INTRODUCTION

Inflammatory bowel disease (IBD) is a group of chronic systemic diseases involving inflammation of gastrointestinal tract. It includes ulcerative colitis (UC), Crohn’s disease (CD), and indeterminate colitis. The etiology of the disease is unknown, but interplay of genetic, environmental and immunologic factors is crucial in its pathogenesis. Standard medical treatment is directed towards nonspecific suppression of inflammation (1, 2). However, a substantial number of patients have serious side effects or do not respond to this therapy (3).

Tumor necrosis factor \( \alpha \) (TNF-\( \alpha \)) is a typical pro-inflammatory cytokine. The hypothesis that it may be of particular importance in the induction and perpetuation of intestinal inflammation has led to the development of treatments directed at blocking its proinflammatory actions. Three anti-TNF-\( \alpha \) molecules are used currently to treat IBD. Infliximab (Remicade®, Centrocor) is administered as an intravenous infusion for the treatment of UC and CD. Adalimumab (Humira®, Abbott), a fully human TNF-\( \alpha \) antagonist, and certolizumab pegol (Cimzia®, Celltech), a pegylated humanized anti-TNF-\( \alpha \) antibody fragment, are administered subcutaneously for the treatment of CD. Biological therapeutics has a number of safety issues that differ from those of standard drugs, such as sulfasalazine, mesalazine, steroids, azathioprine and methotrexate (1, 2). Moreover, biologics are frequently given to patients who are refractory to the former treatment and are usually added to the standard drugs. Due to the combination of very potent drugs and long treatment, patients may experience cumulative toxicities of the different medications used. The safety of CD therapies emerged as an important issue in clinical management of this special group of patients very early. In order to gather more information, two large registries, the TREAT registry in North America and ENCORE registry in Europe were established.

Although short- and long-term anti-TNF-\( \alpha \) therapy is generally well tolerated, clinicians must be vigilant for the occurrence of infrequent but serious events. Antibodies to infliximab interfere with the safety and efficacy of the drug and may lead to infusion reactions, loss of response, and delayed serum sickness-like reactions. The optimal strategy to overcome the production of antibodies is systematic maintenance treatment. The most effective way to minimize the risk of opportunistic infection is to vaccinate the patients and to avoid the use of corticosteroids. All patients should receive varicella vaccination, annual influenza vaccination (also pandemic influenza A – H1N1), and pneumococcal vaccination every 3 to 5 years. In addition, HPV vaccine should be administered to young females, and hepatitis B vaccine to HBV seronegative patients. Unlike corticosteroids, infliximab does not pose an increased risk for serious infection. Treatment with anti-TNF-\( \alpha \) agents increases the risk of activation of latent TB. Therefore, all patients should be screened for TB infection before starting with therapy. The use of anti-TNF-\( \alpha \) agents in combination with immunomodulators is associated with an increased risk of non-Hodgkin’s lymphoma, but the absolute rate remains low. There is no evidence that other malignancies and death rates in patients treated with anti-TNF-\( \alpha \) strategies are increased. Reported data from 300 pregnant women treated with infliximab have not shown any untoward effects of treatment on pregnancy outcome.

Key words: safety; anti-TNF-\( \alpha \), infections, malignancy, mortality

HOW TO IMPROVE THE SAFETY OF BIOLOGIC THERAPY IN CROHN’S DISEASE

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Short- and long-term anti tumor necrosis factor-alpha (TNF-\( \alpha \)) therapy in Crohn’s disease is generally well tolerated. However, clinicians must be vigilant for the occurrence of infrequent but serious events. Antibodies to infliximab interfere with the safety and efficacy of the drug and may lead to infusion reactions, loss of response, and delayed serum sickness-like reactions. The optimal strategy to overcome the production of antibodies is systematic maintenance treatment. The most effective way to minimize the risk of opportunistic infection is to vaccinate the patients and to avoid the use of corticosteroids. All patients should receive varicella vaccination, annual influenza vaccination (also pandemic influenza A – H1N1), and pneumococcal vaccination every 3 to 5 years. In addition, HPV vaccine should be administered to young females, and hepatitis B vaccine to HBV seronegative patients. Unlike corticosteroids, infliximab does not pose an increased risk for serious infection. Treatment with anti-TNF-\( \alpha \) agents increases the risk of activation of latent TB. Therefore, all patients should be screened for TB infection before starting with therapy. The use of anti-TNF-\( \alpha \) agents in combination with immunomodulators is associated with an increased risk of non-Hodgkin’s lymphoma, but the absolute rate remains low. There is no evidence that other malignancies and death rates in patients treated with anti-TNF-\( \alpha \) strategies are increased. Reported data from 300 pregnant women treated with infliximab have not shown any untoward effects of treatment on pregnancy outcome.

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INVESTIGATIONS BEFORE THE USE OF TNF-\( \alpha \) BLOCKERS

Before the use of TNF-\( \alpha \) blockers, detailed history of heart failure, chronic liver disease, neurological disorders and neoplasia is mandatory. TNF-\( \alpha \) blockers are contraindicated in heart failure of NYHA III or IV class and have to be used with caution in patients with chronic liver disease, neurological disorders or history of malignancy, especially lymphoma. Moderate and severe infections require appropriate treatment before biologic therapy is started, because active and quiescent infections may worsen during therapy. If an abscess is suspected, an MRI is indicated. All abscesses should be cured before starting anti-TNF-\( \alpha \) therapy (4).
In presence of colitis relapse, a super infection with Clostridium difficile or CMV should be ruled out. Anti TNF-\(\alpha\) agents carry an increased risk of activation of latent tuberculosis (TB) and careful evaluation (including history of epidemiological risk factors, physical examinations, and chest X-ray and tuberculosis skin test according to national guidelines) for active or latent TB before their use is mandatory. Interferon-gamma release assays are likely to complement the tuberculosis skin test and are preferred in BCG vaccinated individuals, if available. False negative tests can occur in patients treated with steroids and/or immunosuppressants. Patients with a positive screening should be treated with isoniazid for at least 4 weeks, before starting TNF-\(\alpha\) blocker therapy. TB must also be excluded in the event of persistent fever or non specific clinical deterioration occurring during immunomodulator therapy. If TB is diagnosed, patient should be given anti-TB drugs and anti TNF-\(\alpha\) therapy should be stopped and resumed only after two months, if needed.

Reactivation of latent HBV infection is a serious threat for the patients treated with TNF-\(\alpha\) blockers, therefore the serological tests to rule out hepatitis B viral infection should be performed. Patients with negative serology should be vaccinated. Efficacy of vaccination is influenced by the number of immunomodulators given and additional vaccine doses may be necessary to obtain an adequate response. A three-dose vaccination is recommended with evaluation of response 1 month after final injection. Patients with a positive HBsAg and elevated liver enzymes must receive antiviral treatment. No consensus was however reached for HCV screening prior starting with immunomodulators. Some anecdotal reports of increased risk and severity of HIV-related infections in HIV positive patients treated with immunomodulators were published. Therefore, prior to start with immunomodulation therapy, testing for HIV should be considered. In patients with negative history of chickenpox, shingles and varicella zoster virus vaccination, immunization with vaccine (live vaccine!) should be performed at least 3 weeks before introduction of immunomodulator therapy. Patients should receive influenza vaccine annually and pneumococcal vaccine every 3–5 years. During the course of anti TNF-\(\alpha\) and other immunosuppressant therapy live vaccines are contra-indicated. However usual scheduled and routine maintenance vaccinations with inactivated (killed) vaccines can be carried out. IBD patients, who are immunocompromised due to underlying disease and/or treatment are considered at higher risk of complications from influenza A (H1N1). They should be offered prevention (vaccination, post-exposure prophylaxis), or treatment with antiviral drugs if affected. Withdrawal of immunosuppressive treatment appears advisable during severe active infection if possible.

Owing to the risk of cervical cancer caused by human papilloma virus, young women who are not yet sexually active should be vaccinated before anti TNF-\(\alpha\) therapy is started - (according to national guidelines). Women should also have a regular gynaecological examination with a cervical smear with cytodiagnosis (PAP) every year.

Patients should be informed about possible adverse effects and be monitored regularly every two weeks at the initial phase of treatment and every two months later to check efficacy and safety.

**IMMUNOGENICITY**

Infliximab is a genetically constructed IgG1 marine-human chimeric anti TNF-\(\alpha\) monoclonal antibody, which binds to soluble and membrane bound receptors of TNF-\(\alpha\) and neutralizes its biological activity. An important proportion of patients (18%–61%) develop antibodies to infliximab (ATI) because of the presence of foreign sequences in the variable, complementarity-determining regions of the antibody. ATI predispose to acute infusion reactions and delayed serum sickness-like reactions as well as secondary loss of response.

Several treatment strategies, including scheduled maintenance therapy every 8 weeks, concomitant immunosuppression (azathioprine/6-MP for first 6 months), and prophylactic systemic steroids, have been proposed to decrease the incidence and the impact of ATI. Nevertheless, annually in 10% of patients the treatment has to be withdrawn because of intolerance and/or loss of response even on scheduled maintenance therapy. In these patients, the infusion should be stopped and switched to adalimumab, which is a fully humanized IgG1 antibody and is considered to be less immunogenic than infliximab.

Immunogenicity is more problematic with infliximab than with the other drugs, but none should be administered on an episodic basis.

**INFECTIONS**

Infections are a common problem in patients with chronic diseases treated with drugs that interfere with immune system. Many of patients who are receiving biologics alongside with immunomodulators and have moderate or severe disease activity, are at increased risk for opportunistic infections. However, data concerning the risk of infection in patients treated with infliximab are conflicting. In different clinical studies up to 36% of patients treated with infliximab and 28% of patients treated with placebo experienced infections that required therapy. Data from the TREAT registry indicate that during a 2-year follow-up period, the risks for serious infection associated with infliximab were similar to those of conventional immunomodulators. Possible factors implicated with a significantly increased risk of serious infections include use of prednisone, use of narcotic analgesics, advanced age and a severe form of the disease. In contrast to that, an interim safety analysis of the ENCORE registry has not confirmed increased risk for serious infection in patients treated with infliximab. When however the patients received corticosteroids, this risk was high. Fidder et al. also found that concomitant treatment with steroids was the only independent risk factor for infections in patients treated with infliximab.

In the report of adalimumab safety including 6 global clinical trials, 1.8% of patients had experienced opportunistic infections, oral candidiasis being the most common among them. Serious infections were reported in 5.8% of patients. The most common was abscess, followed by gastrointestinal (abscess excluded), pulmonary and viral infections. Thus, the most effective way to minimize the risk of opportunistic infection in IBD is to avoid the use of corticosteroids. Although biologics alone double the risk of infection, adding steroids to the therapy increases the risk nearly 15-fold. The risk of opportunistic infections also dramatically increases when anti TNF-\(\alpha\) therapy is combined with additional immunosuppressive therapy. Future trials to determine the effects of anti TNF-\(\alpha\) monotherapy versus combination therapy, such as anti-TNF, corticosteroids, thiopurines, and methotrexate, will be important to guide this strategy.

The best way of reducing the risk of opportunistic infection is to avoid corticosteroids and to vaccinate all IBD patients: in addition to hepatitis B vaccination in HBV seronegative patients, patients should be vaccinated for varicella, annually for seasonal and pandemic influenza and pneumococcal every 3–5 years.
MALIGNANCY

In IBD patients, the risk of lymphoproliferative disorders (LD) is similar to or only slightly higher than in the general population. The role of immunosuppressants in lymphoma genesis is difficult to individualize because other potentially involved factors are interlinked. Concordant data suggest that azathioprine-6-mercaptopurine therapy is associated with a moderately increased risk of LD (19). Data regarding methotrexate are scarce and available for diseases other than IBD, but the risk seems to be low. All anti TNF-α drugs used in adult CD patients appear to be associated with an increased risk of non-Hodgkin’s lymphoma (NHL) too. A recently presented meta-analysis of 26 studies of infliximab, adalimumab and certolizumab including 8843 patients reported an increased risk. Although the risk was statistically significant when compared with the general population, the absolute risk remained small (6.1 per 10 000 patient-years) (20). When compared with CD patients taking immunomodulators alone, there is a statistically insignificant increase in the rate of NHL for those treated in addition with anti TNF-α agents. Anyhow, the use of anti TNF-α agents with immunomodulators is associated with an increased risk of NHL, but absolute rate remains low and should be weighed against the substantial benefits of the treatment. The relative contribution of many risk factors for the development of lymphomas remains to be determined, such as the duration of anti TNF-α therapy, concomitant immunosuppressive therapy, and the activity of the underlying disease.

Seventeen cases of hepatosplenic T-lymphoma were reported in adolescent and young adult patients with Crohn’s disease treated with infliximab and adalimumab (one patient) (19). This rare type of T-cell lymphoma (150 cases are reported in the literature) has a very aggressive disease course and is usually fatal. All of them occurred in patients on concomitant treatment with azathioprine or 6-mercaptopurine. In global clinical trials, close to 1% of patients (35) treated with adalimumab developed a malignant neoplasm (16). The standardized incidence rates for all malignancies was 1.56 (95%, CI=94-2.43), indicating that these patients are not at increased risk for malignancies compared with age- and sex-matched controls. The types of malignancies reported varied and affected many different organ systems (except for skin cancers - 11). These results suggests a small increase in the incidence of non-melanoma skin cancer, driven by a significant increase for squamous cell carcinoma in patients treated with adalimumab for CD compared with the general population. There is no evidence that malignancy rates in patients treated with anti TNF-α agents are increased but regular screening colonoscopies should begin 8-10 years after the onset of IBD symptoms. Advances in endoscopic imaging techniques (high resolution endoscopy, magnifying endoscopy and chromoendoscopy) are already underway, and may potentially aid in dysplasia or early cancerous changes detection (21).

MORTALITY

Patients with CD may also have an increased risk of mortality compared to the general population (22). The mortality rate in Mayo clinic study is generally comparable with the expected surplus of mortality reported in patients with CD, particularly when considering that infliximab therapy is indicated only for patients with moderate to severe form of the disease (12). In the TREAT registry, mortality rates were similar for patients who had received infliximab and those who had not and only prednisone treatment was associated with a significantly increased risk for death (13). The number of deaths (4) observed in adalimumab-treated patients in CD clinical trials was also not different compared with what would be expected in an age- and sex-matched general population (16). Consequently, there is no evidence that death rates in patients treated with anti TNF-α strategies are increased.

PREGNANCY

IBD female patients should be advised to plan their pregnancy. The conception is generally recommended at the time of minor disease activity or in remission. Data on the safety of infliximab during pregnancy are scarce. Large antibodies do not pass through the placenta during the first two trimesters of pregnancy and therefore the risk for the fetus seems to be low (10). There is no data on the effects if infliximab therapy on lactation. Post-marketing reports from approximately 300 pregnant women treated with infliximab, do not indicate untowards effects on pregnancy outcome, however, the available clinical experience is limited. At present, the use of infliximab and possibly adalimumab also does not appear to represent an increased risk for fecundity, pregnancy, or fetal development (23). Since the available data on toxicity and long-term effects during pregnancy and in newborns are limited, a restrictive approach of using anti TNF-α therapy prior to and during pregnancy seems appropriate (24). Women of childbearing potential should use adequate contraception to prevent unplanned pregnancy.

CONCLUSIONS

The efficacy and safety profile of the TNF-α inhibitors can be considered, in general, as a class effect. Nevertheless, some differences may exist among the three agents. Physicians who treat patients with biologic therapies should be aware of the possible safety problems and the ways to avoid and treat them. Benefit-risk profile of them is well-defined and positive, but clear communication to patients is critical. In individual patients, the risk/benefit analysis needs to be carefully assessed and discussed prior to commencement of therapy.

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