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EDITORIAL

Safety of anti-tumor necrosis factor therapy in inflammatory bowel disease

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Abstract

Inflammatory bowel disease (IBD), in particular Crohn's disease refractory to conventional therapy, fistulizing Crohn's disease and chronic active ulcerative colitis, generally respond well to anti-tumor necrosis factor (TNF) therapy. However, serious side effects do occur, necessitating careful monitoring of therapy. Potential side effects of anti-TNF therapy include opportunistic infections, which show a higher incidence when concomitant immunosuppression is used. Furthermore, antibody formation against anti-TNF is associated with decreased efficacy and an increased frequency of infusion reactions. The hypothesis of a slightly increased risk of lymphomas in IBD patients treated with anti TNF-therapy is debatable, since most studies lack the specific design to properly address this issue. Alarmingly, the occurrence of hepatosplenic T-cell lymphomas coincides with combined immunosuppressive therapy. Despite the potential serious side effects, anti-TNF therapy is an effective and relatively safe treatment option for refractory IBD. Future research is needed to answer important questions, such as the long-term risk of malignancies, safety during pregnancy, when to discontinue and when to switch anti-TNF therapy, as well as to determine the balance between therapeutic and toxic effects.

Key words: Anti-tumor necrosis factor; Biologics; Inflammatory bowel diseases; Crohn's disease; Infliximab

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INTRODUCTION

Inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis, is an idiopathic chronic relapsing inflammatory disorder of the intestinal tract[1]. The chronic and relapsing course of disease makes IBD a disabling disease that is complex to treat. Conventional therapy, including corticosteroids and thiopurines, is aimed at control of inflammation but does not appear to change the natural course of disease. Moreover, many patients become refractory to conventional therapies during the course of disease.

Infliximab was introduced in the late 1990s as the first result in the development of biologic therapies, and changed the therapeutic potential in IBD dramatically. Anti-tumor necrosis factor (TNF) therapy is currently used for the treatment of corticosteroid-refractory, active, corticosteroid-dependent, fistulizing Crohn's disease, as well as refractory ulcerative colitis[2,3]. Anti-TNF therapy is remarkably effective in patients who do not respond to conventional treatment. However, the use of biologics is associated with significant, but rarely, fatal complications, leading to serious concerns about safety and long-term consequences (Table 1). This review will discuss the current knowledge and safety issues as well as future directions for the role of anti-TNF therapy in the treatment of IBD.

SIDE EFFECTS OF BIOLOGIC THERAPY

Infections

The immunosuppressive effect of currently used biologics leads to an increased risk of specific infections during therapy. Most commonly, these infections arise from the upper respiratory tract and the urinary tract. Forty-eight patients had an infectious event and

Table 1 Side effects associated with anti-TNF therapy

Side effect	Example
Infections	Tuberculosis, histoplasmosis
Antibody formation	Antibodies to infliximab, antibodies to adalimumab
Infusion reactions	Anaphylaxis, delayed-type hypersensitivity
Autoimmunity	Antinuclear antibodies
Malignancies	Hepatosplenic T-cell lymphoma
Demyelization	Guillain-Barré syndrome
Abnormal liver function tests	Hepatitis, cholestatic disease
Cardiac abnormalities	Heart failure
Skin eruptions	Psoriasiform dermatitis

20 patients had a serious infection (an infection that requires antimicrobial therapy or hospitalization) during anti-TNF therapy, including fatal sepsis in two patients, in 500 Crohn's disease patients receiving infliximab[4]. In contrast, the CHARM study included 854 Crohn's disease patients, 517 of whom received adalimumab[5], and infectious adverse events occurred in 36%-44% of these patients. Serious infectious adverse events occurred in 2.7% of patients, and both types of adverse events were comparable to those in the placebo group. Serious infectious complications occurred in six of 216 patients (3%) treated with certolizumab[6].

Serious infections during anti-TNF therapy include the reactivation of latent tuberculosis. The increased awareness of this complication has led to a decrease in the number of reports of tuberculosis during biologic therapy. The risk of reactivation of latent tuberculosis was increased by seven-fold when the screening recommendations were not completely followed, as demonstrated by the Spanish national registry for anti-TNF therapy in rheumatoid arthritis[7]. After initiation of guidelines for tuberculosis screening prior to anti-TNF therapy, the rate of tuberculosis decreased by 78% in this registry[8]. Latent tuberculosis was identified by positive skin test and/or fibrotic lesions on chest X-ray in 16 patients in a single center cohort study including 734 IBD patients receiving infliximab. After chemoprophylaxis, none of these patients developed tuberculosis during infliximab therapy[9]. These findings suggest that the current treatment guidelines are indeed effective in preventing reactivation of latent tuberculosis. From 2001 to 2006, 130 patients with tuberculosis during anti-TNF therapy were reported in the USA[10]. The most important risk factor for disease reactivation was concomitant immunosuppressive therapy. Ominously, 34 patients in this group demonstrated a negative tuberculin skin test prior to anti-TNF therapy. Currently, every patient undergoing anti-TNF therapy should be screened by a careful medical history revealing any tuberculosis contact, followed by a chest X-ray and tuberculin skin test. As mentioned, this test is controversial due to reader variability and false-negative results. The recent T-cell-based interferon-γ assay seems more reliable with better sensitivity and specificity than the skin test, as shown in a group of 97 rheumatoid arthritis patients before initiation of anti-TNF therapy[11]. Patients with latent tuberculosis should start with chemoprophylaxis, for example isoniazid for 6 mo, during which anti-TNF medication can be introduced. Active tuberculosis should be fully treated before the start of anti-TNF therapy.

Data on the risk of fungal infections during anti-TNF therapy is limited. A database search identified 226 patients with fungal infections during infliximab therapy[12]. The most common pathogens were those causing histoplasmosis (30%), candidiasis (23%), and aspergillosis (23%). The majority of patients in this group were on concomitant immunosuppressive therapy (98%). Pneumonia was the most common manifestation of infection[12].

The reported risk of opportunistic infections in IBD patients treated with infliximab varies between 0.3% and 0.9%[13]. Interestingly, the risk of opportunistic infections dramatically increases when anti-TNF therapy is combined with additional immunosuppressive therapy, such as corticosteroids or thiopurine therapy[14]. The odds ratio for an opportunistic infection during infliximab therapy was 4.4, compared to 14.5 when combined with corticosteroids or thiopurines in 100 IBD patients with opportunistic infections, compared with a matched control group of IBD patients without opportunistic infections. The TREAT registry, which enrolled 6290 patients who received infliximab, showed that the increased risk for infections during anti-TNF therapy was associated with the use of corticosteroids and disease activity but not with the use of infliximab[15].

In summary, concomitant immunosuppression appears to be an important risk factor for infections during anti-TNF therapy. In daily practice, moderate to severe infectious complications prior to or during anti-TNF therapy require appropriate treatment of the infection before biologic therapy can be initiated or resumed safely.

Antibody formation

The monoclonal antibodies used for anti-TNF therapy frequently induce the formation of antibodies [antibodies to infliximab (ATI); antibodies to adalimumab (ATA)]. Sixty one percent of patients developed ATI in a study of 125 Crohn's disease patients who received on average four infusions of infliximab[16]. This development of ATI was associated with a shorter duration of response to therapy (35 d *vs* 71 d) and a higher rate of infusion reactions (relative risk 2.4)[16]. However, this correlation was not linear and did not predict infusion reactions in an individual patient. Importantly, immunosuppression in the latter study did decrease the formation of ATI.

Interestingly, recent data suggest that IBD patients who discontinued thiopurine therapy while continuing anti-TNF therapy did not show statistically significant clinical differences, compared to the group of patients receiving combination therapy[17]. This was demonstrated during a 2-year trial of 80 Crohn's disease patients. However, it should be noted that the infliximab

monotherapy group demonstrated lower infliximab trough levels and higher levels of C-reactive protein at 18-mo follow-up. We speculate that a prolonged follow-up period might have shown significant differences in the latter trends. ATI formation did not influence the pharmacokinetics of infliximab retreatment, although the authors discuss the influence of serum infliximab on the ATI assay in their paper, leading to an inability to draw firm conclusions[17]. Feagan *et al*[18] demonstrated that the efficacy of infliximab monotherapy was comparable to combination therapy with infliximab and methotrexate after 50 wk of treatment in Crohn's disease patients. Thus, although concomitant immunosuppression does reduce the formation of ATI, the clinical impact has recently been questioned. To further investigate the rationale for combination therapy with azathioprine and biologics, the SONIC trial included Crohn's disease patients who were naïve to immunosuppressive agents and biologic therapy with moderate to severe disease[19]. Patients were started on either azathioprine, infliximab, or a combination of both, and each group included 169 patients. At 26 wk, patients treated with infliximab monotherapy or infliximab plus azathioprine were more likely to achieve steroid-free remission and complete mucosal healing than those receiving azathioprine alone, whereas infliximab plus azathioprine was more effective than infliximab monotherapy. Further investigation in this field is warranted in order to guide patients in evidence-based choices to advise mono- or combination therapy.

Dosage and interval play a role in the development of ATI. For example, infliximab appears to be less immunogenic with increasing dose, as shown with different doses (1, 3 and 10 mg/kg) of infliximab in rheumatoid arthritis patients[20]. The immunological phenomenon of high-dose tolerance may explain this inverse dose-response correlation. Episodic treatment with anti-TNF therapy will also lead to an increased chance of developing antibodies to anti-TNF upon rechallenge. Therefore, scheduled maintenance rather than episodic therapy is recommended[21].

Adalimumab is a fully humanized IgG1 antibody to TNF and is considered less immunogenic than infliximab. The CLASSIC-2 trial demonstrated 2.6% antibody development in 269 patients receiving maintenance therapy for 56 wk[22]. All patients who developed antibodies in this study were not on concomitant immunosuppressive therapy. Yet, an ELISA was used for the detection of antibodies in this study. This technique has significant limitations due to the lack of discrimination between antibodies and anti-TNF medication[23]. This phenomenon may lead to underestimation of the true concentration of antibodies. Therefore, it is recommended that serum samples should be tested shortly before the next dose of anti-TNF in order to reduce the interference of anti-TNF medication[23]. A radioimmunoassay (RIA) is another technique to measure antibodies to anti-TNF medication. This technique measures specific high-avidity IgG antibodies against infliximab or adalimumab by an antigen-binding test[24]. The advantages of this assay are that it includes IgG4 antibodies, and it is more sensitive than ELISA due to a higher protein-binding capacity[23]. RIA measurements led to the detection of a higher percentage of patients who developed ATI or ATA when compared to previously reported findings[23]. Indeed, West *et al*[25] looked at 30 Crohn's disease patients who lost response to infliximab and were subsequently started on adalimumab. ATA were detected in five patients using RIA, four of these were non-responders to adalimumab. In this study, 17 patients were not on concomitant immunosuppression, and this subgroup included four patients with ATA. The authors concluded that ATA negatively influenced responses to adalimumab. In patients treated with certolizumab as maintenance therapy, 12% developed antibodies without concomitant immunosuppression, while 2% developed antibodies with immunosuppression[6].

Of interest, Aarden *et al*[23] demonstrated that low levels of anti-TNF, just prior to administration of the next dose, preceded the detection of ATI or ATA. Given the need for prevention of antibody formation during maintenance therapy and the technical challenges in the measurement of antibodies, assessment of trough levels rather than antibody development could be used as a biomarker for therapy adjustment. Therapeutic drug monitoring to guide therapy efficacy has not yet been elaborated.

Infusion reactions

The overall percentage of infusion reactions with infliximab was 6.1% in a group of 165 IBD patients[26]. These reactions included a burning sensation, itching, erythema, and pain. The estimated occurrence of serious adverse reactions (including shortness of breath, hypotension, or stridor) was 1.0%. In the latter study, all reactions were effectively treated[26]. Prophylactic antihistamines or a single-dose of hydrocortisone can be considered. In addition, patients who are off treatment for more than 4 mo are more susceptible to developing ATI and infusion reactions and should preferably receive these precautions. Most patients can be rechallenged after the appropriate precautions. Rarely, a genuine allergic reaction occurs, which is characterized by shortness of breath and urticaria[26]. These reactions are IgE-mediated and due to mast cell or basophil degranulation. In this case, the infusion should be stopped and switching to a different anti-TNF agent, such as adalimumab[27].

Delayed hypersensitivity-like reactions occur 3-14 d after anti-TNF therapy. Arthralgia and muscle ache are the most common symptoms[26]. It is believed that immune complex depositions take place and cause the latter symptoms[27]. Most patients with a large interval after the first administration of anti-TNF therapy develop delayed hypersensitivity upon rechallenge. Symptoms can be treated by acetaminophen and high-dose corticosteroids; symptoms usually resolve after 1-2 wk[27]. This group of patients will benefit from switching to a fully humanized anti-TNF therapy since poor responses to infliximab can be expected due to circulating ATI[16].

As a rule, adalimumab and certolizumab are administered subcutaneously. Injection site reactions, attributed to local irritation, were observed in 4% during adalimumab and 3% during induction therapy with certolizumab[5,28]. However, in our experience, injection site reactions are a frequently reported bothersome side effect of long-term adalimumab use. Injection site reactions regarded as a direct toxic effect do not improve following administration of antihistamines.

Autoimmunity

Anti-TNF therapy leads to cell lysis, in turn inducing circulating DNA and cell fragments, followed by the formation of autoantibodies such as antinuclear antibodies (ANAs). The percentages of autoantibodies differ depending on the therapy administered. Antibodies developed in 8% of certolizumab-treated patients after 6 mo, while infliximab led to > 50% of patients testing positive for autoantibodies[29,30]. Antibodies against double-stranded DNA were observed in 33% of 43 ANA-positive Crohn's disease patients receiving infliximab[30]. The development of antibodies is not limited to IBD patients or the use of infliximab; adalimumab induced ANAs in 45% of patients after 24 wk of treatment, and for infliximab, this number was 63% in a group of 91 rheumatoid arthritis patients[31]. Forty-one of 43 rheumatoid arthritis patients receiving infliximab and methotrexate demonstrated ANAs on at least one occasion, suggesting that concomitant immunosuppression does not reduce the formation of autoantibodies[32]. Furthermore, the formation of autoantibodies did not affect the efficacy of anti-TNF therapy and did not predispose to autoimmune diseases, in particular, systemic lupus erythematosus.

Malignancies

TNF plays a role in apoptosis and tumor suppression; it is believed that interference with these pathways can potentially lead to an increased risk of malignancies. However, the small size of clinical trials relative to the low incidence of lymphomas, the underlying risk of malignancies due to IBD, and the concomitant immunosuppressive therapy make it difficult to estimate the true effect, if any, of anti-TNF therapy on the genesis of malignancies in IBD patients. A large population-based study including 47 000 Crohn's disease and ulcerative colitis patients showed a standardized incidence ratio for lymphomas of 1.0 and 1.3 for ulcerative colitis and Crohn's disease, respectively[33,34]. The odds ratio for all types of cancer was 3.3 in a pooled analysis of both Crohn's disease and rheumatoid arthritis patients receiving infliximab or adalimumab[35]. Ten lymphomas were detected in 3493 patients receiving anti TNF therapy, whereas no lymphomas were reported in the control group. However, rheumatoid arthritis is associated with an increased risk of lymphomas, the latter being a disputed association in Crohn's disease[36,37]. The TREAT registry demonstrated that there was no significant increase in the relative risk for lymphoma (1.3) in 3272 patients treated with infliximab[15].

IBD patients undergoing immunosuppression are at increased risk for infections, including Epstein-Barr virus, which in turn may be associated with an increased risk of developing lymphomas. Seven of 18 lymphomas detected in IBD patients were Epstein-Barr-virus-positive, five patients in this group underwent therapy with azathioprine or 6-mercaptopurine[38]. However, the use of anti-TNF agents was not recorded in this study.

Hepatosplenic T-cell lymphoma is a rare type of non-Hodgkin's lymphoma with an aggressive and mostly fatal outcome. Until recently, 16 patients, mostly Crohn's disease patients who were exposed to infliximab, developed this type of lymphoma[39]. All patients received concomitant immunosuppressive therapy with thiopurines, and most patients also received corticosteroids. Of interest, three patients in this group received adalimumab, including two patients who previously received infliximab. It is alarming that nine cases were reported in the last 2 years, although increased awareness and subsequent reporting might play a role in this recent increase. Currently, it is unclear whether infliximab, thiopurine therapy, concomitant immunosuppressive therapy, the underlying disease, separately or in combination, are risk factors for the development of these lymphomas.

Taken together, the hypothesis of a slightly increased risk of lymphomas in IBD patients treated with anti TNF-therapy is debatable. Most studies lack the specific design to properly address this issue. The relative contribution of many risk factors for the development of lymphomas remains to be determined, such as the duration of anti-TNF therapy, concomitant immunosuppressive therapy, and the activity of the underlying disease.

Pregnancy and biologic therapy

Large-sized antibodies do not pass the placenta in the first trimester of pregnancy, but placental transfer is indeed possible in the second and third trimester of pregnancy. However, infliximab was not detected in breast milk[40,41]. To date, limited data are available to address the safety of anti-TNF medication during pregnancy. Live births occurred in 67%, miscarriages in 15%, and therapeutic terminations in 19% in a series of 96 pregnant patients receiving infliximab for either Crohn's disease or rheumatoid arthritis[42]. These results are comparable to Crohn's disease patients not receiving infliximab. However, it should be noted that most women stopped infliximab after conception. The TREAT registry reported 66 pregnancies including 36 during infliximab infusions[15]. The number of miscarriages and neonatal complications were similar in the infliximab-receiving *versus* infliximab-naïve patients. In another study of 10 pregnant Crohn's disease patients intentionally receiving infliximab during pregnancy, all had live births, of which three infants were premature and one had a low-birth weight[43]. Infliximab was detectable in newborns from 2 to 6 mo after delivery in a group of five mothers who were followed from the sixth month of pregnancy until

after delivery[44]. The decreasing levels of infliximab in newborns despite continuous breastfeeding do suggest placental transfer rather than transfer *via* breast milk. According to the FDA drug safety classification, infliximab is a drug without documented human toxicity, and is therefore considered category B.

Data on the use of adalimumab is limited, although case reports do not show adverse effects after the use of adalimumab during pregnancy[45,46]. No increased risk for adverse pregnancy outcomes was observed in a prospective cohort including 30 pregnant adalimumab-exposed rheumatoid arthritis patients, compared to a control group. A similar outcome was detected for an additional 66 pregnant patients exposed to adalimumab who did not meet the study cohort criteria[47].

Until now, the use of infliximab and possibly adalimumab does not appear to lead to an increased risk for fecundity, pregnancy, or fetal development. The available data on toxicity and long-term effects during pregnancy and in newborns are limited, therefore, a restrictive approach of using anti-TNF therapy prior to and during pregnancy seems appropriate. However, it is also important to realize that active IBD is documented to be detrimental to fecundity and pregnancy, and active disease can potentially do more harm to the embryo, fetus and mother than anti-TNF therapy.

Other safety issues

Neurological disorders following anti-TNF therapy have been described. Nineteen cases of demyelinating events following administration of anti-TNF agents were revealed in a review of the Adverse Events Reporting System of the Food and Drug Administration[48]. The latter observation was associated with a variety of neurological symptoms, including paresthesia, cognitive dysfunction, ocular symptoms, difficulty walking, incontinence, and hemiparesis[48]. Most, but not all, patients demonstrated partial or full recovery. Furthermore, nine patients on infliximab and one patient on adalimumab developed Guillain-Barré syndrome[49]. Also, optic neuritis was described in eight patients receiving infliximab and in two patients receiving adalimumab[50].

Abnormal liver function tests are associated with infliximab therapy. These abnormalities include cholestatic disease[51] as well as hepatitis-like syndromes[52]. Five patients receiving infliximab for Crohn's disease (one), rheumatoid arthritis (three) and psoriatic arthritis (one) developed liver disease, including one with autoimmune hepatitis and one with cholestatic liver disease leading to liver failure[53]. In addition, mildly elevated liver enzymes do occur, and it is recommended that anti-TNF infusions are stopped when these increases exceed three times the upper limit of normal in the case of alanine aminotransferase[54]. Abnormal liver functions tests generally return to normal after discontinuation of anti-TNF therapy. Reactivation of viral hepatitis[55,56] has been described in patients treated with anti-TNF therapy. Therefore, it is advocated that in high-risk groups, patients receiving anti-TNF therapy should be screened for hepatitis B prior to the initiation of therapy, and if positive, nucleoside analogs should be prescribed prior to the start of biologic therapy[56]. Interval monitoring of serum aminotransferases and viral load is recommended[56].

Data on the use of anti-TNF therapy in HIV-positive patients are limited. No clinical adverse effects or changes in CD4 count and viral load were detected in eight patients with rheumatic disease that were followed during their therapy with infliximab or etanercept. In this group, five patients received concomitant methotrexate, and five patients were using highly active antiretroviral therapy[57].

Dermatological symptoms have been reported as a side effect of infliximab therapy. 150 patients developed a wide variety of skin eruptions in a single-center cohort study including 734 infliximab-treated patients[58]. The majority of these patients (61%) were diagnosed with psoriatic dermatitis. Most skin lesions responded well to topical corticosteroids.

Anti-TNF therapy can lead to an increase in the rate of heart failure with an increased risk of death. Worsening of congestive heart failure was reported through the FDA's MedWatch in a number of postmarketing reports. Of 47 reported cases, 38 were new and nine were exacerbations[59]. Therefore, its use is contraindicated in patients with class Ⅲ-Ⅳ New York Heart Association congestive heart failure.

FUTURE DIRECTIONS

The potential risk for malignancies and infections during anti-TNF therapy appears strongly increased with concomitant immunosuppressive therapy, such as thiopurines. Therefore, risk stratification in order to reduce side effects in IBD patients requiring immunosuppressive therapy will become an important part of long-term treatment in these patients. For example, previous and latent infections (Epstein Barr virus, tuberculosis, and hepatitis B), previous malignancies and comorbidity should be taken into account to decide whether to withdraw immunosuppressive agents in order to reduce long-term side effects and maintain remission in IBD patients. Studies that address the reduction of immunosuppressive agents, like the withdrawal of thiopurines and continuation of infliximab in the study by Van Assche *et al*[17], provide valuable data for the potential reduction of concomitant therapies in IBD patients. Future trials to determine the effects of monotherapy *versus* combination therapy, such as anti-TNF, thiopurines, and methotrexate, will be important to guide this strategy. Furthermore, goals of therapy need to be defined. Should physicians aim for more aggressive therapy to ultimately achieve mucosal healing while increasing the risk of side effects, or should clinical remission remain the goal? Future research will help to provide patients with optimal therapy leading to quiescent disease and minimal side effects.

CONCLUSION

Anti-TNF therapy is a robust and effective therapy for

refractory IBD patients. The side effects can be severe, therefore, careful consideration and monitoring can partially prevent damage. Abscesses and opportunistic infections should be treated, and screening for tuberculosis as well as hepatitis B and HIV in high-risk patients is mandatory before the start of treatment. Antibody formation against anti-TNF agents can be prevented with concomitant immunosuppressive therapy, and the majority of infusion reactions due to infliximab can be prevented with antihistamines and corticosteroids. The risk of lymphomas requires careful consideration before the start of biologic therapy. Information on anti-TNF therapy in pregnancy is limited, although no adverse effects have been reported so far.

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