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EXPERT OPINION

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Immunogenicity of infliximab and adalimumab: what is its role in hypersensitivity and modulation of therapeutic efficacy and safety?

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Introduction: TNF- α inhibitors have demonstrated efficacy both as monotherapy and in combination with disease-modifying antirheumatic drugs (DMARDs) in the treatment of chronic inflammatory immune-mediated diseases such as rheumatoid arthritis, Crohn's disease, ankylosing spondylitis, psoriasis and/or psoriatic arthritis, and may be administered off-label to treat disseminated granuloma annulare systemic lupus erythematosus and systemic sclerosis. There are several TNF- α inhibitors available for clinical use including infliximab, adalimumab, golimumab, certolizumab pegol and etanercept.

Areas covered: infliximab and adalimumab can induce the development of anti-infliximab (anti-IFX) and anti-adalimumab (anti-ADA) monoclonal antibodies (mAbs). In this review, we discuss the impact of anti-IFX and anti-ADA mAbs upon efficacy and safety of these biological agents.

Expert opinion: IgG/IgE neutralizing antibodies against infliximab and adalimumab decrease the possibility of achieving a minimal disease activity state or clinical remission, decrease drug survival, increase the need for doctors to prescribe a higher drug dosage and, finally, favor the occurrence of adverse events. Concomitant administration of DMARDs such as methotrexate or leflunomide prevents the development of neutralizing Abs against infliximab and adalimumab.

Keywords: adalimumab, hypersensitivity reactions, immune-mediated diseases, immunogenicity, infliximab

Expert Opin. Drug Saf. [Early Online]

1. Introduction

TNF- α inhibitors have demonstrated efficacy both as monotherapy and in combination with disease-modifying antirheumatic drugs (DMARDs) in the treatment of chronic inflammatory immune-mediated diseases such as rheumatoid arthritis (RA), Crohn's disease (CD), ulcerative colitis, ankylosing spondylitis, psoriasis and/or psoriatic arthritis.[1–10] TNF- α inhibitors, particularly infliximab (IFX), may be administered off-label to treat other chronic inflammatory immune-mediated diseases such as disseminated granuloma annulare, systemic lupus erythematosus and systemic sclerosis.[11–14] There are several TNF- α inhibitors available for clinical use. IFX, adalimumab (ADA) and golimumab are anti-TNF- α monoclonal antibodies (mAbs). In particular, IFX is a chimeric human/murine IgG1 mAb, ADA is a fully recombinant human IgG1 anti-TNF- α -specific mAb and golimumab is a human gamma-1 immunoglobulin- κ anti-TNF- α mAb.[1–14] Certolizumab pegol is composed of the fragment antigen binding (Fab) domain of



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Article highlights.

- Infliximab (IFX) is a chimeric anti-TNF- α mAb and induces the secretion of human anti-IFX Abs favoring the occurrence of adverse reactions or gradually leading to loss of therapeutic efficacy.
- Despite its humanized structure, adalimumab (ADA) may also induce the appearance of anti-ADA Abs.
- Anti-IFX and anti-ADA Abs mainly belong to the IgG and IgE isotypes.
- anti-IFX IgM Abs were found in anti-IFX IgE Abs-negative patients.
- Early appearance of anti-IFX and anti-ADA Abs was associated with subsequent discontinuation of the drugs due to treatment failure and the risk of reaction is relatively high during episodic reinitiation treatment especially at the second infusion.
- Active inflammation and genetics factors play a key role in the production of anti-IFX Abs, while the patient age seems to play a minimal role in the appearance of anti-IFX Abs.
- Methotrexate or leflunomide prevents the development of neutralizing Abs against IFX and ADA.

This box summarizes key points contained in the article.

a humanized monoclonal anti-TNF- α antibody combined with polyethylene glycol to increase its half-life in the body.[15] Finally, etanercept is a fusion protein that acts as a “decoy receptor” for TNF- α . [1–14] Two distinct TNF receptors, a 55-kDa protein and a 75-kDa protein, exist naturally as monomeric molecules on cell surfaces and in soluble form. [16] Etanercept is a dimeric fusion protein (approximately 150 kDa) consisting of extracellular ligand-binding portion of human 75-kDa protein TNF receptor linked to the Fc portion of human IgG1. [11] Notably, only etanercept is able to neutralize lymphotoxin (LT)- α as we have shown in psoriatic arthritis patients. [17] Indeed, etanercept binds to both TNF- α (primarily to its soluble form) and LT- α , rendering these cytokines biologically inactive by inhibiting their interaction with cell surface TNF receptors. [3,11–20] T-helper (Th)-1 and Th-17 lymphocytes have been associated with autoimmune diseases such as RA and expressed LT- α . [21–23] Depletion of LT- α -expressing Th-1 and Th-17 lymphocytes with LT- α -specific mAb, reducing the secretion of interleukin-17, interferon- γ and TNF- α , may be beneficial in the treatment of autoimmune disease such as RA. [22] CD8⁺CD28[−] T regulatory cells are involved in the control of pathologic chronic immune responses, contributing in some cases to the pathogenesis of immune-mediated diseases such as multiple sclerosis, systemic lupus erythematosus, systemic sclerosis and RA. [24,25] Despite an *in vivo* abundance of CD8⁺CD28[−] T regulatory cells in RA patients they are functionally deficient, but their function can be improved by TNF- α inhibitors. [24,25] Furthermore, TNF- α may promote progression of endothelial dysfunction and,

thus, of accelerated atherosclerosis. [26–30] TNF- α inhibitors seem to have a beneficial role in the treatment of accelerated atherosclerosis, decreasing the serum TNF- α levels and increasing the tissue expression of endothelial nitric oxide (NO) synthase and vasodilatory response to bradykinin. [28,31–33] TNF- α inhibitors are able to reduce the expression and production of vascular endothelial growth factor (VEGF), NO and inducible NO synthase. [34] VEGF is a critical mediator of inflammation in both chronic immune-mediated and allergic diseases. [27,35,36] It is known that VEGF is a pro-angiogenic factor which alters the microvascular network and, thus, correlates and may contribute to the development and progression of atherosclerosis. TNF- α inhibitors reduce the systemic inflammation in patients with chronic immune-mediated diseases, improve both the clinical course of the disease itself and the endothelial function and, thus, may decrease the risk of acute cardiovascular and/or cerebrovascular events. [27,34–36]

Although TNF- α inhibitors are generally well tolerated, physicians should be aware of the potential adverse events of these drugs, such as infusion reactions with IFX, injection site reactions to subcutaneously administered drugs (i.e., local erythema and swelling), opportunistic infections, malignancies, autoimmune diseases, demyelinating diseases, few cases of neutropenia and rare cases of severe fibrosing alveolitis. [1,11,37,38] IFX is a chimeric anti-TNF- α mAb containing 25% murine sequences that can induce the production of human anti-IFX Abs, [3] favoring the occurrence of adverse reactions or gradually leading to loss of therapeutic efficacy. [3] Despite its human structure, ADA may also induce the appearance of anti-ADA Abs. [39] It still remains unclear which part of ADA induces the production of anti-ADA Abs. Immunogenicity of ADA and its clinical significance in daily clinical practice are poorly investigated compared to the immunogenicity of IFX. [39] These agents have also the potential to cause delayed hypersensitivity reaction (HR). [40] In this article, we will briefly discuss the immunogenicity of IFX and ADA and the impact of both acute and delayed HRs on the efficacy and safety of these biological agents.

2. Anti-infliximab antibodies and acute hypersensitivity reactions

Anti-IFX Abs neutralize the function of IFX, preventing the drug from entering the sites of inflammation. [41–44] Indeed, anti-IFX Abs may decrease the clinical response to the treatment with IFX and, thus, the control of disease activity. [41,44] Van der Laken et al. [45] investigated *in vivo* the role of anti-IFX Abs by using radiolabeled IFX in two responder and two nonresponder IFX-treated RA patients. The scintigrams demonstrated a trend of faster blood clearance and higher liver and spleen uptake of 99mTc-IFX in one nonresponder patient. Anti-IFX Abs levels were high in the nonresponders and low or not detectable in the

responders. Sucrose gradients of serum revealed anti-IFX Ab-IFX complexes in both nonresponders. However, in some cases, anti-IFX Abs do not interfere with the pharmacologic action of IFX possibly because they have a low affinity for the drug or fail to interact with it. Moreover, concomitant administration of DMARDs such as methotrexate (MTX) or leflunomide decreases the appearance of anti-IFX Abs. [3,9,42,44,46,47] Maini et al. [48] first investigated whether MTX could reduce the immunogenicity of IFX in RA. In a 26-week, double-blind, placebo-controlled, multicenter trial, they evaluated the efficacy, pharmacokinetics and safety of different IFX regimens, given alone or in combination with MTX, by randomizing 101 patients into 7 groups of 10–15 patients each. The development of Abs was inversely associated with IFX dose (53%, 21% and 7% in patients receiving 1, 3 and 10 mg/kg monotherapy, respectively) and the concomitant administration of MTX at a dose of 7.5 mg/week greatly decreased the appearance of anti-IFX Abs, with incidence rates of 15%, 7% and 0% at the three dose levels. Bendtzen et al. [49] analyzed sera from 106 IFX-treated RA patients. After the first two intravenous infusions of IFX at 3 mg/kg, only 13% of patients were anti-IFX Abs-positive. With subsequent infusions, the frequency of Ab positivity rose to 30% and 44% at 3 and 6 months, respectively, accompanied by diminished trough IFX levels. The authors reported that at 6 months of treatment, anti-IFX Abs-positive patients receiving MTX had lower anti-IFX Abs compared with those not receiving MTX (11% vs 5%). Pascual-Salcedo et al. [50] evaluated the effect of long-term immunogenicity in a cohort of 85 RA patients receiving IFX. The concomitant administration of MTX 15 mg/week was associated with lower levels of anti-IFX Abs and longer survival. Finally, the development of immunogenicity was strongly linked to infusion reactions. What is the influence of anti-IFX Abs on the occurrence and severity of adverse events? The real role of anti-IFX Abs remains still inconsistent. However, the formation of immune complexes following the binding of anti-IFX Abs to IFX induces the appearance of acute infusion reactions occurring 1–2 h after administration. [1,42,44,51,52] Because of the different ways in which they were collected, the data concerning the immunogenicity of IFX are heterogeneous. If blood samples are collected soon after administration, anti-IFX Abs may not be detectable because they form immune complexes with the drug. [44] Vultaggio et al. reported that some acute severe infusion reactions to IFX may be caused by a type 1 HR mediated by anti-IFX IgE Abs. [53] They analyzed 71 patients treated with IFX suffering from RA, spondyloarthropathies and systemic vasculitis. Fifteen acute reactions out of 1041 infusions were observed. Two reactions were classified as mild (urticaria), eight as moderate (urticaria, chest tightness and dyspnea, vomiting) and five as severe (oxygen desaturation, hypotension with systolic blood pressure < 90 mmHg and confusion). IgE anti-IFX were detected in 3 out of the 11 reactive patients, who also developed a positive intradermal test at immediate

lecture performed with 1/10 diluted drug. Furthermore, significantly higher levels of IgM anti-IFX Abs were demonstrated in the reactive patients compared with unreactive subjects and controls. In particular, high levels of IgM anti-IFX Abs were found in three IgE anti-IFX Abs-negative patients. Anti-IFX Abs were not detected before the first IFX infusion. However, Abs anti-IFX were detected in the sera collected before the second and third infusion and their appearance resulted strictly related to the timing of reaction. The authors define a timing relationship between the Abs anti-IFX appearance and the IFX reaction. The progressive but quite fast decrease of Abs including IgE starting from 7 days after the reaction was observed. These findings suggest that immunological mechanisms other than type 1 HR may be involved in protein-induced fatal anaphylaxis. [54,55] Finally, in two anti-IFX Abs-positive but IgE- and IgM-negative subjects, a role for IgG anti-IFX Abs may be envisaged. Notably, the detection in three patients of anti-IFX Abs at the second course of treatment after the first infusion suggested a sensitization phase (first course of treatment) and a challenge phase (second course of treatment). These findings confirmed an effect of treatment interruption on the prevalence of IFX reaction. [56] The majority of reactions could be predicted by the appearance of anti-IFX Abs. By monitoring these Abs, at least for the first five infusions, it is possible to identify potentially reactive patients and, thus, improve the IFX safety profile. Matucci et al. [57] investigated the usefulness of skin testing in patients who have experienced IFX-related immediate HRs. Thirty patients who had a previous immediate HR after IFX treatment were enrolled (group I). Furthermore, 20 non-exposed disease-matched patients (group II), 15 IFX-treated disease-matched tolerant patients (group III) and 15 IFX-treated patients who lost the response to the treatment (group IV) were also included as control groups. Cutaneous and respiratory symptoms represented the most frequent clinical features, particularly flushing, dyspnea, throat constriction and itching. The authors reported the same incidence of mild, moderate and severe reactions. The majority (26/30, 86.6%) of the reactions were recorded before the 10th infusion, but never at the first dose of the drug, and eight of them (26.6%) at the re-exposure after a period of interruption. The reaction within 1–15 min after the starting of the infusion was reported in 17 patients, within 15–30 min in 3 and within 30–60 min in 10 patients. Twenty-three of the 30 reactive patients displayed anti-IFX-positivity at the non-isotype-specific assay. Moreover, six reactive patients developed anti-IFX IgE Abs, whereas 3 of the 30 patients belonging to groups III and IV had anti-IFX IgE Abs. The drug concentration for skin prick testing was from 0.01 to 10 mg/ml and, if negative, intradermal testing (IDT) was performed by using 0.02 ml of 0.01 mg/ml dilution and proceeding to 0.1, 1 and 10 mg/ml. Notably, irritant weals were noted in three subjects at IDT by using undiluted concentration (10 mg/ml) of IFX. Therefore, in the analysis of reactive patients, the

authors used only diluted solution of IFX (up to a maximum of 1 mg/ml). In both skin prick testing and IDT, a minimum weal area of 3 mm in diameter or an increase of area > 3 mm was considered as positive compared to the negative response obtained with the saline solution. The authors suggested the use of IFX 1 mg/ml, since this concentration has not been shown to give false-positive results in healthy donors and IFX-tolerant patients. All 23 of the 30 reactive patients accepted to be submitted to skin testing. All six patients who developed anti-IFX IgE Abs resulted positive to IDT and one reactive patient who did not have detectable anti-IFX IgE Abs was positive to both skin prick testing and IDT. Furthermore, 1 of the 30 patients with no HRs (group III and IV) resulted positive to skin testing. The positive and negative predictive values of skin testing could be estimated as being about 55% and 90%, respectively.

To better define the role of skin testing for IFX in reactive patients, the authors compared the skin positivity with the presence of circulating specific IgE and non-IgE anti-IFX. The majority of reactive patients (group I) displayed anti-IFX Abs positivity (23/30; 76.6%) at the non-isotype-specific assay. Overall, by using a cut-off value of 0.10 kUA/l for the anti-IFX-IgE, the *in vitro* test showed a sensitivity of 26% (6/23; CI: 10.2–48.4%) and a specificity of 90% (27/30; CI: 72.6–97.8%). The estimated positive and negative predictive values would be about 26% and 89%, respectively.

Regarding the timing of the development of reaction, the authors showed that skin testing–positive patients displayed HRs significantly earlier (2.4 ± 0.2 infusions) during the course of treatment than both anti-IFX-positive IgE-negative (5.3 ± 0.7 ; $p < 0.02$) and anti-IFX-negative patients (6.6 ± 0.6 ; $p < 0.02$). Furthermore, the majority of skin test–positive patients (5/7; 71.4%) as opposed to skin testing–negative patients (2/16; $p < 0.02$) developed HRs at the re-exposure to IFX. Among anti-IFX-positive patients, all skin testing–positive individuals ($n = 7$) developed the reaction before or during the third infusion compared to 5 of 16 skin testing–negative patients (31.2%, $p < 0.005$). It is essential to perform IDT in subjects with immediate reactions, as the prick test is usually negative.

These findings confirmed that not all HRs to IFX are IgE-driven, thus leading to the low sensitivity and positive predictive value of the skin testing. Finally, the authors showed that the IgE-mediated reactions usually occur at the beginning of the treatment, particularly within the first three administrations, suggesting that the immune response against IFX which leads to the development of anti-IFX IgE Abs is a quite early phenomenon. None of the patients showed skin testing positivity to IFX and specific serum IgE when studied 8 months after the first analysis, confirming that the allergological work-up of reactive patients should be performed quite early. Indeed, IFX-reactive patients showed a rapid decrease of IFX-specific IgE antibodies.[53]

Steenholdt et al. [58] investigated the role of anti-IFX Abs in the development of acute severe infusion reactions in 315 patients with inflammatory bowel disease (IBD). Twenty-five of 315 patients presented acute severe infusion reactions and anti-IFX IgG Abs were detected in 19 of 20 patients shortly after the reactions. The authors excluded that the IgE had a pivotal role in inducing severe infusion reactions. Indeed, anti-IFX IgE Abs resulted negative in all patients with reactions. Furthermore, patients who reacted were younger as compared to those who did not react (19 vs 26 years). The risk of reaction was relatively high during episodic reinitiation treatment, especially at the second infusion in a new series and the negative anti-IFX Abs before reinitiation did not exclude potential reactions. However, the risk of reactions increased with time between IFX series. Which factors promote the synthesis of anti-IFX Abs? Various factors may influence the immunogenicity of IFX and include the lack of development of “tolerance” by patients’ immune system to biologics,[59] high inflammatory burden (i.e., elevated C-reactive protein, low serum albumin) [60,61] and genetic factors (i.e., HLA-DR β S13 residues) [62] that favor the production of anti-IFX Abs. The effect of age on the anti-IFX Abs incidence is sparsely studied. Fasanmade et al. [63] reported a difference in the prevalence of anti-IFX Abs in children (2.9%) and adults (11%) affected by CD treated with IFX. However, community-based studies of pediatric populations and predominantly older populations find similar prevalence of anti-IFX Abs.[63,64] These studies suggest that patient age may only play a minimal role in anti-IFX Abs production. Pallagi-Kunstár et al. [65] examined in patients with IBD the correlation loss of response, the development of side effects or hypersensitivity and serum TNF- α , IFX trough levels and anti-IFX Abs concentrations. In particular, anti-IFX Abs positivity was significantly correlated with low trough IFX levels. Furthermore, anti-IFX Abs were detected in 25% of IBD patients with loss of response, side effects or hypersensitivity. These findings suggested that the simultaneous measurement of serum TNF- α , IFX levels and anti-IFX Abs concentrations may help to optimize the treatment.

3. Anti-adalimumab antibodies and acute hypersensitivity reactions

ADA is a fully recombinant human IgG1 mAb specific for human TNF- α , which binds soluble and membrane-bound TNF- α with high specificity and affinity. In spite of its fully human sequence, the production of anti-ADA Abs has been also reported, which may reduce the efficacy of the drug and induce the development of adverse drug reactions and exanthema.[66] Jani et al. [67] analyzed 331 RA patients receiving TNF- α inhibitors (ADA or etanercept). Anti-ADA Abs were detected in 31 out of the (24.8%) 125 patients who

had completed 12-month follow-up and none of the etanercept patients. At 3 months, anti-ADA Abs formation and low ADA concentrations were significant predictors of poor treatment response at 12 months. Bartelds et al. [68] examined the long-term impact of anti-ADA Abs on ADA concentrations in 272 RA patients receiving ADA. After 3 years, 76 of 272 patients (28%) developed anti-ADA Abs and presented lower ADA concentration and, thus, more often discontinued the drug due to treatment failure. In particular, after 4, 16 and 28 weeks of treatment, approximately 10%, 15% and 20% of patients, respectively, developed anti-ADA Abs. Finally, 51 of 76 (67%) patients developed anti-ADA Abs during the first 28 weeks of therapy. Patients without anti-ADA Abs had significantly higher ADA concentrations compared with patients having both Abs titers from 13 to 100 AU/ml ($P < 0.001$) and greater than 100 AU/ml ($P < 0.001$), with regression coefficients of -4.5 (95% confidence interval [CI]: -6.0 to -2.9) and -7.1 (95% CI: -8.4 to -5.8), respectively. Notably, 8 of 45 patients (18%) with anti-ADA Abs titers from 13 to 100 AU/ml and 2 of 31 patients (6%) with anti-ADA Abs titers greater than 100 AU/ml achieved minimal disease activity ($\text{DAS28} < 3.2$) compared with 95 of 196 anti-ADA Abs-negative ones ($P < 0.001$). Furthermore, 3 of 76 patients (4%) with anti-ADA Abs achieved sustained remission ($\text{DAS28} < 2.6$) compared with 67 of 196 (34%) anti-ADA Abs-negative ones ($P < 0.001$). Papp et al. [69] enrolled 1468 patients with moderate-to-severe chronic plaque psoriasis receiving ADA and investigated the influence of anti-ADA Abs on the therapeutic response. The authors confirmed that the loss of efficacy observed in patients on long-term ADA treatment was associated with the development of anti-ADA Abs. Moreover, van Kuijk et al. [70] and Kneepkens et al. [71] also confirmed the role of anti-ADA Abs in influencing the response to ADA treatment. Karmiris et al. [72] investigated the relationship between serum ADA concentrations and clinical efficacy in 168 CD patients receiving ADA, who were followed up for a period of 2 years: 71% were judged to be responders in week 4 and 67% in week 12, and 61.5% of these presented a sustained clinical benefit until the end of the follow-up. Discontinuations were directly related to low serum through ADA concentrations, which were more frequent in the patients who developed anti-ADA Abs. However, the impact of ADA immunogenicity on the infusion reactions remains still unclear. Benucci et al. [73] enrolled 90 RA patients receiving TNF- α inhibitors and investigated the different incidence of HRs (infusion reactions to IFX and injection site reactions to ADA and etanercept) in atopic patients versus non-atopic patients. Among the 26 patients treated with ADA, only three patients had specific IgE. However, injection site reactions were reported in five patients without specific IgE. These findings confirmed that injection site reactions to ADA are rare with a percentage from 6.6%. [74] Furthermore, Weinblatt et al. [75] reported 15.3% of injection site reactions in patients

receiving ADA plus MTX. The concomitant administration of MTX decreases the production of anti-ADA Abs in patients receiving ADA. Notably, the titer of anti-ADA Abs is much lower in patients receiving higher doses of MTX. [76] Furthermore, cases of urticaria, angioedema and anaphylaxis have been reported in subjects treated with ADA. [77–79] Bartelds et al. [80] confirmed in RA patients that the use of concomitant MTX favored a lower production of anti-ADA Abs compared with the patients receiving ADA monotherapy. Krieckaert et al. [81] demonstrated a clear dose-dependent relationship with MTX and a reduction in anti-ADA Abs production in 272 RA patients receiving ADA. The patients were stratified according to the baseline MTX dose: 70 patients did not receive concomitant MTX, 40 received 5–10 mg/week, 54 received 12.5–20 mg/week and, finally, 108 received ≥ 22.5 mg/week. The ≥ 22.5 mg/week group contained the lowest percentage of patients developing anti-ADA Abs. Garc  s et al. [82] confirmed that immunogenicity of TNF- α inhibitors reduces the therapeutic response to these agents, an effect that is attenuated by the concomitant administration of DMARDs.

4. Effects of anti-IFX and anti-ADA Abs on drug efficacy

Anti-IFX and anti-ADA Abs can reduce treatment efficacy by two possible mechanisms. First, neutralizing anti-IFX and anti-ADA Abs block binding of IFX and ADA to its target, reducing treatment efficacy. Second, binding of both neutralizing and non-neutralizing Abs to IFX and to ADA can result in the formation of immune complexes, which are then cleared from the circulation, reducing the drug's half-life. Kosma   et al. [83] enrolled 21 pediatric patients treated with IFX for the treatment of rheumatic diseases. Nine patients tested positive for anti-IFX Abs, which were predominantly IgG isotype and the majority of the isolated IgG Abs were subtypes IgG1 (36–65%) and IgG4 (20–55%). As IFX is a chimeric human/murine IgG1 mAb, we would assume that neutralizing anti-IFX Abs will be directed against the variable domains that are foreign to the human body. The authors confirmed the ability of anti-IFX Abs to neutralize the binding of IFX Fab fragment to immobilized TNF- α . All serum samples that tested positive for anti-IFX Abs showed neutralizing Abs, while none of the anti-IFX-negative sera and none of the negative control sera showed inhibition of IFX binding. Finally, Abs bound IFX Fab fragment with a 32-fold higher affinity when it was in its native, rather than denatured, form. van Schouwenburg et al. [84] demonstrated in RA patients that the IgG1/IgG4 Abs response to ADA is restricted to the idiotype. Furthermore, the authors also demonstrated that small immune complexes – the size of dimers – between anti-ADA Abs and ADA can be detected in patients 2 weeks after the last injection of ADA, suggesting that these immune complexes are not rapidly cleared from the circulation. The large immune complexes were cleared from the circulation more rapidly than the small complexes. [85] van der Laken et al. [86] confirmed

in RA patients that the size of immune complexes formed between anti-IFX Abs and IFX varies between patients. The authors reported that a patient developed a severe infusion reaction associated with large immune complexes. Indeed, the large immune complexes rather than the small ones are rapidly cleared in the liver, and this affects both the half-life and the efficacy of the drug.

5. Anti-IFX and anti-ADA Abs and delayed type hypersensitivity reactions

Delayed reactions to IFX occur 24 h to 14 days after an infusion and imitate serum sickness, a type III HRs.[87] These tend to be associated with episodic treatment that predisposes to the development of anti-IFX Abs and are generally reported only after repetitive treatment with IFX.[58] However, Ally et al. [88] described a case of delayed HR occurring after the first IFX administration. Steenholdt et al. [40] described a patient with CD who developed an acute severe anaphylactoid reaction (severe malaise and dyspnea, precordial chest pain, tachycardia, urticaria and nausea) after the ninth infusion of IFX and a delayed HR (urticaria involving the whole body, headache, and severe fatigue) 12 days after the first ADA administration. The authors suggested that both reactions were favored by IgG Abs against IFX and ADA. One year after the HRs, the serum levels of both anti-IFX and anti-ADA Abs were reassessed. The anti-IFX IgG Ab serum level was still high, while anti-ADA IgG Ab was undetectable. However, the kinetics by which anti-IFX and anti-ADA Abs are produced remains still largely unexplored. Disappearance of anti-IFX Abs during maintenance treatment has been reported and anti-IFX Abs may have a relatively short half-life after the discontinuation of IFX treatment.[89,90]

6. Expert opinion

TNF- α inhibitors have demonstrated efficacy both as monotherapy and in combination with DMARDs in the treatment of chronic inflammatory immune-mediated diseases. IFX is a chimeric anti-TNF- α mAb containing 25% murine sequences that can induce the secretion of human anti-IFX Abs, favoring the occurrence of adverse reactions and/or gradually leading to loss of therapeutic efficacy. Despite its human structure, ADA may also induce the appearance of anti-ADA Abs. An immune reaction is the primary factor limiting the administration of TNF- α inhibitors. Anti-IFX and anti-ADA Abs may impact the clinical efficacy, depending on whether Abs are neutralizing or non-neutralizing. Neutralizing Abs decrease the possibility of achieving a minimal disease activity state or clinical remission, decrease drug survival, increase the dosage of the drug one needs and, finally, favor the occurrence of adverse events. Anti-IFX and anti-ADA Abs mainly belong to the IgG isotype.

However, the existence of anti-IFX and anti-ADA IgE has been demonstrated. Indeed, a proportion of acute adverse reactions in patients receiving IFX were associated with the appearance of anti-IFX IgE. However, we have to consider the potential role of IgM and IgG isotype in the development of adverse reaction in patients who are anti-IFX IgE negative. Notably, the appearance of anti-IFX IgE Abs is a quite early phenomenon, as confirmed by the fact that IgE-mediated reactions usually occur at the beginning of the treatment, particularly within the first three administrations. However, anti-IFX IgM Abs were found in anti-IFX IgE Abs-negative patients. Furthermore, early appearance of anti-IFX and anti-ADA Abs was associated with subsequent discontinuation of the drugs due to treatment failure and the risk of reaction is relatively high during episodic reinitiation treatment especially at the second infusion. Active inflammation and genetic factors play a key role in the production of anti-IFX Abs, while the patient age seems to play a minimal role in the appearance of anti-IFX Abs. Although ADA is a fully recombinant human IgG1 mAb specific for human TNF- α and less immunogenic than IFX, ADA may induce the production of anti-ADA Abs which are associated with the loss of efficacy in patients on long-term ADA treatment. Indeed, discontinuations were directly related to low serum through ADA concentrations in the patients who developed anti-ADA Abs. The concomitant administration of DMARDs, such as MTX or leflunomide, prevents the development of neutralizing Abs against IFX and ADA. Notably, IgG Abs against IFX and ADA may favor the appearance of delayed hypersensitivity reaction. However, the role of anti-IFX Abs in the appearance of delayed hypersensitivity reactions occurring 3–12 days after infusion remains still unclear. The use of pharmacogenetic testing has the potential to increase drug efficiency by identifying genetic factors responsible for a lack of response to, or toxicities from, TNF- α inhibitors, and could be used to individualize therapy. Indeed, some single-nucleotide polymorphisms such as -308 G/G, -857 C/T, +489 GG and GA, and HLA-DRB1-encoding SE (allele *0404 and allele *0101) have been proven to influence the response to TNF- α inhibitors.[91–93] Large clinical studies are needed to confirm the relevance of these associations in order to tailor treatment and to decrease unnecessary toxicity.

Declaration of interest

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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