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Review

Immunogenicity and autoimmunity during anti-TNF therapy

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ABSTRACT

The introduction of anti-tumour necrosis factor (TNF) agents for the treatment of rheumatoid arthritis (RA), Crohn's disease (CD) or spondyloarthritis (SpA) has revolutionised the therapeutic approach to patients with active disease failing to respond to conventional therapy. However, some of the patients treated with selective TNF inhibitors may develop autoantibodies, such as antinuclear antibodies (ANAs) and anti-double-stranded DNA (anti-dsDNA) antibodies. Furthermore, anti-phospholipid antibodies, which are mainly detected by means of anti-cardiolipin assays, have been found in RA patients receiving TNF blockers. There have also been a number of reports of the development of anti-drug antibodies, of which those against infliximab can interfere with the drug's pharmacokinetics (and therefore its effects), and may also cause acute and delayed infusion and injection site reactions. The onset of autoimmune diseases during biological treatment is rare, but it needs to be promptly recognised in order to plan appropriate patient management. The addition of an immunosuppressive drug can reduce the induction of anti-TNF antibodies.

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1. Introduction

Tumour necrosis factor alpha (TNFα) is a 17 kDa protein consisting of 157 amino acids. It is a homotrimer in solution, and its bioactivity is mainly regulated by soluble TNFα-binding receptors. In humans, the gene maps to chromosome 6. TNFα is mainly produced by activated macrophages, T lymphocytes, and natural killer (NK) cells, but is also expressed at lower levels by fibroblasts, smooth muscle cells, and tumour cells. Its complex functions in the immune system include the stimulation of inflammation, cytotoxicity, the regulation of cell adhesion, and the induction of cachexia [1,2]. As it plays a key role in the pathogenesis of chronic inflammatory diseases such as Crohn's disease (CD) and rheumatoid arthritis (RA), a new class of drugs has been

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developed in an attempt to neutralise its biological activities [1–4]. Five TNF blockers have been approved in Europe for treating RA patients: the three monoclonal antibodies (infliximab [INF], adalimumab [ADA] and golimumab [GLM]), the recombinant TNF receptor (etanercept [ETN]), and the pegylated certolizumab (CTZ). INF, ADA and CTZ (the last only in the United States) have also been approved for treating CD patients.

A number of randomised clinical trials (RCTs) and extension studies have shown that anti-TNF drugs are highly effective in patients with early or established RA and CD. Furthermore, large-scale observational and registry studies have confirmed their long-term efficacy in clinical practice [5]. However, although the drugs have similar mechanisms of action, they have different structures, morphology, pharmacokinetic properties and activity, and there are differences in patient responses that may be due to differences in bioavailability, the stability of the drug/TNF complex, the development of anti-drug antibodies and, possibly, treatment compliance [3–5].

The aim of this review was to consider the clinical significance of the development of antinuclear antibodies (ANA), anti-double-stranded DNA (anti-dsDNA) antibodies, anti-phospholipid (aPL) antibodies and anti-drug antibodies, and their relationships with efficacy or adverse events.

1.1. Autoimmunity

A number of studies have shown that the administration of biological agents can lead to the formation of neutralising and non-neutralising antibodies [6,7].

1.2. Neutralising antibodies

The immunogenicity of TNF inhibitors has been widely investigated because of its potential repercussions on efficacy and safety. The various inhibitors have different rates of immunogenicity, which is influenced by factors such as the route of administration, concomitant medications, drug dose and treatment schedule, genetics, age and gender, immune and nutritional status, disease characteristics, the size and structure of the drug, the number of epitopes, the clearance rate of immune complexes, and drug solubility. Furthermore, the detection of anti-drug antibodies may be affected by the type and timing of detection assays.

RCTs have shown that 25–40% of patients with inflammatory bowel disease (IBD) and 12% to 44% of RA patients, develop resistance or adverse reactions to anti-TNF agents, probably because of neutralising antibodies [4,6]. As INF and ETN have been used for a longer time, their immunogenicity is better characterised than that of the other agents. Moreover, the chimeric structure, dose, administration route, and frequency of administration of INF increase its immunogenicity.

1.2.1. Anti-infliximab antibodies

INF is a chimeric antibody containing 25% murine sequences that can induce the secretion of human anti-chimeric antibodies (HACAs) or (ATIs) [5], thus leading to adverse reactions or a gradually increasing lack of efficacy [7] that may or may not be mediated by IgE [8].

ATIs neutralise the function or increase the clearance of INF. They can prevent the drug from entering the bloodstream, enhance clearance by forming precipitated immune complexes in vessels and increasing splenic clearance, prevent the drug from entering sites of inflammation, or neutralise its ability to inhibit TNF [9]. They can therefore impede clinical responses and the control of disease activity by affecting bioavailability, pharmacokinetics, and pharmacodynamics [5,10].

However, in some cases, the clinical efficacy of anti-TNF may not be affected by the presence of ATIs, possibly because they have a low affinity for the drug or fail to interact with it, or because concomitant treatment with immunosuppressive drugs such as azathioprine (AZA) or methotrexate (MTX) decreases antibody formation and increases drug levels, although the exact mechanism is not clearly understood [7,10].

The binding of ATIs to INF favours the formation of immune complexes that give rise to adverse events such as acute infusion reactions, which occur within 1–2 h of administration and include fever, nausea, breathlessness and headache [7–10]. No association has been found between antibodies against anti-TNF drugs and delayed hypersensitivity reactions, which occur 3–12 days after infusion and are characterised by myalgia, arthralgia, pruritus, facial or peripheral oedema, sore throat and headache [10].

Because of the different ways in which they were collected, the data concerning the immunogenicity of INF are heterogeneous. Detecting anti-drug antibodies depends on the pharmacokinetics of the drug itself and, although INF has a circulating half-life of about 10 days, it can still be detected in tissue for up to 12 weeks after discontinuation [10]. If blood samples are collected soon after administration, ATIs may not be detectable because they form immune complexes with the drug. Furthermore, current enzyme-linked immunosorbent assays (ELISAs) are affected by a high rate of false positive results; radio-immunosorbent assays (especially in the fluid phase) are more specific as they do not interact with other immunoglobulins such as rheumatoid factor [10].

The prevalence of ATIs varies from 12% to 44% in INF-treated RA patients, and from 6% to 61% in those with CD [6,7], who may be immunised against INF after only one month of treatment [11]. The RA patients who need higher INF concentrations to control their disease have the highest ATI titres. Furthermore, the immunogenicity of INF in CD patients varies depending on whether it is administered using an episodic (36–61%) or scheduled regimen (18%).

A number of studies have described the prevalence of ATIs in RA and CD patients, and shown their repercussions in clinical practice, although the results are still controversial.

1.2.1.1. HACA in CD patients. Baert et al. [12] conducted a study that included CD patients treated with episodically administered INF, and found that 61% of these were ATI positive after five infusions, but the incidence of ATIs remained stable in the patients undergoing subsequent consecutive infusions. Serum anti-INF antibody concentrations inversely correlated with the duration of response (71 days in patients with ATI levels of <8 μg/mL and 35 days in patients with levels of >8 μg/mL; $P<0.001$). There was also a close correlation between ATI concentrations and acute infusion reactions, for which the patients with levels of >8 μg/mL had a relative risk of 2.4. The infusion reactions were less frequent in CD patients with higher serum INF levels, and in those treated with other immunomodulators, thus suggesting that immunosuppressive therapy should be started before administering INF in order to prevent antibody formation and improve the duration of drug response [11].

Farrell et al. [13] detected ATIs in 36% of their patients after 24 weeks. They stratified the patients on the basis of whether they showed a 'continuous response', a 'secondary loss of response', a 'partial response', or a 'non-primary response', and found an association between the clinical response and the presence of ATIs: none of the patients with a 'continued response' had ATIs, whereas 73% of those with a 'secondary loss of response' developed them. Moreover, all of the patients who experienced an adverse reaction were ATI positive, and a level of >8 μg/mL before a subsequent infusion predicted a four-fold higher risk of a serious infusion reaction [13].

The ACCENT I trial evaluated the use of a new long-term INF treatment regimen for CD patients, and found that the clinical response after 54 weeks was similar in patients with and without ATIs (64% *vs*. 62%) and with and without remission (41% *vs* 39%). ATIs were associated with a 12% absolute increase in infusion reactions. There was a trend towards a lower incidence of the development of INF antibodies in the patients receiving concomitant corticosteroids plus