

Biological Therapy for Inflammatory Bowel Disease in Children

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The pathogenesis of inflammatory bowel diseases is not very well understood; it is currently thought to be caused by the interaction between genetic factors, environmental factors, intestinal microbes, and immune factors. Biological agents such as anti-tumor necrosis factor (anti-TNF) are widely being used as therapeutic agents. Infliximab, a chimeric monoclonal IgG1 antibody against tumor necrosis factor, has been demonstrated to have an effect in the induction and maintenance of remission in Crohn's disease in children. The effects of biological agents, typified by anti-TNFs, in inflammatory bowel disease in children; the recent concern on the administration of biological agents in combination with immunomodulators; and 'Top-down' therapy are some of the topics covered in this review. (**Pediatr Gastroenterol Hepatol Nutr 2012; 15: 13~18**)

Key Words: Inflammatory bowel disease, Infliximab, Children

INTRODUCTION

Approximately 10 to 15% of patients diagnosed with inflammatory bowel disease, 25% of Crohn's disease, are diagnosed in childhood [1]. Although the pathogenesis of inflammatory bowel diseases is not very well understood, it is currently thought to be caused by the interaction between genetic factors, environmental factors, immune factors, and intestinal microbes. It is thought that environmental factors either directly promote inflammation, or damage the individual's immune system through

changes in gene expression causing intestinal microbes to penetrate the intestinal mucosa and cause inflammation. The reason why inflammation is confined to the colon mucosa in ulcerative colitis and why it is transmural and can involve any segment of the digestive tract in Crohn's disease has been so far unclear [2].

The ideal short term therapeutic aim in inflammatory bowel disease is to improve symptoms by inducing remission; while in the long term, the aim is to prevent relapse, maintain remission, minimize surgical procedures and the administration of

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corticosteroids, and prevent complications. In children, pursuing normal development is an additional goal. Classically, 5-ASA, corticosteroids, and immunomodulators have been utilized; and with the recent introduction of the concept of mucosal healing, biological agents such as anti-tumor necrosis factor (anti-TNF) have been used more often.

Corticosteroids are highly effective in the induction of remission in active inflammatory bowel disease, but are inappropriate for long term maintenance therapy due to its side effects. There are studies that show that most patients develop corticosteroid dependence within one year of corticosteroid therapy [3]. Immunomodulators, such as azathioprine and 6-mercaptopurine, are standard in maintenance therapy for they are effective in maintaining remission in Crohn's disease and show reduction in corticosteroid use. In children with moderate to severe ulcerative colitis, azathioprine is effective for maintenance therapy [1]. However, immunomodulators are inappropriate for induction purposes because of their slow onset of action and are ineffective even with 12 to 16 weeks of treatment [4]. Occurrence of opportunistic infections and malignant tumors are also a problem with immunomodulators.

The introduction of biological agents such as infliximab has dramatically changed the treatment of refractory inflammatory bowel disease. It is believed that biological agents correct the imbalance in the gastrointestinal immune system that triggered the disease. Although inflammatory bowel disease cannot be explained by a single cause, biological molecules involved in the manifestations of the disease are being identified, and these are targeted by biological agents. Here, the effects of biological agents, typified by anti-TNFs, in inflammatory bowel disease in children; the recent concern on the administration of biological agents in combination with immunomodulators; and 'Top-down' therapy will be discussed.

THE EFFECT OF ANTI-TNF IN INFLAMMATORY BOWEL DISEASE

To date, biological agents that the FDA has approved for use in inflammatory bowel disease are: anti-TNF agents, such as infliximab, adalimumab, certolizumab; natalizumab, a selective adhesion molecule; and sargramostim, a mucosal barrier enhancer. In children, however, only infliximab is approved for Crohn's disease. Tumor necrosis factor (TNF) is a proinflammatory cytokine that promotes proliferation and differentiation of cells, and promotes the inflammation response in various diseases such as rheumatoid arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, and psoriasis. The aim of anti-TNF agents is to improve symptoms by suppressing the inflammation promoted by TNF.

Infliximab is a chimeric monoclonal antibody specific for TNF and is composed of 25% murine and 75% human IgG. It is only administered intravenously at 5 mg/kg per dose. For induction, it is given at 0, 2, and 6 weeks and if there is a response, it is followed with a maintenance regimen of a scheduled dose every 8 weeks.

In adults, a large number of studies, including ACCENT-1 and ACCENT-2, have demonstrated the effectiveness of infliximab in maintaining response and remission and in fistulizing Crohn's disease [5]. Remission induction and maintenance therapy in children have been shown to be effective as in adults. The REACH study is a well known initial study of infliximab in children. In children with moderate to severe Crohn's disease, 88% showed clinical improvement and 59% were in remission with doses at 0, 2, and 6 weeks; and with a maintenance regimen of a scheduled dose every 8 weeks, 56% maintained remission at 54 weeks. However, when the maintenance dose was administered every 12 weeks, the remission retention rate was lower at 23% [6]. In addition, bone formation was stimulated and after being observed for 54 weeks, growth rate improved [7]. The SONIC study in adults, infliximab monotherapy compared to azathioprine monotherapy showed improved mucosal healing at 26

weeks, and the rate of maintaining remission without corticosteroids was higher up to 50 weeks [8].

A recent study attempting to increase the effectiveness of infliximab showed that the trough level of infliximab in patients with complete mucosal healing were high, and suggested that monitoring the concentration of infliximab and modifying the dose to increase the rate of mucosal healing should be carried out [9]. In the 2011 guidelines of the British Society of Gastroenterology, in the absence of response after the initial two doses (primary non-responder) of infliximab, considering increasing the dose to 10 mg/kg, surgical treatment, or a change to adalimumab is recommended. Where response is lost, decreasing the interval to 6 weeks, increasing the dose to 10 mg/kg, or switching medications is recommended [10].

In ulcerative colitis, a Cochrane review of 7 adult randomized clinical trials has shown that administering infliximab at 0, 2, and 6 weeks is effective for the induction of clinical and endoscopic remission. In the ACT1 and ACT2 studies, for patients with moderate or severe disease unresponsive to corticosteroids and immunomodulators, infliximab showed effects in mucosal healing and remission at 8 and 30 weeks [11], and a recent follow-up study reported a lower risk of bowel resection at 54 weeks [12]. Although research is limited in children and it may not be as effective as it is in Crohn's disease, infliximab is valued as a medication that can be used in patients with severe ulcerative colitis refractory to conventional treatment [1], and is reported to decrease the frequency of bowel resection [13].

In summary, the indications for treatment with infliximab are as follows: refractory Crohn's disease, corticosteroid dependent Crohn's disease, fistulizing Crohn's disease, severe ulcerative colitis, and inflammatory bowel disease with extra-intestinal systemic symptom. Recently, it is also being considered for first line therapy, and for post operative maintenance therapy.

Infection, hypersensitivity reaction, and malignancy are some of the safety issues associated

with anti-TNFs. Adverse effects such as tuberculosis and opportunistic infections, which are also present with corticosteroids and immunomodulators, must be taken into consideration. In a study of risk factors for opportunistic infections, any one of either corticosteroids, or thiopurines, or infliximab raise the risk of infection by three, and in combinations of two or three drugs, the risk of infection raises to 15 times [14]. Screening for latent tuberculosis through medical history, chest radiography, and tuberculin skin test must be done before starting infliximab treatment. T-cell interferon- γ release assay can improve the diagnosis of latent tuberculosis infection. If present, tuberculosis must be treated before the starting infliximab therapy [10]. In fistulizing Crohn's disease, before administering infliximab, it must be first ascertained that there are no problems with infection and that actions such as drainage are not required. For this purpose, radiologic studies such as MRI and collaborating with an experienced surgeon may be necessary.

Formation of antibodies to biologic drugs can cause both acute hypersensitive reactions and delayed serum sickness-like reactions. If mild, slowing the rate of infusion and administering antihistamines and corticosteroids will suffice. A skilled medical staff member carefully monitoring the patient and slowly administering the drug with an infuser over 2 hours is recommended. Administration of corticosteroids in all patients as a pretreatment is not recommended. When treatment is interrupted for more than 12 months as a 'drug holiday,' the chances of forming antibodies increase. In adults, the cumulative rate of antibody formation over a 72 week period reaching 30% has been reported [5]. In the long term, antibody formation is a problem that is associated with a loss of response.

Associations with Non-Hodgkin lymphomas (NHL), especially hepatosplenic T-cell lymphomas are also reported. Hepatosplenic T-cell lymphomas are rare but have high mortality rates and the success rates for hematopoietic stem cell transplan-

tation are low. In a recent review of 36 cases of hepatosplenic T-cell lymphoma in patients with inflammatory bowel disease, the patients were mostly young men aged 10 to 35, and had hepatosplenomegaly, elevated liver enzymes, fever, weight loss, and night sweats, but no palpable lymph nodes. In 20 cases, they were treated with a combination of azathioprine and anti-TNF and in 16 cases they were given azathioprine only [15]. It is still unclear whether it is a thiopurine problem or a combination problem, but there are no reported cases in anti-TNF monotherapy. In a recent meta-analysis, anti-TNF therapy has been shown to have a higher incidence of NHL compared to that of the general population, but the risk is low (6.1 per 10,000 patient years), and was not significantly higher than immunomodulator monotherapy [16].

Central nervous system demyelinating disorders, optic neuritis, and congestive heart failure has also been reported, but rarely.

ANTI-TNF AND IMMUNOMODULATOR COMBINATION THERAPY

In the aforementioned SONIC study, the remission rate reported at week 26 with infliximab/azathioprine combination therapy, infliximab monotherapy, and azathioprine monotherapy was 56.8%, 44.4%, and 30.0%, respectively. The treatment outcome of the combination therapy was better [8], but other studies have reported no differences between the treatment groups [5,11]. This question has not yet been resolved for long-term effects, safety and other factors must all be considered. As noted earlier, since there were no cases of hepatosplenic T-cell lymphoma in the patient group treated with anti-TNF alone without azathioprine, clinicians should be cautious in recommending azathioprine combination therapy, especially to young males. Some authors suggested that the combination therapy is appropriate in those with short duration of disease, extensive lesions, perianal involvement, females, history of

surgery, and in older adults; and is inappropriate in relatively healthy young males [17].

BEGINNING AND DURATION OF ANTI-TNF TREATMENT

The traditional management of Crohn's disease is to start treatment with corticosteroids, adding immunomodulators such as azathioprine and methotrexate, and then administering biological agents in a sequential 'step-up' therapy. However, with increased emphasis on mucosal healing in inflammatory bowel diseases, a 'top-down' therapy of emphasizing biological agents that target the inflammatory cascade, is emerging as a possibly more efficient therapy in the treatment of Crohn's disease.

Studies of Crohn's disease in adults comparing the top-down therapy (administration of immunomodulators in combination) and the step-up therapy (administer corticosteroids twice then immunomodulators) show higher rates of remission at 26 and 52 weeks with the top-down therapy, but no difference at 78 and 104 weeks [18]. Although there are almost no studies done in children, an early pilot study, comparing a group inducted with infliximab and maintained with azathioprine or in combination with methotrexate with a group inducted with corticosteroids or nutritional therapy and maintained with azathioprine, has shown that after one year, 12 of the 13 patients in the top-down therapy maintained remission while only 2 of 19 patients maintained remission in the step-up therapy group. It concluded that with the top-down therapy, remission duration is longer, corticosteroid use is reduced, endoscopic improvement rate is higher, and is also beneficial to growth [19]. However, it has been pointed out that the duration of treatment must be established, and that adverse effects and complications with aggressive treatment still exist.

Another problem is identifying the patients who will benefit from the top-down therapy. In some

analysis, over 30% of patients are over treated and thus can be an economic burden. Since, in our country, infliximab is covered by the national health insurance only in severe Crohn's disease unresponsive to 2 other medications and fistulizing Crohn's disease, the top-down therapy as a first line protocol is not yet feasible. Further, large-scale studies on the indications for early administration of infliximab, analysis of long term effects, method and timing of termination of treatment are needed.

When maintaining remission with biological agents alone or in combination, the duration of treatment and whether the biological agent or the immunomodulator can be discontinued is still an unresolved issue. One study (n=80), after administering azathioprine/infliximab in combination for 6 months, discontinued azathioprine in one group of patients. They reported that there was no difference between infliximab monotherapy and combination therapy at 104 weeks, and concluded that azathioprine did not add any benefit [20]. However, a smaller, yet a similar study (n=48) reported that after discontinuation of azathioprine, infliximab failure was 15% and 59% at 1 and 2 years, respectively [21]. The National Institute for Clinical Excellence (NICE) guide, which states that infliximab treatment should be maintained for at least 12 months or until treatment failure and in cases of relapse after discontinuation restarting the treatment is an option, is carefully endorsed by the British Society of Gastroenterology, which in some aspects, there is a paucity of strong evidence [10].

CONCLUSION

Anti-TNF agents raised expectations in the improvement of long-term outcomes for it is superior to conventional therapies in mucosal healing by effectively controlling intestinal inflammation. It is anticipated to reduce the frequency of hospitalizations and surgeries; moreover, by improving bone formation, it is also expected to reduce growth disorders in children. Further long term studies are re-

quired to evaluate whether anti-TNF can alter the natural course of the disease.

Preparing for resistance to anti-TNF agents, research into other biological agents in adults is very active. However, in children, there are no medications that can replace infliximab and data into other anti-TNF agents such as adalimumab is inadequate.

Research into topical administration of nanobodies (single domain antibody) that are one tenth the size of a human antibody, IL-10, and other molecules through genetically modified *Lactococcus lactis*, hematopoietic stem cell transplantation, and other treatments are being carried out [2]. In addition, the genetic factors of inflammatory bowel disease are being identified, leading to a better understanding of the pathogenesis of the disease. In the future, understanding the interaction between genetic and environmental factors leading to various phenotypes is anticipated to result in an individualized treatment.

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