Antitumor necrosis factor treatment for pediatric inflammatory bowel disease

Zdravljenje kroničnih vnetnih črevesnih bolezni s protitelesi proti faktorju tumorske nekroze pri otrocih

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Abstract

Over the last 10 years, biologic treatment with the antitumor necrosis factor (anti-TNF) antibodies has dramatically changed the therapeutic approach in pediatric patients with inflammatory bowel disease (IBD). Currently, infliximab and adalimumab are the only anti-TNF drugs that have been approved for use in refractory pediatric Crohn's disease (CD) and infliximab the only anti-TNF agent for use in refractory pediatric ulcerative colitis (UC). According to the current treatment recommendations, anti-TNF therapy is indicated for moderate and severe pediatric IBD when remission is not achieved using conventional treatment or conventional therapy is not tolerated by the patients.

Despite the demonstrated efficacy of anti-TNF drugs in pediatric IBD patients, the potential development of serious adverse events, such as severe immune reactions, infections, and malignancies, limit the possibility of a wider use of anti-TNF drugs. Moreover, a substantial percentage of patients gradually develop non-responsiveness to these therapeutics, due to generation of antibodies against anti-TNF antibodies. Therefore, treatment of pediatric IBD patients with biologics should be undertaken in specialized tertiary medical centers, which are specially qualified for this purpose.

Izvleček

V zadnjem desetletju je zdravljenje s protitelesi proti faktorju tumorske nekroze (anti-TNF) pomembno vplivalo na terapevtski pristop pri otrocih s kroničnimi vnetnimi črevesnimi boleznimi (KVČB). Trenutno sta infliximab in adalimumab edini biološki zdravili, ki sta registrirani za zdravljenje Crohnove bolezni (CB), ki je neodzivna na standardno terapijo, pri otrocih, infliximab pa je registriran tudi za zdravljenje refraktornega ulceroznega kolitisa (UK) pri otrocih. Sodobne strokovne smernice priporočajo zdravljenje z anti-TNF zdravili v primeru zmernih in hudih oblik otroške KVČB, če s standardnimi zdravili ne moremo doseči remisije, ali pa takšnega zdravljenja bolnik ne prenaša.

Kljub dokazani učinkovitosti anti-TNF zdravil njihovo širšo uporabo omejuje možnost pojava resnih neželenih učinkov, kot so imunogenost, hude okužbe in malignomi. Poleg tega sčasoma pomemben delež bolnikov postane slabše odziven na ta zdravila zaradi tvorbe lastnih protiteles proti proti TNF protitelesom. Zato naj se zdravljenje otrok s KVČB z biološkimi zdravili izvaja le v specializiranih terciarnih ustanovah, ki so zanj ustrezno usposobljene.

Introduction

Inflammatory bowel disease (IBD) may present during childhood or adolescents in up to 20–30 % of all patients.[1] The incidence of pediatric IBD has been rapidly increasing over the last few decades. The highest incidence of childhood IBD has been observed in developed countries of North America and Europe and it seems that it is still on the rise, mainly that of CD.[2-11]

Certain features are unique to pediatric IBD compared to adult onset disease, such as growth failure (which is present at diagnosis in 10–40 % of affected children), delay in puberty and altered bone health.[12]

Although the treatment of pediatric IBD is quite similar to adult IBD, special considerations in the treatment of pediatric population are needed regarding optimal growth and pubertal development.[13] In pediatric CD, exclusive enteral nutrition (EEN) is widely used due to its significant advantages over steroids, especially due to fewer side effects and its beneficial effect on growth.[14] In the managment of pediatric IBD corticosteroids should not be used for long-term treatment such as maintenance of remission. For maintenance of remission, thiopurines (azathioprine or 6-mercaptopurine) are most commonly used and are frequently introduced at the time of remission induction in CD. Methotrexate is an alternative to thiopurines when these drugs are ineffective or not tolerated.[15]

In children and adolescents with severe IBD who are refractory to or intolerant of the conventional medical treatment and EEN, anti-TNF drugs have been effectively used in the last years. Currently, infliximab and adalimumab are approved and licensed to treat refractory CD in children, whereas only infliximab is approved to treat pediatric UC. Despite this fact, adalimumab has also been used off-label in clinical practice in some refractory childhood UC.

The present European Crohn's and Colitis Organization (ECCO) and the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) guidelines recommend anti-TNF treatment only in pediatric IBD patients who failed conventional treatment.[16]

Mechanism of action of anti-TNF drugs

Tumor necrosis factor alpha (TNF-α) exerts a wide spectrum of effects in the body. These include immunoregulatory effects, such as the induction of immunoregulatory molecules and other cytokines, cellular proliferation, and apoptosis, as well as clinical signs and symptoms such as fever, shock, and anorexia.[17] TNF-α is produced by macrophages, monocytes, and by T-and B-lymphocytes. The increased concentrations of TNF-α have been found in the stools, serum and the inflamed intestinal mucosa in patients with IBD.[17-19]

Infliximab is a chimeric monoclonal immunoglobulin G_1 antibody to TNF-α and is the first biological drug that was approved for IBD. It is composed of a (75 %) human constant and (25 %) murine variable region and binds to human TNF-α with a half-life of 10 days. In a week 12 after the infusion of the dose of 5 mg/kg, its levels are usually not detectable.[20] Adalimumab is a fully humanized monoclonal anti-TNF antibody.[21] Both anti-TNF drugs can bind and neutralize soluble and transmembrane TNF-α.[17]

Infliximab and adalimumab are found to exert other mechanisms of action as well which are probably more important, such as induction of apoptosis in T cells and monocytes,[22] antibody-dependent cytotoxicity, and complement-dependent cytotoxicity.[17,23]

In a recent Dutch study, a novel mechanism of action of anti-TNF drugs was reported. A significant induction of regulatory macrophages was observed in IBD patients with mucosal healing after treatment with infliximab. These regulatory macrophages had immunosuppressive capacities, such as production of anti-inflammatory cytokines and inhibition of T-cell proliferation.[24]

Clinical efficacy of infliximab in pediatric Crohn's disease

Several clinical trials have shown the beneficial effect of infliximab therapy in adult IBD.[25-31] Two large, multicentric, placebo-controlled studies have confirmed the efficacy of infliximab not only for induction but also for maintanance of remission.[27,28] In pediatric IBD population, placebo-controlled trials in patients with severe disease activity requiring biological treatment have not been considered ethical and therefore, such trials have not been performed.

The earliest trial of infliximab in pediatric CD was retrospective, multicenter study of 19 children with moderate to severe CD (7 medically refractory, 12 steroid dependent, 14 were on immunomodulator treatment with thiopurines). They received three infusions (5 mg/kg of infliximab) over the 12-

week study and achieved remission at week 4 and a mild disease activity at week 12.[32]

In the first multicenter, randomized, dose-ranging study in 21 children with CD, performed by Baldassano et al., all 21 children achieved clinical response during the course of the study (a decrease in the Pediatric Crohn's Disease Activity Index (PCDAI) of ≥ 10 points from baseline). Clinical remission (PCDAI < 10) was seen in 10 patients (48 %), with numerically higher remission rates in the groups of patients receiving 5 mg/kg and 10 mg/kg of infliximab compared to the group of patients with the dose of infliximab of 1 mg/kg.[33]

Subsequent studies confirmed the corticosteroid-sparing effect of infliximab in pediatric CD.[34-37] Early studies examined the effect of infliximab on fistulizing disease as well. A multicenter Italian study reported complete closure of the fistulae in 54 % (7 of 13) of CD patients treated with 1–8 infusions of infliximab and a partial response in the additional 23 % of patients.[37] Cezard et al. prospectively enrolled 21 patients with severe CD, 12 of whom had fistulizing disease. They were given 5 mg/kg infusions of infliximab at 0, 15, and 45 days. All fistulae were closed by day 45.[34]

The largest, most comprehensive trial of infliximab in children and adolescents with CD is the REACH study (A randomized, multicenter, open-label study to evaluate the safety and efficacy of infliximab).[38] The study evaluated infliximab efficacy and safety in 112 pediatric patients with moderate to severe CD. Patients were given induction therapy consisting of 5 mg/kg of infliximab at 0, 2, and 6 weeks. At week 10, responders were randomized to receive either 5 mg/kg of infliximab every 8 weeks (group 1) or every 12 weeks (group 2). The primary end-point was clinical response (a decrease in PCDAI of ≥ 15 points from baseline and a total PCDAI ≤ 30) at week 10. Secondary end-points were response and remission (PCDAI ≤ 10) at week 54. Eighty-eight percent of pateints responded to infliximab by week 10, with 59 % achieving remission. At week 54, 64 % of patients in group 1 and 33 % in group 2, respectively, had responded. The remission was achieved in 56 % of pateints in group

1 compared to 24 % of patients in group 2. Quality of life (measured by the IMPACT III questionnaire) showed significant improvement at weeks 10 and 54. Additionally, a significant growth improvement was seen during the observational period.

During the study, 32 (31 %) of CD patients needed dose adjustments due to loss of response (dosage increase to 10 mg/kg or reduction of dose interval to 8 weeks, or both adjustments). These adjustments were successful in 75 % (24/32) of CD patients.

After the REACH study, several randomized and observational studies were published and confirmed the efficacy of infliximab in the treatment of active CD in children.[39-42]

In 2011, investigators of the REACH study published the data on long-term effects of maintenance infliximab therapy in children with moderately-to-severely active Crohn's disease (REACH open-label extension study). Sixty CD patients, who completed the treatment in the first part of the REACH study through the week 46 and experienced the benefit from continued treatment, entered the study and were given infliximab continuously for up to 3 years during the study period. Approximately eighty percent of them had remission or response with mild disease activity per the physician's global assessment at the end of the study. Additionally, patients with ≥ 1-year delay in bone age at baseline trended toward improvement in height during the study.[43]

Current international guidelines recommend infliximab for induction and maintenance treatment in pediatric CD patients with moderate to severe disease, refractory or intolerant to conventional treatment.[44] The induction treatment consists of administration of infliximab infusions (5 mg/kg) at 0, 2 and 6 weeks. When this three-dose induction treatment has been effective, patients continue with scheduled maintenance infusions every 8 weeks.[38,43,15,44]

Clinical efficacy of infliximab in pediatric ulcerative colitis

In the last years, infliximab has been successfully used in the treatment of adult

ulcerative colitis. The first large, multicenter, randomized, placebo-controlled trials in adult UC were ACT 1 and ACT 2, which confirmed the efficacy and safety of infliximab in inducing and maintaining remission in adult patients with UC.[45] In 2005, infliximab therapy was approved in the USA in adult patients with UC. After that time, several retrospective studies and case reports have shown its efficacy in preventing colectomy in pediatric patients with severe UC.[46-49]

In a prospective study by Turner et al., thiry-three of 37 pediatric patients with severe UC failing intravenous corticosteroid therapy were treated with infliximab. Seventy-six percent of these patients had short-term response to infliximab. A sustained response was seen in 52 % of patients during a 1-year follow-up period.[50]

In 2012, a multicenter prospective study on the efficacy and safety of infliximab for inducing and maintaining treatment in children with moderately to severely active UC has been published.[51] Patients with UC (6–17 years old) who had active UC (Mayo scores of 6–12; endoscopic subscores ≥ 2) and had not responded to or tolerated conventional treatment were given 5 mg/kg infliximab at weeks 0, 2, and 6. The primary end point was response at week 8 (decreases in Mayo scores ≥ 30 % and ≥ 3 points). At week 8, only responders were randomly assigned to groups given infliximab every 8 or 12 weeks and followed through week 54. Maintenance end points included pediatric UC activity index scores < 10 points, defined as remission. At week 8, infliximab induced a response in 73.3 % of UC patients. At week 54, remission was achieved in 38.1 % of those patients who were in the group with every 8-week infusions compared to 18.2 % of those patients who were in the group with every 12-week infusions.[51] These results have confirmed the role of infliximab in the management of children with moderate to severe UC, though it appears to be less effective than in pediatric CD. Further pediatric studies will be needed to confirm these results and determine the long-term effect and safety of infliximab in pediatric UC. The dose and time schedule of induction and mainte-nance treatment with infliximab in pediatric UC is similar to that in pediatric CD.[50,51,15]

Safety of infliximab therapy

Immunogenicity

Several studies have shown that some patients treated with infliximab generate antibodies to infliximab (ATI). The prevalence of ATI in adult studies varies from 16–59 %.[15,52,53]

The presence of ATI may lead to acute infusion reactions, delayed hypersensitivity reactions, and decreased serum drug levels leading to a shorter duration of response or even to a complete loss of response to infliximab therapy.[52,53] In a recent adult study, ATI levels were measured retrospectively in 1,232 serum samples of 90 patients with IBD (64 CD and 26 UC). Antibodies to infliximab were present in 59 % of patients. In twenty-eight percent of ATI positive patients, ATI disappeared over time. In the group of patients with sustained ATI, 68 % of them needed to discontinue treatment with infliximab compared to 13 % of patients with transient ATI. Sustained high levels of ATI led to permanent loss of response to infliximab.[52]

The prevalence of ATI in children receiving infliximab was determined by Miele et al. to be 35 %.[54] Candon et al. have found a very similar rate of ATI (35.7 %) in CD children after infliximab administration. The presence of ATI was clearly associated with a loss of response to infliximab. In two patients presenting with high titers of ATI, severe infusion reactions were observed, precluding further use of the medication.[55]

Infusion reactions

Infusion reactions have been one of the most consistent adverse effects of anti-TNF therapy. Acute infusion reactions (AIR) may be mild with symptoms such as flushing, dizziness, shortness of breath, nausea, headache, and feeling hot, or severe such as hypotension, hypoxemia and anaphylactic shock.[55,56] In pediatric studies, the incidence of infusion reactions ranges from 0 %[33,36] to 38,6 %.[57] In the REACH study, 17–18 % of

CD patients experienced an infusion-related reaction.[38] Premedication (antihistamines, antipyretics, corticosteroids) did not seem to prevent the development of AIR.[15]

The symptoms of delayed hypersensitivity reactions are usually similar to serum sickness-like disease with fever, joint pain and swelling, and sometimes with rash. These serum-sickness-like reactions occur more than 1 day after the infusion of infliximab and have been reported in 0–8 % of pediatric patients receiving infliximab.[38,40,57]

Infections

Infections remain the most commonly reported adverse events during the infliximab therapy. While most infections are minor, serious infections including pneumonia, sepsis, histoplasmosis, disseminated tuberculosis, listeria and other opportunistic infections have been reported. The combination of infliximab with other immunosuppressive medications, such as thiopurines, increases the risk for opportunistic infections.[15,58,59]

The TREAT (Therapy, Resource, Evaluation and Assessment Tool) registry, published in 2006, evaluated safety in > 6000 adult IBD patients, half of them were treated with infliximab for about 1.9 years. Patients treated with infliximab had an increased risk of infections and this was associated with disease severity and concomitant prednisone use.[60]

The recently published TREAT registry confirmed an increased risk of serious infections in patients treated with infliximab, although the severity of IBD and the use of prednisone or narcotic analgesics carried higher risks.[61]

In the REACH study, the frequency of serious infections (requiring hospitalization) was 5.7 % in the group of patients with 8-week intervals and 8 % in the group with 12-week intervals. During the 36 months of follow-up in the REACH open-label extension study, the most prevalent adverse events were respiratory infections.[38]

Three infections with herpes zoster and Lysteria monocytogenes meningitis have been reported in 82 pediatric patients receiving infliximab at the Children's Hospital of Philadelphia.[62]

One of the most severe complications of anti-TNF therapy is the reactivation of latent tuberculosis. Therefore, testing for tuberculosis prior to anti-TNF therapy should be performed. Evaluation for tuberculosis should include not only tuberculin skin test, but also chest radiography and detailed history of travel, tuberculosis exposure, and symptoms such as chronic cough and weight loss. A high incidence of anergy after administration of intradermal purified protein derivate in IBD patients limits the usefulness of tuberculin skin tests, therefore, more sensitive tests such as gamma interferon release assays (IGRAs) are recommended.[63]

Malignancy

Tumor necrosis factor-α plays an important role in host defense and tumor growth control and, therefore, anti-TNF therapy may increase the risk of malignancies. Adult studies have yielded conflicting results. Several large IBD cohort studies did not find an increased risk of malignancy in contrast to some studies on anti-TNF therapy in patients with rheumatoid atrhritis.[64-66]

There is evidence that the use of thiopurines and anti-tumor necrosis factor (TNF) agents is associated with an increased risk of hepatosplenic T-cell lymphoma (HSTCL), especially in young male patients with Crohn's disease.[67] This is a rare form of very aggressive non-Hodgkin's lymphoma. Twenty-nine cases of HSTCL have been reported until now. All patients with HSTCL were treated with thiopurines, and the combination therapy with anti-TNF-alpha and thiopurines was found in 23 patients (79 %). Twenty-six patients were men, mostly between 18 and 25 years of age.[68,69] Therefore, monotherapy with anti-TNF may be a safer therapeutic strategy that can help to minimize possible risks of combination therapy. However, clear guidelines regarding this issue are still missing. Randomized controlled trials in pediatric IBD will be needed to elucidate this important question. Adult studies including a large multicenter randomized SONIC study have confirmed that combina-

tion therapy with immunosupresives, such as thiopurines, increases the efficacy of anti--TNF therapy.[70,71]

Adalimumab in pediatric Crohn's disease

Adalimumab is a fully humanized IgG1 monoclonal antibody to TNF and is considered less immunogenic than infliximab. It binds to soluble TNF-α and has apoptotic properties similar to infliximab.[60] Its lower immunogenicity and the possibility of a home-based administration are advantages when compared to intravenous anti-TNF treatment. In adult IBD patients, adalimumab was proven to be an effective induction and maintenance therapy for both CD and UC.[72-74]

Unill 2009, some small pediatric studies on the efficacy and safety of adalimumab have been published and have shown that adalimumab was effective even in pediatric CD patient who had lost the response to infliximab.[75,76]

So far, the largest multicenter study on adalimumab safety and efficacy in pediatric CD patients is the RESEAT (Retrospective Evaluation of the Safety and Effect of Adalimumab Therapy) study.[77] There were 115 pediatric patients with moderate and severe CD from 12 IBD pediatric centers included in the study. Ninety-five percent of them were treated with infliximab (with a mean of 12 infliximab infusions) prior to the introduction of adalimumab. Infliximab discontinuation was due to loss of response (47 %), infusion reaction or infliximab intolerance (45 %), or preference for a subcutaneous medication (9 %). Concomitant medications at the commencement of adalimumab were corticosteroids (38 %), azathioprine/6--mercaptopurine (41 %), and methotrexate (23 %). The most common dosing frequency was every other week with induction doses of 160/80 mg in 19 %, 80/40 mg in 44 %, and 40/40 mg in 15 % of patients. Maintenance dosing was 40 mg every other week in 88 % of patients. Clinical response measured by physician's global assessment (PGA) at 3, 6, and 12 months was 65 %, 71 %, and 70 %, respectively, with steroid-free remission at 3, 6, and 12 months of 22 %, 33 %, and 42 %, respectively. There were no malignancies, serious infections, or deaths in the study subjects. In this study, adalimumab was a well--tolerated and effective rescue therapy for moderate-to-severe pediatric CD patients previously treated with infliximab.

The study was retrospective with some limitations of a retrospective approach, however, it should be pointed out that because of the severity of pediatric CD, placebo-controlled biological trials have not been considered ethical.[77] Further trials on adalimumab efficacy will be needed in pediatric UC. Until now, only infliximab has been approved for use in refractory pediatric UC.

Conclusion

In the last years, anti-TNF therapy has significantly improved the therapeutic approach in pediatric patients with inflammatory bowel disease (IBD). Current international guidelines recommend anti-TNF therapy for induction and maintenance treatment in pediatric IBD patients with moderate to severe disease, refractory to or intolerant of conventional treatment. Infliximab is used in both pediatric CD and UC, however, adalimumab has been recently approved only for pediatric CD. During the maintenance treatment with both anti-TNF drugs, a substantial number of patients lose initial response and require dose adjustments to maintain clinical response. Optimal patient selection and timing of anti-TNF therapy requires clinical judgment. The safety profile of infliximab and adalimumab is overall favorable although continued vigilance, especially for the occurrence of infrequent but serious and even dangerous adverse events, including opportunistic infection, remains necessary. Therefore, treatment with anti--TNF should be undertaken in specialized tertiary medical centers, which are specially qualified for this purpose.

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