Treatment of Psoriasis with Anti-TNF Alpha Blocking Agents: Impact of Immunogenicity

Clara De Simone¹, Giacomo Caldarola¹, Francesca Perino¹ and Ketty Peris¹

Abstract — Psoriasis is an immune-mediated chronic inflammatory skin disorder, affecting 2–3% of the world population, with roughly one third of the patients suffering from moderate-to-severe disease and a high impact on quality of life. Since Tumor Necrosis Factor (TNF) alpha has been recognized as a pivotal cytokine in the pathogenesis of the disease, treatment of psoriasis has improved considerably with the introduction of anti-TNF alpha biologic agents. They include two monoclonal antibodies (infliximab and adalimumab) and a fusion protein (etanercept). Despite the efficacy of these drugs has been demonstrated in randomized controlled trials and observational studies, a consistent proportion of patients loses the therapeutic response, one of the reasons possibly being the immunogenicity of the molecule. In fact, as foreign proteins they can induce the production of anti-drug antibodies, both neutralizing and non-neutralizing, which probably also play a role in some side effects of treatment. However, immunogenicity of anti-TNF alpha agents is influenced by numerous factors related not only to the drug used and treatment modalities but also to the patient’s disease and individual characteristics. A better knowledge of the implications of biologic immunogenicity in psoriasis would allow a more rational approach to management of an individual patient.

Keywords — Psoriasis, anti-TNF alpha, immunogenicity

INTRODUCTION

Psoriasis is a common chronic inflammatory skin condition with a relapsing and remitting course that affects approximately 2% of the population in western countries [1]. The most common clinical presentation of the disease, observed in more than 80% of patients, consists of well-demarcated, erythematous and desquamative plaques on the head and extensor surfaces of trunk and limbs which are characterized by hyperproliferation of epidermal keratinocytes, neoangiogenesis, and inflammation on histology. Psoriasis is probably a complex multifactorial disease, where various environmental triggers (e.g. trauma, stress, infections and drugs) promote, in genetically predisposed individuals, the activation of an exaggerated and poorly controlled immuno-inflammatory response in the skin, which leads to excessive keratinocyte proliferation. The current model of psoriasis implicates cellular elements of both the innate and adaptive immunity and several cytokines that drive the uncontrolled inflammation and proliferation of keratinocytes (fig. 1) [2]. Tumor Necrosis Factor (TNF) alpha is a pivotal cytokine in the pathogenesis of psoriasis, being an important mediator of cutaneous inflammation and acting synergistically with other cytokines [3]. TNF alpha is derived from activated dendritic cells, Th1 and Th17 cells and keratinocytes and TNF alpha mRNA is increased in human psoriatic skin relative to normal controls [4].

Psoriasis may cause a significant psychosocial morbidity and is associated with numerous co-morbidities, including psoriatic arthritis, inflammatory bowel disease, cardiovascular disease, metabolic syndrome, lymphoma and depression [5, 6]. Treatment of psoriasis depends on severity of the disease which is defined on the extent of the skin involvement and impact on patient’s quality of life. However, therapeutic approaches should also take into account the concomitant co-morbidities and triggering factors such as psychological stress or infections. In general mild disease can be treated with topical drugs while treatments for moderate-to-severe disease include systemic drugs such as methotrexate, cyclosporin, acitretin and, more recently, biologics [7]. Over the past decade, in fact, biological drugs - therapeutic products made by biotechnology...
IMMUNOGENICITY OF ANTI-TNF ALPHA AGENTS

The term immunogenicity refers to the ability of a molecule to induce a specific humoral or cellular immune response, which is triggered by differences between the structure of the exogenous drug molecules and the body’s natural proteins [12]. Antibodies, which are part of the adaptive immune system, can recognize even small molecular differences in exogenous substances, which can be then eliminated through various mechanisms such as direct neutralization or phagocytosis of the drug-antibody complex or complement activation. The main immune system’s defence against exogenous drugs are immunoglobulin (Ig) G antibodies [3]. All biotechnology-derived therapeutic proteins, whether entirely of human origin, chimeric or ‘humanized’ contain unique sequences that can elicit an immune response that generate anti-drug antibodies (ADAs). ADAs may target allotypes, idiotypes, or even epitopes generated by the formation of new structures, as occurs in the case of fusion proteins. However, it is important to note that different types of ADAs, targeting different parts of the same drug, may coexist in certain patients.

One of the key determinants of immunogenicity is the molecular structure of the drug; in fact, the different molecular structures of the various anti-TNF alpha agents translate to different immunogenicity profiles, with distinctive clinical implications. Chimeric drugs such as infliximab may induce the production of antibodies against the murine component of Fab fragments [13], whereas fully human anti-TNF alpha monoclonal antibodies such as adalimumab elicit antibodies against the idiotype which is the set of the epitopes in the hypervariable portion of the therapeutic monoclonal antibody [14]. In fact, anti-idiotypic antibodies target the drug binding site, as this does not belong to the immunoglobulin repertoire of the host. Therefore, although adalimumab have less immunogenic potential compared with infliximab, it can still induce the formation of human anti-human antibodies [15]. For etanercept, which combines a naturally occurring TNF alpha receptor to the Fc region of a fully human immunoglobulin, epitopes recognized by the immune system as foreign may be present in the joining region of the molecule [16].

However, immunogenicity of the targeted drug is influenced not only by drug-related factors but also by patient and disease characteristics and treatment protocol. A patient’s genetic background, for example, will determine the likelihood and nature of the immune response to the exogenous molecules. According to currently used assays, not all patients receiving the same biologic under similar conditions will develop ADAs. However, those who develop ADAs against a first TNF alpha inhibitor are more likely to develop ADAs against a second agent, possibly due to genetic susceptibility [17]. There is no evidence that ADAs can cross-react between the various

...
anti-TNF alpha agents; therefore, the presence of an ADA does not contraindicate switching to another drug of the same class. The underlying disease is also a factor, and certain diseases, such as RA, are known to be particularly associated with immunogenicity. Finally, treatment-related factors that may influence the risk of sensitization include the drug dose (and serum concentration), administration route, frequency of administration, and duration of treatment. A lower dose administered intermittently is typically more immunogenic compared with a larger dose administered without interruption [8, 18]. Intravenous administration is generally considered less immunogenic than the subcutaneous route because the latter favours antigen-presenting cell uptake and presentation [19]. Accordingly, the European Medicines Agency underlines that long term rather than short term and continuous rather than intermittent treatment appears to decrease the risk of immunogenicity [8].

**CLINICAL IMPACT OF IMMUNOGENICITY**

One of the most important aspects of ADAs is the fact that they can be either neutralizing or non-neutralizing. Infliximab and adalimumab can induce neutralizing ADAs that bind the hypervariable region of the Fab fragment, essential for the link to TNF alpha, thus interfering directly with the drug’s therapeutic activity [20]. In RA and spondyloarthritides, development of ADAs in 19–26% of patients treated with infliximab has been shown to be associated with low trough drug levels during the initiation period, poor clinical response, increased infusion reactions and a greater likelihood of drug discontinuation [21, 22]. In a large series of 249 patients with severe plaque psoriasis, higher rates of ADAs were recorded among patients receiving low drug dosage (3 mg/kg) in an intermittent regimen in comparison with patients receiving higher dose (5 mg/kg) in scheduled treatments [23].

Similarly, development of ADAs against adalimumab in 28% of RA patients was associated with lower drug concentrations and a lower likelihood of minimal disease activity or clinical remission [24]. An ADA incidence as high as 45% was reported in a small series of adalimumab-treated patients with psoriasis, with a significant inverse correlation with serum drug level and clinical response [25]. Non-neutralizing ADAs, by contrast, bind to a portion of the drug molecule that is not essential to its therapeutic activity. In such cases, antibodies can be directed against the allotope and be triggered, even when the structure of the molecule is fully human, by polymorphisms expressed in the constant portion of the light and heavy chains, which vary between individuals.

Finally, another potential target of non-neutralizing ADAs are the new epitopes found in fusion proteins such as etanercept. The joining region is not involved in drug binding; consequently, only non-neutralizing ADAs against etanercept have been detected [26]. ADAs have been detected in as many as 18% of etanercept-treated psoriasis patients and these have been shown to be non-neutralizing [27]. Lack of clinical response, however, may also be related to mechanisms other than the direct blockage of the idotype by antibodies: immune-complex formation between anti-TNF alpha agents and ADAs, which are eliminated by the reticuloendothelial system, leads to an increased drug clearance through the reticuloendothelial system. The presence of ADAs, therefore, through one or more different mechanisms, can reduce the likelihood of achieving a sufficient number of free drug molecules to bind to the therapeutic targets [28].

At the present time, it is not yet possible to measure antibodies against biologics in a simple, efficient manner in routine clinical practice. It is important to test for ADAs just before the drug is administered, when drug levels are presumably at their lowest level otherwise the ADAs will be bound to drug molecules and will not be detected. In patients who experience problems with efficacy, drug concentrations should be first measured and then, if unusually low, ADAs should be tested. The presence of ADAs does not preclude a clinical response as long as they do not bring the concentration of the unbound active drug below the therapeutic level [29].

Regarding the methods used to measure ADAs, many studies have used standard ELISAs. However, while sensitive, these are not very specific and are prone to false-positive results and non-specific binding [30]. More recently, two alternative types of assay have been widely used. The two-site (bridging) ELISA is highly specific and sensitive, but it is very susceptible to interference by the drug present in the patient’s serum that results in immune complex formation [15]. The radioimmunoassay antigen binding test can detect clinically relevant antibodies, but the use of radioactivity is a disadvantage [15]. Whereas the bridging ELISA can only detect ADAs in the absence of detectable amounts of circulating drug, the radioimmunoassay is less susceptible to drug interference [31].

ADA formation may have various clinical effects. The potential impact of immunogenicity on safety is another very important issue. Overall, it can be stated that the presence of ADAs has only been associated with a high frequency of infusion-related reactions during treatment with infliximab but not with adalimumab or etanercept [32].

Several factors may influence the clinical impact of drug immunogenicity, and their identification may be useful for the optimization and personalization of biologic therapies. The addition of methotrexate to biologic regimens is an example of how adjunctive therapy can be used to interfere with the immune system and reduce its ability to recognize and eliminate foreign molecules by forming ADAs [33].

Typically, the immune reaction against a therapeutic protein is reduced when immunosuppressive agents are used concomitantly [8, 10, 34]. A meta-analysis conducted in 936 patients (40% RA and 47% IBD) treated with adalimumab or infliximab showed that concomitant methotrexate or azathioprine/mercaptopurine reduced detectable ADA frequency by about 47% (64% for ADAs assessed by radioimmunoassay) [35]. Beside adding immunosuppressive agents to the anti-TNF alpha therapeutic regimen, increasing the dose of the biologic can counterbalance the effects ADAs
since it also increases the plasma through level necessary for clinical efficacy.

Presence of ADAs should be considered before switching biological agents. Only a limited amount of data is available in the literature, with the greatest part coming from patients affected by RA. In particular, in a study of 292 patients who initiated treatment with etanercept (some of whom were receiving their first anti-TNF agent and others who had been switched from infliximab or adalimumab), anti-TNF alpha-naïve patients and switchers with ADAs had a similar response, which was better than that of the switchers without ADAs [36]. These findings suggest that lack of responsiveness in absence of ADAs could drive switching to a biologic different from a TNF alpha blocking agent, since in these cases TNF alpha could not be involved in the pathomechanisms of the disease. By contrast, in patients with ADAs against anti-TNF alpha monoclonal antibodies the option of using a drug with a similar mechanism of action but a different molecular structure (in this case etanercept) would be justifiable.

Although ADA or drug serum level is not routinely performed, recommendations for switching in clinical practice have also been suggested for patient with psoriasis. Particularly, when therapy with a biologic is not effective, increasing the drug dosage and/or shortening the interval between doses can be tried before switching to another biologic. In these patients, switching can be performed with the same administration protocol used for “naïve” patients, without observing a washout period. When switching is considered because of side effects, a washout period is suggested before starting the new biologic treatment [37].

CONCLUSIONS

In conclusion, immunogenicity may affect the pharmacokinetics of anti-TNF alpha agents used to treat psoriasis, may result in reduced clinical efficacy and drug survival and need of dose escalation. In some cases, immunogenicity is associated with a higher risk of adverse events, especially infusion reactions. Infliximab and adalimumab are associated with development of neutralizing ADAs; in contrast, antibodies to etanercept are non-neutralizing and appear unrelated to clinical response. Drug trough levels supported by ADA testing may help optimize psoriasis management with biological therapy. Flexible biological dosing in response to clinical response and life events is desirable in a long-term condition like psoriasis. Immunogenicity should be taken into account alongside factors such as the clinical efficacy of the drug, the impact on comorbidities and the safety profile.

References


