

WJG 20th Anniversary Special Issues (3): Inflammatory bowel disease**Risk of infections associated with biological treatment in inflammatory bowel disease**

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Received: June 19, 2014 Revised: July 28, 2014

Accepted: September 5, 2014

Published online: November 21, 2014

Abstract

Tumor necrosis factor- α (TNF- α) inhibitors are biological agents introduced in the late 1990s for the treatment of different immune-mediated diseases as inflammatory bowel disease, rheumatoid arthritis and psoriasis. The most commonly used TNF- α antagonists are infliximab, adalimumab, and certolizumab pegol, and though highly effective in lowering inflammation, the efficacy must be weighed against the potential for adverse events. The treatment-induced immunosuppression is suspected to increase the risk of infections, including the risk of reactivation of latent tuberculosis, as the TNF- α cytokine plays an important role in the immune function. In this topic highlight a short overview of the infection risk associated with TNF- α inhibitor therapy is outlined with a focus on the overall risk of serious infections, mycobacterial infection and latent viral infections.

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Key words: Inflammatory bowel disease; Biological treatment; Tumor necrosis factor- α inhibitors; Risk; Infections; Ulcerative colitis; Crohn's disease

Core tip: The use of tumor necrosis factor- α (TNF- α)

inhibitors are increasing worldwide for the treatment of several chronic immune-mediated diseases as rheumatoid arthritis and inflammatory bowel disease (IBD). As the drugs are relatively new on the market, their long-term safety profile remains uncertain. In particular, a concern regarding an increased infections risk has been debated. In the current topic highlight, a brief overview of the current literature regarding the risk of infections in patients with IBD exposed to TNF- α inhibitors is outlined.

Andersen NN, Jess T. Risk of infections associated with biological treatment in inflammatory bowel disease. *World J Gastroenterol* 2014; 20(43): 16014-16019 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v20/i43/16014.htm> DOI: <http://dx.doi.org/10.3748/wjg.v20.i43.16014>

INTRODUCTION

Inflammatory bowel disease (IBD), comprising ulcerative colitis (UC) and Crohn's disease (CD) are relapsing inflammatory conditions affecting the gastrointestinal tract. Since their introduction in the late 1990s, tumor necrosis factor- α (TNF- α) inhibitors have altered the treatment paradigm in IBD and other chronic inflammatory conditions as rheumatoid arthritis and psoriasis. TNF- α inhibitors are chimeric, partly or fully humanized monoclonal antibodies or antibody fragments impairing the pro-inflammatory cytokine, TNF- α . Initially, TNF- α inhibitors were approved for treating fistulizing CD but rapidly their indication expanded and currently, infliximab, adalimumab, certolizumab pegol and golimumab are approved for the treatment of moderate to severe active IBD in adults (certolizumab pegol solely approved for CD and golimumab solely approved for UC)^[1-5], and recently infliximab has been approved for refractory CD and UC in pediatric patients^[6,7]. Assembled, the benefits

of TNF- α inhibitors in the management of IBD are indisputable, but concerns about potential adverse events remain an important issue. TNF- α has a central role in the immune system stimulating the differentiation of monocytes into macrophages, recruitment of neutrophils and creation of granulomas^[8]. Inhibiting this cytokine in the case of inappropriate immune responses as seen in IBD, could potentially impair the effectiveness of the host immune function in the defense against infectious organisms, thereby leading to an increased risk of infections, including the risk of opportunist infections. Shortly after the introduction of infliximab a concern regarding the risk of reactivation of latent tuberculosis (TB) was raised and has led to obligate screening for latent TB prior to TNF- α inhibitor exposure^[9]. Early randomized clinical trials examining the risk of infectious complications have primarily suggested that there is no overall increased risk of infections after treatment with TNF- α inhibitors, but, the true risk profile often relies on ongoing surveillance during the post marketing period with the accumulation of a large number of unselected exposed patients. For this purpose, population- and register-based observational studies are useful, though residual confounding often challenges the interpretation of these studies. Further, drug specific analyses are complicated by the fact that the majority of IBD patients receiving TNF- α inhibitors have concurrent exposure to other immunomodulators as azathioprine and prednisolone, drugs also known to possess an infection risk *per se*^[10-12]. Hence, multiple factors must be taken into account when analyzing and interpretation the infectious risk estimates related to biological treatment.

The aim of the current topic highlight is to give a brief up-date on the existing evidence on the potential increased risk of infections, including the risk of reactivation of latent TB and viral pathogens in IBD patients treated with TNF- α inhibitors.

OVERALL INFECTION RISK

Prior to the approval of infliximab for IBD in the late 1990's, several large, randomized pivotal phase 3 clinical trials were conducted in order to assess the effectiveness of the drug and outline a safety profile. Lichtenstein *et al*^[13] performed a pooled analysis of infections risk based on these sponsor-initiated trials, including the ACCENT I^[3,14], ACCENT II^[15] and SONIC^[1] trials in CD and the ACT I and ACT 2^[2] trials in UC. Authors found that a larger proportion of infliximab- than placebo-treated UC patients had at least one infection (50.1% *vs* 36.3%; $P < 0.001$) whereas the proportion of CD patients treated with infliximab *vs* placebo who had one infection was similar (49.1% *vs* 45.3%; $P = 0.402$). The proportion of IBD patients having one serious infection was similar in infliximab *vs* placebo treated patients (4.7% *vs* 3.7%; $P = 0.427$). Infections expressed as incidences per 100 person-years revealed that infliximab-treated IBD patients had an incidence of 113.80 (95%CI: 109.12-118.62)

vs 115.79 (95%CI: 104.26-128.25) in placebo-treated IBD patients. Similarly, no significant difference between infliximab-treated and placebo-treated IBD patients in incidence of serious infections was observed and authors concluded that infliximab treatment in patients with IBD did not appear to affect incidences of infections. However, the design of randomized clinical trials is often with stringent inclusion and exclusion criteria, and limited follow-up and sample size, hence presenting selected patients populations, that are not optimal for evaluation of the overall, long-term risk of adverse events. In 2009, Fidler *et al*^[16] conducted a single-centre cohort study, evaluating the long-term safety of infliximab in 734 exposed IBD patients followed for a median of 58 mo. The study suggested that the infection rate was similar in IBD patients treated with infliximab compared to IBD patients treated with conventional therapies. In contrast, a prospective, observational study with equivalent follow-up time, based on data from the North American TREAT (Crohn's Therapy, Resource, Evaluation, and Assessment Tool) registry found that infliximab treatment was associated with a significant 43% increased risk of serious infections (HR = 1.43; 95%CI: 1.11-1.84) but authors pointed out that CD severity and use of prednisone and narcotic analgesic carried higher risks, thus the increased risk of serious infection might be attributed to disease severity rather than the infliximab treatment *per se*^[17]. Another North American study including combined data from four large databases in the SABER (Safety Assessment of Biologic Therapy) project investigated the rate of serious infections in patients with different autoimmune disease (IBD, RA, psoriasis, psoriatic arthritis, and ankylosing spondylitis) exposed to TNF- α inhibitor treatment compared with the rate in propensity score matched non-users^[18]. Among 2323 patients with IBD exposed to TNF- α inhibitors no increased risk of serious infections was observed (365 d risk window) following exposure, with an adjusted HR of 1.13 (95%CI: 0.85-1.50) whereas an insignificant trend towards an increased risk was observed for those with concomitant glucocorticoid treatment (> 10 mg/d) with a HR of 1.38 (95%CI: 0.98-1.95). Only for RA patients did the study have sufficient power to analyze the risk of serious infections for the different TNF- α inhibitors separately and stratified analyses revealed that exposure to infliximab was associated with a 25% significant increased risk of serious infections when compared to non-biological treatment (HR = 1.25; 95%CI: 1.07-1.48). There were no increased risk of serious infections related to adalimumab. A small cohort study from Korea compared the risk of serious infections between infliximab and adalimumab in 175 patients with different autoimmune disorders (including 54 with IBD) and found similar infections rates in patients exposed to adalimumab and infliximab but no analyses with a comparison group were performed^[19].

From the Food and Drug Administration Adverse Event Reporting System, Deepak *et al*^[20] studied the association between infections risk and different drugs, in-

cluding TNF- α inhibitors in patients with IBD. Authors found that the risk of serious infections was increased in IBD patients treated with TNF- α inhibitors as monotherapy (OR = 1.95; 95%CI: 1.06-3.59) and further revealed that there was no incremental increase in risk, when combining the treatment with other immunomodulators. A register-based study from the United Kingdom compared the risk of serious infections in patients with rheumatoid arthritis (RA) exposed to TNF- α inhibitors with those exposed to conventional treatments and found a small, significant increased risk related to TNF- α inhibitor exposure (HR = 1.2; 95%CI: 1.1-1.5) with no significant difference between the different TNF- α inhibitors^[21]. Further, when limiting the follow-up to the first 90 days after exposure to TNF- α inhibitors revealed a augmented increased risk of serious infections (HR = 1.8; 95%CI: 1.3-2.6) suggesting that the risk of serious infections is dependent on time since exposure with an increased risk in the early post-treatment period. The study also studied the effect of age on risk of infections and although increasing age was an independent risk factor for serious infections in both treatment groups, there was no difference in relative risk of infection in patients on TNF- α inhibitor therapy in the older population.

To summarize, the overall risk of infections related to TNF- α inhibitor exposure in patients with IBD tend to be limited during long follow-up and mostly driven by patient factors including comorbidities and steroid use. However, the potential for TNF- α inhibitor therapy to improve disease control and allow for steroid dose reduction or elimination, could even out the risk estimates and mask a more substantial increased infections risk related to TNF- α inhibitors *per se*. There is a need of further longitudinal observational studies examining the risk in the different TNF- α inhibitors separately and during different risk windows to assess the potential of a time varying effect.

MYCOBACTERIAL INFECTIONS

According to the World Health Organization, an estimated 8.6 million people developed Tuberculosis (TB) and 1.3 million died from the disease in 2012 making the disease a major global health problem^[22]. Shortly after introduction of infliximab, the concern of reactivation of latent TB in patients receiving TNF- α inhibitors was raised as reports from the Food and Drug Administration Adverse Events Reporting System revealed higher rates of TB in patients exposed to infliximab compared to the background rates^[9]. There were 70 reported cases of TB in patients exposed to infliximab for a median of 12 wk and in 48 patients, TB developed after three or fewer infusions. Of the 70 cases, 91% were from countries with low incidence of TB. The association is further strengthened by the biological plausible link, as TNF- α plays an important role in granuloma formation, which is responsible for the sequestration of mycobacteria. The risk of TB reactivation following TNF- α inhibitor

treatment is mostly studied in patients with rheumatoid arthritis^[23-25] and there is a wide variation in TB rates observed amongst the different studies and a consensus report stated that the relative risk of TB increases 1.6-25 times with exposure to TNF- α inhibitors depending on the clinical context, the drug used and the patient's country of origin^[26]. Interestingly, two studies investigating the risk of reactivation of latent TB in patients with CD did not find any cases of TB and this raises the possibility of a substantial lower risk of TB in patients with IBD compared to those with rheumatoid arthritis, possibly partly because of the younger age of IBD patients^[27,28]. In light of the significant morbidity and mortality associated with TB reactivation, current guidelines demand that patients with IBD who are to be treated with TNF- α inhibitors should first be screened for latent TB with a chest x-ray and tuberculin skin test^[29,30] (in case of a negative test in patients at high TB risk a Quantiferon test should be considered^[29,31-33]). If there is evidence of latent TB infections, patients should begin treatment with isoniazid therapy prior to introducing TNF- α inhibitor treatment.

LATENT VIRAL INFECTIONS

An increased risk of viral infections has also been associated with TNF- α inhibitor exposure as TNF- α has an important role in viral clearance. Particularly the risk of reactivation of varicella zoster virus (VZV), cytomegalovirus (CMV) and viral chronic hepatitis B has received attention.

TNF- α plays a role in the immune response against VZV as it blocks antigen expression and viral virus replication^[34]. Infection with VZV in children causes chickenpox (primary infection) and the infection then becomes latent and may be reactivated in adults causing herpes zoster (shingles). The potential association between TNF- α inhibitors and herpes zoster is mainly studied in patients with RA. A German study including 5040 patients with RA revealed that exposure to the TNF- α inhibitors infliximab and adalimumab was associated with an 82% significant increased risk after adjustment for age, disease severity and glucocorticoid use (HR = 1.82; 95%CI: 1.05-3.15)^[35]. However a more recent study, including 33324 new users of TNF- α inhibitors in patients with RA, IBD, psoriasis, psoriatic arthritis, or ankylosing spondylitis did not find a higher risk of herpes zoster in patients with IBD or other inflammatory diseases who initiated TNF- α inhibitor therapies compared with patients who initiated non-biologic treatment regimens^[36]. As the evidence is not clear, clinicians should be aware of the potential increase risk of herpes zoster, particularly in the light of the high prevalence of VZV seropositive patients. Prior to initiation of TNF- α inhibitor treatment, VZV vaccine may be administered to all adults without evidence of immunity to VZV, but administration of live attenuated VZV vaccine is contraindicated during TNF- α inhibitor therapy and should be given at least 3 wk prior to initiation of any immunosup-

Table 1 Testing to undertake prior to initiation of tumor necrosis factor- α inhibitor treatment

Infection	Tests	Consequences
TB	Latent TB infection should be tested by a combination of patient history, chest X-ray, tuberculin skin test and interferon-gamma release assays (Quantiferon test) according to local prevalence and national recommendations. The Quantiferon test is preferred in patients receiving immunosuppressive therapy and in BCG immunized patients	Patients diagnosed with latent TB infection prior to TNF- α inhibitor exposure should be treated with a complete therapeutic regimen for latent TB. TNF- α inhibitor treatment should not be initiated prior to one month after the introduction of anti-TB treatment When active TB is diagnosed, anti TB-therapy must be started, and TNF- α inhibitor therapy must be stopped but can be resumed after two months if needed
HBV	Blood test for HBsAg, anti- HBsAb and HBeAb to determine HBV status. In patients with positive HBsAg, viremia (HBV-DNA) should also be quantified	Patients with acute HBV infection (HBsAg positive) should be treated with antiviral drugs and treatment with TNF- α inhibitors should not be initiated before a test of HBV DNA is negative In case of evidence of quiescent HBV infection patients should be regularly monitored for evidence of HBV replication during treatment with TNF- α inhibitors
HIV	Blood test for HIV serology	In patients with uncontrolled HIV infection, treatment with TNF- α inhibitors is contra-indicated
VZV	In case of a negative history of chicken pox/herpes zoster infection VZV serology should be tested	Patients with negative serology for VZV should be vaccinated and treatment with TNF- α inhibitor should be awaited three weeks

TB: Tuberculosis mycobacterium; TNF- α : Tumor necrosis factor- α ; HBV: Hepatitis B virus; HBsAg: Hepatitis B surface antigen; HBsAb: Hepatitis surface antibody; HBeAb: Hepatitis B core antibody; HIV: Human immunodeficiency virus; VZV: Varicella zoster virus.

pressant including TNF- α inhibitors.

Cytomegalovirus is another member of the Herpes virus family and has a high seroprevalence in adults^[37]. The primary infection in immune-competent patients is nearly always asymptomatic or comparable to mild mononucleosis-like symptoms but afterwards the infection often becomes latent. Treatment with TNF- α inhibitors has been related to reactivation of latent CMV infections in patients with IBD^[37,38]. The handling of CMV infection in IBD patients remains a challenge as the distinction between active CMV infection and active CMV disease (the presence of both CMV infection and the presence of clinical signs and symptoms, such as fever, leukopenia, or end organ involvement) may be difficult. As there are no current consensus on how to manage active CMV infections/CMV disease in IBD patients treated with TNF- α inhibitors or other immunosuppressant drugs large, controlled trials on antiviral treatment are needed to clearly elucidate the benefits of antivirals in this setting, and to possibly identify risk factors that help identify patients who need antiviral therapy^[39].

The awareness of hepatitis B virus (HBV) infections has increased because of several case reports of severe hepatitis B virus reactivation in patients exposed to TNF- α inhibitors^[40-42]. Although the role of TNF- α in chronic viral hepatitis is limited, there is evidence that TNF- α synergizes with interferons in suppressing viral replication^[43] and is essential in clearing HBV^[44]. Hence, inhibiting the TNF- α cytokine could potentially increase HBV replication leading to active disease. Currently, it is recommended that all patients with IBD are screened for HBV before introducing TNF- α inhibitor therapy and if active HBV replication is detected, antiviral treatment should be administered prior to introducing TNF- α inhibitor therapy.

Table 1 summarizes which tests to undertake prior to initiation of treatment with TNF- α inhibitors.

Based on the current ECCO (European Crohn Colitis Organisation) consensus on preventing opportunistic infections in patients with IBD the following vaccinations are recommended to be given prior to the initiation of TNF- α inhibitors: Influenza (annual), Pneumococcal, Hepatitis B, Varicella, HPV (only women)^[45].

CONCLUSION

There is limited evidence of a substantial increased overall risk of serious infections in patients with IBD exposed to TNF- α inhibitors, however, a small increased risk may not be ruled out, particularly in patients receiving concomitant treatment with corticosteroids and comorbidity. Additionally, it seems that there is an association between exposure to TNF- α inhibitors and different site- and pathogen-specific infections. The risk of reactivation of latent TB infections should be recognized and minimized by TB testing prior to the initiation of TNF- α inhibitor treatment, particularly in countries with high TB incidence. Likewise, it is recommended to screen for latent hepatitis B virus infection and VZV prior to TNF- α inhibitor treatment. The magnitude of the risk of reactivation of CMV in IBD patients exposed to TNF- α inhibitors and other immunosuppressant drugs is not clear and there is no current consensus on how to manage these patients.

In the future, with a growing number of patients exposed to TNF- α inhibitors and hence increasing power, there is need for studies examining the risk of infections following TNF- α inhibitor exposure in patient sub-groups, as for example the elderly. Further there is a need of studies investigating the risk of infections according to specific TNF- α inhibitors separately.

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P- Reviewer: Gaertner W, Limdi JKK, Lucendo AJ, Perse M
S- Editor: Ma YJ **L- Editor:** A **E- Editor:** Liu XM





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ISSN 1007-9327

