EXCLI Journal 2014;13:111-122 – ISSN 1611-2156
Received: October 21, 2013, accepted: December 11, 2013, published: February 13, 2014

Guest editorial:

SELECT A SUITABLE TREATMENT STRATEGY FOR CROHN'S DISEASE: STEP-UP OR TOP-DOWN

Qian-Qian Chen, Li Yan, Jun Wan*

Department of Nanlou Gastroenterology, Chinese PLA General Hospital, Beijing 100853, China
* Corresponding author: e-mail:wanjun301@126.com; phone.: +86-10-66876266; Fax: +86-404-68295664.

ABSTRACT

Crohn's Disease (CD) is a chronic immune-mediated disorder with progressive and destructive course. Current guidelines on the treatment strategy still recommend a step-up approach with sequential prescription of corticosteroids and immunosuppressives. However, mounting evidences manifested that top-down therapy with early administration of anti-TNF or combination of immunosuppressives can achieve more rapid and higher rate of mucosal healing and has the potential of modifying the natural course of disease. Therefore, who is suitable to accept and when to start anti-TNF therapy have attracted the attention of gastroenterologists. And what benefit/risk can be expected from the two strategies should be carefully taken into account by clinicians. Age stratification, special patients, disease location and extension, genetic and serologic testing are predictors of disease progression and complication and thus guide a personalized treatment approach in CD. A definition of early CD has been proposed to select an algorithm for treatment of moderate-to-severe CD with a suitable strategy. To date mucosal healing has been widely used, the Lémann score, which assesses the extent and severity of bowel damage at a specific time-point and over time, and is a new disability index for patients with CD, will be considered as a new endpoint for future studies of treatment strategies. Besides medicines of the two strategies, surgery, vaccine, Leukocytapheresis and stem cell therapy are all effective therapeutic approaches which lead to another thinking about what should they be putted in the conditional pyramid. However, we are trying to answer these questions.

Keywords: Crohn's disease, step-up therapy, top-down therapy, biologic therapy, immunosuppressive agents, treatment strategy

TREATMENT STRATEGY FOR CROHN'S DISEASE

Crohn's Disease (CD), which is one type of inflammatory bowel disease (IBD), is an immune-mediated disorder that mainly affects any part of gastrointestinal tract. Asia is witnessing a rapid rise in occurrence of CD with time. In China, the recent incidence and prevalence rates are 0.848/10(5) and 2.29/10(5) person/year, respectively (Ng et al., 2013; Zheng et al., 2010). The pathogenesis of CD mainly involves genetic, environmental and immunological factors (Kaser et al., 2010). The disease has a chronic relapsing course with the period of acute exacerbation, remission or less active status and can finally lead to disability, surgeries, long-term hospitalization, poor quality of life and even death (Cosnes et al., 2011). Current treatment, comprised of

EXCLI Journal 2014;13:111-122 – ISSN 1611-2156
Received: October 21, 2013, accepted: December 11, 2013, published: February 13, 2014

medical and surgical procedures, is largely directed at symptom relief rather than modifying or reversing the underlying pathogenic mechanism. The goal of treatment includes inducing remission (active treatment of acute disease) and maintaining remission (treatment of preventing relapse) (Mayberry et al., 2013).

During the past decade, the development of biologic therapies for CD has brought hope to patients and also led to an argument between step-up therapy and top-down therapy. Many trials of biologic therapies (including the combination of immunomodulators) are still in progress, but other than anti-TNF therapies, very few are likely to reach the clinic in the near future (De Vroey and Colombel, 2011). Step-up therapy is a traditional therapeutic approach which has still been recommended by current guidelines (Mayberry et al., 2013; Dignass et al., 2010). It has focus on induction of a clinical remission using a progressive intensification of treatment as the disease severity. 5-Aminosalicylates (5-ASA), corticosteroids, immunosuppressive drugs (e.g., Thiopurines) and biological agents (e.g., Infliximab, IFX) were used sequentially to treat mild-to-severe CD (Bar-Meir, 2009). But this strategy cannot positively induce mucosal healing and alter the natural history of CD (Lin et al., 2010). Therefore, mounting preliminary studies have showed that reversing the treatment paradigm from step-up approach to top down approach may remedy the defect (Lin et al., 2010; D'Haens et al., 2008; Present et al., 1999; Colombel et al., 2007; Ford et al., 2011). Top-down therapy refers to aggressive and early use of biological agents and immune modulators in order to avoid complications or surgery, decrease hospitalization and improving quality of life (Fascì Spurio et al., 2012; Blonski et al., 2011).Though this strategy is associated with better clinical outcomes, these drugs have rare but potentially serious side effects (Lin et al., 2010; D'Haens et al., 2008; Present et al., 1999; Colombel et al., 2007; Ford et al., 2011).

For the treatment of CD, there is no "one size fits all". What gastroenterologists can do is to select a suitable treatment strategy for every patient. So new questions occurred: What is the rationale for selecting step-up therapy or top-down therapy? What benefit/risk can be expected from the two strategies? Is top down approach a good idea for all CD patients? At what points in the natural history of CD should one be started and ended? Is early therapy in CD only biologics and immunomodulators? However, we are trying to answer these questions.

WHICH ONE IS BETTER? STEP-UP VERSUS TOP-DOWN THERAPY

Step-up therapy is done first with less effective and limited systemic toxicity drugs, such as 5-ASA, antibiotics or glucocorticosteroids, mainly to suppress the symptoms of the disease. Then it moved to next step in non-responders by using more aggressive but higher toxicity immunosuppressive agents (azathioprine, mercaptopurine and methotrexate) and biologic agents (antitumor necrosis factor antibody, anti-TNF antibody, including infliximab, adalimumab, certolizumab pegol; monoclonal antibodies directed against the α4-integrin, natalizumab; monoclonal antibodies targets the α4β7-integrin, vedolizumab;etc.) in order to both induce and maintain remission (Mayberry et al., 2013; Bar-Meir, 2009; D'Haens, 2010; Gionchetti et al., 2011). Although this strategy is usually effective for symptom control with less adverse events and can avoid overtreatment of low-risk patients. The failure to optimize conventional therapy can lead to patients' being not receiving the optimal initial therapy before experiencing complications (structuring or penetrating) and intestinal resections at final and being unnecessarily exposed to potentially toxic and/or expensive biologic drugs, which is seriously impact their quality-of-lives (QOL) patients (Domènech et al., 2009; Taylor and Irving, 2011).

EXCLI Journal 2014;13:111-122 – ISSN 1611-2156
Received: October 21, 2013, accepted: December 11, 2013, published: February 13, 2014

The top-down strategy has been adopted for managing rheumatoid arthritis where there is a focus on treat-to-target to achieve early remission (Knevel et al., 2010). Lessons from rheumatoid arthritis can be translated to Crohn's disease. Recently many trials (Mayberry et al., 2013; Lin et al., 2010; Kim et al., 2011; Yang et al., 2012; Xiao et al., 2012; Orlando et al., 2012) (Supplementary Table 1) have shown that patients who were administrated of immunosuppressive or biologic agents in the earlier phases of CD achieved less clinical relapse, less steroid use, better mucosal healing, fewer hospitalizations, fewer complications and surgeries than those with the same disease that were further given those drugs. These findings have stimulated efforts in the field of CD towards to intensive and early top-down approach. However, the evidence of wide use is still not strong enough, because the studies (Supplementary Table 1) are somewhat susceptible to several methodological criticisms:

(1) lack of large scale and multi-center trails;
(2) often being open label studies;
(3) not always giving sufficient consideration of maintenance therapy especially in step-up group; and
(4) always being short follow-up term.

Several arguments exist against the top-down approach in CD. First, Lin et al. (2010) and Kim et al. (2011) reported that approximately 30 % of patients might have been over treated by applying this therapy. Second, infliximab was found to be associated with 3-fold increase in malignancy and 2-fold increase in serious infection in treatment of in rheumatoid arthritis (Bongartz et al., 2006). Therefore, future therapies of CD will be individualized and targeted to optimize treatment outcomes and to reduce the disadvantages related to the two strategies.

WHAT ARE THE LONG-TERM CONSIDERATIONS FOR PATIENT WITH CD?

CD is a chronic and life-time of recurrent disease with flare-ups and remission, so we cannot just consider the short-term induction therapy. Long-term efficacy, safety and cost are main concerns of risk/benefit assessment of different treatment strategies (Supplementary Figure 1). In step-up approach, infections associated with corticosteroids and lymphoma caused by azathioprine are commonly seen adverse events. In top-down approach, serious infections, lymphoma and malignancies are side effects of anti-TNF agents and immunosuppressives. In a more than 5 years of follow-up study, 36.273 patients (3.420 infliximab and 2.853 other-treatments-only) have been enrolled into the TREAT registry, mortality was similar for infliximab and other-treatments only patients (0.58 vs. 0.59/100 patient-years of follow-up), an increased risk of serious infection with infliximab was observed (HR=1.43), and severity of CD at baseline (HR=2.24) and use of narcotic analgesics (HR=1.98) or prednisone (HR=1.57) carried higher risks for serious infection (Lichtenstein et al., 2012). In a cohort study (1996–2009), data showed that use of anti-TNF with thiopurine and current use of thiopurine alone were associated with increased risk of lymphoma, including diffuse large B-cell lymphoma (44 %), follicular lymphoma (14 %), and Hodgkin's disease (12 %) (Herrinton et al., 2011).

In addition, the economic burden of patients with CD is very high not only in China but also in developed countries. Because patients must spend a lot of money on medicine, especially biologics, which most of them do not belong to the scope of medical insurance medicine. Meanwhile, some of patients with CD would experience disability, loss of work productivity, surgery and hospitalization (Ordás et al., 2011). Therefore, it is important to offset the high cost by selecting a suitable treatment strategy to

maintain long-term remission and prevent poor outcomes of CD.

In conclusion, many studies have shown the direction of administrating biologics and immunomodulators, which offer an important clinical benefit for patients with severe CD. But the risk-benefit ratio and cost-effectiveness should be carefully taken into account by clinicians when treatment strategies are established.

WHICH IS THE TAILORED THERAPY FOR SPECIFIC SUBGROUP OF PATIENTS WITH CD? AGE SECTION, BIOLOGICAL MARIKERS OR LOCATION OF DISEASE

CD is a disease affecting all age groups, but there is a bimodal peak in incidence rates by age group with the first peak occurring between the second and third decades of life (teenagers and young adults) and a second peak occurring between 55-59 years (Day et al., 2012; Quezada et al., 2011). In addition, we should accurately distinct elderly-onset CD and elderly people with disease starting at a younger age. A population-based study showed that 1/20 incident cases of elderly-onset CD occurred in people>60 years of age (Charpentier et al., 2014). The heterogeneity of manifestations, a potentially insidious onset, the presence of overlapping features, extraintestinal symptoms and different features of every age stage can make the diagnosis and treatment of CD difficult (Charpentier et al., 2014; Dretzke et al., 2011). So we should take specific consideration to children, adolescents, adults, and elderly when determining a treatment strategy (Supplementary Table 2) (Day et al., 2012; Krupoves et al., 2011; Sherlock and Griffiths, 2012; Day et al., 2013; Sprakes et al., 2012; Assa et al., 2013). For children and adolescents, optimizing nutritional status and growth, minimizing psychological concerns and possible side effects of treatment are critical considerations of selecting a suitable treatment strategy (Mayberry et al., 2013; Day et al., 2012; Charpentier et al., 2014; Krupoves et al., 2011; Sherlock and Griffiths, 2012; Day et al., 2013; Sprakes et al., 2012; Assa et al., 2012; Beaugerie et al., 2009; Setshedi et al., 2012; Cottone et al., 2011). For adults, optimizing conventional “step-up” therapy is still the recommendation, and the benefit of combination therapy has been demonstrated by many studies. But new “top-down” therapy is appropriate in moderate-to-severe CD and more data supporting the efficacy and safety are needed before combination therapy becomes the first choice treatment. To persuade the patient to quit smoking is also effective for treatment (Lakatos et al., 2013; Pithadia and Jain, 2011; Danese, 2012; Melmed et al., 2010). For the elderly, especially those>65 years, anti-TNF therapy would be a dangerous choice and improving quality of care should be taken (Charpentier et al., 2014; Beaugerie et al., 2009; Setshedi et al., 2012; Cottone et al., 2011).

In addition, the medical managements of pregnancy and post operation in CD require careful discussions with individual patients. During pregnancy, it is necessary to optimize disease control by treating aggressively to prevent adverse outcomes (Mowat et al., 2011).The conventional medicine (5-ASA) is safe in pregnancy and breast feeding (Selinger et al., 2012). Metronidazole is considered safe after the first trimester (Mowat et al., 2011). In a recent population-based study, children born to mothers with CD got an increased risk of congenital abnormalities in women exposed to both corticosteroids and acetazolamide (Norgard et al., 2007). Methotrexate is strictly contraindicated because of the serious side effects of teratogenicity (Selinger et al., 2012). Infliximab and Adalimumab are rated as a second line medicine for pregnancy, which considered probably safe during the first two trimesters (Vermeire et al., 2012). There are need more evidence of the use of these during breast feeding. Approximately 80 % of patients with CD would finally accept operation, of whom 70 % will require a further surgery (De

Cruz et al., 2013). Therefore, it is necessary to select appropriate treatment strategies to prevent postoperative recurrence. In a cohort study, step-up approach consisted of antibiotics, 5-ASA, thiopurine and methotrexate has been recommended (De Cruz et al., 2013). Lakatos and Lakatos (2010) demonstrated that anti-TNF agents may be appropriate for postoperative prevention and therapy in most severe cases. Savarino et al. (2012) further reported a case series of six patients who were given Adalimumab at the dose of 160/80/40mg every 2 weeks after resection for an ileocecal stricture caused by CD have been disease-free for about 3 years after surgery on clinical, radiological, and endoscopic/histological grounds (Crohn's Disease Activity Index ≤ 110 in all occasions). Such therapeutic benefits of strategies remain to be proven by further large controlled studies.

There is accumulating evidence that current treatment strategy is guided by the disease location, severity, associated complications and concurrent therapy taken by patients (Lin et al., 2010). Patient with CD involved of terminal ileum are strongly associated with an increased risk of stricture or penetrating behavior (Louis et al., 2010). Patients with rectal disease (92 %), colonic disease (41 %) and ileal disease (12 %) are associated with perianal disease (Hellers et al., 1980). They both lead to an increased risk of surgical resection (Lin et al., 2010, Hellers et al., 1980). In Loly's study (Loly et al., 2008), the multivariate analysis showed that selected ileocolonic location needed steroids to treat the first flare. Costantino et al. (2012) indicated that administration of thiopurines among disease- and patient-related parameters a shorter disease duration, female gender and ileal disease in Crohn's patients had resulted in better response.

Although clinical parameters have some predictive value for prognosis and guiding treatment strategies in CD, their application still have some unsolved problems. The search for genetic polymorphisms and cytokine profiles in CD has led to direction of potential predictors of prognosis and thus of identifying patients who should be treated more aggressively early on (top-down). Genome-wide association studies have identified approximately 71 CD-associated gene susceptibility loci and some of these have been studied their relation to CD phenotype and disease course (Franke et al., 2010). The nucleotide oligomerization domain 2 (NOD2) or caspase-activating recruitment domain 15 (CARD15) is known as a major susceptibility gene associated with worse CD prognosis and more likely to require surgical resection (Tamboli et al., 2011). Recently, Plantinga et al. (2011) indicated that variation in the autophagy gene ATG16L1 had been another major genetic susceptibility factor for CD and the risk variant of ATG16L1 is associated with an impaired induction of autophagy specifically after NOD2 engagement. And it is relevant to IL-1β, IL-6 and TNF-α production in CD (Plantinga et al., 2011). These findings suggest that patient's genetic profile can assess risk of complicated disease which contributes to patient stratification and individualized care. Prieto-Pérez et al. (2013) demonstrated that gene polymorphisms can predict response to anti-TNF therapy in patients with immune disease, such as psoriasis (Ps), rheumatoid arthritis (RA) and CD. Gutiérrez et al. (2013) further confirmed that intensified anti-TNF therapy is more frequent in patients with mutated NOD2/ ATG16L1-combined genotypes.

Current data have shown that genetic mutations could lead to alteration in the expression of some serological predictors, such as antibodies to microbial antigens (Tamboli et al., 2011). These antibodies include anti-Saccharomyces cerevisiae antibody (ASCA, glycan antibody), antibodies to the Escherichia coli outer-membrane point C (OmpC), the Pseudomonas fluorescens CD-related protein [anti-CD related bacterial sequence (I2)] and the CBir1 flagellin, which are mostly associated with

early disease onset CD, CD with earlier complications and relapsing CD (Beaugerie et al., 2012). So these can also be used as predictors of CD course to guide the selection of treatment strategy.

In conclusion, age stratification, special patients, disease location and extension, genetic and serologic testing all have potential to predict disease progression and complication, and thus response to medical therapies, particularly biologic agents. In future, the combination of these would significantly contribute to a personalized treatment approach in CD.

WHEN TO INTRODUCE BIOLOGICAS AND WHERE IS THE ENDING POINT?

The key to step-up therapy and top-down therapy is whether earlier administrated with biologics or immunosuppressive agents. Population-based studies have shown that it is crucial to relate treatment instructions to the natural course of the disease for newly diagnosed CD. For the reason that the heterogeneous clinical course associated with high risk of disease progression is a guide to identify the beginning point of early intervention with highly effective treatment strategies (Ordás et al., 2011). Recently, a definition of early CD has been proposed to select an algorithm for treatment of moderate-to-severe CD with a suitable strategy (Supplementary Figure 2) (Ordás et al., 2011; Peyrin-Biroulet 2009; Burger and Travis, 2011; Yang et al., 2011). It is defined as disease duration<2 years and no previous use of immunosuppressive or TNF antagonists. And early surgical resection is another common choice for serious patients (Ordás et al., 2011; Burger and Travis, 2011; Yang et al., 2011).

CD therapy is based on the primary goals of achieving every remission endpoint and ultimate goal of altering the long-term disease history course. The primary goals should include:

(1) eliminate all symptoms related to a patient's CD;
(2) induction and maintenance of mucosal healing;
(3) maintenance of normal gastrointestinal function;
(4) avoidance of cumulative bowel damage;
(5) prevention of disability and surgery; and
(6) improving patients' QOL and reducing hospitalization (Ordás et al., 2011; Devlin and Panaccione, 2010).

Nowadays, many studies confirmed that mucosal healing is becoming a valuable end point for accessing therapeutic efficacy in CD (Fascì Spurio et al., 2012; Blonski et al., 2011; Domènech et al., 2009). It has been widely used in clinical trials and basic researches to assess the severity of CD (Fascì Spurio et al., 2012; Blonski et al., 2011; Domènech et al., 2009; Hébuterne et al., 2013; Danese and Peyrin-Biroulet, 2012). Mucosal healing is considered to be the first step towards clinical symptom and to guide treatment strategies. Because it could measure changes in the disease, including predicting the risk of clinical relapse, occurrence of complications, require for surgical resection or re-operations and potential for cancer and mortality (Reenaers et al., 2012). However, mucosal healing could only reflect the external closure of fistulous tracts and not correspond to complete healing of the penetrating bowel disease. Therefore, gastroenterologists are considering finding another end point of measuring the cumulative bowel damage. The International Program to develop New Indexes in Crohn's disease (IPNIC) group has conducted a new instrument, called the Crohn's Disease Digestive Damage Score (the Lémann score), to take into account damage location, severity, extent, progression, and reversibility by using computed tomography or magnetic resonance imaging enterography, and colonoscopy. The Lémann score could be used as a more reliable endpoint to assess efficiency of various treatment strategies on the progression of bowel damage (Pariente et al., 2011a, b).

Hommes et al. (2012) suggest that we should change Crohn's disease management by applying new goals and indices, such as the Lémann score, to prevent disability and patient's QOL.

In conclusion, though gastroenterologists have proposed an algorithm for treatment of early CD, there are still some modifications to every individual patient. Even if mucosal healing has been widely used to date, the Lémann score, which assesses the extent and severity of bowel damage at a specific time-point and over time, and is a new disability index for patients with CD, will be considered as a new endpoint for future studies of treatment strategies.

IS EARLY THERAPY IN CD ONLY BIOLOGICS AND IMMUNOMODULATORS?

Though biologics and immunomodulators have shared the main part of CD treatment, and led to an argument between step-up therapy and top-down therapy. There are many other effective therapeutic approaches, such as surgery, vaccine, Leukocytapheresis (LCAP) therapy and stem cell therapy.

The long term need of surgery in patients with CD could be decreased in the era of biologics (Jones and Finlayson 2010). In a population-based study, the surgery rate of patients newly diagnosed with CD in Cardiff between 1986 and 2003 at 5 years decreased significantly from 59 % (1986-91) to 25 % (1998-2003) by induction of infliximab (Jones and Finlayson, 2010). But surgery may still be a valid option in respect to a refractory CD with complications or failure of the medical therapy. Different disease location and extension also appear to influence the need for surgery (Bernstein et al., 2012). In future, the minimally invasive surgery, which aims at further reducing hospitalization and improving the cosmetic outcomes, will become standard clinical practice (Gardenbroek et al., 2012).

Patients with CD are at increased risk of infection, partially due to the disease itself, but mostly because of treatment with immunosuppressive drugs (Gisbert et al., 2013). Because vaccine can prevent many of infections, some clinical trials have been carried out to examine vaccine strategies for CD treatment (de Bruyn et al., 2012). Live vaccines are contraindicated in immunocompromised individuals, but inactivated vaccines can be safely to patients under immunotherapy (Rahier, 2013). But vaccination status should be checked and updated upon diagnosis of CD (Gisbert et al., 2013).

LCAP is a recent modality for treatment of patients with CD, especially those refractory to conventional therapies (including steroids) (Fukunaga and Matsumoto, 2012).The removal of circulating leukocytes to suppress immunological response is primary aim of LCAP (Mitsuyama and Sata, 2009). In Japan, it has been accepted by authority government organizations. In a preliminary clinical trial of LCAP for CD patients, significant clinical efficacy together with recovering peripheral immune response has been reported (Fukunaga ans Matsumoto, 2012). It is predicted that unique non-pharmacological and non-surgical strategy of LCAP has both effective and safety. And future strategies to optimize processing conditions and with or without combining biologics should now be studied (Muratov et al., 2012).

Mesenchymal stem cells (MSCs) are the focus of intensive efforts worldwide by developing cell-based therapies for a diverse range of disease, including graft-versus-host disease, Crohn's disease, myocardial infarction, and etc. Many basic and early clinical trails of MSCs therapy in CD have proven to be beneficial effects on mucosal healing and no result of toxicity or ectopic tissue growth (Duijvestein et al., 2010; Dalal et al., 2012). Local injection of MSCs is a novel and promising therapeutic strategy for refractory and fistulizing CD, offering hope to patients who have this notoriously difficult to treat and disabling manifestation of CD (Wood, 2011; Ciccocioppo et al.,

2011). MSCs have the potentials of homing to injured gut tissues, actively participate in tissue repair, and regulating immune and inflammatory responses (Frenette et al., 2013). So MSCs may serve as a candidate therapy for patients who have failed to respond to biological therapy. Currently, scholars are making great efforts to translate the science of MSCs into medicine (Bianco et al., 2013).

In conclusion, the development of novel therapeutic strategies is leading to another thinking about what should they be putted in the conditional pyramid.

CONCLUSIONS AND FUTURE DIRECTIONS

CD which is a global epidemic disease with rapidly progressive course and disabling complications attracted more attention to gastroenterologists all over the world. Conventional step-up approach with sequence use of low-toxicity drugs and novel top-down approach with early use of biologicals are both effective to inducing remission in the short term, but the latter one is more effective to maintain remission, decrease the rate of relapse, reduce administration of corticosteroids, prevent occurrence of complications and minimize operation in the long term. Due to the heterogeneity of CD, it is necessary to select a suitable treatment strategy for different patient. Current data have shown that age stratification, special patients, disease location and extension, genetic and serologic markers could be used as predictors of disease course. But little clinical trials are associated them with the two treatment strategies. In future, the management strategies to CD will be based on these predictors to evaluate therapeutic efficacies. The proposition of early CD provides a cue to determine when to start anti-TNF therapy or combination with immunosuppressives. This need more evidence to support. Furthermore, Lémann score (a tissue damage score) should be considered for a further study and be putted into widely use in CD to assess adequately the ability of treatment strategies to change natural history. Despite use of a traditional step-up therapy may has better the risk-benefit and cost-effectiveness ratio in the short term, most CD patients eventually require surgery at some time in their disease course. But new top-down therapy has remarkably achieving a long time efficacies. Therefore, further studies should pay more attention to the long-term benefits. Medical therapy is not the only treatment in CD, surgery, vaccine, LCAP and stem cell therapy are all effective therapeutic approaches which some of them are understudy. This lead to a further direction of changing the two classic paradigms:

1) Optimizing the traditional step-up approach by combination with vaccine.
2) Changing the top-down approach by early use of LCAP and stem cell therapy and re-evaluation of surgical timing.

ACKNOWLEGEMENTS

The first author would like to acknowledge professor Wan for giving instructions of designing and associate professor Yan for profiting language. This article is supported by grants from the National Natural Science Foundation of China, No. 81050027.

REFERENCES

Assa A, Hartman C, Weiss B, Broide E, Rosenbach Y, Zevit N et al. Long-term outcome of tumor necrosis factor alpha antagonist's treatment in pediatric Crohn's disease. J Crohns Colitis 2013;7:369-76.

Bar-Meir S. Mild to moderate Crohn's disease: still room for step-up therapies? Dig Dis 2009;27:347-50.

Beaugerie L, Sokol H. Clinical, serological and genetic predictors of inflammatory bowel disease course. World J Gastroenterol 2012;18:3806-13.

Beaugerie L, Brousse N, Bouvier AM, Colombel JF, Lémann M, Cosnes J et al. Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. Lancet 2009;374:1617-25.

Bernstein CN, Loftus EV Jr, Ng SC, Lakatos PL, Moum B. Epidemiology and Natural History Task Force of the International Organization for the Study of Inflammatory Bowel Disease (IOIBD). Hospitalisations and surgery in Crohn's disease. Gut 2012; 61:622-9.

Bianco P, Cao X, Frenette PS, Mao JJ, Robey PG, Simmons PJ et al. The meaning, the sense and the significance: translating the science of mesenchymal stem cells into medicine. Nature Med 2013;19:35-42.

Blonski W, Buchner AM, Lichtenstein GR. Inflammatory bowel disease therapy: current state-of-the-art. Curr Opin Gastroenterol 2011;27:346-57.

Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. JAMA 2006;295:2275-85.

Burger D, Travis S. Conventional medical management of inflammatory bowel disease. Gastroenterology 2011;140:1827-37.e2.

Charpentier C, Salleron J, Savoye G, Fumery M, Merle V, Laberenne JE et al. Natural history of elderly-onset inflammatory bowel disease: a population-based cohort study. Gut 2014;63:423-32.

Ciccocioppo R, Bernardo ME, Sgarella A, Maccario R, Avanzini MA, Ubezio C et al. Autologous bone marrow-derived mesenchymal stromal cells in the treatment of fistulising Crohn's disease. Gut 2011; 60:788-98.

Colombel JF, Sandborn WJ, Rutgeerts P, Enns R, Hanauer SB, Panaccione R et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. Gastroenterology 2007;132:52-65.

Cosnes J, Gower-Rousseau C, Seksik P, Cortot A. Epidemiology and natural history of inflammatory bowel diseases. Gastroenterology 2011;140:1785-94.

Costantino G, Furfaro F, Belvedere A, Alibrandi A, Fries W. Thiopurine treatment in inflammatory bowel disease: response predictors, safety, and withdrawal in follow-up. J Crohns Colitis 2012;6:588-96.

Cottone M, Kohn A, Daperno M, Armuzzi A, Guidi L, D'Inca R et al. Advanced age is an independent risk factor for severe infections and mortality in patients given anti-tumor necrosis factor therapy for inflammatory bowel disease. Clin Gastroenterol Hepatol 2011;9:30-5.

Dalal J, Gandy K, Domen J. Role of mesenchymal stem cell therapy in Crohn's disease. Pediatr Res 2012;71:445-51.

Danese S. New therapies for inflammatory bowel disease: from the bench to the bedside. Gut 2012;61:918-32.

Danese S, Peyrin-Biroulet L. IBD: Mucosal healing--extending our knowledge in Crohn's disease. Nature Rev Gastroenterol Hepatol 2012;9:309-11.

Day AS, Burgess L. Exclusive enteral nutrition and induction of remission of active Crohn's disease in children. Expert Rev Clin Immunol 2013;9:375-84.

Day AS, Ledder O, Leach ST, Lemberg DA. Crohn's and colitis in children and adolescents. World J Gastroenterol 2012;18:5862-9.

De Bruyn JC, Hilsden R, Fonseca K, Russell ML, Kaplan GG, Vanderkooi O et al. Immunogenicity and safety of influenza vaccination in children with inflammatory bowel disease. Inflamm Bowel Dis 2012;18:25-33.

De Cruz P, Bernardi MP, Kamm MA, Allen PB, Prideaux L, Williams J et al. Postoperative recurrence of Crohn's disease: impact of endoscopic monitoring and treatment step-up. Colorectal Dis 2013;15:187-97.

De Vroey B, Colombel JF. IBD in 2010: optimizing treatment and minimizing adverse events. Nature Rev Gastroenterol Hepatol 2011;8:74-6.

Devlin SM, Panaccione R. Evolving inflammatory bowel disease treatment paradigms: top-down versus step-up. Med Clin North Am 2010;94:1-18.

D'Haens GR. Top-down therapy for IBD: rationale and requisite evidence. Nature Rev Gastroenterol Hepatol 2010;7:86-92.

D'Haens G, Baert F, van Assche G, Caenepeel P, Vergauwe P, Tuynman H et al. Belgian Inflammatory Bowel Disease Research Group; North-Holland Gut Club. Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. Lancet 2008;371:660-7.

Dignass A, Van Assche G, Lindsay JO, Lémann M, Söderholm J, Colombel JF et al. European Crohn's and Colitis Organisation (ECCO). The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: current management. J Crohns Colitis 2010;4:28-62.

Domènech E, Mañosa M, Cabré E. Top-down therapy: is the evidence strong enough? Dig Dis 2009; 27:306-11.

Dretzke J, Edlin R, Round J, Connock M, Hulme C, Czeczot J et al. A systematic review and economic evaluation of the use of tumour necrosis factor-alpha (TNF-α) inhibitors, adalimumab and infliximab, for Crohn's disease. Health Technol Assess 2011;15:1-244.

Duijvestein M, Vos AC, Roelofs H, Wildenberg ME, Wendrich BB, Verspaget HW et al. Autologous bone marrow-derived mesenchymal stromal cell treatment for refractory luminal Crohn's disease: results of a phase I study. Gut 2010;59:1662-9.

Fascì Spurio F, Aratari A, Margagnoni G, Doddato MT, Papi C. Early treatment in Crohn's disease: do we have enough evidence to reverse the therapeutic pyramid? J Gastrointestin Liver Dis 2012;21:67-73.

Ford AC, Sandborn WJ, Khan KJ, Hanauer SB, Talley NJ, Moayyedi P. Efficacy of biological therapies in inflammatory bowel disease: systematic review and meta-analysis. Am J Gastroenterol 2011;106: 644-59.

Franke A, McGovern DP, Barrett JC, Wang K, Radford-Smith GL, Ahmad T et al. Genome-wide meta-analysis increases to 71 the number of confirmed Crohn's disease susceptibility loci. Nature Genet 2010;42:1118-25.

Frenette PS, Pinho S, Lucas D, Scheiermann C. Mesenchymal stem cell: keystone of the hematopoietic stem cell niche and a stepping-stone for regenerative medicine. Annu Rev Immunol 2013;31:285-316.

Fukunaga K, Matsumoto T. Current status and future perspectives of leukocytapheresis for inflammatory bowel disease. J Gastroenterol Hepatol 2012;27:997-1003.

Gardenbroek TJ, Tanis PJ, Buskens CJ, Bemelman WA. Surgery for Crohn's disease: new developments. Dig Surg 2012;29:275-80.

Gionchetti P, Calabrese C, Tambasco R, Brugnera R, Straforini G, Liguori G et al. Role of conventional therapies in the era of biological treatment in Crohn's disease. World J Gastroenterol 2011;17: 1797-806.

Gisbert JP, Chaparro M. Vaccination strategies in patients with IBD. Nature Rev Gastroenterol Hepatol 2013;10:277-85.

Gutiérrez A, Scharl M, Sempere L, Holler E, Zapater P, Almenta I et al. Genetic susceptibility to increased bacterial translocation influences the response to biological therapy in patients with Crohn's disease. Gut 2014,63;272-80.

Hébuterne X, Lémann M, Bouhnik Y, Dewit O, Dupas JL, Mross M et al. Endoscopic improvement of mucosal lesions in patients with moderate to severe ileocolonic Crohn's disease following treatment with certolizumab pegol. Gut 2013;62:201-8.

Hellers G, Bergstrand O, Ewerth S, Holmström B. Occurrence and outcome after primary treatment of anal fistulae in Crohn's disease. Gut 1980;21:525-7.

Herrinton LJ, Liu L, Weng X, Lewis JD, Hutfless S, Allison JE. Role of thiopurine and anti-TNF therapy in lymphoma in inflammatory bowel disease. Am J Gastroenterol 2011;106:2146-53.

Hommes D, Colombel JF, Emery P, Greco M, Sandborn WJ. Changing Crohn's disease management: need for new goals and indices to prevent disability and improve quality of life. J Crohns Colitis 2012;6(Suppl 2):S224-34.

Jones DW, Finlayson SR. Trends in surgery for Crohn's disease in the era of infliximab. Ann Surg 2010;252:307-12.

Kaser A, Zeissig S, Blumberg RS. Inflammatory bowel disease. Annu Rev Immunol 2010;28:573-621.

Kim MJ, Lee JS, Lee JH, Kim JY, Choe YH. Infliximab therapy in children with Crohn's disease: a one-year evaluation of efficacy comparing 'top-down' and 'step-up' strategies. Acta Paediatr 2011;100:451-5.

Knevel R, Schoels M, Huizinga TW, Aletaha D, Burmester GR, Combe B et al. Current evidence for a strategic approach to the management of rheumatoid arthritis with disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis 2010;69:987-94.

Krupoves A, Mack DR, Seidman EG, Deslandres C, Bucionis V, Amre DK. Immediate and long-term outcomes of corticosteroid therapy in pediatric Crohn's disease patients. Inflamm Bowel Dis 2011; 17:954-62.

Lakatos L, Lakatos PL. Postoperative recurrence of Crohn's disease, and its prevention. Orv Hetil 2010;151:870-7.

Lakatos PL, Vegh Z, Lovasz BD, David G, Pandur T, Erdelyi Z et al. Is current smoking still an important environmental factor in inflammatory bowel diseases? Results from a population-based incident cohort. Inflamm Bowel Dis 2013;19:1010-7.

Lichtenstein GR, Feagan BG, Cohen RD, Salzberg BA, Diamond RH, Price S et al. Serious infection and mortality in patients with Crohn's disease: more than 5 years of follow-up in the TREAT™ registry. Am J Gastroenterol 2012;107:1409-22.

Lin MV, Blonski W, Lichtenstein GR. What is the optimal therapy for Crohn's disease: step-up or top-down? Expert Rev Gastroenterol Hepatol 2010;4: 167-80.

Loly C, Belaiche J, Louis E. Predictors of severe Crohn's disease. Scand J Gastroenterol 2008;43:948-54.

Louis E, Belaiche J, Reenaers C. Do clinical factors help to predict disease course in inflammatory bowel disease? World J Gastroenterol 2010;16:2600-3.

Mayberry JF, Lobo A, Ford AC, Thomas A. NICE clinical guideline (CG152): the management of Crohn's disease in adults, children and young people. Aliment Pharmacol Ther 2013;37:195-203.

Melmed GY, Spiegel BM, Bressler B, Cheifetz AS, Devlin SM, Harrell LE et al. The appropriateness of concomitant immunomodulators with anti-tumor necrosis factor agents for Crohn's disease: one size does not fit all. Clin Gastroenterol Hepatol 2010; 8:655-9.

Mitsuyama K, Sata M. Therapeutic leukocytapheresis in inflammatory bowel disease: clinical efficacy and mechanisms of action. Cytotherapy 2009;11: 229-37.

Mowat C, Cole A, Windsor A, Ahmad T, Arnott I, Driscoll R et al. IBD Section of the British Society of Gastroenterology. Guidelines for the management of inflammatory bowel disease in adults. Gut 2011; 60:571-607.

Muratov V, Paulsson JM, Elvin K, Löfberg R, Lundahl J. Kinetics of the soluble IL-1 receptor type I during treatment with an LCAP filter in patients with inflammatory bowel disease. J Clin Apher 2012;27:61-3.

Ng SC, Bernstein CN, Vatn MH, Lakatos PL, Loftus EV Jr, Tysk C et al. on behalf of the Epidemiology and Natural History Task Force of the International Organization of Inflammatory Bowel Disease (IOIBD). Geographical variability and environmental risk factors in inflammatory bowel disease. Gut 2013;62:630-49.

Norgard B, Hundborg HH, Jacobsen BA, Nielsen GL, Fonager K. Disease activity in pregnant women with Crohn's disease and birth outcomes: a regional Danish cohort study. Am J Gastroenterol 2007;102: 1947-54.

Ordás I, Feagan BG, Sandborn WJ. Early use of immunosuppressives or TNF antagonists for the treatment of Crohn's disease: time for a change. Gut 2011;60:1754-63.

Orlando A, Armuzzi A, Papi C, Annese V, Ardizzone S, Biancone L et al. Italian Society of Gastroenterology; Italian Group for the Study of Inflammatory Bowel Disease. The Italian Society of Gastroenterology (SIGE) and the Italian Group for the Study of Inflammatory Bowel Disease (IG-IBD) Clinical Practice Guidelines: The use of tumor necrosis factor-alpha antagonist therapy in inflammatory bowel disease. Dig Liver Dis 2011;43:1-20.

Pariente B, Cosnes J, Danese S, Sandborn WJ, Lewin M, Fletcher JG et al. Development of the Crohn's disease digestive damage score, the Lémann score. Inflamm Bowel Dis 2011a;17:1415-22.

Pariente B, Peyrin-Biroulet L, Cohen L, Zagdanski AM, Colombel JF. Gastroenterology review and perspective: the role of cross-sectional imaging in evaluating bowel damage in Crohn disease. AJR Am J Roentgenol 2011b;197:42-9.

Peyrin-Biroulet L, Loftus EV Jr, Colombel JF, Sandborn WJ. Early Crohn disease: a proposed definition for use in disease-modification trials. Gut 2010;59:141-7.

Pithadia AB, Jain S. Treatment of inflammatory bowel disease (IBD). Pharmacol Rep 2011;63:629-42.

Plantinga TS, Crisan TO, Oosting M, van de Veerdonk FL, de Jong DJ, Philpott DJ et al. Crohn's disease-associated ATG16L1 polymorphism modulates pro-inflammatory cytokine responses selectively upon activation of NOD2. Gut 2011;60:1229-35.

Present DH, Rutgeerts P, Targan S, Caenepeel P, Vergauwe P, Tuynman H et al. Infliximab for the treatment of fistulas in patients with Crohn's disease. N Engl J Med 1999;340:1398-405.

Prieto-Pérez R, Cabaleiro T, Daudén E, Abad-Santos F. Gene polymorphisms that can predict response to anti-TNF therapy in patients with psoriasis and related autoimmune diseases. Pharmacogenomics J 2013;13:297-305.

Quezada SM, Steinberger EK, Cross RK. Association of age at diagnosis and Crohn's disease phenotype. Age Ageing 2013;42:102-6.

Rahier JF. Prevention and management of infectious complications in IBD. Dig Dis 2012;30:408-14.

Reenaers C, Belaiche J, Louis E. Impact of medical therapies on inflammatory bowel disease complication rate. World J Gastroenterol 2012;18:3823-7.

Savarino E, Dulbecco P, Bodini G, Assandri L, Savarino V. Prevention of postoperative recurrence of Crohn's disease by Adalimumab: a case series. Eur J Gastroenterol Hepatol 2012;24:468-70.

Selinger CP, Leong RW, Lal S. Pregnancy related issues in inflammatory bowel disease: evidence base and patients' perspective. World J Gastroenterol 2012;18:2600-8.

Setshedi M, Epstein D, Winter TA, Myer L, Watermeyer G, Hift R. Use of thiopurines in the treatment of inflammatory bowel disease is associated with an increased risk of non-melanoma skin cancer in an at-risk population: a cohort study. J Gastroenterol Hepatol 2012;27:385-9.

Sherlock ME, Griffiths AM. Medical therapy for pediatric inflammatory bowel disease. Curr Gastroenterol Rep 2012;14:166-73.

Sprakes MB, Ford AC, Warren L, Greer D, Hamlin J. Efficacy, tolerability, and predictors of response to infliximab therapy for Crohn's disease: a large single centre experience. J Crohns Colitis 2012;6:143-53.

Tamboli CP, Doman DB, Patel A. Current and future role of biomarkers in Crohn's disease risk assessment and treatment. Clin Exp Gastroenterol 2011;4:127-40.

Taylor KM, Irving PM. Optimization of conventional therapy in patients with IBD. Nature Rev Gastroenterol Hepatol 2011;8:646-56.

Vermeire S, Carbonnel F, Coulie PG, Geenen V, Hazes JM, Masson PL et al. Management of inflammatory bowel disease in pregnancy. J Crohns Colitis 2012;6:811-23.

Wood NJ. IBD: Stem cell therapy feasible, safe and beneficial for fistulizing Crohn's disease. Naure Rev Gastroenterol Hepatol 2011;8:181.

Xiao YL, Chen BL, He Y, Gao X, Huang MJ, Hu PJ et al. The clinical and endoscopic efficacy of step-up and top-down infliximab therapy in Crohn's disease. Zhonghua Nei Ke Za Zhi 2012;51:100-3.

Yang CH, Ding J, Gao Y, Chen X, Yang ZB, Xiao SD. Risk factors that predict the requirement of aggressive therapy among Chinese patients with Crohn's disease. J Dig Dis 2011;12:99-104.

Yang LS, Alex G, Catto-Smith AG. The use of biologic agents in pediatric inflammatory bowel disease. Curr Opin Pediatr 2012;24:609-14.

Zheng JJ, Zhu XS, Huangfu Z, Shi XH, Guo ZR. Prevalence and incidence rates of Crohn's disease in mainland China: a meta-analysis of 55 years of research. J Dig Dis 2010;11:161-6.