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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

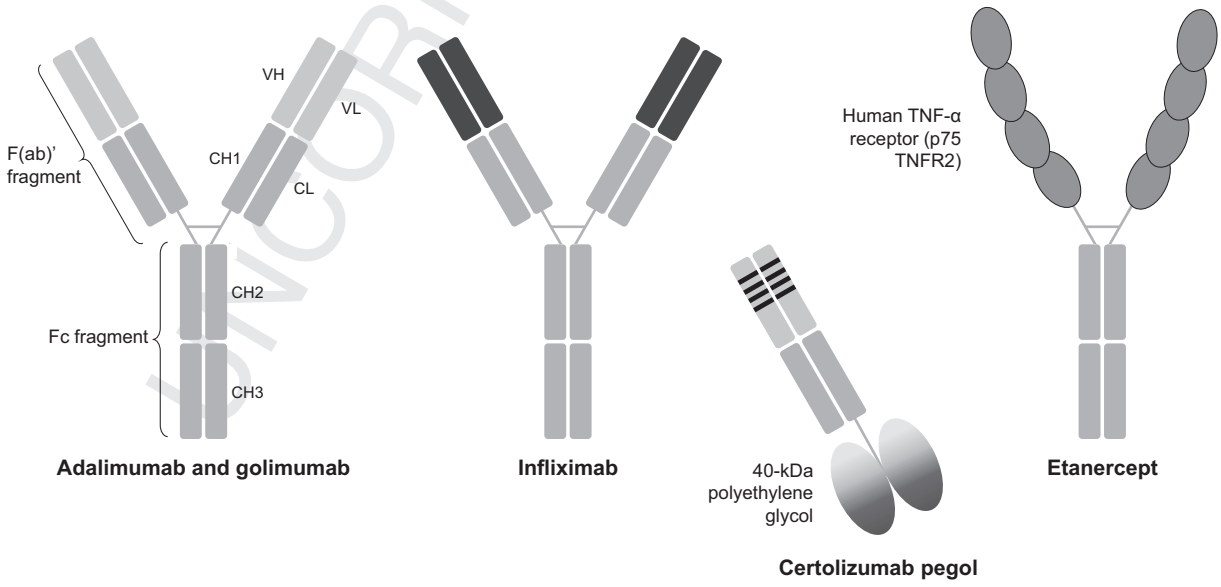

Fig. 1. Structure of different anti-tumour necrosis factor-α (TNF-α) agents. Adalimumab and golimumab are fully human IgG1 antibodies. Infliximab is a chimeric antibody composed of a antigen-binding murine variable region and the human IgG1 constant region. Certolizumab pegol is a recombinant humanized 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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