Gastroenterology and Hepatology

Dissertation for Exit Assessment

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Crohn's Disease

Local Retrospective and

Future Prospective

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Abstract

Crohn's disease (CD) is more common in the Western than the Asian countries. Limited data is available about CD in the Hong Kong Chinese population. A retrospective study was performed in a regional hospital from the year 1993 to 2000 and 15 new cases of CD were diagnosed, giving an estimated annual incidence rate of 0.43 per 100,000 population. No apparent gender difference was observed (M:F; 1.1:1). The main presenting symptoms were abdominal pain (67%), diarrhoea (46%), blood in stool (40%) and weight loss (33%). Ileocolonic CD was the commonest pattern of gastrointestinal involvement (56%). Colonic or small bowel disease alone constituted 33% and 13% of all the cases of CD, respectively. A predilection to involve the colon (87%) is a distinct feature in contrast to our western counterparts and some other Asian countries where a comparatively higher frequency of small bowel disease was observed. Extraintestinal manifestations were rare in our patients. The histologic hallmark of non-caseating granuloma was infrequently seen in the biopsy specimens (18%). Seven patients had no relapse while on maintenance medical therapy. Intestinal resection was undertaken in 5 patients (45%), of which 4 (80%) had the operation performed before the diagnosis of CD. Medical therapy remains the mainstay of treatment for CD. Therapeutic modalities used to treat CD act at various locations along the inflammatory pathway. Advance has been made in recent years in the medical therapy of CD in particular the development of biological treatment directed to alter the specific pathogenic mechanisms that have the potential to modify the natural course of the disease.

1 Introduction

Crohn's disease (CD) is an inflammatory disorder of the gastrointestinal tract of unknown aetiology at the moment. The epidemiology of CD varies among different geographic areas and distinct populations. Collected studies from Europe and North American yielded annual incidence figures between 2 to 6 per 100,000 population (1). Countries in southern Europe, South African, and Australia have lower incidence rates with a range of 0.9 to 3.1 per 100,000 population (2, 3, 4). CD is thought to be rare in Asia. Incidence rate of 0.08 per 100,000 population has been reported in a Japanese study (5). As it was a rare disease here, publications were scanty concerning CD in the Chinese population. Only three cases of CD were reported in Hong Kong Chinese over a 25-year period from 1950s to 1970s (6). However, a recent report of 15 ethnic Chinese with CD over a period from 1987 to 1992 in a regional hospital suggested a rising incidence of this condition in the Chinese population in Hong Kong (7). With these backgrounds, a retrospective study was therefore performed in a regional hospital in Hong Kong with an objective to study the latest incidence of CD and to explore its characteristics in the ethnic Chinese. Medical therapy is the mainstay of treatment for CD. In recent years, we have witnessed a series of breakthrough in the medical therapy of CD. Although a definitive curative therapy is still lacking, adverse effects on the health and quality of life of the patient can be substantially lessened by meticulous medical therapy. A critical review on the current update about the medical therapy of CD will be included in the dissertation.

2 A Retrospective Study of Crohn's Disease in a Regional Hospital

2.1 Patients and Methods

A retrospective study was performed on all consecutive cases of ethnic Chinese with CD diagnosed and treated in Pamela Youde Nethersole Eastern Hospital (PYNEH) from the year 1993 to 2000. Our hospital serves a population of 500,000 in the eastern part of Hong Kong Island. The diagnosis of CD was established on the basis of

compatible clinical, endoscopic, radiological and pathological features including the following characteristics: 1) a history of chronic gastrointestinal symptom of abdominal pain and or diarrhoea; 2) inflammatory changes of the small intestine or large bowel with features such as ulcerations, skip lesions, intestinal strictures and fistula formation suggestive of CD; 3) histologic features of chronic inflammation and 4) response to anti-inflammatory therapy. Bacterial and mycobacterial infections as well as parasitic infestations were excluded in all cases by repeated stool microscopy together with cultures at initial presentation and subsequent episodes of relapse. The extent of small bowel involvement was assessed by upper endoscopy and small bowel enema. Colonic disease was evaluated by colonoscopy and/or barium enema. All patients were followed up regularly in our specialty outpatient clinic to document their response to medical therapy and the presence of any complications.

2.2 Results

A total of 15 Chinese patients were diagnosed and treated for CD from the year 1993 to 2000 in our hospital. There were 8 males and 7 females (M:F, 1.1:1). The mean age at presentation was 41.1 years (range, 10-74). The median duration between the onset of symptom and the establishment of diagnosis of CD was 12 months (range, 1-52). One patient was a smoker at presentation and two were ex-smoker. There was no history of chronic intake of nonsteroidal anti-inflammatory drugs in any of the patients. None of these patients had a family history of chronic inflammatory bowel disease. The main presenting symptoms included abdominal pain (67%), diarrhoea (47%), blood in stool (40%) and weight loss (33%) (figure 1).

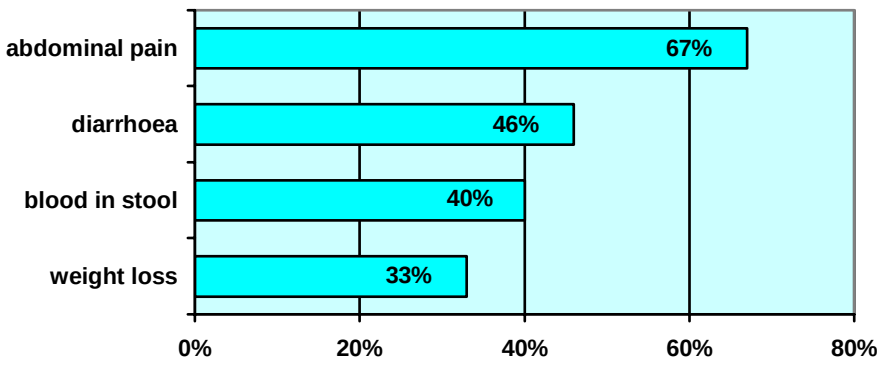

Figure 1 **Symptom at presentation in the fifteen cases of CD in PYNEH**

Macroscopic features of colitis were detected by colonoscopy and/or barium study. Evidences of small intestinal involvement were evaluated by small bowel enema. The pattern of disease involvement is shown in figure 2. Ileocolonic disease was the commonest pattern of gastrointestinal involvement and was documented in 8 patients (54%). Small bowel disease alone or colonic disease alone was found in 2 (13%) and 5 patients (33%) respectively. Radiographic evidence of small bowel strictures was seen in 4 out of 10 patients (40%) with small bowel diseases. In contrast, only 1 out of 13 patients (7.7%) with colonic disease was found to have a mild stricture on colonoscopy. Intestinal obstruction due to stricture occurred in 3 out of 10 patients (30%) with small bowel diseases. All patients who developed intestinal obstruction failed to respond to medical treatment and required laparotomy with surgical resection. The patient with colonic stricture had no symptom of intestinal obstruction. Two patients had recurrent oral aphthous ulcerations. Two patients had perianal disease in the form of perianal fistula. One patient developed enterocutaneous fistula after laparotomy and required surgical excision of the fistula with satisfactory result.

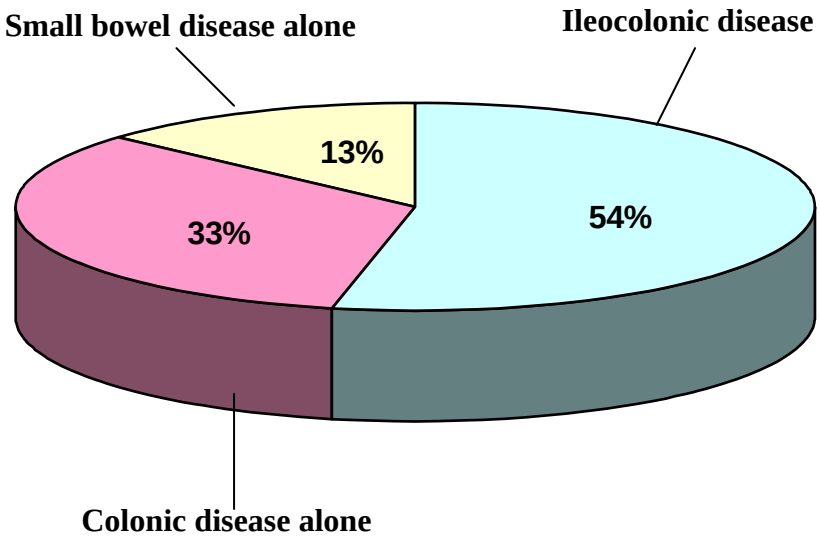

Figure 2 **Anatomical involvement in the fifteen cases of CD**

Common features on colonoscopic examination were multiple mucosal ulcerations less than 1cm, which occurred in a skipped pattern. One patient was found to have a

large caecal ulcer of 3 cm in diameter on endoscopic examination. Characteristic cobblestone appearance was only found in one patient. Histologic examination revealed the presence of non-caseating granuloma in only two patients (13%).

Extraintestinal manifestations were uncommon. No patient had characteristic dermatological vasculitic lesions like erythema nodosum or pyoderma gangrenosum, nor was there any patient with ocular involvement like scleritis or uveitis. One patient had inflammatory bowel disease related spondylarthritis with symptom of low back pain. Radiological examination of the sacroiliac spine revealed sacroiliitis with sclerotic changes and widening of joint space in the sacroiliac joint.

Complete blood counts, liver and renal function tests as well as assays of inflammatory markers were performed in all patients at presentation with results as shown in figure 3. Anaemia (Hb <12.5g/dl), thrombocytosis (platelet <150x10^9/l) and hypoalbuminemia (albumin < 35g/l) were detected in 9(60%), 5(33%) and 4(27%) patients, respectively. Elevated inflammatory markers, including ESR and C-reactive protein (CRP), were almost universal and found in 13 patients (86%).

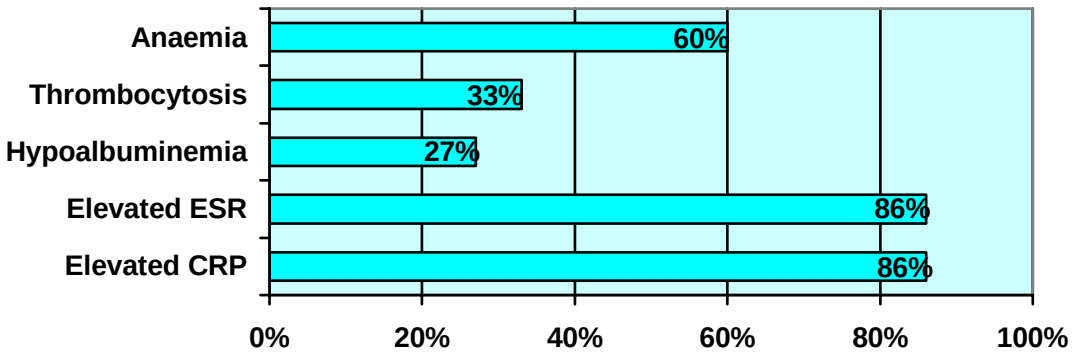

Figure 3 **Laboratory parameters at presentation in the fifteen cases of CD**

Most patients responded initially to medical therapy with systemic corticosteroids and high dose oral 5-aminosalicylate (5-ASA) compounds. Maintenance therapy with oral 5-ASA was instituted in all patients. Eight patients were on Salofalk® 2-4g/d and 7 patients were on Pentasa® 2-4g/d. Immunosuppressive therapy in the form of

azathioprine therapy was commenced in 8 patients, 5 for steroid dependent disease or frequent relapses and 3 for prophylaxis after surgical resection for an active disease. Most patients tolerated to azathioprine at the dosage of 1.0-1.5mg/kg/d. One patient developed cytopenia requiring withdrawal of azathioprine. Antibiotics in the form of metronidazole 400 to 800mg/d or ciprofloxacin 500mg/d were prescribed to 4 patients, 2 for perianal disease and 2 for frequent relapses.

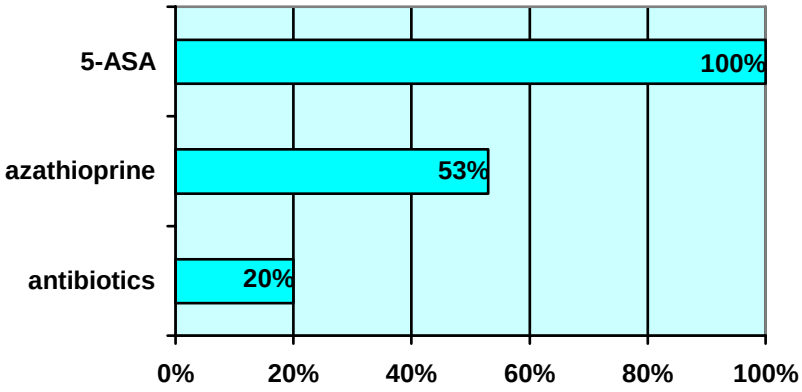

Figure 4 **Maintenance medical therapy in the fifteen cases of CD**

Seven patients had no relapse during a mean follow-up period of 22 months (range, 3-60). The remaining 8 patients had an average of 0.68 relapse per year over a mean follow-up duration of 31 months (range, 18-60). Five patients (33%) had surgical resection (figure 5) of which 4 had the operation performed before the diagnosis of CD was made. Two patients had more than one operation. Intestinal obstruction was the commonest acute complication and occurred in 3 patients. All of them had disease involving the small bowel. All patients having intestinal obstruction failed to respond to medical therapy and ended up in laparotomy and surgical resection (figure 6). One patient had massive bleeding from a colonic ulcer with emergency hemicolectomy performed. Excision of enterocutaneous fistula was undertaken in one patient. Another patient had fistolotomy for a perianal fistula. One patient had CD related mortality. He was a 71 years old man who had repeated acute flares not responding to medical therapy but reluctant for surgical intervention. He followed a progressively downhill course and eventually succumbed. Postmortem examination of the bowel

specimens showed histologic features of transmural inflammation, deep fissuring ulcer and non-caseating granuloma typical of CD.

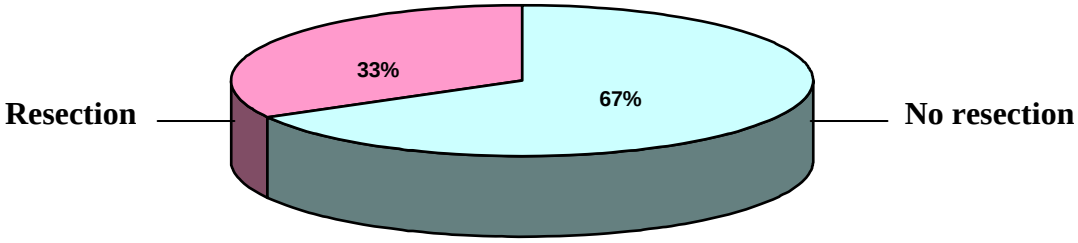

Figure 5 **Proportion of CD patients requiring intestinal resection**

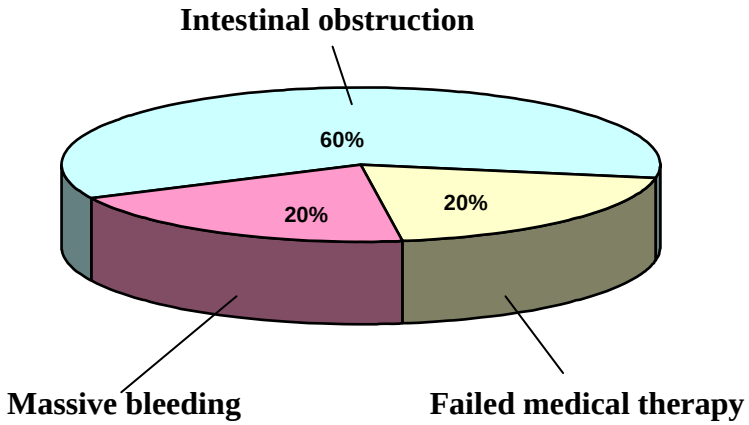

Figure 6 **Indication for operation in the 5 CD patients with intestinal resection**

2.3 Discussion

CD is uncommon among the Oriental population and there have been only a limited number of English publications focusing on the epidemiology of the disease in Asia. In Hong Kong, a publication two decades ago by Chan *et al* revealed only 3 cases of suspected CD over a 25-year survey (6). In a study at the Prince of Wales hospital,

Shatin, Hong Kong, 15 patients were diagnosed to have CD over a 5-year period from 1987 to 1992, giving an estimated annual incidence of 0.25 per 100,000 population (7). Our study revealed 15 cases of Crohn's disease over a 7-year period from 1993 to 2000, giving an estimated incidence of 0.43 per 100,000 population. These figures were still lower than the reported annual incidences of 0.9 to 3.1 per 100,000 in southern Europe, South African, and Australia. However, it has represented a dramatic rise compared with previous data in Hong Kong. The observed rise in the incidence of CD may represent an actual increase in the incidence of this disease here or it may be due to an increase in the awareness of this condition among physicians as well as a wider availability of diagnostic tools especially endoscopy together with small bowel enema in Hong Kong. However, our study included only hospitalised patients in a regional public hospital. The true incidence of the disease in the population could still be underestimated as patients treated in the private sectors were not included.

Our study showed no apparent difference in the incidence of CD in both gender, and was consistent with data in the western countries. It has been shown that genetic factors play a role in the aetiology of inflammatory bowel diseases and susceptibility loci on chromosomes 1, 3, 7, 12 and 16 have been demonstrated (8). The risk of a second first-order family member being affected is estimated to lie between 1 in 15 and 1 in 10 in the western countries. In view of the relatively small number of affected patients in our series, it is not surprising that none of our patients had a family history of inflammatory bowel disease. On the other hand, our patients may belong to the entity of the "sporadic CD", which could exhibit distinct characteristics, compared with the "familial CD". In one study, patients with "sporadic CD" was found to be associated with significantly later onset and higher proportion of colonic CD in comparison with "familial CD" (9). If this is true, it may explain a higher age at presentation in our patients compared with that of the western countries.

It is generally agreed that smokers are over-represented amongst patients with CD but the exact mechanism remains speculative. However, only one out of fifteen patients was a chronic smoker in our study. Use of non-steroid anti-inflammatory drug has been identified as one of the predisposing factors for the development of

inflammatory bowel disease. However, none of our patients was a chronic user of non-steroidal anti-inflammatory drugs. These could be explained by the multifactorial nature and the interplay of other environmental factors leading to the development of CD.

Common presenting symptoms were abdominal pain, diarrhoea, blood in stool and weight loss in our study. These were similar to the western figures. Extra-intestinal manifestations were rare in our patients. Only one of our patients had inflammatory bowel disease related spondylarthritis. She is a 28 years old girl with symptom of low back pain and radiological features of sacroiliitis. The joint symptom was quite mild and simple analgesic was adequate for satisfactory pain relief. The figure of extraintestinal manifestation in our CD patients was slightly lower than the series reported from the Prince of Wales Hospital (7) where inflammatory disease related arthropathy was noticed in 4 patients (27%) (table 2). Dermatological and ocular features were not found in any one of our patients. In Sung's series ocular and dermatologic manifestation of CD were not reported as well (7).

The pattern of gastrointestinal involvement was found to be quite different from that of our western counterparts. Disease with colonic involvement was over-represented in our patients. In our series, only two patients had small bowel disease alone. All the others had either colonic or ileocolonic diseases (table 1). In contrast, CD with small bowel involvement is more common in the western population.

	Our series	**Sung '94**[7]	**Farm '75**[10]	**Lashner '95**[11]
Ileocolonic disease	53%	47%	40-55%	40%
Colonic disease alone	33%	53%	15-25%	25%
Small bowel disease	13%	0%	30-40%	30%

Table 1 **Pattern of gastrointestinal involvement of CD in different series**

The pattern of involvement in our patients was in keeping with Sung's series, in which colonic diseases were seen in all of their CD patients and no single case of small bowel CD alone was found (table 1). This is an interesting finding as a rising incidence of Crohn's colitis has been reported in several recent series. Nevertheless, colonic involvement seems to be a dominant characteristic pattern in our Chinese patients in Hong Kong in contrast to the western CD patients.

Interestingly, small bowel predominant pattern was observed in the series reported in our neighborhood Asian countries. For instances, small bowel involvement alone was found in 38% and 44% of the CD patients in studies reported in Singapore (12) and Japan (13), respectively (table 2).

	Our Series	**Law '98**[12] **Singapore**	**Okada '87**[13] **Japan**
No of patients	15	32	93
Ileocolonic disease	53%	34%	40%
Colonic disease alone	33%	28%	14%
Small bowel disease alone	13%	38%	44%

Table 2 **Pattern of gastrointestinal involvement in other Asian countries**

The underlying reason of why colonic disease is more common in the Hong Kong series is not entirely certain. In Sung's series, the absence of small bowel CD alone may be due to the fact that not all their patients underwent small bowel series at that period. Since all of our patients had undergone radiologic evaluation of the small bowel, the results was probably not due to under-diagnosis of small bowel CD. In one study, patients with "sporadic CD" was found to be associated with higher proportion of colonic CD in comparison with "familial CD" (14). In our series, none of the patients had a family history of inflammatory bowel disease. The solely "sporadic CD" in our series may partly explain the observed difference in the anatomic distribution of the disease.

On endoscopic evaluation, the most commonly identified features were small patchy ulcerations and skipped lesions. Characteristic cobblestone stone appearance was only seen in one patient. Although the presence of non-caseating granuloma is a key histologic feature of CD, it was infrequently seen in our biopsy specimens. Granulomas were identified in only two of our patients. These emphasise the fact that a combination of clinical, endoscopic, radiologic and histological assessment was required for the diagnosis of CD in our Chinese population. Assay of inflammatory markers was found to be sensitive indicator of activity at the presentation of CD. Eight-seven percents of our patients were found to have raised ESR and CRP on presentation.

Because of the relatively lower incidence of CD in our locality in comparison with gastrointestinal infections such as bacterial dysentery and even intestinal tuberculosis, it is mandatory to exclude gastrointestinal infection by repeated examination of stool microscopy and cultures. Intestinal tuberculosis should be carefully excluded by smears and cultures of biopsy specimens. In some occasions, it may be difficult to make a definitive distinction of CD from intestinal tuberculosis. In one of our CD patients, he presented with marked weight loss and colonoscopy showed inflammation at the ileocecal region. Histological examination was however not conclusive of CD and tuberculosis. We commenced on empirical anti-tuberculosis therapy without any improvement. The diagnosis of CD was eventually made after repeated colonoscopic biopsies to exclude tuberculosis and the dramatic response to subsequent corticosteroid therapy.

The median duration of symptom before the diagnosis of CD was 12 months. However, one patient had 3 years history of on and off abdominal pain before the definitive diagnosis of CD was made. Surgical resection was undertaken in 5 patients (45%) of which 4 patients (80%) were not yet diagnosed to have CD at the time of surgery. One patient was attended by surgeons with two laparotomy and bowel resection before the diagnosis CD was made. The relatively long symptomatic period before the final diagnosis of CD was very often due to delay referral of patients from primary physicians to secondary and tertiary centres for detailed work-up.

Majority of our patients responded reasonably well initially to medical therapy with systemic corticosteroids and 5-ASA. Seven patients had no relapse while on maintenance medical therapy. We commenced 5-ASA on all of our CD patients as a maintenance therapy with no major side effects being reported. For patients having frequent relapses or difficulty in tailing down corticosteroids, we instituted immunosuppressive therapy in the form of azathioprine at the dosage of 1.0mg/kg/d with gradual increase according to the response. We found that that most of our patients responded well to azathioprine at 1.0-1.5mg/kg/d, which is lower than the generally recommended dosage of 2.0-2.5mg/kg/d for CD in the western countries. We tend to commence azathioprine early rather than late in our patients with active CD requiring surgical resection. Most of our patients tolerate well to azathioprine except for one patient, who developed cytopenia while on azathioprine of 1.0mg/kg/d and subsequently diagnosed to have myelodysplastic syndrome on bone marrow biopsy. He was a 71 years old patient who encountered frequent and troublesome relapses requiring frequent systemic steroid therapy. He was intolerant to azathioprine because of myelodysplastic syndrome. We did put on cyclosporin for that patient during an episode of acute relapse but no improvement was noticed. He followed a progressively downhill course and eventually succumbed.

2.4 Conclusion

CD is traditional thought to be rare in the Chinese population. Our local figures showed an increasing incidence of CD in the Hong Kong Chinese population in recent years. Nevertheless bacterial gastrointestinal infection, mycobacterial infection as well as parasitic infestation should be cautiously excluded in our sub-tropical region. Our series revealed that CD in the Hong Kong Chinese population exhibited a distinct pattern with a predilection to involve the colon and affected an older age group in comparison with that in the western population. Extra-intestinal manifestations were rare. Most of our patients responded satisfactorily to medical therapy. Intestinal obstruction secondary to small bowel stricture was the most common acute surgical complication, which required surgical resection.

3 Current Update on the Medical Therapy of Crohn's Disease

The aetiology of CD remains unknown but the current leading hypothesis is that this disorder may be due to a dysregulated mucosal immune response to enteric bacterial antigens in a genetically susceptible host. Therefore, the pathogenesis involves complex interactions among immunologic, environmental and genetic components. The therapeutic modalities used to treat CD act at various locations along the inflammatory pathway. Traditional therapies included the use of aminosalicylates and corticosteroids. Immunomodulators, such as azathioprine and 6-mercaptopurine, have demonstrated increasing importance in the setting of steroid-resistant and steroid-dependent disease. Recent advance has led to the development of biologic treatments directed at altering specific pathogenic mechanisms that have the potential to modify the natural course of the disease.

3.1 Aminosalicylates

The prototypic 5-ASA compound, sulphasalazine, was initially synthesized for use in rheumatoid arthritis. Svartz first used this compound to treat rheumatoid arthritis and demonstrated an unanticipated reduction of gastrointestinal symptoms in patients with co-existing ulcerative colitis. Sulphasalazine was subsequently found to have beneficial effect in the treatment of CD.

The specific mechanism of action of 5-ASA remains undefined. Particular attention has been played to its effect on the arachidonic acid cascade and lipoxygenase pathway and inhibition of the platelet-activating factor synthase. Other proposed mechanism includes inhibition of free oxygen radicle production and inhibition of interleukin (IL)-1 production. It also has the effect of impairing leucocytes and monocytes function and reducing immunoglobulin production.

Although highly effective for ulcerative colitis, randomised controlled trials showed that sulphasalazine was only marginally effective for the induction of remission in

active CD. The efficacy of sulphasalazine for CD is influenced by the site of disease activity. The requisite for colonic bacteria to cleave the compound likely limits the utility of sulfasalazine for CD confined to the small intestine. Accordingly two large randomised placebo-controlled trials, the National Crohn's Disease Cooperative Study (15) and the European Cooperative Crohn's Disease Study (16), evaluated more than 500 patients with active CD, sulphasalazine at doses of 3 to 5 g/d proved superior to placebo for patients with ileocolonic and colonic CD, whereas no benefit was observed in isolated small bowel disease.

Since the sulfa related adverse effects of sulphasalazine often limit the maximum drug dose that can be administered, the development of 5-ASA formulations which lack a sulfa moiety are often better tolerated. Differences between the more recent 5-ASA compounds also relate to different delivery mechanisms resulting in some differences in the site of release and maximum concentration which are designed to deliver the active drug topically to the small intestine. Comparisons of some of the newer 5-ASAs with placebo have shown favorable response, particularly among patients with small bowel disease. Salofalk® is a 5-ASA coated with an acrylic-based resin (Eudragit-L) that dissolves at pH 6 and is released in the terminal ileum and colon. In randomised controlled trials, Salofalk® at a dosage 3g/d has demonstrated efficacy in patients with Crohn’s ileitis or ileocolitis (17). Asacol® is a 5-ASA coated with an acrylic-based resin (Eudragit-S) and dissolves rapidly above pH 7.0. Asacol® 3.2 g/d was found to be effective for active Crohn's colitis and ileocolitis as compared with placebo (18). The slow-release form, Pentasa®, in ethylcellulose-coated micro-particles, is released throughout the small bowel and colon. Benefit in induction of remission was observed in patients with active small bowel CD who received Pentasa® at a dosage of 4g/d (19).

Although 5-ASA is commonly prescribed as maintenance for quiescent CD, the evidence of its benefit is less well established. Neither the National Crohn's Disease Cooperative Study nor the European Cooperative Crohn's Disease Study demonstrated significant maintenance benefit from sulfasalazine at dosage of 1.5 to 3g/d. It appears that there is dose-response effect in the use of 5-ASA in maintaining

remission of CD. 5-ASA at a dosage of at least 2.0 to 2.4g/d is generally required for maintenance of remission (20, 21, 22, 23).

A meta-analysis (24) evaluating 15 randomised, controlled trials, which included a total of 2097 patients showed a slight benefit with an overall relative risk reduction of 6.3% per year. The results of a subgroup analysis demonstrated that the benefit of 5-ASA was most apparent in the post-surgical setting. However, the most recently published European Cooperative Crohn's Disease Study IV (25), investigating the long-term treatment with high-dose mesalamine on the risk of clinical relapse of CD after surgical resection in 318 patients, 18 months of mesalamine, 4 g daily, did not significantly affect the postoperative course of CD.

The benefit of 5-ASA in maintaining remission of CD seems to be marginal. Nevertheless, 5-ASAs are generally well tolerated. Hypersensitivity reaction occurs rarely with rash, hepatitis, pneumonitis, pancreatitis, interstitial nephritis and agranulocytosis. The safety of 5-ASA regarding its use in human pregnancy was examined in one case-controlled study (26). In a prospective follow up of 165 women exposed to mesalamine during pregnancy, 146 of whom had first trimester exposure, no increase in major fetal malformations was observed.

Although, the efficacy of 5-ASA in maintaining remission of CD is likely to be marginal, we instituted 5-ASA in the form of Salofalk® or Pentasa® at a dosage of 2-4g/d for all of our patients as maintenance therapy. For patients if extensive small bowel disease, we prefer to use Pentasa® rather than Salofalk® because of the slow releasing property of Pentasa® starting from the proximal small bowel. Altogether, we had eight patients being put on Salofalk® and 7 patient on Pentasa®. No major side effects have been reported in any one of our patients.

3.2 Corticosteroids

Corticosteroids are the first medications to be evaluated systematically in patients with CD and are well established as being efficacious for the treatment of active CD,

regardless of disease distribution. The exact mechanism of action is not completely understood and likely to be multifactorial. Corticosteroids modify almost every part of the inflammatory response, including cell-mediated immunity and the production of inflammatory mediators such as prostaglandins, leukotrienes, platelet activating factors, and cytokines.

The National Crohn's Disease Cooperative Study (15) and the European Cooperative Crohn's Disease Study (16) both showed that approximately 70% of patients who are treated with 40-60 mg/d of prednisolone for 3-4 months enter remission. Prednisolone is the most commonly used oral steroid and is usually initiated at a dose of 40mg/d. Initial prednisolone therapy is usually continued for 2 to 3 weeks, by which time a successful response should be seen. Prednisolone can then be slowly tapered to avoid unnecessary toxicity. It is well established that there is no role for corticosteroids in remission maintenance in CD. Hence, corticosteroid therapy is indicated primarily for the short-term induction of a remission of CD and not as maintenance therapy.

The beneficial effects of corticosteroids can be counterbalanced by their side effects. Recent attention has been focused on newer formulations of steroids, which are poorly absorbed or extensively inactivated by the liver to minimize systemic side effects. Budesonide was developed as a novel corticosteroid. It is readily water-soluble and has high topical antiinflammatory activity as a result of its strong affinity for corticosteroid receptors. Its systemic bioavailability, however, is low (10 to 15 %) because it is rapidly metabolised by cytochrome P-450 enzymes in the liver. Budesonide has been formulated into a coated-capsule preparation (Entocort®) containing acid-stable microgranules composed of an inner sugar core surrounded by a layer of budesonide in ethylcellulose and an outer acrylic-based resin coating (Eudragit L100-55) that dissolves at a pH of 5.5 or higher. Budesonide, in this formulation, is delivered in a controlled manner in the ileum resulting in absorption of 52-79% in the terminal ileum and right side of the colon.

A Canadian multicentre dose finding study (27) found that 9mg/d of budesonide was more effective than placebo for the induction of remission in patients with moderately

active CD. The proportion of patients experiencing glucocorticoid related adverse effects was not greater than with placebo treatment. In another European study (28), 9mg/d of budesonide was found to have comparable effect with prednisolone in induction of remission. The central conclusions from the authors in these two studies are that budesonide is better than placebo and comparable to prednisolone in the treatment of active CD with fewer side effects and less suppression of the hypothalamic-pituitary-adrenal axis.

From my impression, budesonide might be less encouraging than it might seem at first glance. First, by no outcome criterion was budesonide as efficacious as prednisolone. In the European study, for example, the rates of complete and partial remission were higher in the prednisolone group at every follow-up interval, as were specific improvements in bowel movements and overall well-being. Second, trials also suggested that the peak remission rates were not achieved with budesonide before eight weeks, whereas in the European study the remission rates with prednisolone therapy were maximal by four weeks. Third, the adrenal suppression with budesonide treatment is not entirely absent. In the Canadian trial, for instance, 69 percent of the patients receiving 9 mg of budesonide daily had suppressed morning plasma cortisol levels, and 50 percent had impaired responses to corticotropin stimulation. Whether the systemic actions of corticosteroids play a greater role than their local mucosal actions is still uncertain.

If budesonide can maintain long-term remissions without toxicity, then perhaps it may have a greater value. Three randomised placebo controlled trials have evaluated the use of either 6mg/d or 3mg/d of budesonide for 1 year of treatment (29,30,31). Taken collectively, these studies suggested that budesonide treated patients remained in remission longer than those who received the placebo did. However, the response was not durable. The greatest difference in remission rates was observed 3 months after randomisation whereas at 1 year no significant differences were present. There is no evidence, therefore, at present to support the routine use of budesonide as a maintenance therapy for CD.

We have prescribed Entocort® controlled-ileal-release (CIR) formulation in one of our CD patients, who suffered from ileocecal CD associated with frequent relapse. He had some Cushingoid appearance as well as symptom of low back pain secondary to osteoporosis, which will probably aggravated by systemic steroid therapy. Apparently, his back pain was not worsen with several courses of Entocort® CIR but it took an average longer period of over eight weeks to wean off the Entocort® each time. My impression is that budesonide may be of value in a selective group of CD patients. It should be limited to patients with mild to moderate disease involving the terminal ileum and or the right side of the colon. It may be desirable for patients that are steroid dependent or having complications of chronic steroid use like Cushingoid features. It may be of value in patients with osteoporosis but the actual benefit has not yet been proven. It is important to note that most of the studies on budesonide included patients with mild to moderate CD involving the terminal ileum and right side of the colon. Its actual benefit for severe, extensive CD, fistulizing CD and patients who have undergone extensive bowel resection has not been established.

3.3 Azathioprine and 6-mercaptopurine

Immunomodulators that suppress the immune system and down-regulate inflammation, such as 6-mercaptopurine (6-MP) and azathioprine, are now considered front-line drugs for the long-term therapy of CD. Azathioprine and 6-MP are purine analogues, that competitively inhibit the biosynthesis of purine nucleotides and cell proliferation. These agents alter the immune response via inhibition of natural killer cell activity and suppression of cytotoxic T-cell function, which likely explains the 3-6 months delay in their onset of clinical efficacy.

Both azathioprine and 6-MP have been shown to be effective in active CD patients by improving their overall symptoms. A meta-analysis of nine randomised placebo-controlled trials showed efficacy in treating active CD and in maintaining remission (32). Azathioprine and 6-MP have also proven to be effective steroid sparing agents in CD. There are also data to support the use of these agents to treat active perineal disease and fistulas (33). Reports on the use of azathioprine or 6-MP seem to be of

benefit in postoperative prophylaxis of disease recurrence, but additional controlled studies are required (34).

The primary role of azathioprine and 6-MP have been reserved for patients with active CD who failed to respond to aminosalicylates, antibiotics, or corticosteroids, or who are dependent on corticosteroids. These medications take four to six months to demonstrate their full effect, although some patients respond more quickly. The delayed onset of action of the purine analogues is an obstacle when using these agents for the management of active CD. A small uncontrolled study showed an initial promise in induction therapy with intravenous loading in steroid dependent or refractory CD patients (35). However, a subsequent randomised controlled trial (36), which evaluated 96 patients, showed equally low remission rate at 8 weeks in patients who received either loading or conventional azathioprine regimens. Furthermore, the proportion of patients entering remission did not increase after 8 weeks of treatment.

Recent recognition of the metabolic pathways of azathioprine and 6-MP along with the identification of genetic polymorphisms of an important enzyme thiopurine methyltransferase (TPMT) has opened the door for potential therapeutic monitoring of these agents in this disease setting (37). Once absorbed, azathioprine is rapidly absorbed and converted to 6-MP in the liver, by sulphydryl compounds such as glutathione. 6-MP is then metabolised by TPMT to 6-methylmercaptopurine, by xanthine oxidase to the inactive 6-thiouric acid or by a series of steps to active 6-thioguainine nucleotides.

The production of TPMT is genetically determined, whereas xanthine oxidase and the enzymes that convert 6-MP to 6-thioguanine are not genetically regulated. Myelosuppression in patients treated with azathioprine has been attributed to low activity of TPMT. Congenital deficiency of TPMT or inhibition of xanthine oxidase by allopurinol predispose to accumulation of 6-MP with the potential for severe bone marrow suppression. Mutant alleles of the TPMT gene has recently been demonstrated in association with enzyme deficiency (38). Approximately 1/300 individuals produce low levels of TPMT and, hence, convert 6-MP directly to 6-

thioguanine (6-TG), the active metabolite. 6-methylmercaptopurine, in contrast, is not thought to influence the immune activity but is associated with hepatotoxicity.

A recent study has suggested that there may be a therapeutic level of 6-TG associated with remissions in CD (39). If these studies bear out in prospective series, therapeutic monitoring for 6-TG may be an important advance. Compared with corticosteroids, azathioprine and 6-MP have less long-term toxicity. Intolerance to azathioprine or 6-MP has been noted in up to 10% of patients and includes fever, rash, nausea, and headaches. Pancreatitis occurs in 2-4% of patients on azathioprine or 6-MP and typically presents within the first few weeks of therapy and promptly resolves on drug withdrawal leading to chronic symptoms. The patient should never be restarted on either medication. Bone marrow depression is dose related and may be delayed. Mild hepatitis can usually be reversed by lowering the drug dosage. Long-term side effects occur in less that 2% of patients, but the development of opportunistic infections in patients on immunomodulators plus steroids should be watched out carefully.

The incidence of various cancers, especially non-Hodgkin lymphoma, is higher among patients who receive azathioprine for immunosuppression after organ transplants than in the general population. In a study of the risk of neoplasia after azathioprine in 755 patients treated for inflammatory bowel disease, no significant excess of cancer was observed and no single case of lymphoma was identified (40). The results were consistent with that of the Oxford series disclosed in the recent British Society of Gastroenterology Spring Meeting, in which a total of 2205 patients with inflammatory bowel diseases treated with azathioprine at a mean duration of 26 months were evaluated. Reassuringly, no increased risk of colorectal cancer or other tumours were observed. (41)

We had 8 CD patients on maintenance azathioprine, 5 for frequent flare and 3 for prophylaxis after surgery for an active disease. Most of our patients tolerated well to azathioprine except one patient who developed cytopenia. Although a meta-analysis supports the use of azathioprine at a maintenance dosage of 2.0-2.5mg/kg/d for CD, we found that our Chinese patients responded to a lower dosage of 1.0-1.5mg/kg/d.

3.4 Methotrexate

Methotrexate is another immunomudulator that has been found to be effective for treatment of CD. It is an anti-metabolite that inhibits dihydrofolate reductase resulting in impaired DNA synthesis. It has molecular homology to IL-1 and interferes with inflammatory action of IL-2. Dose which has been used in CD is 25mg intramuscularly once a week for short course, i.e., 12 weeks, and the beneficial effect is usual apparent within 2 to 4 weeks.

A multicentre, placebo-controlled trial enrolling 141 patients with active CD demonstrated that parenteral methotrexate 25mg intramuscularly or subcutaneously weekly over 16 weeks was twice as likely to allow steroid tapering and maintenance of remission (42). The effective of methotrexate in maintaining remissions for CD was supported by a recent multicentre randomised-controlled study, in which patients with chronically active CD who had entered remission were included. Treatment with a low dose of methotrexate was found to maintain remission (43).

Potential toxicity of methotrexate includes leucopenia, and hepatic fibrosis. Hypersensitivity pneumonitis is a rare but potentially serious complication of the therapy. Methotrexate is a known teratogen and abortifacient and should not be used during pregnancy or in men or women planning conception.

Methotrexate, I believe, is probably a good alternative drug for patients who are intolerant to or not responding well to azathioprine. However, we have so far no experience in using this drug in any one of our CD patients. We had one patient who was intolerant to azathioprine because of cytopenia and hence not suitable for methotrexate.

3.5 Cyclosporin

Cyclosporin is a lipid soluble fungal derivative with potent immumosuppressive effect, which acts primarily on T-cell function and proliferation, mainly through inhibition of

IL-2 gene transcription. Its efficacy in CD is less clear. Oral absorption is variable and incompletely understood.

In uncontrolled series, up to 60% response to cyclosporin in patients with refractory CD was reported. In one randomised placebo-controlled trial, 38% response rate was reported with treatment of cyclosporine in patients with active chronic CD who were resistant to or intolerant of corticosteroids (44). However, two large controlled trials failed to demonstrate any benefit from oral cyclosporin 5mg/kg/d at preventing CD relapse (45,46). Nevertheless, there is some evidence to suggest healing of Crohn's fistula with treatment of intravenous cyclosporin (47).

Hypertension, gingival hyperplasia, hypertrichosis, paresthesia, tremor, headache, electrolytes disturbances are common side effects. Nephrotoxicity is an important potential complication necessitating dose reduction or discontinuation of therapy, particularly if significant rise in serum creatinine. Seizures may also complicate therapy particularly if serum cholesterol values are less than 120mg/dl. Opportunistic infections, most notably pneumocystis carini pneumonia have occurred.

We had tried oral cyclosporin at a daily dosage of 4mg/kg/d in one of our CD patients who suffered from chronic active CD not responding to systemic therapy but reluctant for surgery. However, he had no response to cyclosporin and followed a gradual downhill course and eventually succumbed.

3.6 Antibiotics

Experimental and clinical evidence suggests that bacterial flora may play a role in the pathogenesis of CD. Antibiotics, including metronidazole and ciprofloxacin, are being used successfully in patients with active CD. Beneficial effect has been observed in perianal and fistulous CD. Metronidazole at dosage of 20mg/kg/d can be effective in inducing remission in active Crohn's colitis and in treating fistulae, sinus tracts, and abscesses that occur in CD involving the perineum. (48,49). Metronidazole also

decreases the endoscopic recurrence of aphthous ulcerations associated with early disease at the site of the anastomosis following intestinal resection for CD (50).

Common side effects include nausea, epigastric dsicomfort, metallic taste and disulfuram-like reaction. The patient must avoid alcohol while on this agent. Peripheral neuropathy from long-term administration of metronidazole (3 to 6 months at 750 mg/d or greater) is the most severe side effect. Neuropathy is a dose-cumulative side effect and is seen in one-third of patients. An additional one-third of patients may have subclinical neuropathy detected after formal neurologic testing. The neuropathy reverses very slowly (6 to 18 months) and sometimes only incompletely after metronidazole is discontinued. Therefore, every attempt should be made to keep long-term doses of metronidazole at less than 750 mg/d.

Ciprofloxacin is a very good alternative antibiotic therapy for CD patients with perineal disease or fistulae, who have either become refractory to metronidazole or who can no longer tolerate its side effects. Ciprofloxacin has been used successfully in the treatment of active CD with improvement in symptoms in 50-60% of patients. Metronidazole plus ciprofloxacin has been examined for the treatment of active, refractory CD. In a comparison trial with steroids, ciprofloxacin, 500 mg bid plus metronidazole, 250 mg qid were evaluated (51). Ten out of 22 CD patients treated with antibiotics (45.5%) compared with 12 out of 19 CD patients treated with steroids (63%) obtained clinical remission as defined by a Crohn's Disease Activity Index of less than 150. Therefore, ciprofloxacin plus metronidazole may be useful in some patients with active CD.

Antibiotics were prescribed to 4 of our CD patients, 2 for perianal disease and 2 for frequent relapses. We usually commence metronidazole at a dosage of 20mg/kg/d for and try to decrease to maintenance dosage of 10mg/kg/d to minimize the risk of neuropathy. Switching to ciprofloxacin 250mg twice daily was found to be useful on occasion when the fistula discharges worsens while the patient was on metronidazole. We had 2 patients who were on antibiotics for frequent relapses with switching therapy between metronidazole 10-20mg/kg/d and ciprofloxacin 500mg/d.

3.7 Nutritional therapy

Several studies have found similar efficacy between elemental diets and corticosteroids in achieving remission of active CD (52). Elemental diets consist of completely predigested nutrients such as glucose, amino acids and fatty acids. The mechanism of action is not fully understood. The efficacy of elemental diet may be due to decreased presentation of complex antigenic stimuli found in whole food, alternations in the composition of the colonic flora and nutritional repletion. Elemental diets have several disadvantages. The presence of free amino acids and limited fat content make these preparations hyperosmolar and unpalatable. Flavouring supplement is required when given orally and a feeding tube is often necessary to achieve dietary compliance. Meta-analysis of randomised controlled trials, nevertheless, revealed that elemental diet was inferior to corticosteroid therapy in achieving remission (53,54).

Enteral nutrition in the form of non-elemental diet preparations has also been used in treatment of active CD. Semi-elemental formulations contain peptides, oligosaccharides, and medium chain triglycerides. Polymeric diets consist of starches, protein, long-chain and medium-chain triglycerides, vitamins and minerals. The theoretical advantage of oligomeric formulas is related to the absorption of di-peptides and tripeptides, which have specific transport mechanisms for their intact uptake and are absorbed more efficiently than are amino acids or whole protein. A meta-analysis of randomised controlled trials in patients with active CD treated with elemental versus nonelemental formulations however showed no difference in the likelihood of achieving remission (54).

It is important to note that neither elemental diet nor total parenteral nutrition is effective in maintenance of remission. Long term remission rates were generally poorer among patients who underwent therapy with elemental diets compared to conventional therapy.

We have tried to institute oligomeric diet in the form of Vital® in 2 of our CD patients during an acute flare, as an adjuntive therapy in addition to conventional systemic corticosteroid treatment. The major complaint from both patients was poor taste of the diet, which lead to unsatisfactory compliance.

3.8 Anti-tumour necrosis therapy

In the past, medical treatment has focused on nonspecific suppression of the inflammatory process. Recently, there is increasing evidence that a disturbance in the balance between proinflammatory and anti-inflammatory cytokines occurs in CD. It was found that during chronic intestinal inflammation, large amounts of the proinflammatory cytokines tumour necrosis factor(TNF)-alpha, IL-1, and IL-6 are synthesized and secreted by activated lymphocytes and macrophages within the inflamed intestinal mucosa. The biologic effects of TNF-alpha, IL-1, and IL-6 result in the amplification of immunologic and inflammatory processes.

Biologic therapy has emerged into clinical practice with development of anti-TNF-alpha antibody. The most extensively studied anti-TNF-alpha antibody is infliximab. It is a mouse-human chimeric monoclonal IgG_1 antibody directed against TNF-alpha. The monoclonal antibody is made in mice (55). Mouse monoclonal antibodies can not be infused into a human because a very severe reaction against the xenogeneic molecules would occur. Therefore, the monoclonal antibodies are chimerised, which means that the Fab part of the antibody which recognises the TNF-alpha is still mouse. However, the other two-thirds of the chimeric antibody is a human, IgG_1 F_C fragment. The IgG_1 F_C fragment is important because it is able to activate complement.

The mechanism of action of infliximab is not entirely clear. Originally, it was thought that it would neutralise soluble TNF. However, the clinical effect is too long lasting for that to be the case. It is therefore currently theorised that the monoclonal antibody recognises TNF-alpha, which has attached to TNF-alpha receptors present on activated macrophages and T cells, which themselves are capable of producing large amounts of TNF. There is some evidence that the IgG_1 F_C fragment may trigger the

activation of complement-pathway components leading to macrophage and/or T-cell lysis (56).

In a multicentre, randomised, placebo-controlled trial, a single intravenous dose of infliximab was administered in regimens of 5 mg/kg, 10 mg/kg, 20 mg/kg, or placebo to individuals with moderate to severe CD. Overall, clinical remission occurred in 33% of all patients compared with 4% of patients receiving placebo. (57). The most efficacious dose studied was the 5-mg/kg schedule. In generalisation with other studies, the percentage of CD patients responding to infliximab is approximately 70% with approximately 40% achieving remission. The time to response is approximately 2 weeks, with relapses occurring in the range of 6 to 8 weeks following initial response.

One of most significant therapeutic breakthroughs is that clinical improvement after infliximab therapy in active CD patients has been demonstrated to be accompanied by significant healing of endoscopic lesions and disappearance of the mucosal inflammatory infiltrate. Crohn's ulcerations in the colon were found to have significant improvement within 4 weeks of infliximab treatment (58). This is in contrast to treatment with corticosteroids, the mainstay of therapy, where only 29% of patients with colonic CD showed endoscopic healing in two studies. (59,60). In addition to providing mucosal healing, infliximab has been shown to restore the mucosa and submucosa. In a study that evaluate the effect of histologic healing, a single infusion of infliximab resulted in disappearance of histologic signs of active inflammation, accompanied by a downregulation of inflammatory mediators. (58, 61).

Subsequent study demonstrated efficacy with repeated infusions of infliximab, given at 8 weeks intervals (62). Of the 108 patients initially treated with 5, 10, or 20 mg/kg of infliximab, 73 patients who had responded during the initial treatment were entered into a retreatment trial. The medication was administered up to 36 weeks on an every-8 week basis and the patients were followed until week 48. Both the clinical response rate and also the clinical remission rate were maintained by giving the infliximab infusions, whereas placebo infusions resulted in a gradual loss of clinical response and/or clinical remission. In general, enterocutaneous fistulae can be serious

complications of CD and often are quite difficult to treat. Infliximab has also been shown to be an effective treatment for enterocutaneous fistulae in patients with CD. (63).

Adverse events following use of infliximab include upper respiratory tract infections, nausea, abdominal pain, fatigue and fever. There may be a moderate immunosuppressive effect of infliximab, although the peripheral white blood cell count is not suppressed. Any ongoing infection is a contraindication to the use of this agent due to the possibility of dissemination of the infection. If infliximab is being used to treat fistulae, the patient should not have an abscess due to the potential risk of spread of infection.

As infliximab is a chimeric antibody with a 75% human and 25% murine component, it has the potential to induce the development of human antibodies directed against infliximab, otherwise known as human anti-chimeric antibodies (HACAs). Approximately 13% of CD patients infused with this antibody develop HACAs. Infusion reactions have been observed in HACA-positive patients consisting of shortness of breath, chest pain, fever, and/or urticaria. These reactions are seen in about 15% of patients and are easily treated by stopping the infusion, treatment with benadryl, and restarting after resolution of symptoms. The incidence of infusion reactions is positively correlated with the number of infusions received and the presence of HACAs, and negatively correlated with the use of concurrent immunosuppressants (azathioprine, 6-MP, methotrexate, and possibly corticosteroids).

A more serious delayed hypersensitivity reaction has been observed in patients with CD who had previously received a single infusion and then delay retreatment after a "drug holiday" for 2 to 4 years (64). Subsequent to their initial infusion, 10/40 (25%) patients who were retreated after a long infliximab-free interval, developed a "delayed hypersensitivity reaction." This reaction did not occur immediately; but develop 3 to 12 days after infusion. Initial HACA status after the first infusion did not correlate with the likelihood of developing this adverse event. The HACA was negative immediately before infusion but markedly elevated after the delayed hypersensitivity reaction. Six patients were hospitalised and received antihistamines and/or

corticosteroids. One patient also received epinephrine. All patients improved after receiving therapy in 1 to 4 days. Such delayed hypersensitivity reaction is a major concern in the retreatment after a drug holiday.

The other autoantibody that can occur is antinuclear antibody (ANA), with a positive ANA being seen in approximately 9% of infliximab-infused patients. Systemic lupus erythematosus (SLE) has not been reported from using infliximab and no serologic markers consistent with active SLE have been observed to date. However, a "lupus-like reaction" has been observed in a small number of patients. These individuals have double stranded DNA positivity with negative Ro, La, RNP, Sm, and Rheumatoid Factor serologies. The complement levels are also unaffected and there are no other organ systems affected other than the joints. This temporary reaction, which is similar to other drug-induced lupus-like reactions, resolves after treatment with corticosteroids without permanent sequelae.

The potential risk of malignancies has been an initial concern. Five lymphomas were reported in the initial formal studies of approximately 900 patients. More reassuring is that lymphoma has been reported in only 6 patients in the post-marketing surveillance where over 50,000 patients have been treated (39) and such patients were mainly patients suffering from rheumatoid arthritis or HIV infection. The actual risk of lymphoma seems to be illusive. A particular concern is the treatment of patient with active inflammatory strictures. The use of this biologic might cause conversion to a fibrotic stricture if the healing process leads to increased collagen production and vigorous scarring.

For special problematic CD patients, infliximab seems to be a promising novel therapy. Although the drug is not yet launched in Hong Kong, as information from the Department of Health, it could be used on a named patient basis.

3.9 Emerging therapy

There is another anti-TNF-alpha agent that is currently under investigation: CDP571. CDP 571 is a humanised monoclonal antibody with approximately 95% human and 5% mouse in composition. Only a small portion of the Fab TNF binding site is murine. It is currently undergoing phase II/III trials (65). Infusion reactions are uncommon. There is no formation of anti-DNA antibodies and no lupus-like reactions have been reported. Its efficacy is yet to be determined.

The recently released anti-TNF-alpha therapy approved for the treatment of rheumatoid arthritis, Etanercept, is also undergoing evaluation in patients with CD. This agent is a fusion protein of soluble tumor necrosis factor receptors to the Fc fragment of IgG immunoglobulin. It is 100% human. Etanercept is administered subcutaneously at a dose of 25 mg twice weekly. A phase II placebo-controlled study is underway in patients with active CD.

IL-10 is an important cytokine that is involved in regulation of pro-inflammatory cytokines and T-cell responses. The most remarkable effect of IL-10 is its ability to downregulate macrophage functions. This includes inhibiting the production of pro-inflammatory cytokines such TNF-alpha, IL-1, IL-6 and antigen presentation by these professional antigen presenting cells. Three studies of recombined human IL-10 have been reported in CD. The first study included steroid refractory CD patients with treatment of daily intravenous dosing for 1 week period. The response rate at 3 week was higher among treated patients than those receiving placebo (66). A second study examined the efficacy of a 28-day course of daily subcutaneous injection in patients with mild to moderate disease activity on no other medication. Greatest efficacy was seen at a median dosage of 5mg/kg/d (67). The third study replicated the dosing regimen of the second, but included only patients with chronic, active, steroid-resistant disease. No significant beneficial effect was observed (68).

The success of anti-TNF antibody in CD has led to an interest in thalidomide as a potential treatment. Thalidomide inhibits the transcription of TNF-alpha. It

inhibits TNF-alpha production by lipopolysaccharide-stimulated monocytes. This agent increases the degradation of TNF mRNA and inhibits IL-12 production. In addition, thalidomide is antiangiogenic (69,70). Two, small open-label studies of thalidomide in CD suggest it may be beneficial (71,72). The drug has a positive therapeutic effect in refractory CD and is particularly good in patients with fistulas. Thalidomide was used as a sedative/hypnotic in the 1950s and is highly teratogenic. It causes drowsiness and sedation along with rash and polyneuropathy. The sedative side effects were debilitating for some patients in the studies. This drug is not FDA-approved for treating CD. As an information, this drug is not available in Hong Kong.

3.10 Conclusion

Use of non-specific anti-inflammatory drugs is the foundation of the traditional therapy for Crohn's disease. However, recent advances in molecular biology have yielded novel therapy, which may be more relevant to tackle the underlying pathophysiologic abnormality of the disease. Hopeful, with a better understanding of the pathogenesis of CD, curative medical therapy can be developed in the future.

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