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Review

The impact of immunogenicity of TNFα inhibitors in autoimmune inflammatory disease. A systematic review and meta-analysis

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ABSTRACT

Background: Monoclonal antibodies drugs directed against TNFα, TNFα inhibitors, are immunogenic, and consequent anti-drug antibodies (ADA) formation may decrease the functional drug concentration, resulting in a loss of response. We evaluated the impact of ADA on TNFα therapeutic response.
Methods: We considered studies enrolling adult patients affected by autoimmune inflammatory disease in therapy with TNFα inhibitors. We collected data about study and population characteristics, treatment dosage, determination of ADA and adverse events (AE). We combined data in meta-analysis, calculating risk ratios (RR) for each study. p-Values < 0.05 were considered as statistically significant. Methodological quality was evaluated. Analyses were performed with the STATA 11 and RevMan 5.3 softwares.
Results: We included 34 studies enrolling 4273 patients. Of these, 794 (18.6%) developed ADA. Our analysis showed a significant reduction of response (RR 0.43, 95%CI 0.3–0.63) in patients with ADA respect to patients without, especially in patients treated with Infliximab (RR 0.37) or Adalimumab (RR 0.40). Furthermore, the administration of TNFα inhibitors produced a reaction at the infusion site in 17%, infection in 30% and serious AE in 5% of patients.
Conclusion: Detectable ADA significantly reduced TNFα inhibitors response. Drug administration can also cause injection site reaction and infections. Early detection of serum ADA levels may improve patients' management. Currently, there are many indications about the use of immunogenicity tests to guide the therapy, but information regarding how to implement it in clinical practice is needed.

Contents

Abbreviations: ADA, antidrug antibodies; AEs, adverse events; ADL, Adalimumab; AS, ankylosing spondylitis; ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CI, confidence interval; CTZ, Certolizumab; DAS28, Disease Activity Score; ELISA, enzyme-linked immunosorbent assay; ETA, Etanercept; GOL, Golimumab; IS, immunosuppressor; IFX, Infliximab; mAbs, monoclonal antibodies; MD, mean difference; MTX, methotrexate; PEG, polyethylene glycol; PASI, Psoriasis Area Severity Index; Ps, Psoriasis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; RCT, randomized control trial; RIA, radioimmunoassay; RR, risk ratio; SE, standard error; TNFα, tumor necrosis factor alpha; sTNFα, soluble TNFα; tmTNFα, transmembrane TNFα; TNFR, TNF receptor; UC, ulcerative colitis.

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1. Introduction

Tumor necrosis factor alpha (TNFα) inhibitors are monoclonal antibodies (mAbs) binding the TNFα neutralizing its pro-inflammatory effects. TNFα is a member of a cytokines family that take part in some regulatory mechanisms, such as the stimulation of inflammation, cytotoxicity and cell adhesion [1]. TNFα exerts its effects by binding onto two receptors, the type 1 (TNFR1 or p55) and the type 2 (TNFR2 or p75) TNF receptors, which are found on immune, inflammatory, and endothelial cells [2]. When it is in excess, TNFα plays a pivotal role in the pathogenesis of some autoimmune inflammatory diseases, such as rheumatoid arthritis (RA), ulcerative colitis (UC), Crohn's disease (CD), psoriatic arthritis (PsA), ankylosing spondylitis (AS). TNFα inhibitors bind to two types of TNFα: the precursor transmembrane TNFα (tmTNFα) and the soluble TNFα (sTNFα), derived from the tmTNFα. Thus, this connection interferes with the interaction between TNFα and its receptors, TNFR1 and TNFR2, as well as a soluble receptor (sTNFR), neutralizing TNFα effects and inhibiting the expression of inflammatory genes [3].

There are five TNFα inhibitors (Box 1). These mAbs exhibit different structural features, and also functional and action mechanisms and pharmacokinetic properties. Infliximab (IFX) was the first agent licensed by regulatory agencies. IFX (Remicade) is a chimeric (human–murine) IgG1 antibody, and is administered intravenously. Adalimumab (ADL, Humira) and Golimumab (GOL, Simponi) are humanized mAbs, produced by recombinant DNA technologies, and are administered subcutaneously. Etanercept (ETA, Enbrel) is a fusion protein, developed by the TNFR2 linked to the Fc portion of human IgG1. Finally, Certolizumab (CTZ, Cimzia) is a recombinant humanized antibody Fab fragment conjugated to PEG [4].

Although mAbs are highly effective for induction and maintenance of clinical remission in about 60–70% of patients [5], in a substantial part of cases TNFα inhibitors is either associated with primary failure (immediate therapy failure) or patients do not tolerate the possible adverse events (AEs). Moreover, a high proportion of patients experience secondary failure (loss of response over time, despite an initial good response).

TNFα inhibitors have features that can generate antibodies against themselves (antidrug antibodies, ADA), eliciting an immune response. This event is known as immunogenicity [6]. ADA development results in the formation of immune complexes blocking the interaction between the drug and the TNFα, and may lead to a reduction in the serum drug levels to below levels required to therapeutic efficacy. ADA, influencing the drug pharmacokinetic and pharmacodynamic, can neutralize the therapeutic action and decrease the efficacy of TNFα [7]. This is not the case in all patients with ADA, as some are however, good responders.

The main objective of this systematic review is to explore the impact of ADA on therapeutic response. Therefore, we evaluate the impact of

Box 1
Main characteristics of TNFα inhibitors.

	Infliximab	Adalimumab	Golimumab	Etanercept	Certolizumab
Structure	Monoclonal antibody	Monoclonal antibody	Monoclonal antibody	P75TNFR/Fc fusion protein	Monoclonal antibody Pegylated humanized Fab
Fully human	No	Yes	Yes	Yes	No
Ligand	sTNF, mTNF	sTNF, mTNF	sTNF, mTNF	sTNF, mTNF and LTα3	sTNF, mTNF
Weight (kDa)	150	150	150	150	95
Half life (days)	8–10	10–14	12 ± 3	3	14
Approved indications	CD, UC, RA, PsA, AS	CD, UC, RA, PsA, AS	RA, PsA, AS, UC	RA, AS, PsA	CD, RA
Reverse signaling	High	High	Moderate	Moderate	Moderate
Apoptosis	High	High	Moderate	Moderate	Moderate
Dosage	5 mg/kg	40 mg	50 mg	25–50 mg	400 mg
Administration	Iv	Sub-cut	Sub-cut	Sub-cut	Sub-cut every
Frequency (weeks)	8 wks following loading at wks 0, 2 and 6	2	4	1	2