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**Risk of infections associated with biological treatment in inflammatory bowel disease**

Andersen NN *et al*.IBD and risk of infections

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**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 inhibiter 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.

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**INTRODUCTION**

Inflammatory bowel disease (IBD), comprising ulcerative colitis (UC) and Crohn’s disease (CD) are replapsing 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 of 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 is not optimal for evaluation of the overall, long-term risk of adverse events. In 2009, Fidder *et al*. 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[16]. 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 2,323 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, including 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 strengthen 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 5,040 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 weeks prior to initiation of any immunosuppressant 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 in case of evidence of active HBV replication; antiviral treatment should be administered prior to introducing TNF-α inhibitor therapy.

Table 1 summarizes the testing to be performed 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 recieving 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.

**REFERENCES**

1 **Colombel JF**, Sandborn WJ, Reinisch W, Mantzaris GJ, Kornbluth A, Rachmilewitz D, Lichtiger S, D'Haens G, Diamond RH, Broussard DL, Tang KL, van der Woude CJ, Rutgeerts P. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med* 2010; **362**: 1383-1395 [PMID: 20393175 DOI: 10.1056/NEJMoa0904492]

2 **Rutgeerts P**, Sandborn WJ, Feagan BG, Reinisch W, Olson A, Johanns J, Travers S, Rachmilewitz D, Hanauer SB, Lichtenstein GR, de Villiers WJ, Present D, Sands BE, Colombel JF. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2005; **353**: 2462-2476 [PMID: 16339095 DOI: 10.1056/NEJMoa050516]

3 **Rutgeerts P**, Diamond RH, Bala M, Olson A, Lichtenstein GR, Bao W, Patel K, Wolf DC, Safdi M, Colombel JF, Lashner B, Hanauer SB. Scheduled maintenance treatment with infliximab is superior to episodic treatment for the healing of mucosal ulceration associated with Crohn's disease. *Gastrointest Endosc* 2006; **63**: 433-42; quiz 464 [PMID: 16500392 DOI: 10.1016/j.gie.2005.08.011]

4 **Sandborn WJ**, Feagan BG, Stoinov S, Honiball PJ, Rutgeerts P, Mason D, Bloomfield R, Schreiber S. Certolizumab pegol for the treatment of Crohn's disease. *N Engl J Med* 2007; **357**: 228-238 [PMID: 17634458 DOI: 10.1056/NEJMoa067594]

5 **Sandborn WJ**, van Assche G, Reinisch W, Colombel JF, D'Haens G, Wolf DC, Kron M, Tighe MB, Lazar A, Thakkar RB. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. *Gastroenterology* 2012; **142**: 257-65.e1-3 [PMID: 22062358 DOI: 10.1053/j.gastro.2011.10.032]

6 **Hyams J**, Damaraju L, Blank M, Johanns J, Guzzo C, Winter HS, Kugathasan S, Cohen S, Markowitz J, Escher JC, Veereman-Wauters G, Crandall W, Baldassano R, Griffiths A. Induction and maintenance therapy with infliximab for children with moderate to severe ulcerative colitis. *Clin Gastroenterol Hepatol* 2012; **10**: 391-9.e1 [PMID: 22155755 DOI: 10.1016/j.cgh.2011.11.026]

7 **Hyams JS**, Lerer T, Griffiths A, Pfefferkorn M, Kugathasan S, Evans J, Otley A, Carvalho R, Mack D, Bousvaros A, Rosh J, Mamula P, Kay M, Crandall W, Oliva-Hemker M, Keljo D, LeLeiko N, Markowitz J. Long-term outcome of maintenance infliximab therapy in children with Crohn's disease. *Inflamm Bowel Dis* 2009; **15**: 816-822 [PMID: 19107783 DOI: 10.1002/ibd.20845]

8 **Roach DR**, Bean AG, Demangel C, France MP, Briscoe H, Britton WJ. TNF regulates chemokine induction essential for cell recruitment, granuloma formation, and clearance of mycobacterial infection. *J Immunol* 2002; **168**: 4620-4627 [PMID: 11971010 DOI: 10.4049/jimmunol.168.9.4620]

9 **Keane J**, Gershon S, Wise RP, Mirabile-Levens E, Kasznica J, Schwieterman WD, Siegel JN, Braun MM. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. *N Engl J Med* 2001; **345**: 1098-1104 [PMID: 11596589 DOI: 10.1056/NEJMoa011110]

10 **Glazier KD**, Palance AL, Griffel LH, Das KM. The ten-year single-center experience with 6-mercaptopurine in the treatment of inflammatory bowel disease. *J Clin Gastroenterol* 2005; **39**: 21-26 [PMID: 15599205]

11 **Stuck AE**, Minder CE, Frey FJ. Risk of infectious complications in patients taking glucocorticosteroids. *Rev Infect Dis* 1989; **11**: 954-963 [PMID: 2690289]

12 **Warman JI**, Korelitz BI, Fleisher MR, Janardhanam R. Cumulative experience with short- and long-term toxicity to 6-mercaptopurine in the treatment of Crohn's disease and ulcerative colitis. *J Clin Gastroenterol* 2003; **37**: 220-225 [PMID: 12960720]

13 **Lichtenstein GR**, Rutgeerts P, Sandborn WJ, Sands BE, Diamond RH, Blank M, Montello J, Tang L, Cornillie F, Colombel JF. A pooled analysis of infections, malignancy, and mortality in infliximab- and immunomodulator-treated adult patients with inflammatory bowel disease. *Am J Gastroenterol* 2012; **107**: 1051-1063 [PMID: 22613901 DOI: 10.1038/ajg.2012.89]

14 **Hanauer SB**, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, Rachmilewitz D, Wolf DC, Olson A, Bao W, Rutgeerts P. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet* 2002; **359**: 1541-1549 [PMID: 12047962 DOI: 10.1016/S0140-6736(02)08512-4]

15 **Sands BE**, Anderson FH, Bernstein CN, Chey WY, Feagan BG, Fedorak RN, Kamm MA, Korzenik JR, Lashner BA, Onken JE, Rachmilewitz D, Rutgeerts P, Wild G, Wolf DC, Marsters PA, Travers SB, Blank MA, van Deventer SJ. Infliximab maintenance therapy for fistulizing Crohn's disease. *N Engl J Med* 2004; **350**: 876-885 [PMID: 14985485 DOI: 10.1056/NEJMoa030815]

16 **Fidder H**, Schnitzler F, Ferrante M, Noman M, Katsanos K, Segaert S, Henckaerts L, Van Assche G, Vermeire S, Rutgeerts P. Long-term safety of infliximab for the treatment of inflammatory bowel disease: a single-centre cohort study. *Gut* 2009; **58**: 501-508 [PMID: 18832524 DOI: 10.1136/gut.2008.163642]

17 **Lichtenstein GR**, Feagan BG, Cohen RD, Salzberg BA, Diamond RH, Price S, Langholff W, Londhe A, Sandborn WJ. Serious infection and mortality in patients with Crohn's disease: more than 5 years of follow-up in the TREAT™ registry. *Am J Gastroenterol* 2012; **107**: 1409-1422 [PMID: 22890223 DOI: 10.1038/ajg.2012.218]

18 **Grijalva CG**, Chen L, Delzell E, Baddley JW, Beukelman T, Winthrop KL, Griffin MR, Herrinton LJ, Liu L, Ouellet-Hellstrom R, Patkar NM, Solomon DH, Lewis JD, Xie F, Saag KG, Curtis JR. Initiation of tumor necrosis factor-α antagonists and the risk of hospitalization for infection in patients with autoimmune diseases. *JAMA* 2011; **306**: 2331-2339 [PMID: 22056398 DOI: 10.1001/jama.2011.1692]

19 **Yoo IK**, Choung RS, Hyun JJ, Kim SY, Jung SW, Koo JS, Lee SW, Choi JH, Kim H, Lee HS, Keum B, Kim ES, Jeen YT. Incidences of serious infections and tuberculosis among patients receiving anti-tumor necrosis factor-α therapy. *Yonsei Med J* 2014; **55**: 442-448 [PMID: 24532516 DOI: 10.3349/ymj.2014.55.2.442]

20 **Deepak P**, Stobaugh DJ, Ehrenpreis ED. Infectious complications of TNF-α inhibitor monotherapy versus combination therapy with immunomodulators in inflammatory bowel disease: analysis of the Food and Drug Administration Adverse Event Reporting System. *J Gastrointestin Liver Dis* 2013; **22**: 269-276 [PMID: 24078983]

21 **Galloway JB**, Hyrich KL, Mercer LK, Dixon WG, Fu B, Ustianowski AP, Watson KD, Lunt M, Symmons DP. Anti-TNF therapy is associated with an increased risk of serious infections in patients with rheumatoid arthritis especially in the first 6 months of treatment: updated results from the British Society for Rheumatology Biologics Register with special emphasis on risks in the elderly. *Rheumatology* (Oxford) 2011; **50**: 124-131 [PMID: 20675706 DOI: 10.1093/rheumatology/keq242]

22 **World Health Organisation (WHO)**. Global tuberculosis repart 2013. Geneva. WHO; 23 oct 2013. Availble from: URL: http: //apps.who.int/iris/bitstream/10665/91355/9789241564656\_eng.pdf

23 **Askling J**, Fored CM, Brandt L, Baecklund E, Bertilsson L, Cöster L, Geborek P, Jacobsson LT, Lindblad S, Lysholm J, Rantapää-Dahlqvist S, Saxne T, Romanus V, Klareskog L, Feltelius N. Risk and case characteristics of tuberculosis in rheumatoid arthritis associated with tumor necrosis factor antagonists in Sweden. *Arthritis Rheum* 2005; **52**: 1986-1992 [PMID: 15986370 DOI: 10.1002/art.21137]

24 **Desai SB**, Furst DE. Problems encountered during anti-tumour necrosis factor therapy. *Best Pract Res Clin Rheumatol* 2006; **20**: 757-790 [PMID: 16979537 DOI: 10.1016/j.berh.2006.06.002]

25 **Gómez-Reino JJ**, Carmona L, Valverde VR, Mola EM, Montero MD. Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may predispose to significant increase in tuberculosis risk: a multicenter active-surveillance report. *Arthritis Rheum* 2003; **48**: 2122-2127 [PMID: 12905464 DOI: 10.1002/art.11137]

26 **Solovic I**, Sester M, Gomez-Reino JJ, Rieder HL, Ehlers S, Milburn HJ, Kampmann B, Hellmich B, Groves R, Schreiber S, Wallis RS, Sotgiu G, Schölvinck EH, Goletti D, Zellweger JP, Diel R, Carmona L, Bartalesi F, Ravn P, Bossink A, Duarte R, Erkens C, Clark J, Migliori GB, Lange C. The risk of tuberculosis related to tumour necrosis factor antagonist therapies: a TBNET consensus statement. *Eur Respir J* 2010; **36**: 1185-1206 [PMID: 20530046 DOI: 10.1183/09031936.00028510]

27 **Seiderer J**, Göke B, Ochsenkühn T. Safety aspects of infliximab in inflammatory bowel disease patients. A retrospective cohort study in 100 patients of a German University Hospital. *Digestion* 2004; **70**: 3-9 [PMID: 15297773]

28 **Seminerio JL**, Loftus EV, Colombel JF, Thapa P, Sandborn WJ. Infliximab for Crohn's disease: the first 500 patients followed up through 2009. *Dig Dis Sci* 2013; **58**: 797-806 [PMID: 23053885 DOI: 10.1007/s10620-012-2405-z]

29 **Clark M**, Colombel JF, Feagan BC, Fedorak RN, Hanauer SB, Kamm MA, Mayer L, Regueiro C, Rutgeerts P, Sandborn WJ, Sands BE, Schreiber S, Targan S, Travis S, Vermeire S. American gastroenterological association consensus development conference on the use of biologics in the treatment of inflammatory bowel disease, June 21-23, 2006. *Gastroenterology* 2007; **133**: 312-339 [PMID: 17631151]

30 **Van Assche G**, Lewis JD, Lichtenstein GR, Loftus EV, Ouyang Q, Panes J, Siegel CA, Sandborn WJ, Travis SP, Colombel JF. The London position statement of the World Congress of Gastroenterology on Biological Therapy for IBD with the European Crohn's and Colitis Organisation: safety. *Am J Gastroenterol* 2011; **106**: 1594-602; quiz 1593, 1603 [PMID: 21844919 DOI: 10.1053/j.gastro.2007.05.006]

31 **Jauregui-Amezaga A**, Turon F, Ordás I, Gallego M, Feu F, Ricart E, Panés J. Risk of developing tuberculosis under anti-TNF treatment despite latent infection screening. *J Crohns Colitis* 2013; **7**: 208-212 [PMID: 22677117 DOI: 10.1016/j.crohns.2012.05.012]

32 **Qumseya BJ**, Ananthakrishnan AN, Skaros S, Bonner M, Issa M, Zadvornova Y, Naik A, Perera L, Binion DG. QuantiFERON TB gold testing for tuberculosis screening in an inflammatory bowel disease cohort in the United States. *Inflamm Bowel Dis* 2011; **17**: 77-83 [PMID: 20848501 DOI: 10.1002/ibd.21329]

33 **Schoepfer AM**, Flogerzi B, Fallegger S, Schaffer T, Mueller S, Nicod L, Seibold F. Comparison of interferon-gamma release assay versus tuberculin skin test for tuberculosis screening in inflammatory bowel disease. *Am J Gastroenterol* 2008; **103**: 2799-2806 [PMID: 18684188 DOI: 10.1111/j.1572-0241.2008.02050.x]

34 **Ali T**, Kaitha S, Mahmood S, Ftesi A, Stone J, Bronze MS. Clinical use of anti-TNF therapy and increased risk of infections. *Drug Healthc Patient Saf* 2013; **5**: 79-99 [PMID: 23569399 DOI: 10.2147/DHPS.S28801]

35 **Strangfeld A**, Listing J, Herzer P, Liebhaber A, Rockwitz K, Richter C, Zink A. Risk of herpes zoster in patients with rheumatoid arthritis treated with anti-TNF-alpha agents. *JAMA* 2009; **301**: 737-744 [PMID: 19224750 DOI: 10.1001/jama.2009.146]

36 **Winthrop KL**, Baddley JW, Chen L, Liu L, Grijalva CG, Delzell E, Beukelman T, Patkar NM, Xie F, Saag KG, Herrinton LJ, Solomon DH, Lewis JD, Curtis JR. Association between the initiation of anti-tumor necrosis factor therapy and the risk of herpes zoster. *JAMA* 2013; **309**: 887-895 [PMID: 23462785 DOI: 10.1001/jama.2013.1099]

37 **Papadakis KA**, Tung JK, Binder SW, Kam LY, Abreu MT, Targan SR, Vasiliauskas EA. Outcome of cytomegalovirus infections in patients with inflammatory bowel disease. *Am J Gastroenterol* 2001; **96**: 2137-2142 [PMID: 11467645 DOI: 10.1111/j.1572-0241.2001.03949.x]

38 **Helbling D**, Breitbach TH, Krause M. Disseminated cytomegalovirus infection in Crohn's disease following anti-tumour necrosis factor therapy. *Eur J Gastroenterol Hepatol* 2002; **14**: 1393-1395 [PMID: 12468964]

39 **Kandiel A**, Lashner B. Cytomegalovirus colitis complicating inflammatory bowel disease. *Am J Gastroenterol* 2006; **101**: 2857-2865 [PMID: 17026558 DOI: 10.1111/j.1572-0241.2006.00869.x]

40 **Esteve M**, Saro C, González-Huix F, Suarez F, Forné M, Viver JM. Chronic hepatitis B reactivation following infliximab therapy in Crohn's disease patients: need for primary prophylaxis. *Gut* 2004; **53**: 1363-1365 [PMID: 15306601 DOI: 10.1136/gut.2004.040675]

41 **Michel M**, Duvoux C, Hezode C, Cherqui D. Fulminant hepatitis after infliximab in a patient with hepatitis B virus treated for an adult onset still's disease. *J Rheumatol* 2003; **30**: 1624-1625 [PMID: 12858469]

42 **Ostuni P**, Botsios C, Punzi L, Sfriso P, Todesco S. Hepatitis B reactivation in a chronic hepatitis B surface antigen carrier with rheumatoid arthritis treated with infliximab and low dose methotrexate. *Ann Rheum Dis* 2003; **62**: 686-687 [PMID: 12810441 DOI: 10.1136/ard.62.7.686]

43 **Wong GH**, Goeddel DV. Tumour necrosis factors alpha and beta inhibit virus replication and synergize with interferons. *Nature* 1986; **323**: 819-822 [PMID: 2430188]

44 **Schlaak JF**, Tully G, Löhr HF, Gerken G, Meyer zum Büschenfelde KH. HBV-specific immune defect in chronic hepatitis B (CHB) is correlated with a dysregulation of pro- and anti-inflammatory cytokines. *Clin Exp Immunol* 1999; **115**: 508-514 [PMID: 10193426 DOI: 10.1046/j.1365-2249.1999.00812.x]

45 **Rahier JF**, Magro F, Abreu C, Armuzzi A, Ben-Horin S, Chowers Y, Cottone M, de Ridder L, Doherty G, Ehehalt R, Esteve M, Katsanos K, Lees CW, Macmahon E, Moreels T, Reinisch W, Tilg H, Tremblay L, Veereman-Wauters G, Viget N, Yazdanpanah Y, Eliakim R, Colombel JF. Second European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. *J Crohns Colitis* 2014; **8**: 443-468 [PMID: 24613021 DOI: 10.1016/j.crohns.2013.12.013]

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

|  |  |  |
| --- | --- | --- |
| **Infection** | **Tests** | **Consequences** |
| TB  | Latent TB infection should betested 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 bestarted, 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 HBcAb to determineHBV 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; HBcAb: Hepatitis B core antibody; HIV: Human immunodeficiency virus; VZV: Varicella zoster virus.