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Review

ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an infectious diseases perspective (Soluble immune effector molecules [I]: anti-tumour necrosis factor-α agents)

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ABSTRACT

Background: The present review is part of the ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies.
Aims: To review, from an Infectious Diseases perspective, the safety profile of agents targeting tumour necrosis factor-α (TNF-α) and to suggest preventive recommendations.
Sources: Computer-based MEDLINE searches with MeSH terms pertaining to each agent or therapeutic family.
Content: Preclinical and clinical evidence indicate that anti-TNF-α therapy (infliximab, adalimumab, golimumab, certolizumab pegol and etanercept) is associated with a two-to four-fold increase in the risk of active tuberculosis and other granulomatous conditions (mostly resulting from the reactivation of a latent infection). In addition, it may lead to the occurrence of other serious infections (bacterial, fungal, opportunistic and certain viral infections). These associated risks seem to be lower for etanercept than other agents. Screening for latent tuberculosis infection should be performed before starting anti-TNF-α therapy, followed by anti-tuberculosis therapy if appropriate. Screening for chronic hepatitis B virus (HBV) infection is also recommended, and antiviral prophylaxis may be warranted for hepatitis B surface antigen-positive individuals. No benefit is expected from the use of antibacterial, anti-*Pneumocystis* or antifungal prophylaxis. Pneumococcal and age-appropriate antiviral vaccinations (i.e. influenza) should be administered. Live-virus vaccines (i.e. varicella-zoster virus or measles–mumps–rubella) may be contraindicated in people receiving anti-TNF-α therapy, although additional data are needed before definitive recommendations can be made.
Implications: Prevention measures should be implemented to reduce the risk of latent tuberculosis or HBV reactivation among individuals receiving anti-TNF-α therapy. **J.W. Baddley, Clin Microbiol Infect 2018;▪:1**

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Introduction

The present review paper is part of a larger effort launched by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Study Group for Infections in Compromised Hosts (ESGICH) and aimed at analysing, from an Infectious Diseases perspective, the safety profile of biological and targeted therapies. By means of a set of unrestricted computer-based MEDLINE (National Library of Medicine, Bethesda, MD) searches based on the MeSH terms appropriate for each agent or therapeutic family, we identified literature pertaining to the subject. In addition, package information and boxed warning alerts from regulatory agencies (European Medicines Agency and US Food and Drug Administration) were reviewed. Methodological details are provided in the Introduction section of the present Supplement issue [1]. For each agent (or class of agents), a common outline is offered: (a) summary of mechanism of action, approved indications and most common off-label uses; (b) theoretically expected impact on the host's susceptibility to infection; (c) available evidence emerging from the clinical use of that agent (i.e. randomized clinical trials (RCTs), post-marketing studies, case series and single case reports); and (d) suggested preventive and risk minimization strategies. This section is the first one specifically focused on the risk of infection entailed by the use of agents targeting soluble immune effector molecules, such as pro-inflammatory cytokines.

Tumour necrosis factor-α-targeted agents: infliximab, adalimumab, golimumab, certolizumab pegol and etanercept

Mechanism of action, approved indications and off-label uses

Tumour necrosis factor-α (TNF-α) is a naturally occurring homotrimeric cytokine involved in inflammatory and immune responses. TNF-α is generated as a 26-kDa non-glycosylated, membrane-bound monomeric polypeptide that is later assembled at the cell surface to constitute the homotrimeric form (pro-TNF-α). This precursor is processed by proteolytic cleavage to its 51-kDa trimeric soluble/secreted form in a process controlled by the membrane metalloprotease TNF-α converting enzyme (TACE or ADAM17) [2]. Although this soluble form elicits most TNF-α-mediated responses, the membrane-bound molecule also exerts functional effects, which are not necessarily comparable to those of its soluble counterpart. Two structurally related, but functionally distinct receptors mediate the activities of TNF-α: TNFR1 (p55) and TNFR2 (p75). Both receptors exist as monomeric molecules on most cells, with the exception of red blood cells [3].

Biological activities attributed to TNF-α include: induction of pro-inflammatory cytokines such as interleukin-1 and interleukin-6, enhancement of leucocyte migration by increasing endothelial layer permeability and expression of adhesion molecules by endothelial cells and leucocytes, functional activation of neutrophils and eosinophils, and induction of acute-phase reactants and other liver proteins as well as tissue-degrading enzymes produced by synoviocytes and/or chondrocytes [3–8]. Elevated concentrations of TNF-α have been found in involved tissues and fluids of patients with rheumatoid arthritis (RA), inflammatory bowel disease (IBD), ankylosing spondylitis, psoriatic arthritis and plaque psoriasis.

The TNF-α-targeted (i.e. anti-TNF-α) agents inhibit these biological activities by binding with high affinity to the cytokine itself or by blocking the binding of TNF-α with its receptors (either both or just one, as is the case of etanercept) (Fig. 1) [8–13]. *In vivo*, such approaches reduce tissue infiltration by inflammatory cells as well as expression of cell adhesion molecules and tissue degradation. However, the mechanistic relationship linking these effects with the clinical impact exerted by TNF-α-targeted agents remains partially unknown [6].

Infliximab (Remicade®; Janssen Biotech, Horsham, PA, USA; and biosimilar versions), adalimumab (Humira®; AbbVie, North Chicago, IL, USA) and golimumab (Simponi®; Merck Sharp & Dohme, Kenilworth, NJ, USA) are IgG1 monoclonal antibodies (either chimeric or fully human) that target both the soluble and membrane-bound forms of TNF-α [8–14]. They do not neutralize TNF-β, a related cytokine that uses the same receptors as TNF-α. In the presence of complement, all of them are also able to lyse membrane-bound TNF-α-expressing cells by inducing

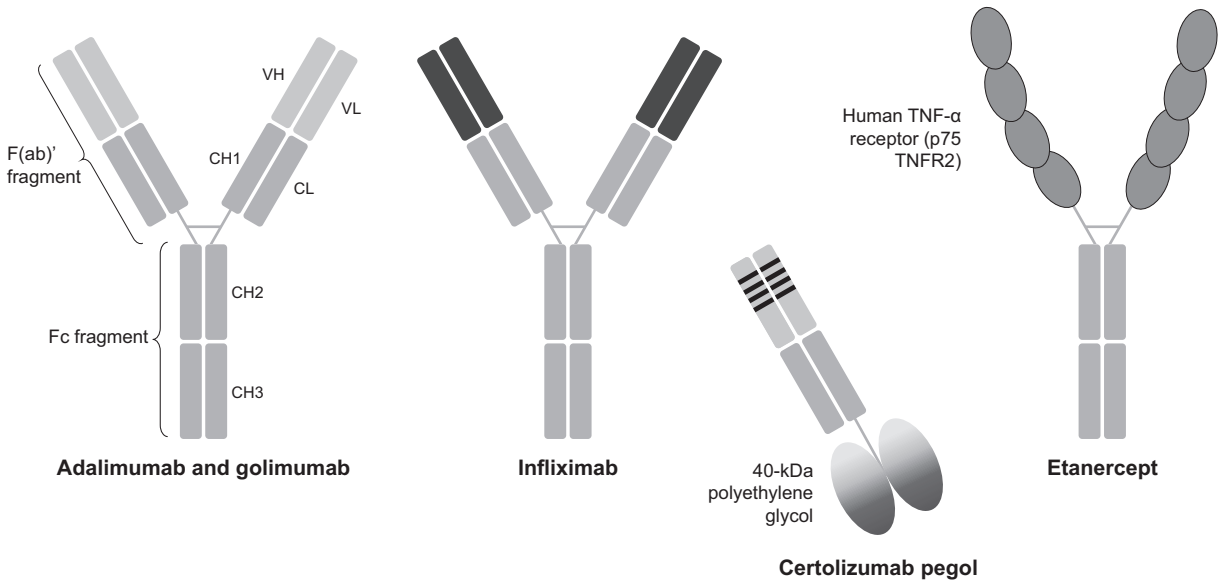

Fig. 1. Structure of different anti-tumour necrosis factor-α (TNF-α) agents. Adalimumab and golimumab are fully human IgG1 antibodies. Infliximab is a chimeric antibody composed of a antigen-binding murine variable region and the human IgG1 constant region. Certolizumab pegol is a recombinant humanized F(ab') fragment conjugated to two 20-kDa polyethylene glycol molecules. Etanercept is a dimeric soluble form of the 75-kDa TNF-α receptor (p75 TNFR2) linked to the hinge and Fc portions of human IgG1 antibody. Human origin is shown in grey, murine origin in black.

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complement-dependent cytotoxicity, with a weaker apoptotic effect observed for golimumab [15]. Infliximab is approved for the treatment of IBD (both Crohn's disease and ulcerative colitis), RA, ankylosing spondylitis, psoriatic arthritis and plaque psoriasis [9–11]. Adalimumab is approved for the treatment of IBD (both Crohn's disease and ulcerative colitis), RA, ankylosing spondylitis, juvenile idiopathic arthritis, psoriatic arthritis, plaque psoriasis, hidradenitis suppurativa and uveitis [12,13]. Golimumab is indicated for the treatment of ulcerative colitis, RA, ankylosing spondylitis, juvenile idiopathic arthritis and psoriatic arthritis [14].

Certolizumab pegol (Cimzia®; UCB Pharma, Brussels, Belgium) is a recombinant humanized F(ab') IgG1 fragment composed of single light and heavy chains targeting TNF-α (both soluble and membrane-bound forms) that is conjugated to an approximately 40-kDa polyethylene glycol (PEG2MAL40K) [16]. In opposition to the other anti-TNF-α antibodies, certolizumab pegol does not contain the IgG fragment crystallizable (Fc) and does not fix complement, being therefore unable to induce complement-dependent cytotoxicity or antibody-dependent cell-mediated cytotoxicity *in vitro* [15,16]. In addition, it lacks activity against TNF-β. Certolizumab pegol is approved for the treatment of RA, ankylosing spondylitis and psoriatic arthritis. The US Food and Drug Administration has also granted approval for Crohn's disease [16].

Etanercept (Enbrel®; Amgen, Thousand Oaks, CA, USA, and biosimilar versions) is a dimeric soluble form of the p75 TNFR2 receptor linked to the hinge and fragment crystallizable (Fc) regions of human IgG1 that can bind both TNF-α and TNF-β [8]. Both full-length antibodies and etanercept possess the Fc portion of IgG1, which contains the CH2 domain that is responsible for the activation of C1 (first component of the classical pathway of complement activation). However, etanercept is unable to activate C3 (the pivotal component of such a pathway) because it lacks the CH1 domain of the Fc region. Hence, etanercept is significantly worse than full-length antibodies at inducing complement-dependent cytotoxicity on membrane-bound TNF-α-expressing cells. It is approved for the treatment of RA, ankylosing spondylitis, juvenile idiopathic arthritis, psoriatic arthritis and plaque psoriasis (Table 1).

Expected impact on the infection risk

Tumour necrosis factor-α is involved in a number of adaptive immune responses, including formation of granulomas, development of phagosomes, activation and differentiation of macrophages, and immune response against viral pathogens [17]. The role of anti-TNF-α therapies in immune response is best studied in the context of tuberculous granuloma formation and maintenance, a process that requires the activation of lymphocytes and their recruitment, along with monocytes, to the site of the infection [18]. TNF-α plays a critical role in attracting and activating CD4+, CD8+ and γ/δ T cells, which in turn strengthen T-cell adhesion and antigen presentation and facilitate further T- and B-cell recruitment [17–19]. However, as mycobacteria survive within macrophages in patients with latent tuberculosis infection (LTBI), anti-TNF-α agents may cause *Mycobacterium tuberculosis* reactivation or dissemination in the form of active tuberculosis (TB) [19,20]. Conversely, TNF-α has not been implicated in the innate immune response against extracellular bacterial pathogens.

Therefore, patients receiving anti-TNF-α agents are at increased risk for granulomatous infections, namely TB, that mostly result from the reactivation of a latent infection. In addition, this therapy would theoretically increase susceptibility to other intracellular pathogens such as bacteria (i.e. *Listeria monocytogenes* or *Salmonella* spp.) and viruses (i.e. hepatitis B virus (HBV), varicella zoster virus and John Cunningham human polyomavirus) [17]. On the other hand, anti-TNF-α therapy may cause neutropenia, which would lead in turn to the occurrence of invasive fungal infection. However, we are still learning the impact of this armamentarium in clinical practice, as well as the potential effect of differences in structure, mechanisms of action and pharmacokinetic properties across available agents [21]. For example, etanercept only forms 1:1 stoichiometric complexes with the homotrimeric form of membrane-bound TNF-α, leaving one receptor-binding site free even when the agent is present in excess. In contrast, each molecule of infliximab is able to bind either one or two molecules of the homotrimeric and/or monomeric membrane-bound forms, and up to three molecules of infliximab can bind each TNF-α homotrimer, leaving few or no receptor-binding sites free [22]. Moreover, the TNF-α association/dissociation rates are approximately 20-fold faster from the p75 TNFR2 receptor than from the p55 TNFR1 [23], suggesting that etanercept only transiently neutralizes the activity of an individual TNF-α molecule.

Available clinical data

Tuberculosis

Meta-analyses of RCTs, open-label extension studies [24–29], post-marketing registries [28–39] and retrospective cohort studies [40–45] have consistently shown that patients with LTBI receiving anti-TNF-α therapy for RA, ankylosing spondylitis or psoriatic arthritis have approximately a four-fold increase in the risk of developing active TB compared with healthy patients (Table 2). Interestingly, the first relevant report of increased TB susceptibility among patients with Crohn's disease or RA while on anti-TNF-α agents emerged from the MedWatch reporting system rather than from pivotal RCTs [46]. The subsequent formulation of

Table 1
Summary of currently available anti-tumour necrosis factor-α therapies

Agent (trade mark)	Type and mode of action	Approved indications	Off-label uses
Infliximab (Remicade®)	Human–mouse chimeric IgG1 monoclonal antibody	IBD (CD and UC), RA, AS, PsA, plaque psoriasis	Graft-versus-host disease, uveitis, Behçet's disease, skin disorders
Etanercept (Enbrel®)	Fusion protein of the soluble 75-kDa TNF-α receptor and human IgG1 antibody (hinge and FC regions)	RA, AS, JIA, PsA, plaque psoriasis	Pemphigus vulgaris, Behçet's disease, skin disorders
Adalimumab (Humira®)	Fully human IgG1 monoclonal antibody	IBD (CD and UC), RA, AS, JIA, PsA, plaque psoriasis, hidradenitis suppurativa and uveitis	Sarcoidosis, Behçet's disease, skin disorders
Golimumab (Simponi®)	Fully human IgG1 monoclonal antibody	UC, RA, AS, JIA, PsA	Plaque psoriasis, systemic lupus erythematosus, uveitis
Certolizumab pegol (Cimzia®)	Pegylated F(ab') fragment of humanized monoclonal antibody	CD (only FDA), RA, AS, PsA	Plaque psoriasis

AS, ankylosing spondylitis; CD, Crohn's disease; FDA, US Food and Drug Administration; IBD, inflammatory bowel disease; JIA, juvenile idiopathic arthritis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; TNF-α, tumour necrosis factor α; UC, ulcerative colitis.

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Table 2
Summary of estimated risks of infection in patients with rheumatoid arthritis and other systemic inflammatory diseases treated with anti-tumour necrosis factor-α therapy across randomized controlled trials and observational studies

Reference, year	Study design, no. of patients, type of anti-TNF-α agent, time period	Risk estimate for serious infection	Risk estimate for opportunistic infection[a]	Risk estimate for TB
RCTs		OR; 95% CI	OR; 95% CI	OR; 95% CI
Singh et al., 2011 [25]	Meta-analysis of 163 RCTs and 46 OLEs (61,964 patients); biological vs. non-biological DMARDs until 2010	1.37; 1.04–1.82 (SS) overall 3.51; 1.59–7.79 (SS) for certolizumab	NR	4.68; 1.18–18.60 (SS)
Michaud et al., 2014 [9]	Meta-analysis of 44 RCTs; only RA (11,700 patients); anti-TNFs vs. non-biological DMARDs until 2013	1.42; 1.13–1.78 (SS) overall 1.69; 1.12–2.54 (SS) for adalimumab 1.98; 0.99–3.96 (NS) for certolizumab 1.63; 1.07–2.47 (SS) for infliximab	NR	NR
Singh et al., 2015 [26]	Meta-analysis of 106 RCTs; only RA (42,330 patients); biological vs. non-biological DMARDs until 2014	1.31; 1.09–1.58 (SS) for standard dose 1.90; 1.50–2.39 (SS) for high dose 0.93; 0.65–1.33 (NS) for low dose	NR	NR
Ai et al., 2015 [8]	Meta-analysis of 50 RCTs and 13 registries and cohort studies; only RA (82,590 pts); infliximab, etanercept, adalimumab, golimumab and certolizumab vs. no anti-TNFs or general population	NR	NR	17.1; 13.9–21.0 (SS) vs. general population 4.03; 2.36–6.88 (SS) vs. RA patients not exposed to anti-TNFs
Minozzi et al., 2016 [7]	Meta-analysis of 71 RCTs plus 7 OLEs; RA, PsA and AS (22,760 plus 2236 patients); infliximab, adalimumab, etanercept, golimumab, certolizumab vs. no anti-TNFs until 2014	1.41; 1.16–1.73 (SS)	0.94: 0.33–2.64 (NS)	3.53; 1.58–7.85 (SS) (32 TB cases)
Observational registries		aRR/aHR; 95% CI	aRR/aHR; 95% CI	aRR/aHR; 95% CI
BIOBADASER (Spain), 2003 [30]	Multicentre registry; only RA (1,540 patients); anti-TNFs vs. non-biologicals from 2001 to 2003	NR	NR	4.13; 2.59–6.83 (SS)
ARTIS (Sweden), 2005 [31]	Multicentre registy (1,565 patients); infliximab or etanercept vs. non-biologicals from 1999 to 2001	NR	NR	4.0; 1.3–12.0 (SS) (15 TB cases)
ARTIS (Sweden), 2007 [67]	Multicentre registry; only RA (4167 patients); anti-TNFs vs. non-biologicals from 1999 to 2003	1.43; 1.18–1.73 (SS) for the first year of therapy 1.15; 0.8–1.51 (NS) for the second year of therapy 0.82; 0.62–1.08. (NS) thereafter	NR	NR
PharMetrics (Canada), 2006 [33]	Pharmaceutical claims database (3,423 patients); infliximab or etanercept vs. no anti-TNFs from 1998 to 2003	NR	NR	1.6; 1.0–2.6 (SS) for infliximab 1.2; 0.9–1.8 (NS) for etanercept
BSRBR (UK), 2007 [9]	Multicentre registry; only RA (8659 patients); anti-TNFs vs. non-biologicals	4.6; 1.8–11.9 (SS) 1.22; 0.88–1.69 (NS)	NR	NR
RATIO (France), 2009 [36]	Multicentre registy (no. of patients. NR); infliximab, etanercept or adalimumab	NR	NR	12.2; 9.7–15.5 (SS) for infliximab or adalimumab vs. etanercept (69 TB cases)
BSRBR (UK), 2010 [37]	Multicentre registry (10,712 patients); infliximab, etanercept or adalimumab vs. no anti-TNFs	NR	NR	3.1; 1.0–9.5 (SS) for infliximab vs. etanercept 4.2; 1.4–12.4 (SS) for adalimumab vs. etanercept (40 TB cases)
Bernatsky et al., 2010 [146]	Meta-analysis of six observational cohorts (124,374 patients); anti-TNFs vs. non-biologicals until 2009	1.37; 1.18–1.60 (SS)	NR	NR
Grijalva et al. (US), 2011 [64]	Multicentre retrospective cohort (10,484 RA patients, 3215 patients with other conditions); anti-TNFs vs. non-biologicals from 1998 to 2007; risk estimates adjusted by corticosteroids	1.05; 0.91–1.21 (NS) for RA 1.05: 0.76–1.45 (NS) for other diseases	NR	NR
RABBIT (Germany), 2011 [63]	Multicentre registry, only RA (5044 patients); anti-TNFs vs. non-biologicals until 2010; risk stimates adjusted by corticosteroids	1.8; 1.2–2.7 (SS)	NR	NR
GISEA (Italy), 2012 [8]	Multicentre registry (2769 patients); infliximab, etanercept or adalimumab vs. no anti-TNFs	NR	NR	4.91; 2.71–8.90 (SS) for infliximab 2.22; 1.12–4.42 (SS) for adalimumab (9 TB cases)

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Table 2 (*continued*)

Reference, year	Study design, no. of patients, type of anti-TNF-α agent, time period	Risk estimate for serious infection	Risk estimate for opportunistic infection[a]	Risk estimate for TB
RCTs		OR; 95% CI	OR; 95% CI	OR; 95% CI
Kaiser Permanente Northern California (US), 2013 [39]	Multicentre registry (8,418 patients); infliximab, etanercept or adalimumab vs. no anti-TNFs	NR	NR	2.0; 0.8–5.4 (NS) for infliximab 0.6; 0.2–1.5 (NS) for etanercept 2.0; 0.8–5.4 (NS) for adalimumab (16 TB cases)
US Veterans (US), 2014 [7]	Multicentre registry, only RA (3111 patients); different anti-TNFs vs. non-biologicals from 1998 to 2011	1.4; 0.9–2.2 (NS) for adalimumab 2.3; 1.3–4.0 (SS) for infliximab	NR	NR
Post-marketing cohorts		aRR/aHR; 95% CI	aRR/aHR; 95% CI	aRR/aHR; 95% CI
Kim et al. (South Korea), 2011 [43]	Retrospective cohort (354 patients); infliximab, etanercept or adalimumab vs. no anti-TNFs	NR	NR	0.53; 0.14–1.91 (NS) (10 TB cases)
Alawneh et al. (Jordan), 2014 [44]	Retrospective cohort (199 patients); infliximab, etanercept or adalimumab vs. no anti-TNFs	NR	NR	1.9; 1.06–4.0 (SS) (3 TB cases)

Abbreviations: anti-TNFs, anti-TNF-α agents; aRR/aHR, adjusted relative risk/hazard ratio; AS, ankylosing spondylitis; DMARD, disease-modifying antirheumatic drugs; NR, none reported; NS, non significant; OLE, open-label extension study; OR, odds ratio; PsA, psoriatic arthritis; pts, patients; RA, rheumatoid arthritis; RCT, randomized clinical trial; SS, statistically significant; TB, active tuberculosis.

[a] Includes active tuberculosis, progressive multifocal leucoencephalopathy, nocardiosis, cytomegalovirus or Epstein–Barr virus infection, oral or oesophageal candidiasis, varicella-zoster virus infection, *Pneumocystis jiroveci* pneumonia, *Histoplasma capsulatum* infection, *Legionella* spp. pneumonia, herpes simplex virus infection, or other unspecified opportunistic infection.

recommendations for LTBI screening and treatment before administering anti-TNF-α therapy has reduced, but not completely eliminated, such risk [34,35]. This is in part because current guidelines are not universally applicable across different countries, considering disparate social and economic backgrounds, individual host conditions, baseline TB prevalence rates and treatment practices [47]. In addition to the impact of TNF-α blockade, additional factors contributing to the occurrence of TB in this patient population include increasing age, co-morbidities and the previous or concurrent use of traditional (non-biological) disease-modifying antirheumatic drugs (DMARDs) [48–50]. The role of the cumulative corticosteroid dose in this increased incidence should be particularly noted, which may even exceed that associated with the use of anti-TNF-α agents [33,51]. Underlying inflammatory rheumatic disease is associated with an increased relative risk of TB (2.0 to 8.9 in RA, 3.1 in psoriatic arthritis, and 3.9 in ankylosing spondylitis) [47]. Unfortunately, defective or incomplete LTBI screening and treatment procedures have been frequently observed in RCTs and registries [24,34]. The lack of compliance with guidelines has been associated with a seven-fold increase in the incidence of TB [34]. In accordance with its theoretical less potent impact on TNF-α functionality, etanercept seems to entail a lower risk of TB in comparison with anti-TNF-α monoclonal antibodies [49].

In an early meta-analysis of individuals with IBD (including more than 4000 individuals), the relative risk of developing active TB with anti-TNF-α monoclonal antibodies was 2.52 (95% CI 0.62–10.21) [52]. Two more recent meta-analyses have also confirmed an increased risk for both TB and overall opportunistic infection among people with IBD who are receiving anti-TNF-α agents, with this association being particularly evident in the presence of Crohn's disease [53,54] (Table 3).

The optimal diagnostic approach for LTBI among patients starting anti-TNF-α agents is unclear. Interferon-γ release assays (IGRAs), which may be performed in an ELISA (QuantiFERON-TB® in various versions; Qiagen, Hilden, Germany) or an enzyme-linked immunospot assay (ELISpot) format (T-SPOT®.TB; Oxford Immunotec, Abingdon, UK), are increasingly used on the basis of their better reproducibility and increased specificity compared with the traditional tuberculin skin test (TST). The IGRA tests are based on the *in vitro* quantification of IFN-γ release by sensitized T cells upon stimulation with specific *M. tuberculosis* antigens. However, the concordance between TST and IGRAs is relatively low, particularly among bacillus Calmette–Guérin-vaccinated subjects or those infected with non-tuberculous mycobacteria [47]. Similarly to other immunocompromised hosts, most experts support a dual screening strategy at the pretreatment evaluation regardless of the presence of underlying TB risk factors [47,55]. A 10-year longitudinal study including 726 patients from Spain compared three different screening strategies over consecutive periods. The authors concluded that a single-step TST followed by an ELISA-based IGRA offered a substantial reduction in unnecessary courses of LTBI treatment compared with two-step TST-based strategies (with or without subsequent IGRA). In addition, systematic periodic re-testing did not appear to be needed following a negative initial testing in a setting with low to intermediate endemicity [56]. The best re-screening strategy while on anti-TNF-α therapy in countries with high endemicity is less established in the literature. Recent recommendations support annual re-screening among people with RA with negative baseline screening if there are ongoing or future risk factors for TB exposure [57]. A prospective study carried out in Greece (a country with a relatively high population TB incidence) showed that a significant proportion of patients with RA converted at least one LTBI screening assay during the first year of therapy (21%–29% depending on the criteria used). Nevertheless, none of these patients developed active TB during the follow up, despite the fact that only 40% received therapy for LTBI [58]. Therefore, the clinical significance of these LTBI test conversions remains to be assessed, as these results might represent true-positive conversions indicative of an underlying LTBI or false-positive results due to within-subject assay variability.

Other serious bacterial infections

Risk estimation for other infections with shorter incubation periods is more accurately made through RCTs and open-label extension studies, though such approaches may be limited by small sample size and insufficient statistical power to detect

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Table 3
Summary of estimated risks of infection in patients with inflammatory bowel disease treated with anti-tumour necrosis factor-α therapy across randomised controlled trials and observational studies

Reference, year	Study design, no. of patients, type of anti-TNF-α agent, time period	Risk estimate for overall infection	Risk estimate for serious infection	Risk estimate for opportunistic infection[a]	Risk estimate for TB
RCTs		OR; 95% CI	OR; 95% CI	OR; 95% CI	OR; 95% CI
Zhang et al., 2013 [62]	Meta-analysis of 13 RCTs; only CD (4257 patients); different anti-TNFs until 2013	NR	0.96; 0.65–1.41 (NS)	NR	NR
Ford et al., 2013 [52]	Meta-analysis of 22 RCTs; all forms of IBD (4135 patients); different anti-TNFs until 2013	NR	NR	2.05; 1.10–3.85 (SS)	2.52; 0.62–10.21 (NS)
Bonovas et al., 2016 [54]	Meta-analysis of 49 RCTs; all forms of IBD (8897 patients); different anti-TNFs until 2016	1.19; 1.10–1.29 (SS)	0.89: 0.71–1.12 (NS) Low risk of bias: 0.56; 0.35–0.90 (SS)	1.90; 1.21–3.01 (SS)	2.04; 0.71–5.89 (NS)
Osterman et al., 2016 [53]	Meta-analysis of 10 RCTs; only CD (2266 patients); adalimumab until 2016; risk estimates adjusted by disease severity and other IS	NR	Multivariate analysis at day 56: 0.43; 0.17–1.11 (NS); non CD-related: 0.49; 0.15–1.59 (NS)	Univariate analysis at day 56: 2.02; 0.75–5.45 (NS)	NR
Observational registries and retrospective cohorts		aRR/aHR; 95% CI	aRR/aHR; 95% CI	aRR/aHR; 95% CI	aRR/aHR; 95% CI
Grijalva et al., 2011 [64]	US retrospective cohort (1998–2007); all forms of IBD (2323 patients); different anti-TNFs vs. non-biologicals	NR	1.10; 0.83–1.46 (NS)	NR	NR
Billioud et al., 2013 [81]	Meta-analysis of 7 observational studies; all forms of IBD (4251 patients); pre-operative anti-TNFs vs. non-biologicals until 2012	NR	1.45; 1.03–2.05 (SS) for post-operative infection	NR	NR
Waterland et al., 2016 [86]	Meta-analysis of 14 observational studies; only CD (1024 patients); pre-operative anti-TNFs vs. non-biologicals until 2015	NR	1.22: 0.87–1.72 (NS) for post-operative abdominal sepsis	NR	NR

Abbreviations: anti-TNFs, anti-tumour necrosis factor-α agents; aRR/aHR, adjusted relative risk/hazard ratio; CD, Crohn's disease; IBD, inflammatory bowel disease; NR, non reported; NS, non significant; OR, odds ratio, RCT, randomized clinical trial; SS, statistically significant; TB, active tuberculosis.

[a] Includes active tuberculosis, progressive multifocal leucoencephalopathy, nocardiosis, cytomegalovirus or Epstein–Barr virus infection, oral or oesophageal candidiasis, varicella-zoster virus infection, *Pneumocystis jiroveci* pneumonia, *Histoplasma capsulatum* infection, *Legionella* spp. pneumonia, herpes simplex virus infection, or other unspecified opportunistic infection.

uncommon events. In addition, underlying disease usually confers an increased risk for specific infections (i.e. septic arthritis and/or skin and soft-tissue infections in RA, or intra-abdominal abscesses in IBD). A 2011 meta-analysis found that certolizumab pegol was the only individual anti-TNF-α agent that significantly increased the risk of serious infection apart from TB [25]. Nevertheless, a meta-analysis that included RCTs published until 2013 reported an increased individual risk not only for certolizumab pegol but also for adalimumab and infliximab [59]. A more recent meta-analysis of 106 RCTs of targeted therapies (mostly anti-TNF-α) in RA patients demonstrated a two-fold increase in the risk of serious infections, particularly when high doses were used, compared with traditional DMARDs [26]. In ankylosing spondylitis, a meta-analysis failed to show an increased risk of infection between anti-TNF-α-treated patients compared with untreated controls [60]. A meta-analysis evaluating individuals with psoriatic arthritis and plaque psoriasis reported a crude odds ratio (OR) for infection of 1.18 (95% CI 1.05–1.33) in patients exposed to anti-TNF-α therapy (versus not exposed) [61]. In people with IBD a recent meta-analysis concluded that the risk of serious non-opportunistic infections was not increased, but even decreased, when studies with low risks of bias were selected [54]. Other meta-analysis focused on individuals with Crohn's disease reported that anti-TNF-α therapy did not increase risk, and that perhaps provided a protective effect in comparison with other immunosuppressive agents [62]. A pooled analysis of ten RCTs of adalimumab for Crohn's disease highlighted the deleterious effect on the susceptibility to serious and opportunistic infections of higher disease activity (with each 100-point increase in the Crohn's Disease Activity Index being associated with a 30% increase in the risk of infection) and the concomitant use of immunomodulators and corticosteroids [53].

In RA observational studies, methodological heterogeneity and the absence of adequately matched control groups makes it difficult to account for confounding factors associated per se with increased infection risk [63–65]. The occurrence of serious infection in patients receiving anti-TNF-α therapy compared with those receiving conventional DMARDs has been recently evaluated (Table 2). In these scenarios, the risk assessment period is critical [61,66]. Studies focused on the first year of therapy show adjusted rate ratios ranging from 1.5 to 5.0, whereas those with longer follow-up periods yielded contrasting results [63,67,68]. The clinical benefit in terms of disease activity derived from TNF-α blockade allows for dose tapering or withdrawal of other immunosuppressive agents (i.e. corticosteroids) and decreases underlying pro-inflammatory status, thereby reducing the overall risk of infection because disease activity acts as an independent predisposing factor for this complication in RA [63,69,70] and IBD [53]. Such advantages of anti-TNF-α therapy mostly counterbalance the intrinsic increase in the risk of infection [71,72]. Studies on the incidence of infection among new users of anti-TNF-α agents have been rather inconclusive [32,38,64,73,74]. The analysis of a large cohort of patients with RA that had previously suffered from an episode of infection while on anti-TNF-α therapy revealed that most of them continued to use the same agent, whereas only a small proportion switched to another biological DMARD (5%) or did not receive any biological over the following months (16%). Of note, the use of etanercept and abatacept (a T-cell co-stimulation blocker) was associated with a significantly lower risk of subsequent infection compared with

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infliximab. Interestingly, the risk of infection seemed to decline with the duration of therapy in this study, suggesting the beneficial impact of controlling the activity of the underlying inflammatory condition [75].

In a Canadian cohort of axial spondyloarthritis [76], the overall rate of serious infection was 1.3 per 100 patient-years, with no significant differences after multivariate adjustment between patients receiving anti-TNF-α therapy and those never on biological DMARDs. In another multivariate-adjusted analysis of infection, predictors in psoriatic arthritis or psoriasis, the OR for patients treated with biological DMARDs (largely anti-TNF-α agents) versus those not treated was 1.56 (95% CI 1.22–2.00) for those with psoriatic arthritis and 1.50 (95% CI 0.64–3.54) for patients with psoriasis without arthritis [77].

Information on the risk of non-TB infection for patients with IBD receiving anti-TNF-α therapy is limited. The analysis of a US cohort did not demonstrate a significant effect [64]. Additional research has focused on post-surgical infectious complications in patients with IBD (mostly Crohn's disease) previously treated with anti-TNF-α agents, with some studies reporting a higher risk [78–81] and others failing to demonstrate such an association [82–85]. The first of two published meta-analyses yielded an increase in the pooled risk for postoperative infection [81]. Nevertheless, a more recent one, focused on patients with Crohn's disease, did not confirm these results [86].

Many RCTs and observational studies fail to detail the precise nature of infectious syndromes or their causative agents. However, case series have reported either site-specific infections or specific pathogens. Pneumonia and soft-tissue infections are the most common serious infections observed among patients on anti-TNF-α agents, similarly to the pre-biological era [87]. Again, the detrimental impact of baseline therapy on the individual susceptibility to infection should be highlighted, with a dose-dependent relationship between cumulative prednisone use and the incidence of pneumonia in patients with RA [88]. The role of these agents in the development of septic arthritis in RA was evaluated in the British Society for Rheumatology Biologics Register, yielding an adjusted hazard ratio for septic arthritis (versus traditional DMARDs) of 2.3 (95% CI 1.2–4.4). Most episodes were due to *Staphylococcus aureus* [89]. A post-authorization description of severe listeriosis revealed a four-fold increased risk in comparison with the general population [90–93]. In addition, the rate of *Legionella pneumoniae* infection was 37-fold higher in patients receiving anti-TNF-α therapy (mostly adalimumab) [94]. Other granulomatous bacterial infections, including nocardiosis and non-tuberculous mycobacteria, have also been reported [90]. A recent systematic review of published literature reporting the incidence and epidemiology of opportunistic infection within the setting of biological therapy for rheumatic diseases (including 368 RCTs and open-label extension studies, 195 observational studies and numerous case reports/series) found that only 11 studies provided a precise definition for this complication in the methods section. In addition, no consistent definition for opportunistic infection was identified across studies. In this document, a consensus methodological agreement upon how to report different opportunistic infections was reached by an ad hoc committee, and specific case definitions for each opportunistic pathogen were proposed to facilitate comparison between therapies in future studies [95].

Viral infections

Contradictory results have been published reporting the eventual association between anti-TNF-α therapy and herpes zoster (HZ). The largest multicentre US cohort study, which included more than 30 000 individuals treated or not with anti-TNF-α agents for RA, IBD or other inflammatory diseases, did not demonstrate an increased risk of HZ [96]. In contrast, data from European registries suggest an average two-fold increase in the risk of HZ [97–100]. In addition, a nationwide Spanish study reveals that patients with rheumatic diseases exposed to anti-TNF-α therapy were hospitalized due to HZ significantly more frequently than expected in the general population (32 episodes per 100,000 patient-years versus an expected rate of 3.4 per 100,000 patient-years). Differing practices in the use of corticosteroid therapy between European and US practitioners have been suggested as a plausible explanation for such conflicting results [71]. Interestingly, it has been found in the general population that the risk of stroke increases shortly after the occurrence of HZ [101,102]. A similar association has been recently described for patients with autoimmune diseases, in which the crude incidence of stroke was as high as 2.30 episodes per 100 patient-years within the first 90 days from HZ in the presence of certain risk factors (i.e. HZ-related cranial nerve complications and lack of early antiviral treatment) [103]. The contribution of anti-TNF-α therapy to the risk of infection due to other herpesviruses (such as cytomegalovirus (CMV) or Epstein–Barr virus(EBV)) is controversial, although a direct causal relationship seems unlikely [104,105]. Corticosteroids, rather than the TNF-α blockade, have been suggested as the culprit [106].

The inhibition of the TNF-α-mediated biological effects may influence the odds of clearance or reactivation of chronic HBV infection. Cases of HBV reactivation while on therapy have been reported for different indications [107–111], prompting specific recommendations for monitoring and treatment [57,112,113]. In contrast, worsening of hepatitis C virus infection has been rarely reported while on anti-TNF-α therapy [114–119]. In a recent systematic literature review that pooled data from 153 hepatitis C virus-infected patients treated with anti-TNF-α agents (mostly etanercept for RA), only one definitive and five suspected cases of hepatitis C virus infection worsening were identified. However, the authors acknowledged the lack of high-quality information [120].

Data on the attributable risk of CMV or EBV reactivation are scarce, in part due to the lack of specific information on these types of opportunistic infection in most studies [95]. Although TNF-α is involved in controlling CMV replication *in vitro*, concomitant immunosuppressive therapy also increases the risk of reactivation of latent herpesvirus infection [105]. In a 3-year national French registry collecting all cases of opportunistic infection diagnosed in over 55,000 patient-years of use of anti-TNF-α therapy for any indication, only four episodes of disseminated CMV disease were reported (pneumonitis, rectocolitis, retinitis and viral syndrome), mainly among individuals with IBD [121]. The occurrence of CMV colitis in the setting of IBD is well characterized, although the extent of the confounding effect of the underlying condition on the risk of CMV reactivation is unclear, as well as the real clinical relevance of this event. However, some prospective studies in Crohn's disease or RA have shown no evidence of significant CMV reactivation (measured by CMV-PCR) with infliximab [104,122]. A recent study found no apparent association between the use of anti-TNF-α agents and CMV viral load in colonic tissues, suggesting that these drugs may be considered for treating flare-ups of IBD associated with CMV reactivation [123]. Anecdotal cases of symptomatic EBV reactivation in RA [124] or IBD (often associated with B-cell colonic lymphomas or mucocutaneous ulcers [125,126]) have been reported.

Fungal infections

The impact of anti-TNF-α therapy on the risk of granulomatous fungal infection has been highlighted by case reports of cryptococcosis [90,127–129], histoplasmosis and coccidioidomycosis [129–131], particularly among infliximab-exposed patients, which often progressed to disseminated forms [129]. Isolated case reports

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and small series have described invasive aspergillosis associated with anti-TNF agents [90,132], although the concomitant use of other immunosuppressive therapies renders the interpretation of such experiences problematic. Similarly, high-dose corticosteroids were suggested as the main risk factor underlying most cases reported of *Pneumocystis jiroveci* pneumonia [133–136]. A recent meta-analysis of RCTs in patients with RA found that the use of biological DMARDs did not significantly increase the risk of invasive fungal infection (OR 2.58, 95% CI 0.68–11.91) or *Pneumocystis jiroveci* pneumonia (OR 1.77, 95% CI 0.42–7.47) [137].

Conclusions and suggested prevention strategies

- Preclinical and clinical evidence suggests that anti-TNF-α therapy is associated with an increase in the risk of active TB and other granulomatous infections and that may increase the risk of other serious infections (bacterial, fungal, opportunistic and certain viral infections). In addition, the deleterious impact of previous or concurrent non-biological therapies (i.e. cumulative corticosteroid dose) must not be neglected.
- In general terms, anti-TNF-α therapy should be discontinued, at least temporarily, upon the occurrence of serious infection. Therapy should not be restarted until infection has been treated and clinical response is noted.
- Screening for LTBI should be performed before starting anti-TNF-α therapy. A dual strategy including traditional TST and an ELISA- or ELISpot-based IGRA should be used at this baseline evaluation. Clinicians should also individually assess risk factors and systematically exclude active TB.
- The optimal re-testing strategy for LTBI while on anti-TNF-α therapy among patients with negative baseline screening remains to be established, particularly in countries of high endemicity. Although annual re-screening should be generally considered, the clinical significance of LTBI test conversions is unclear due to the presence of within-subject variability of the assays [58,138].
- Anti-TB therapy should be offered to patients diagnosed with LTBI in order to reduce the risk of progression to active TB [138–140]. The individual treatment decision and the choice of regimen must balance the expected benefits against the risk of drug-related toxicity [141].
- Appropriate (i.e. multidrug) anti-TB therapy should be instituted as soon as the diagnosis of active TB is suspected among patients receiving anti-TNF-α therapy. In this scenario, anti-TNF-α therapy should be discontinued and not be restarted, at least until clinical improvement is noted.
- Screening for chronic HBV infection, based on the detection of both hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc), should be performed before starting anti-TNF-α therapy [142]. Antiviral prophylaxis while on therapy should be offered to HBsAg-positive patients to prevent HBV reactivation. Alternatively, specialist referral may be considered. In addition, monitoring for HBV viral load among anti-HBc-positive, HBsAg-negative patients could be indicated to assess the eventual reactivation of occult HBV infection.
- No benefit is expected from the use of antibacterial, anti-*Pneumocystis* or antifungal prophylaxis. However, age-appropriate vaccinations for *Streptococcus pneumoniae* and other pathogens should be administered [143–145].
- Age-appropriate inactivated virus vaccination (i.e. influenza) should also be administered. Some live-virus vaccines (i.e. varicella-zoster virus or measles–mumps–rubella) may be contraindicated in patients receiving anti-TNF-α therapy, although additional data are needed before definitive recommendations can be made [143–146].

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