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Tailoring therapy to the individuals of Crohn's disease

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Abstract

For decades, increasing incidence and prevalence of Crohn's disease (CD) have attracted more attention. Some severe complications such as perforations, fistulas, and abscesses have significantly impaired patients' quality of life. Though the emergence of biologic agents has improved disease course and prognosis to a great extent, different disease manifestations and the economic burden of disease make biologic agents not suitable for all CD patients. The ultimate goal of achieving clinical and endoscopic remission, and even transmural healing is same for every CD patient, but therapeutic decision is so difficult for individual differences. Making a personalized approach based on disease behavior, drug response and other related factors is critical for disease management. This review attempts to summarize the existing clinical trials and data for better tailoring personalized therapy of CD.

Keywords

Crohn's disease, disease activity, personalized therapy, lose of response, medication monitoring

Introduction

Crohn's disease (CD) is characterized by chronic, relapsing inflammatory disease that can involve any part of the gastrointestinal tract. Though CD was regarded as a rare disease, it has become a global disease with increasing incidence and prevalence at the turn of the twenty-first century in developing countries.[1] Since onset of CD, cumulative incidence of

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stricturing and/or penetrating complications increased with times,[2] resulted in bowel surgery, increased psychological and economic burden, and impaired quality of life. Despite the variety of drug options, risks of disease recurrence and loss of response to medication pose a great challenge to doctors and patients. A previous randomized, double-blind, parallel group study showed that scheduled infliximab, a kind of anti-tumor necrosis factors(TNFs) maintenance therapy for CD resulted in higher rates of mucosal healing and a lower rate of CD-related hospitalizations.[3] Guidelines and consensus also recommend biologic agents for patients who are refractory to corticosteroids or immunomodulator therapy.[4,5] However, studies showed that 10–20% of patients have primary loss of response to anti-TNFs,[6] and 40% of patients have a secondary nonresponse to anti-TNFs therapy over time.[7] Dose escalation, combination therapy, or switching to another biologic agent made therapy decision difficult. Moreover, CD patients incurred greater direct cost of care and more out-of-pocket costs compared to non-CD controls.[8] Various medications, interventions, and surgical treatments have been used to treat CD. Cost-effective strategies considering appropriate drugs for specific patients are the aim of this review.

Why should we perform personalized therapy for CD patients?

The definition of personalized therapy is using the right drug, with the right dose, through the right route, at the right time, in the right patient.[9] Patients diagnosed with the same disease differed in clinical manifestations and response to drugs. These individual differences are related to genetic, environmental and other factors. CD is a kind of disease with complex phenotypes. The Montreal classification and Crohn's Disease Activity Index (CDAI) were proposed and used to define CD comprehensively. When CD was diagnosed, its various clinical features should also be described carefully, because clinical patterns of CD are phenotypically variable. CD patients with different subtypes and disease activities differed in the same therapy and prognosis, so be aware of every CD patient's clinical features and make out a personalized therapy was vital.

A meta-analysis showed that mutations of nucleotide-binding oligomerization domain 2(NOD2) were associated with increased risk of developing strictures and fistulae, and even surgery. It also suggested that targeted early-intensive therapy for high-risk patients with two NOD2 mutations might be beneficial.[10] In addition, single-nucleotide polymorphism rs4958847 in the immunity-related GTPase family, M(IRGM) gene correlated with more frequency of surgery in ileocolonic CD patients.[11] Age at diagnosis also played a role on the clinical expression of CD. Previous study found that colonic disease in CD patients over the age of 40 years was increased and upper gastrointestinal tract disease was decreased. Besides, these patients were more inflammatory, but not stricturing or penetrating, whereas the disease behavior in patients under the age of 20 years was more complex, especially with penetrating disease complications.[12]

CD patients of different ages also vary in disease presentations. Elderly CD patients more often suffer from rectal bleeding and less often report abdominal pain at first presentation. Adolescent CD patients often complain about diarrhea, abdominal mass and perianal lesions, and they have growth retardation. Young adult patients are not only suffering from the above mentioned manifestations, but also have more enteral

manifestations.[13] Visceral adiposity is also associated with a significant increase in the risk of penetrating disease and surgery in CD, and negatively impact long-term progression of CD regardless of genetic predisposition.[14]

The behavior of CD is not stable, its phenotype changes over time. A population-based cohort study showed that 18.6% nonstricturing nonpenetrating CD patients experienced stricturing or penetrating complications within 90 days after diagnosis, 50% experienced intestinal complications 20 years after diagnosis.[15] As disease behavior changes, so does therapy. In addition, mental status influences disease conditions. A retrospective study showed that CD patients with anxiety or depression were more likely to require therapy and to utilize healthcare resources, and anxiety and depression were strongly associated with CD patients' surgical history, disease complications.[16]

There are also differences between individuals using the same drug. When patients use the same drug, the dosage is different. Azathioprine (AZA) is a kind of immunosuppressants used in the therapy of CD. Before the treatment, physicians often recommend thiopurine S-methyltransferase (TPMT) testing (genotype and enzyme) to guide AZA dosing,[17] so is the 6-mercaptopurine(6-MP). Among patients with reduced TPMT activity, the drug may be avoided or the dose reduced. The incidence of adverse events is also different in patients using the same drug. A study demonstrated that carriage of any 3 coding nudix hydrolase 15 (NUDT15) variants was associated with an increased risk (OR, 27.2[95% CI, 9.3 to 116.7], $P = 1.1 \times 10^{-7}$) of thiopurine-induced myelosuppression, independent of TPMT genotype and thiopurine dose,[18] suggesting that NUDT15 genotyping should be considered prior to initiation of thiopurine therapy. In addition, different patients may have varies responses to the same drug and even the same individual may have different responses to the same drug at different times. An observational study assessed the effect of infliximab (IFX) in 614 consecutive CD patients and found that 10.9% of patients were primary non-responders to IFX and 21.6% in patients with initial response of IFX developed secondary loss of response.[19]

CD patients have diverse features in terms of severity, phenotype, clinical courses and responses to therapy due to their genetic background, age and other differences. Doctors should develop individualized therapy depending on the patient's age, clinical phenotype and various factors.

How can we perform personalized therapy for CD patients?

The therapeutic goal of CD is to induce and maintain clinical remission and mucosal healing, prevent complications, improve patients' quality of life, and strengthen long-term management of patients. Personalized therapy aims to achieve the same goal through different therapies. Personalized therapy should be carried out as follows, evaluating every patient comprehensively for the risk stratification, selecting the suitable therapy and close monitoring of treatment response.[20]

Step 1: Assess every patient comprehensively to determine risk stratification and draw out an initial plan

Crohn's Disease Activity Index (CDAI), Harvey-Bradshaw index (HBI) are the most common scoring systems used to measure clinical disease activity. These scoring systems

provide a comprehensive evaluation of every patient's condition including symptoms, signs, laboratory examinations and other complications, then physicians put forward a primary treatment target depending on their risk stratifications. For low-to-medium risk patients, we may provide them with proper health instructions to reduce the psychological burden and avoid excessive medical treatment for reducing the economic burden of diseases. Besides, it is necessary to be vigilant that these patients develop into high-risk groups. Early treatment for preventing disease progression, severe complications and maintaining intestinal function is important for high-risk patients.

Some clinical parameters were proposed as prognostic factors to aid in therapeutic decision. Young age at diagnosis less than 40-year-old, perianal disease, significant weight loss, smoking, the presence of deep colonic ulcers, need for steroid use and extensive small bowel involvement is associated with more aggressive CD,[21] indicating a greater propensity for disease extension and a worse prognosis. A specified and timely therapy is essential to these patients.

For pediatric Crohn's disease, exclusive enteral nutrition (EEN) is the induction therapy of first choice due to its excellent safety profile and good for their growth.[22] In addition, a small sample size study suggested that partial enteral nutrition coupled with the CD exclusion diet could also be effective in active paediatric CD patient for inducing remission as EEN group.[23] In children and adolescents with either one of the followings, severe perianal fistulizing disease, severe stricturing/penetrating disease, severe growth retardation, panenteric disease, persistent severe disease despite adequate induction therapy, which is potentially predictive for poor disease outcome, an anti-TNF-based top down approach is recommended.[22] As for maintenance therapy, thiopurines are recommended as one option of steroid free remission in children at risk for poor disease outcome, but not alone as induction therapy. Methotrexate can be also used as a primary maintenance therapy or in thiopurine failure. In addition, using anti-TNF agents regularly scheduled, not episodically, to maintain remission in patients responding to induction therapy with anti-TNF agents is also recommended, but thalidomide in refractory pediatric CD is not recommended.[22] More importantly, the management strategy of pediatric CD patients should consider both the severity of the disease and patients' growth, additional nutritional supplement and/or growth hormone may be considered.

For older-onset CD, patients suffer more severe initial clinical presentations, and are less likely to progress from inflammatory to stricturing or fistulizing disease, but have a higher mortality rate.[24] Though there is no evidence that the efficacy of medical treatment in elderly IBD patients differs from that in younger adult patients, a higher risk of serious adverse events including using of corticosteroids, thiopurines, TNF inhibitors has been verified.[24]

Clinical manifestations vary when different segments of intestine lesioned, so do the treatments and prognosis.[25–27] When localized ileocecal, the choice of treatment depends on disease activity. For mild active localized ileocecal CD patients, oral budesonide is the preferred method[26]; moderately or severely active patients should be treated with systemic corticosteroids or anti-TNF who have previously been steroid-refractory or -intolerant.[26] However, a population-based cohort study concluded that early ileocecal resection for ileal or ileocecal CD was associated with improved long-term outcomes

compared with anti-TNFs, which may have a role as first-line therapy and challenge the current paradigm of reserving surgery for complicated CD refractory or intolerant to medications.[28] As to active colonic CD, patients may choose systemic corticosteroids or anti-TNF if disease relapsed or be refractory to steroids,[26] with the using of 5-aminosalicylic was recommended against for induction of remission and maintenance therapy, which has nearly been a history.[29] When treating extensive small bowel [$>$100 cm] Crohn's disease, systemic corticosteroids are preferred, and an anti-TNF based strategy should be evaluated sooner rather than later who have relapsed or have features indicating a poor prognosis.[26] In addition, mild esophageal or gastroduodenal CD patients may be prescribed with proton pump inhibitors, and additional systemic corticosteroids or an anti-TNF based strategy should be considered in severe or refractory disease.[26]

Scholars put forward that persistent chronic mucosal and transmural inflammation can result in luminal stricture, and the increased intraluminal pressure due to the stricture probably results in fistula and abscess.[30] With the development of disease, inflammatory subtypes possibly developed into narrowing or penetrating. As we know, the occurrence of intestinal stenosis is determined by the disease's biological behavior, but the development of intestinal stenosis is often associated with poor disease control. Therapies for intestinal stenosis patients include medical treatment, endoscopic therapy and surgery. For inflammatory stenosis, the key in medical treatment is to control inflammation with positive anti-inflammatory medicine and parenteral nutritional support, which involves step-up therapy of glucocorticoid and immunosuppressive therapy included, or biological agent initiated step-down therapy.[29] Endoscopic therapy is eligible for patients with a short($\leq$4 cm) fibrotic stricture, benign stricture, single or multiple stricture but straight bowel lumen, or stricture far away from the fistula orifice of the proximal bowel, including endoscopic balloon dilation, endoscopic stricturotomy and endoscopic stent placement.[31] However, it is not recommended to treat naive or anastomotic fibrostenosing small bowel Crohn's disease with bare metal stents, anchored stents, removable stents, biodegradable stents or cutting techniques (for example, needle knife).[32] When the stricture is malignant, angulated, or multiple strictures with angulated lumen, or strictures associated with abscess, endoscopic therapy should be avoided.[31] Surgery may be a choice in some cases. Strictureplasty should be considered as the surgical technique in multiple strictures, and early resection is recommended when small bowel CD complicated with endoscopic therapies ineffective strictures.[33] Lessons from randomized trials in other fibrotic disease of the lung, liver, and skin, several molecular candidates, like growth factor modulators, inflammation modulators, 5-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, intracellular enzymes and kinases, renin-angiotensin system (RAS) modulators, could serve as potential effective antifibrotic therapies for intestinal fibrosis in CD,[34] more clinical studies are needed.

CD is often complicated with fistulas, involving internal and external fistulas. The former includes entero-intestinal fistula, entero-vesical fistula, entero-uterine fistula and entero-vaginal fistula, the latter include anal fistula and entero-abdominal fistula. Assessment of these patients should consider the origin and anatomical structure of the fistula, identify or exclude local sepsis or abscess, determine which organs are affected and the impact on systemic symptoms or impairment of quality of life, evaluate the

nutritional state. For anal fistula, surgical drainage of sepsis in combination with antibiotics is mandatory.[35] In recurrent refractory or complex fistulizing disease, anti-TNFs can be used.[35,36]

Step 2: Select suitable therapeutic strategy, Top-Down or Step-Up?

Traditionally, we treat CD patients with a step-up therapeutic schedule, from 5-aminosalicylic acid, steroids, immunomodulators to biologics. Several clinical trials and guidelines put forward successively that CD patients with certain factors should choose a top-down approach with the early use of biologics, including complicated with perianal lesions, extensive lesions of more than 100 cm small intestine involved, esophageal, gastric and duodenal lesions, the onset age is less than 40 years old, corticosteroid use is needed for the first visit.[37,38] Additionally, ECCO guidelines have recommended against the use of oral 5-aminosalicylic acid for induction of remission and maintenance therapy in CD.[29] A multicenter, open-label, randomized controlled trial that enrolled newly diagnosed active CD patients concluded that top-down treatment with combination infliximab plus immunomodulator achieved substantially better outcomes at 1 year than accelerated step-up treatment.[39] Another open-label, randomized, controlled phase 3 study showed that timely escalation with an anti-tumor necrosis factor therapy on the basis of clinical symptoms combined with biomarkers in patients with early CD resulted in better clinical and endoscopic outcomes than symptom-driven decisions alone.[40] More research is needed on the optimal timing to start biologics.

Step 3: Long-term patient management, including medication monitoring.

Disease treatment should improve the symptoms of discomfort to the greatest extent, protect organ function, reduce adverse drug reactions, and allow patients to return to normal life. Individualized therapy should be centered on patients' needs.

When we choose the appropriate drug based on the above criterion, we also need to consider its adverse effects and optimize drug dosage. Myelosuppression is the most serious adverse reaction of thiopurine. Studies have pointed out that CD patients should detect the thiopurine methyl transferase (TPMT) genotype when there are indications for thiopurine treatment in order to choose appropriate types and dosages, and adjust dosages according to 6-thioguanine, 6-methyl mercaptopurine levels for avoiding the occurrence of adverse reactions.[41,42]

Due to its powerful anti-inflammatory properties, corticosteroids are widely used in the induction therapy for active CD patients. For its complex adverse reactions, patients are often afraid to use it. To maximize corticosteroids' benefits and minimize its disadvantages, fully estimating the incidence of adverse reactions and combining drugs to prevent adverse reactions is of great importance. For example, osteoporosis is a common complication of corticosteroids use, all patients with high risk are suggested to receive an intake of 800–1000 mg calcium and 800 IU vitamin D at the onset of corticosteroid therapy.[4] For patients who intend to use it, we should comprehensively evaluate the disease status, consider their underlying diseases, including diabetes, hypertension, etc., assess the risk of complications, and make plans to reduce the incidence of adverse events.

TNF inhibitors, including infliximab, adalimumab and certolizumab, are recommended to induce remission and as maintenance therapy in patients with

moderate-to-severe CD who have not responded to conventional therapy, IL-12/IL-23 inhibitors (including ustekinumab, risankizumab), anti-integrin therapies (vedolizumab) and janus kinase inhibitors (upadacitinib) are also recommended for these patients.[29] Despite the advent of new advanced therapies, anti-TNF agents still remain the cornerstone of therapy for CD.[43] Data showed that anti-TNFs reached a far from perfect plateau as regards their efficacy (60–70%), meaning that there is still a proportion of patients who either initially lack or in the long-term lose response, so optimization of the therapy should be strongly considered.[44] Optimal trough concentrations (TCs) are associated with a remarkable improvement in the patients' quality of life, which is one of the long-term targets set out in the STRIDE (selecting therapeutic targets in inflammatory bowel disease) consensus.[45] Reactive therapeutic drug monitoring (TDM) has been used in the setting of lose of response (LOR). Assessing TCs and anti-drug antibodies (Abs) helps to identify the possible causes and manage it in a more efficient and documented manner.[46,47] Proactive TDM and empiric use of anti-TNFs have also been studied and compared with reactive TDM in different clinical trials, and showed various results.[44] Therefore, more clinical trials are needed to determine which approach has more clinical efficacy. Switch therapy was considered when dose optimization failed or Abs produced in moderate-severe active CD. As second-line therapy, ustekinumab and vedolizumab are the other biological agents approved for use in CD.[48] Most studies found ustekinumab to be more effective or non-inferior to vedolizumab in treating patients with anti-TNF refractory CD.[49] In addition, multiple classes of advanced therapies, including both monoclonal antibodies and novel oral small molecules, are now available for the treatment of moderately-to-severe active CD and who were refractory to anti-TNF treatment,[50] highlighted by the approvals of selective p19 interleukin-23 antagonists (Guselkumab,[51] Risankizumab[29]), selective Janus kinase inhibitors (Upadacitinib[29,52]) and sphingosine-1-phosphate receptor modulators (Ozanimod[53]). So far, there is no head-to-head research or consensus on the order of choice for switch therapy.

Additionally, there may be a "ceiling effect" of biologic monotherapy, so combination therapy was used in clinical studies. Previous trials have demonstrated that combination therapy with a TNF inhibitor and azathioprine is superior to monotherapy of either agent alone.[54] However, combining TNF antagonists with azathioprine is associated with increased risk of malignancy and infection.[55] Newer biologic therapies such as ustekinumab and oral small-molecule preparations have safety profiles that appear more favorable for combination therapy. Combination therapy of infliximab plus natalizumab for active CD patients showed greater efficacy than treatment with infliximab alone.[56] Triple combination therapy with vedolizumab, adalimumab and methotrexate also produced a higher endoscopic remission rate.[57] Refractory CD patients may benefit from dual biological therapy of adalimumab and ustekinumab,[58] or vedolizumab and ustekinumab,[59] or a biologic combined with a JAK inhibitor.[60] Combination therapy may be a possible option in highly selected, refractory CD patients, but higher quality combination of therapies with a significant improvement in the quality of data is required prior to more widespread use.

In a word, early use of biologics can greatly improve the prognosis of patients, but due to their high price, risk of non-response and the occurrence of malignant tumors, patients are often hesitant to make a choice. With the help of tools, physicians can correctly

predict the risk of disease and decide the appropriate time to use the right medicine for achieving the maximum cost efficiency of drugs, which facilitating the development of individualized treatment plans. C. A. Siegel reported a validated, web-based tool to help providers and patients make personalized decisions about treatment options.[61] The tool collected adult CD patients' clinical, serological and genetic variables to make an individualized predicted outcome. Physicians may choose the right drug timely based on the risk stratification to maximize patients' quality of life. Moreover, an appropriate tool to help making individualized therapy also need to consider treatment accessibility, healthcare disparities and other practical issues.

Conclusion

Individual stratification of CD management is making an individual treatment plan based on the condition of each CD patient. CD personalized management should consider every patient's demographics, genotype, serology, clinical history, and follow the natural history, response to treatment, therapy-related adverse outcomes, and eventually make a specific therapy. By personalizing IBD therapy, we may be able to maximize management efficacy, minimize the risk of adverse events and ultimately decrease costs. However, the limitation of this review is that we didn't consider treatment accessibility, healthcare disparities, and other more cost-effective therapies which are under research.

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Consent

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Author contributions

Xin Gao contributed to the study concept and design, and drafting of the manuscript.
Qi Zhang contributed to revision of the manuscript. Both authors reviewed the manuscript and approved the final manuscript.

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