to appear after 8 to 9 months of therapy, occur in 14% of patients after 1 year, 38% after 2 years and 49% after 3 years 14. The mutant virus has reduced replication competence, but rebound in ALT levels sometimes occurs and serious morbidity and occasional mortality have been reported. HBeAg seroconversion can occur in patients with YMDD variant HBV 15. The long term clinical effects of YMDD variant is unknown.

**Famiclovir**

Long term therapy with Famiclovir 500 mg 3 times daily for 1 year in multi-centre Asian and Caucasian studies failed to demonstrate clinical benefit in chronic hepatitis B.

**Lobucavir**

Trials of lobucavir for chronic hepatitis B have been terminated after findings of possible drug-related tumours in rodent studies.

**Adefovir dipivoxil**

It is a nucleotide analogue with potent inhibition of HBV-DNA replication and has activity against lamivudine resistant mutants. Nephrotoxicity was observed in HIV patients using 80 - 120 mg daily. Use of lower dose for chronic hepatitis B is being investigated.

**Future direction**

Monotherapy with nucleoside analogue suppresses viral replication only, but does not eradicate the ccc DNA in infected hepatocytes. It is unlikely to be curative in many patients. Experience with HIV has shown that combination therapy produces improved viral suppression and dramatic clinical responses. Treatment of CHB appears to be heading in the same direction. Lamivudine may play a key role in these combinations.

Observations of much better HBeAg seroconversion rate in patients with elevated ALT is evidence that an adequate host immune response to HBV is a prerequisite for complete viral clearance by viral suppressive therapy. This host response may be inherent by appropriate selection of patients with high ALT levels, or induced by suitable addition of an immunomodulatory agent.

Although two international multi-centre trials have not shown significantly improved responses with a combination of lamivudine and interferon, they have been criticized for design faults, and they do not necessarily predict results with other modes of combination.

Clinical trials in the near future should include regimens of 2 or more nucleoside analogues, 2 immunomodulatory entires, or a nucleoside analogue plus an immunomodulatory agent.
References


SCIENTIFIC UPDATES

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Update on Management of Irritable Bowel Syndrome (IBS)

Introduction
Irritable bowel syndrome (IBS) is a common disorder characterised by abdominal pain associated with abnormal bowel movement without any identifiable structural or biochemical abnormality. Many patients have mild symptoms on an intermittent basis and neither request nor need drug treatment, while others can be incapacitated with persistent symptoms and seek medical advice with a view to permanent cure. The conventional approach to the management of these patients is summarised in Table 1.

Table 1. Conventional approach to the management of IBS patients

<table>
<thead>
<tr>
<th>1. General measures</th>
<th>2. Exclusion diet</th>
<th>3. Soluble fibre supplement</th>
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<tbody>
<tr>
<td>Explanation of mechanisms of symptom production, reassurance</td>
<td>dairy products, coffee</td>
<td>4. Antidiarrhoeal agents, e.g. loperamide</td>
</tr>
<tr>
<td>5. Antispasmodic agents, e.g. mebeverine, oxiclonton bromide</td>
<td>6. Cortical therapy, e.g. tricyclic antidepressants, hypnotherapy</td>
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Despite multiple tiers of treatment, there remains patients who are disappointed and the search for a magic bullet continues.
New insights in pathophysiology

The past several years have seen a surge in activities aiming at better understanding and more effective treatment for IBS. Classical aetiologies have implicated psychosocial factors and abnormalities in gastrointestinal motility. The prevailing approach to resolve pain has focussed on restoration of normal motility patterns using anti-spasmodics, bulk forming agents and prokinetic agents. The new model is based on a more comprehensive approach encompassing alterations within the central nervous system to manifest as altered neuroendocrine responses to stress, altered autonomic input to the gut and alterations in the central processing or modulations of visceral sensory information. The emerging model can explain alterations in bowel habits (autonomic dysregulation), abdominal pain (enhanced visceral sensitivity) and a variety of constitutional symptoms (e.g. malaise). Over the last decade, the role of enhanced visceral sensitivity in the pathophysiology of irritable bowel syndrome has been largely recognised. Ritchie(1) was the first to show that IBS patients reported pain at a lower volume when a balloon was inflated in the lumen of the bowel as compared with normal control. New insights were obtained in human digestive sensitivity since electronic barostats had been used for distension studies. These barostats could measure the pressure and volume inside the distending device producing discomfort, pain or symptoms such as bloating or rectal urgency. In about 20 human studies comparing healthy controls with IBS patients, about two thirds of the patients exhibited a 20%-25% lower pain threshold to colonic distension.

Neurotransmitters involved in visceral sensation

The neuro-anatomical pathways and neurotransmitters involved in visceral sensation have been studied extensively in animal studies. These studies have highlighted the role of afferent pathways arising from the gut as a possible target for new treatments intended to relieve pain or modify altered reflexes present in these patients. These pharmacological targets have been identified mainly in animal models of visceral hyperalgesia of various origins including local inflammation. Locally several mediators are of paramount importance for sensitization of nerve endings: 5-hydroxytryptamine, bradykinin, tachykinins, calcitonin gene related peptide, and neurotrophins. Other substances like somatostatin, opioid peptides, cholecystokinin, oxytocin and adrenaline modulate the transmission of nociceptive inputs from the gut to the brain and are of great clinical interest.(2)

New treatment

5-Hydroxytryptamine -3 (5-HT3) antagonists

The effects of 5-HT3 antagonists on sensitivity of the lower gut have been extensively investigated. An initial report showed that granisetron reduced sensitivity to colonic distension in patients with diarrhoea predominant IBS(3). On the contrary, ondansetron did not modify sensitivity to rectal distension in this group of patients (4) suggesting that there were subtypes of 5-HT3 antagonists and not everyone worked similarly. Recently, alosetron (5) has been shown to modify perception of colonic distension in patients with IBS. This action was associated with an increased tolerance to volume because the volume of the distending bag was significantly increased on treatment. However the benefit of this group of drugs in treating IBS patients have not been evaluated in large trials. Recently, Mangel (6) conducted a double blind placebo controlled trial on 370 IBS patients using alosetron of different dosages over a period of 12 weeks. They assessed the patients weekly by asking the question "is the pain and discomfort adequately relieved?". The answer was either yes or no. A positive response was defined as "yes" as the answer in at least 6 out of 12 weekly assessment. At the end of the trial, there was significant improvement in the treatment group as compared with the placebo group.

Opioid agonists

Kappa receptor agonists are thought to act on peripheral kappa receptors and are free of the undesirable effects of morphine but they have no effect on GI motility. A double blind placebo controlled trial has shown that fedotizine (7) was superior to placebo in relieving abdominal pain and bloating in IBS patients over a 6 week period. Although the assessment of bowel function appeared to be inadequate in the study, there was no obvious change in bowel frequency and consistency.

Herbal medicine

Bensoussan et al from Australia (8) had compared standard traditional Chinese herbal medicine, individualised Chinese herbal medicine and placebo in 116 IBS patients over a period of 16 weeks. Total bowel symptom scores and global improvement scores were compared at the end of treatment. Both standard traditional Chinese herbal medicine and individualised Chinese herbal medicine groups had statistically significant improvement in both scores as compared to placebo group.

Conclusions

New concepts basing on abnormalities in the central and autonomic nervous system and visceral hypersensitivity have been developed to explain the pathophysiology of IBS. Advances in the understanding of neurotransmitters involved in visceral sensation have led to the development of new drugs like 5-HT3 antagonists and opioid agonists. More clinical trials are needed to assess the efficacy of these new agents before their role in the treatment of IBS can be established.

References:

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3. Prior A, Read NW. Reduction of rectal sensitivity and post-prandial motility by granisetron, 5-HT3 receptor antagonist, in patients with IBS. Aliment Pharmacol Ther 1993;175-180
Endoscopic Management of Bleeding Peptic Ulcer

Endoscopic hemostasis is a major therapeutic advance in the management of bleeding peptic ulcer disease. In the past decade, a substantial number of reports have documented the efficacy of various endoscopic modalities in controlling peptic ulcer bleeding. These modalities include injection therapy using different agents and thermal methods (laser photoagulation or contact thermal devices). Recently argon beam coagulator is becoming available as a non-contact thermal device. In individual randomized studies with small patient numbers, these methods generally improved patients' outcome most notably in reducing the need for emergent surgery. Meta-analyses of pooled data from these studies demonstrated a reduction in mortality (1,2).

A recent National United Kingdom audit revealed a dramatic increase in the proportion of elderly patients with the condition when compared to historic published series (3). In 1940s compared to 68 per cent in 1990s (3). Endoscopic hemostasis is particularly relevant in an aging population with bleeding peptic ulcer.

Injection therapy appeals to many endoscopists for its simplicity. Among the agents used for injection therapy, we recommend the use of dilute epinephrine (1:10,000 or 1:100,000). It is non-tissue damaging and due to its rapid first pass metabolism by the liver, volume of up to 20 ml can be injected with little systemic effect. This is an important advantage as one of the principal modes of action is submucosal volume tamponade. Unfortunately it does not induce vessel thrombosis. Recurrent bleeding following epinephrine injection alone occurs in 15 to 25 per cent of cases. In the past decade, research efforts have been directed at improving permanent hemostasis following epinephrine injection.

Soehendra introduced the concept of combination therapy (4). Epinephrine is injected initially to stop bleeding. A clear view of the bleeding vessel is then possible allowing its targeted treatment by a sclerosant (e.g. polidocanol, sodium tetradecyl sulfate and ethoamidine) or absolute alcohol which causes tissue dehydration. While these agents induce vessel thrombosis, they cause tissue necrosis and ulcer extension in a dose dependent manner. Only a limited volume can be used. Randomized studies in the literature including two from the Prince of Wales Hospital concluded that the addition of a sclerosant after epinephrine injection conferred no benefit when compared to epinephrine alone (5,6). In the literature, there were case reports of gastric necrosis following sclerosant use, some of them were fatal (7).

Recent evidence in the literature suggests that the addition of thrombin or fibrin after epinephrine injection can further reduce recurrent bleeding. A randomized study from Edinburgh compared epinephrine alone to epinephrine plus human thrombin and the dual therapy reduced rebleeding, need for transfusion and deaths (8). In another large-scale multicentre European trial (9), patients were randomized to receive single polidocanol treatment, single epinephrine and fibrin glue treatment and repeated fibrin glue treatment with daily endoscopy until complete fading of bleeding stigmata. Fibrin glue treatment was significantly better than polidocanol only when injected repeatedly at daily control endoscopy. Commercially available fibrin glue is a two-component glue mixed with reconstituted thrombin and fibrinogen. The product is expensive especially when injected repeatedly. Its injection requires the use of a dual channel needle. Clogging of injector is a frequent problem.

In a randomized study, we compared the added coaptive thermocoagulation using a 3.2mm heater probe after epinephrine injection to epinephrine injection alone in 270 patients. We prefer the use of contact thermal probes. Firm mechanical tamponade on the bleeding artery stops bleeding, reduces heat-sink effect by flowing blood and allows heat energy to weld the two walls of artery together i.e. coaptive thermo-coagulation. In a canine model of bleeding peptic ulcer, contact thermal devices are superior to non-contact ones and consistently coagulated arteries up to 2 mm in size. In humans, arteries in larger chronic ulcers often are sub-serosal of around 1 mm in size (10). In combining epinephrine injection and heater probe coagulation, a tendency in less clinical rebleeding and surgery was noted. In the subgroup of spurring hemorrhage, a significant reduction in the need for surgery was seen (11).

To date, we recommend a combination approach in the endoscopic treatment of bleeding peptic ulcer: initial injection of epinephrine to
stop bleeding and targeted treatment to the bleeding vessel using either thrombin or fibrin or a contact thermal device.

Many endoscopists routinely re-endoscopy their patients the next morning after index treatment. Available randomized studies consisted of small number of patients and in some of these trials, epinephrine injection alone was used (12,13). The lack of difference was a consequence of type II error (i.e. inadequate sample size to detect a small difference). A cost-effective analysis is lacking. With more effective index treatment, recurrent bleeding occurs in less than 15 per cent of treated patients. The yield from such an approach is likely to be even smaller. Re-treatment is likely to be associated with more complications e.g. perforation from transmural thermal injury. In a small study from Texas selecting only higher risk patients for re-treatment based on age, co-morbidity, shock at presentation and endoscopic stigmata, rebleeding was significantly reduced by scheduled re-treatment the next morning (14). A selective approach in offering scheduled re-treatment seems more rational.

Surgery assumes an important gate-keeping role in the management algorithm of bleeding peptic ulcer. The relative roles of endoscopic treatment and surgery are complementary to each other. Endoscopic therapy with its proven efficacy should be attempted at index endoscopy. Failure to stop arterial bleeding endoscopically is a clear indication for surgery. After initial endoscopic control of bleeding, recurrent bleeding occurs in about 10 to 15 per cent of patients. It is often a dilemma whether to attempt endoscopic re-treatment or proceed directly to surgery. Avoiding surgery may be beneficial in elderly patients with co-morbid illnesses. On the other hand, further delay with unsuccessful endoscopic treatment would jeopardize patients' survival. In a three-year trial involving more than 3400 patients at the Prince of Wales Hospital, a third of them required endoscopic treatment. Only around 9 per cent of endoscopically treated patients developed recurrent bleeding. They were randomized to endoscopic re-treatment and surgery (15). Re-treatment was successful in three-quarters of patients. With intention-to-treat analysis, endoscopic re-treatment further reduced the need for surgery and its attendant morbidity without increasing mortality. The more pertinent question is to predict patients likely to respond to endoscopic re-treatment. In a logistic regression model, patients with larger ulcers (greater than 2 cm) and rapid exsanguination in shock were less amenable to endoscopic re-treatment. It is suggested that a selective approach can be used in rebleeding patients. Patients with smaller ulcers and subtle signs of rebleeding should be re-endoscoped and therapy repeated often with successful outcome. It remains probable that patients with large chronic ulcers and in shock are better treated by expedite surgery without recourse to endoscopic re-treatment. Some of these patients may benefit from early elective surgery.

References:
**Update on Treatment of Hepatitis C**

**Introduction**
Chronic hepatitis C virus (HCV) infection is a growing health care problem in the world especially in Western countries. It is estimated that around 100 million people worldwide are infected with HCV (1). Eighty-five percent of the infected people will develop persistent infection, in which at least 60% of them develop chronic hepatitis over a 20-year period and 20% may finally progress to cirrhosis and/or hepatocellular carcinoma (HCC) (2). The treatment aims for chronic hepatitis C infection are normalization of aminotransferase, reduction of serum HCV RNA to an undetectable level, improvement of liver histology and thus prevention of progression to cirrhosis and/or HCC. A recent study has shown that interferon-α (IFN-α) treatment reduces the risk of developing cirrhosis-related complications and HCC in chronic hepatitis C patients (3).

**Selection of patients for treatment**
HCV genotype 1b, high level of viraemia and the presence of cirrhosis are independently associated with poor responsiveness to interferon therapy (4). One may hesitate to offer IFN-α treatment for those who have one or more of these unfavourable factors. However, because of lack of long-term data and the flaws inherent in multivariate analyses, withholding therapy based on these baseline features seems to be unwarranted.

Since up to 50% and 77% of patients who have non-cirrhotic liver biopsy will progress to cirrhosis over 10 years and 17 years of follow-up respectively (5), initial histologically mild disease may not run a "benign" course. Therefore, it is reasonable to treat these patients with IFN-α. Moreover, it has been shown that nonfibrotic liver disease is associated with a better response to treatment (6).

It is generally agreed that patients with elevated alanine transaminase (ALT) and positive HCV RNA should be treated with IFN-α. In fact, one study shows that IFN-α may be harmful to HCV patients with normal ALT because of liver injury caused by the immunomodulatory actions of IFN-α (7).

**Therapy for treatment-naïve patients**
A Consensus Report on the treatment of HCV has been published by National Institute of Health. Recent data shows that combination therapy using IFN-α and ribavirin is superior to IFN-α alone.
Four forms of IFN-α [alpha-2b, alpha-2a, alpha-n1 (lymphoblastoid) and consensus interferon] have been evaluated in many studies. Among all the subtypes of IFN-α, IFN-α 2b is the one being studied more extensively. Biochemical and virological responses are defined as normalization of ALT and undetectable HCV RNA by PCR assay respectively. These are evaluated by the end-of-treatment response (ETR) and sustained response (SR), which is usually defined as a response that is maintained up to 6 months after cessation of treatment. In a metaanalysis, after 24 weeks of at least 2 million unit (MU) (most studies were using 3 MU) three times per week of IFN-α 2b, the biochemical ETR and SR are 47% and 23% respectively. These are significantly better when compared to control in which the ETR and SR are only 4% and 2% respectively (p<0.001 and p<0.001 respectively)(8). The virological ETR and SR are also higher in IFN-α 2b-treated patients (i.e. 29% and 8% respectively) when compared to those in untreated patients (5%; p<0.001 and 1%; p<0.001 respectively). More importantly, histological improvement at the end of treatment is observed in 73% of the treated patients compared to only 38% of the controls. Overall, only around 20% of the patients treated with IFN-α have sustained beneficial responses. The low sustained response rate can be further improved by extending the initial treatment to 12 months or even longer. A study has shown that IFN-α 2b (3 MU three times weekly) given for 18 months to patients with chronic non-A, non-B hepatitis results in a better histologic improvement and serum ALT values when compared to regimens using a lower dose or a shorter duration of treatment.(9) Different types of IFN-α may have a different efficacy in treating HCV infection. One study comparing IFN-α 2b and IFN-α n1, shows that though there is no difference in the ETR, SR is higher with IFN-α n1 than with IFN-α 2b (12.0% vs 7.6% at 48 weeks, p=0.02; 10.3% vs. 6.7% at 72 weeks, p=0.04).(10)

Because of the consideration of cost and effectiveness, early termination of the therapy for those who are expected to be nonresponders will be a logical approach. The great majority of ALT normalisations occurs in the early phase of the treatment (i.e. initial 4 to 8 weeks), after which further cases of biochemical response are infrequent. Therefore, termination of therapy may be considered in patients who do not have ALT normalization after 8 weeks of treatment.

As the response to IFN-α is rather unpredictable, factors which predict a greater likelihood of response are being extensively evaluated. Patients without cirrhosis are more likely to respond to IFN-α. Genotype 1b is notoriously more resistant whereas types 2 and 3 are more sensitive to IFN-α. Patients harbouring diverse circulating quasispecies may be less responsive to therapy than those who have only single major species. Low level of HCV RNA is a favourable factor for IFN-α therapy. Long duration of HCV infection and high hepatic iron load are associated with poor response to IFN-α treatment.

Ribavirin is a guanosine analogue with activity against DNA and RNA viruses, including flaviviruses. Though reduction of ALT levels can be achieved by ribavirin monotherapy, there is no reduction of serum HCV RNA levels. Therefore, ribavirin alone is inadequate for the treatment of HCV infection. Recently, a prospective randomized trial involving more than 900 chronic hepatitis C patients showed that combination therapy by using IFN-α 2b and ribavirin was more effective than treatment with interferon alone. The virological SR rates for combination treatment for 24 weeks and 48 weeks (31% and 38% respectively) are significantly higher than those who are treated with IFN-α 2b alone (6% for 24 weeks of treatment and 13% for 48 weeks of treatment).(11)

The side effects of IFN-α include fever, malaise, influenza-like symptoms, alopecia, autoimmune phenomena particularly hyperthyroidism or hypothyroidism, bone marrow suppression, neuropsychiatric disturbance such as depression and liver failure in patients with liver decompensation. The major side effects of ribavirin are haemolysis, fatigue, depression, insomnia, anorexia, nasal congestion and vertigo.

Treatment for nonresponder and relaper after IFN-α therapy
Nonresponders are defined as patients who do not have complete normalization of ALT by the end of the first course of therapy. There is nearly no sustained response if these patients are re-treated with a second course of IFN-α 3 MU three times weekly for 6 months. Even with higher doses and longer duration of treatment, only 2-3% patients achieve sustained response(12). Thus, retreatment with IFN-α monotherapy is generally not advised for these patients. Though combination therapy with IFN-α and ribavirin offers promising results in naïve patients, nonresponders to IFN-α monotherapy seldom achieve sustained responses with the combination treatment.

Relapers are defined as patients who have normalization of ALT at the end of IFN-α therapy, followed by a second elevation of ALT within one year after the treatment has been stopped. Sustained responses can be achieved in 15%, 29% and 43% if they are re-treated with IFN-α 3 MU three times weekly for 6 months, higher doses (5-10 MU three times weekly) for 6 months and for at least 12 months respectively. A recent study has shown that undetectable HCV RNA is achieved in 82% and 47% in relapers who are re-treated with IFN-α plus ribavirin and IFN-α alone respectively (13). Similar to the treatment efficacy for treatment-naïve patients, IFN-α plus ribavirin are more effective in treating relapers when compared to IFN-α monotherapy.

Treatment for special subgroups
For immunocompromized patients, IFN-α treatment is usually not effective though sustained response can occasional occur. The extrahaepatic manifestations of chronic hepatitis C infection e.g. mixed cryoglobulinemia and glomerulonephritis can be treated with IFN-α. Chronic hepatitis C infected patients with cirrhosis have been shown to respond to IFN-α though the rate of response is half that of non-cirrhotic chronic hepatitis C patients. However, IFN-α should be given with extreme caution in cirrhotic patients since IFN-α treatment can cause further liver decompensation, which may be fatal.

Liver transplantation
Liver transplantation remains the last resort for patients with decompensated liver function. Recurrence of HCV infection is almost universal. The 5-year survival rate for patients with transplantation is approximately 80%, which is similar to those who have transplantaions for liver disease of other etiologies. It seems that post-transplantation HCV recurrence is associated with a mild disease activity. However, a certain proportion of patients has significant elevations of ALT with recurrence of HCV infection after transplantation. A pilot study using combination therapy of IFN-α and ribavirin has shown that it is effective in reducing HCV RNA levels, lowering ALT levels and ameliorating liver injury in these patients.(14) However the long-term sequelae needs to be further defined.

Conclusion
IFN-α is the standard modality of treatment for chronic hepatitis C infection. However, in view of the high relapse rate, combination treatment using IFN-α and ribavirin is becoming the first choice of treatment. Retreatment for patients who have relapse of the chronic HCV infection should be considered by using a higher dose and longer period of IFN-α monotherapy or by combination therapy of IFN-α and ribavirin. Liver transplantation remains the last resort for chronic HCV patients with end-stage liver disease.
References:

1. Alter MJ. Epidemiology of Hepatitis C. Hepatology 1997; 26 (3 Suppl): 625-65S.
2. Management of Hepatitis C. Natural Institutes of Health Consensus Development Statement; March 24-26, 1997; Washington, DC.

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HONG KONG SOCIETY OF GASTROENTEROLOGY
SCHOLARSHIP 2000/2001

Objective

The objective of the Scholarship is to facilitate trainees in gastroenterology (physicians, surgeons, radiologists, pathologists) of the Hospital Authority or the Society to undertake overseas training in gastroenterology.

Award

1. The Scholarship is awarded for a study period of 6 months or more.
2. The award is HK$50,000.
3. Simultaneous acceptance of other scholarship is not allowed.
4. The candidate is required to produce evidence of approval to take study leave from his/her serving institution.
5. Upon completion of the training programme, the candidate is required to submit a report to the Society within 2 months, together with original letter of approval on study leave.
6. The award will be paid on satisfactory completion of the training programme
7. An interview may be required by the Scholarship Selection Committee
8. The Scholarship Selection Committee has the sole discretion to grant the Scholarship or to refuse any application.

Qualifications

Application is limited to fellow trainees in Gastroenterology who are:-

1. staff of Hospital Authority or members of the Society
2. holder of a post-graduate diploma (MHKCP/MRCP(UK) or equivalent)
3. in the Hong Kong Academy of Medicine Fellowship Training

Application

1. Interested parties should apply in writing enclosing the curriculum vitae (which should include personal data, professional qualifications, working experience, training experience in gastroenterology, publications and proposed training programme, as well as the reference from at least one supervisor or a referee if the applicant is in private practice)
2. Application should be sent together with supporting documents to the Scholarship Selection Committee, Hong Kong Society of Gastroenterology c/o Miss Clare Wong, Department of Medicine, Queen Mary Hospital, Pokfulam Road, Hong Kong (Tel: 2855-3354, Fax: 2816-2863 and E-mail: mcowong@hkucc.hku.hk)
3. Deadline of application is on April 30, 2000