

Immunogenicity of Anti-TNF- α Agents in Autoimmune Diseases

Nádia Emi Aikawa · Jozélio Freire de Carvalho ·
Clovis Artur Almeida Silva · Eloísa Bonfá

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Abstract Prognosis of several autoimmune diseases, especially rheumatoid arthritis (RA), ankylosing spondylitis, Crohn's disease (CD), and psoriasis, usually refractory to conventional treatment improved considerably with the introduction of tumor necrosis factor alpha (TNF- α) antagonistic agents, which is now available (infliximab, etanercept, and adalimumab). However, a portion of patients persists with active disease, infusion reactions,

Take-home messages • Anti-human anti-chimeric (anti-HACA) antibodies were described in the majority of diseases treated with anti-TNF. • In some cases, anti-HACA may be associated with poor treatment's response to anti-TNF therapy and high frequency of infusion reactions. • Concomitant use of immunosuppressive drug may reduce anti-HACA production.

N. Emi Aikawa · C. Artur Almeida Silva
Pediatric Rheumatology Unit of Instituto da Criança,
Hospital das Clínicas da Faculdade de Medicina da Universidade
São Paulo University,
São Paulo, Brazil

J. F. de Carvalho · E. Bonfá
Rheumatology Division,
Hospital das Clínicas da Faculdade de Medicina da Universidade
São Paulo University,
São Paulo, Brazil

J. F. de Carvalho (✉)
Rheumatology Division,
Faculdade de Medicina da Universidade de São Paulo,
Av. Dr. Arnaldo, no. 455, 3° andar, sala 3190-Cerqueira César,
São Paulo, São Paulo CEP 05403-010, Brazil
e-mail: jotafe@gmail.com

N. Emi Aikawa · J. F. de Carvalho · C. Artur Almeida Silva ·
E. Bonfá
Centro de Dispensação de Medicação de Alto Custo (CEDMAC),
Hospital das Clínicas da Faculdade de Medicina
da Universidade de São Paulo,
São Paulo, Brazil

and relapses even during current biological therapy. One of the reasons for this is the associated immunogenicity to these drugs. The incentive for induction of antibodies against anti-TNF- α agent depends mainly on its constitution. Chimerical drugs have a higher capacity of inducing immunogenicity compared to completely human drugs. Among the three anti-TNF- α agents, this phenomenon has been studied mainly in patients using infliximab, especially in RA and CD. The prevalence of anti-infliximab antibodies in RA varies from 12% to 44% and seems to be inversely proportional to the level of seric infliximab and therapeutic response. The use of etanercept was associated to the development of anti-etanercept antibodies in 0% to 18% of patients, without apparent effect on effectiveness or adverse events. Studies with RA and CD patients show prevalence of anti-adalimumab antibodies from 1% to 87%. Immunosuppressive drug addiction can reduce the induction of anti-TNF- α antibodies.

Keywords Anti-infliximab · Anti-etanercept ·
Anti-adalimumab · Anti-HACA · Anti-TNF- α ·
Autoimmune disease

Introduction

The clinical and radiologic evolution of rheumatologic diseases, especially of rheumatoid arthritis (RA) and spondyloarthropathies, refractory to conventional treatment with disease-modifying anti-rheumatic drugs improved considerably with the introduction of tumor necrosis factor alpha (TNF- α) antagonistic agents which are now available (infliximab, etanercept, and adalimumab) [1–7]. In moderate to severe Crohn's disease (CD), similarly, the use of these agents improved the prognosis

of patients with refractory response to the conventional therapy [8]. However, about 70% of patients with RA continue with the active disease, or relapses, even during current biological therapy [9]. One of the reasons for this kind of evolution is the immunogenicity associated to these drugs [9–17].

Human anti-chimeric antibody and human anti-human antibody pathophysiology

The immunogenicity of each of the anti-TNF- α agents depends mainly on its constitution. This way, after successive applications, chimerical drugs containing murine particles offer greater capacity of inducing development of antibodies (human anti-chimeric antibodies, HACAs) against the drug in relation to completely human ones [10]. Consequently, a reduction in the effectiveness of long-term treatment or even in the induction of allergic reactions can be observed.

The question is what would lead to the formation of antibodies against anti-TNF- α agents in only one group of patients. Immunogenicity seems to be the result of factors associated to the patient and the treatment [8, 18]. Possibly, the association of immunosuppressors inhibits the formation of these antibodies [3, 8, 19–23].

Ebert et al. [24] demonstrated the presence of innate anti-TNF- α immunoglobulin G (IgG) antibodies in patients with ulcerative colitis and CD with no influence on clinical response to infliximab. The role of these antibodies has not been clarified and just some of them have neutralizing activity. It is also not clear if the presence of these antibodies may stimulate the development of anti-HACA.

Methodologies for anti-HACA and anti-HAHA detection

There are several methodologies to detect HACA. Among them, the enzyme-linked immunosorbent assay (ELISA) technique, which is widely used [10, 17], and the radioimmunoassay stand out [25, 26]. ELISA is more frequently truckle to false-positive tests than antigen-binding assays. The current ELISA method usually uses polyclonal rabbit antibodies, specific for infliximab. The sensitivity of detection is of 0.0003 mg/l [25]. With the method previously used, requiring monoclonal human IgG, human anti-human antibody like the IgG rheumatoid factor, and anti-haplotype antibodies could interfere in the quantification of anti-infliximab antibodies in assays using the solid phase, overestimating its value [27]. However, the exact values of the anti-infliximab concentration are not determined precisely by ELISA because the presence of light kappa infliximab chains in the serum interferes in the

gauging, increasing the proportion of false negatives. In the same way, in the radioimmunoassay, the presence of adalimumab interferes in anti-adalimumab concentration, which could underestimate its real concentration.

Svenson et al. [28] demonstrated anti-infliximab antibodies in 18% of patients with RA using the radioimmunoassay method of the liquid phase against 12% using ELISA.

Anti-infliximab antibodies

Infliximab is a chimerical monoclonal antibody (the peptide sequence is 75% human and 25% mice) against TNF- α . Among the three anti-TNF- α agents used in the treatment of autoimmune diseases, now available on the market, infliximab has been the most studied concerning its immunogenicity. Table 1 displays the frequencies of anti-infliximab antibodies, gauging methods and clinical associations found in literature. Studies demonstrate the prevalence of anti-infliximab antibodies varying from 12% to 44% in patients with RA [4, 11, 13, 26, 28–31]. Aybay et al. [28] reported a case of ankylosing spondylitis (AS) undergoing treatment with infliximab, which developed anti-infliximab antibodies during the period in which the level of seric infliximab was below the detectable value. The prevalence in CD varies between 6% and 61% [8, 20–22, 32–34]. There is a study in literature showing the presence of anti-infliximab antibodies in 37.5% of patients with systemic sclerosis after 26 weeks of treatment with infliximab [35]. Neutralizing anti-HACA has also been detected in cutaneous psoriasis patients [36].

A significant percentage of patients with RA (up to 73%) need an increase in the infliximab dose to obtain an appropriate therapeutic response [11, 37]. Elevated doses of this agent were inversely associated with the frequency of anti-chimerical human antibodies (HACA). In a multi-center placebo-controlled randomized study involving 101 individuals with RA, patients receiving infliximab in doses of 1, 3, and 10 mg/kg presented, after 26 weeks of treatment, positive tests for HACAs in 53%, 21%, and 7%, respectively [19]. Bendtsen et al. [31] demonstrated, in patients with RA, that the prevalence of anti-infliximab antibodies was inversely proportional to the infliximab serum levels during the treatment. Patients with positive HACA needed elevation in the infliximab dose more frequently.

Seric levels of infliximab are importantly reduced in patients with positive HACAs [11, 26], suggesting the neutralization of the action of the drug and the acceleration in the clearance, resulting from the immunocomplex formation. The immunogenicity can occur at an earlier stage, as demonstrated previously in about 45% of the cases, 4 weeks after the first infliximab dose in a group of patients with CD [21].

Table 1 Anti-infliximab antibodies in rheumatoid arthritis

Diseases	Frequency	Methodology of assessment	Serum levels of anti-infliximab/association	References
Rheumatoid arthritis	17.4%	ELISA	Inversely correlated with infliximab dosage and use of MTX	Maini et al. [19]
	39%	ELISA	Younger; less prednisone; higher dose of infliximab	Haraoui et al. [11]
	13% (2 weeks), 30% (3 months), 44% (6 months)	Radioimmunoassay	Low serum levels of infliximab; later dose increase; side effects; cessation of therapy	Bendtzen et al. [31]
	43%	Radioimmunoassay	Less antibody, better response; low serum levels of infliximab	Wolbink et al. [26]
	Not specified	Radioimmunoassay	Higher levels in nonresponder	van der Laken et al. [4]
	18% (fluid-phase RIA), 12% (solid-phase RIA)	Radioimmunoassay	Low serum levels of infliximab	Svenson et al. [28]
	22.2%	Radioimmunoassay	Low serum levels of infliximab	van den Bemt et al. [30]
	41.5%	ELISA	No	van der Bijl et al. [29]
	Not specified	Radioimmunoassay	Less antibody, better response; low serum levels of infliximab	Radstake et al. [23]

Hanauer et al. [22] demonstrated in a prospective study of 573 CD patients that the maintenance of the therapy with infliximab reduces the prevalence of anti-infliximab antibodies from 30% to 7%.

Haraoui et al. [11] studied 33 consecutive patients with RA. Concentrations of anti-infliximab antibodies in patients that needed high doses of the drug to obtain, or maintain, a clinical response were significantly higher in relation to the ones that obtained clinical stability with infliximab in the 3-mg/kg dose every 8 weeks (18.5 versus 7.5 µg/ml; $p < 0.001$). Of the patients that needed an increment of the dose, 47% presented anti-infliximab antibodies.

Despite this, the immunogenicity of the infliximab can be significantly reduced with the simultaneous use of immunosuppressive drugs, among which steroids and methotrexate (MTX) stand out. A study with RA patients showed a frequency of 0% of HACA in patients that received concomitantly infliximab and 7.5 mg/week of MTX versus 7% of these antibodies in patients that were treated only with infliximab [19]. On the other hand, other immunosuppressive drugs, like cyclosporine, azathioprine (AZA), and sulfasalazine, did not have any influence on the development of those antibodies in the RA [24]. In CD, on the other hand, 6-mercaptopurine, AZA, and MTX reduced importantly the incidence of anti-infliximab antibodies [8, 21–23, 34], but no association was found between the use of mesalamine and the development HACAs [20, 21]. Baert et al. [21] found an incidence of 43% of these antibodies in patients taking immunosuppressive agents versus 75% in those who were not taking ($p < 0.01$). Vermeire et al. [20] observed that both MTX and AZA were associated with a lower incidence of HACAs and higher levels of serum infliximab. Similarly, Hanauer et al. 2002 [33] demonstrated that patients with CD receiving steroids and immuno-

modulators concomitantly had lower frequency of HACA compared with those who use steroids alone (6% versus 17%). Farrell et al. [34] demonstrated at the first infliximab infusion an incidence of 24% of HACA in CD patients with concomitant use of immunomodulators versus 63% in patients without it ($p = 0.007$). The influence of steroids is controversial. In the study of Haraoui et al. [11], patients with RA who developed anti-infliximab antibodies were about 10 years younger and used steroids in lower doses. Bendtzen et al. [31], on the other hand, did not find any association in the use of steroids with the anti-HACA prevalence in patients with RA. A controlled randomized study of 53 CD patients showed that 26% of the patients who received premedication with hydrocortisone before the first infusion of infliximab developed HACA versus 42% who received placebo ($p = 0.06$). Hydrocortisone group also had better clinical response but with no statistical difference compared to placebo group [34].

The presence of anti-infliximab antibodies seems to be associated to a higher index of therapeutic failure in RA, AS, and CD [4, 21, 23, 25, 26, 38]. In a study of 51 consecutive patients with RA using infliximab, the HACA-negative patients presented a higher number of responders using the Disease Activity Score in 28 joints (DAS28) versus the positive ones (69% versus 36%; $p = 0.04$) [26]. The relationship between immunogenicity and clinical response to infliximab was evaluated in 38 patients with AS. After 54 weeks of treatment with infliximab, the HACA frequency was significantly higher in patients who did not respond to the 20% response criteria (WING-20) of the assessment of ankylosing spondylitis in relation to the responders ($p < 0.04$). Simultaneously, responder patients presented higher medium levels of serum infliximab ($p <$

Table 2 Anti-infliximab antibodies in other autoimmune diseases

Diseases	Frequency	Methodology of assessment	Serum levels of anti-infliximab/association	References
Ankylosing spondylitis	29%	Radioimmunoassay	Decrease clinical response; low serum levels of infliximab; infusion reaction	de Vries et al. [25]
Crohn's disease	6%	ELISA	No	Targan et al. [32]
	61% (fifth infusion)	ELISA	Lower incidence in concomitant use of immunosuppressives; infusion reaction; shorter duration of response	Baert et al. [21]
	36%	ELISA	Inversely correlated with IV hydrocortisone premedication; infusion reaction; loss of initial response	Farrell et al. [34]
	35.3%	ELISA	Infusion reaction; inversely related to concomitant immunosuppressives	Miele et al. [8]
	10% (5 mg/kg), 7% (10 mg/kg)	–	Lower incidence in concomitant use of immunosuppressives	Hanauer et al. 2004 [22]
	55%	ELISA	Lower incidence in concomitant use of immunosuppressives	Vermeire et al. 2007 [20]
	Not specified	Radioimmunoassay	High levels in nonresponder; possible association with infusion reaction	Ainsworth et al. [38]
Systemic sclerosis	33.3%	ELISA	Possible association with infusion reaction	Denton et al. [35]
Psoriasis	Not specified	Not specified	Possible association with low serum levels of infliximab	Langley et al. [36]

0.01) [25]. In a retrospective study of 33 patients with DC treated with infliximab, the patients' percentage with a maintained therapeutic response was inversely proportional to the levels of the serum anti-infliximab antibody ($p<0.0001$) [38]. In the same way, Farrell et al. [34] demonstrated a higher prevalence of HACA in patients with initial response failure (73%) versus the responders (0%; $p<0.0001$).

A meta-analysis of randomized controlled clinical trials including 301 patients with chronic plaque psoriasis clinical response has declined after prolonged use of infliximab. It was associated to lower serum levels of the anti-TNF- α and partially related to the presence of neutralizing antibodies [36].

Unlike the implications of the clinical effectiveness of the medication, anti-infliximab antibodies do not present a clear influence on the frequency and severity of adverse events [29]. Few studies have demonstrated this possible association. Baert et al. [21] showed that infusion reactions were less frequent in CD patients with higher serum levels of infliximab and in association with other immunomodulators. A study with CD patients showed that among 442

patients incidence of infusion reactions was 16% in positive HACA patients compared to 8% in negative ones [33]. Among 38 patients with AS treated with infliximab, six presented mild infusion reactions, all of them being preceded by the development of anti-infliximab antibodies [25]. Miele et al. [8] found a higher incidence of infusion reactions associated with the presence of anti-infliximab antibodies in a population of children and adults with CD ($p<0.01$). In a study including 53 patients with CD, all seven patients who had serious infusion reactions were positive to HACA [34].

In an attempt to reduce the immunogenicity of infliximab, some protocols may be followed, like the use of induction therapy on weeks 0, 2, and 6 and maintenance infusions every 8 weeks or less and association of other immunosuppressive drugs. In patients in whom delayed reactions or loss of response to infliximab has occurred, the use of commercial assays of infliximab serum levels and HACA may be useful in detecting neutralizing antibodies responsible for lowering infliximab levels [39].

van der Bijl et al. [29] carried out a study evaluating the effectiveness of adalimumab in patients that presented a

Table 3 Anti-etanercept antibodies in autoimmune diseases

Disease	Frequency	Methodology of assessment	Association	References
Rheumatoid arthritis	3%	ELISA	No	Keystone et al. [40]
	5.6%	ELISA	No effect on safety/efficacy	Dore et al. [12]
Ankylosing spondylitis	0	Radioimmunoassay	No	de Vries et al. [42]
Juvenile idiopathic arthritis	8%	Not specified	No	Lovell et al. [41]
Psoriasis	18%	ELISA	No	Tyring et al. [43]

Table 4 Anti-adalimumab antibodies in autoimmune diseases

Disease	Frequency	Methodology of assessment	Association	References
Rheumatoid arthritis	12%	ELISA	Lower ACR20	Van de Putte et al. [9]
	<1%	ELISA	No	Keystone et al. [2]
	87%	ELISA	No	Bender et al. [44]
	17%	Radioimmunoassay	Less improvement in DAS28; low serum levels of adalimumab; bad responders	Bartelds et al. [45]
	1%	ELISA	No	Weinblatt et al. [3]
Crohn's disease	2.6%	Not specified	Absent in concomitant use of immunosuppressives	Sandborn et al. [46]

previous poor response to infliximab and the influence of the presence of anti-infliximab antibodies. The percentage of therapeutic failure to adalimumab was higher among the negative HACA patients. Positive and negative patients for anti-infliximab antibodies reached ACR20 in 16 weeks in 47% and 43%, respectively; however, curiously, only 7% of the negative patients obtained ACR50 versus 47% of the positive patients. Statistical significance of these results was not explained.

There is no evidence to affirm that anti-infliximab antibodies react to the other anti-TNF- α agents. Therefore, its presence does not contraindicate the switch of drugs in the same class [29].

Anti-infliximab antibodies in RA and other autoimmune diseases are shown in Tables 1 and 2.

Anti-etanercept antibodies

Etanercept is a dimeric fusion protein with a constant region of human IgG1 and variable regions of mouse antibody. It seems to be less immunogenic than infliximab. In patients with RA, the frequency of anti-etanercept antibodies was demonstrated in 2% to 5.6% [12, 40] (Table 3). No study however showed a clear association of these antibodies formation and lower clinical response. Lovell et al. [41] demonstrated the frequency of 8% of

these antibodies in 25 patients with juvenile idiopathic arthritis. None of the antibodies were neutralizers, i.e., they did not have any effect on the action of the drug and they did not interfere in its profile of safety. In a study involving 214 patients with RA, 12 of them (5.6%) presented, after using etanercept for 24 weeks, antibodies against the positive anti-TNF- α by immunoassay, with low titles (<1:50) in seven of them [12]. A lower prevalence (3%) was observed in a multicenter randomized placebo-controlled study with 16-week duration, without influence from the frequency of the weekly etanercept (one or two doses of 25 mg).

In a study of 53 consecutive patients with AS treated with etanercept, none presented positivity for anti-etanercept antibody after 6 months of therapy. Serum levels of etanercept did not differ between responders and nonresponders [42].

Tyring et al. [43] evaluated 464 patients with psoriasis treated with etanercept and observed a high prevalence (18.3%) of nonneutralizing anti-etanercept antibodies during the study, without any influence on clinical response and adverse events. The positivity of the test is highly dependent on the sensitivity and specificity of the method used, besides the influence of the base disease and associated medications.

Table 3 shows the frequency of anti-etanercept in autoimmune diseases.

Anti-adalimumab antibodies

Although adalimumab, as well as the infliximab, is a monoclonal antibody that blocks the TNF- α molecule directly, its completely human composition makes it apparently less immunogenic. However, immunogenicity of the adalimumab has already been mentioned, possibly related to the development of anti-idiotypal antibodies not directed to the human particles of the drug [44]. The cumulative incidence of anti-adalimumab antibodies in patients with RA varies from 6% to 87% [2, 3, 13, 44, 45] (Table 3). In a study of 209 patients with RA treated with adalimumab (20, 40, or 80 mg every 2 weeks), in association with MTX (average dose of 16.7 mg/week), the

Table 5 Autoimmune diseases where anti-TNF- α was used and anti-human anti-chimeric (anti-HACA) antibodies were not studied

Autoimmune diseases
Psoriatic arthritis
Wegener's granulomatosis
Behcet's disease
Idiopathic uveitis
Still's disease
Inflammatory myopathies
Juvenile systemic lupus erythematosus
Sarcoidosis

values were reduced to <1% (2/209) [3]. The percentage of patients in the concomitant use of MTX was dramatically higher in negative patients with anti-adalimumab versus positive ones (84% versus 52%; $p=0.003$) [45]. Bartelds et al. [45] detected antibodies in 17% (21/121) of patients. Higher concentrations (above 100 AU/ml) were found in 52% of the 21 positive patients with anti-adalimumab. A study with a small population of patients with active RA obtained a frequency of 87% (13/15) in anti-adalimumab antibodies, detected in low levels, through optic density, in 65% of them [44].

The correlation between the immunogenicity of adalimumab and the effectiveness of the drug is controversial. Of the 15 patients with RA using adalimumab, 60% did not present significant improvement in the disease activity score (DAS28). All of them were positive for anti-adalimumab antibodies [44]. In a population of 121 patients with RA, those presenting positive anti-adalimumab antibodies obtained a dramatically worse clinical response in relation to the negative ones, even after sex and MTX dose adjustment. Besides, serum adalimumab concentrations were dramatically lower in patients with anti-adalimumab antibodies (average of 1.2 mg/l in the positive versus 11.0 mg/l in the negative; $p<0.001$) [45]. This evidence is possibly a result of increasing the clearance of the drug after immunocomplex formation. On the other hand, in a double-blind placebo-controlled study including 544 patients with RA, van de Putte et al. [13] did not observe a statistically significant difference in the response to the ACR20 among positive and negative patients with anti-adalimumab, when the drug was used in the recommended dose of 40 mg, every 2 weeks.

In the same way, the influence of the presence of anti-adalimumab antibodies and the development of adverse reactions to the drug are not clear. Bender et al. [44] observed that 85% (11/13) of the patients with RA who interrupted the use of adalimumab presented antibodies against the drug.

Sandborn et al. [46] found anti-adalimumab antibodies in 2.6% of the 269 patients with CD treated with this anti-TNF- α . In the group of 84 patients that used other immunosuppressive drugs simultaneously, none of them presented positivity for the antibody.

Anti-adalimumab antibodies in autoimmune diseases are shown in Table 4.

Other autoimmune diseases treated with anti-TNF- α

There are no studies about the prevalence of anti-TNF- α antibodies in psoriatic arthritis, Wegener's granulomatosis, Behcet's disease, idiopathic uveitis, Still's disease, inflammatory myopathies, juvenile systemic lupus erythematosus, and sarcoidosis (Table 5).

Conclusion

The clinical meaning of the presence of antibodies acting against the anti-TNF- α agents has not been explained in detail. It seems that the immunogenicity of these drugs is greater in CD than in RA. The concept of the occurrence of immune responses to less immunogenic polypeptides in infectious conditions may be an explanation to this finding.

The positivity of anti-infliximab antibodies can suggest, in RA and in CD, a worse therapeutic response and a higher risk of occurrence of infusion reactions. During the treatment with etanercept and adalimumab, on the other hand, such inference does not seem true. These differences can be explained by the drug conformation itself and also by the characteristics of diseases and use of different assay methods used for measuring antibodies.

The immunological tolerance to infliximab and adalimumab can be induced by the concomitant use of immunosuppressive drugs, like AZA and MTX, even in low doses, and promoted, in the case of infliximab, using high drug doses. Such effect could possibly benefit the treatment with other chimerical or merely pure human antibodies. There is no evidence that an anti-HACA antibody specifically for an anti-TNF- α reacts against other anti-TNF- α agents. Therefore, its presence does not contraindicate the substitution of drugs in the same class.

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Competing interest None

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