Prevalence of TNF-α Blocker Immunogenicity in Psoriatic Arthritis

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ABSTRACT. ***Objective.*** The longterm use of tumor necrosis factor (TNF)-α blockers is limited by the formation of neutralizing antibodies. To the best of our knowledge, immunogenicity in psoriatic arthritis (PsA) has not been investigated in depth. Our objective was to evaluate the prevalence and significance of TNF-α blocker immunogenicity in PsA.

Methods. Consecutive patients with PsA treated with either infliximab (IFX), adalimumab (ADA), or etanercept (ETN) > 3 months participated in our cross-sectional study. Their demographic and clinical characteristics, skin and joint disease activity, and records of use of methotrexate (MTX) and other medications were collected. Drug levels (ELISA) and antidrug antibodies (ADAb; Bridging ELISA) were evaluated before the next injection or infusion.

Results. A total of 93 patients with PsA were recruited (48 receiving ADA, 24 IFX, and 21 ETN), with a mean age of 53 years (range 21–83 yrs), composed of 53% women. One-fourth of the patients were concomitantly treated with MTX. Altogether, 77% of the patients demonstrated therapeutic drug levels. High levels of ADAb were found in 29% of patients taking ADA, 21% taking IFX, and 0% taking ETN. ADAb significantly correlated with lower drug levels, higher 28-joint Disease Activity Scores, and higher global assessments. MTX use correlated significantly with a lower prevalence of ADAb.

Conclusion. Significant levels of ADAb were present in up to 29% of patients with PsA treated with ADA or IFX. ADAb clearly correlated with low therapeutic drug levels and higher disease activity variables. The use of MTX significantly decreased ADAb prevalence, and its use should be strongly considered in combination with TNF-α blocker antibodies in patients with PsA. (J Rheumatol First Release Nov 15 2014; doi:10.3899/jrheum.140685)

Key Indexing Terms:

PSORIATIC	ARTHRITIS	IMMUNOGENICITY
INFLIXIMAB	ETANERCEPT	ADALIMUMAB

The management of psoriatic arthritis (PsA) has been revolutionized by the use of tumor necrosis factor (TNF)-α blockers, such as infliximab (IFX), adalimumab (ADA), etanercept (ETN), and others[1]. Moreover, while in the past the use of TNF-α blockers was restricted in some chronic infections, such as latent tuberculosis (TB) and hepatitis C virus (HCV) positivity, today its use is no longer limited and its longterm administration is safe with proper chemoprophylaxis (latent TB) and close monitoring (HCV), as demonstrated by several reports[2,3]. Despite the ability of those agents to decrease disease activity, their longterm effect is limited in some patients. Limited drug efficacy in patients with rheumatoid arthritis (RA), ankylosing spondylitis (AS), and inflammatory bowel disease (IBD) has been partially attributed to the development of immunogenicity[4,5,6]. The creation of antibodies against anti-TNF-α drugs has been associated with low levels of TNF-α blockers[7,8], hypersensitivity reactions[9,10], and decreased therapeutic response (i.e., loss or absence of effect)[11,12,13]. The immunogenicity phenomenon has been described against monoclonal antibodies to TNF-α (IFX and ADA)[14] and rarely to the soluble receptor (ETN)[11,15,16,17,18,19,20,21].

The prevalence of antidrug antibodies (ADAb) in RA is between 20–40%, and it is reportedly reduced significantly by the use of methotrexate (MTX)[11,12,19,22,23,24,25,26]. Similar prevalence levels, and some even higher (up to 61%) have been described in patients with IBD, especially in Crohn disease (CD), while concomitant MTX and azathioprine (AZA) were shown to attenuate immuno-

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genicity[5,27,28,29]. Studies on AS reported an ADAb prevalence of 25–64%[6,13,18,30,31,32]. About one-third of patients with psoriasis who were treated with IFX as monotherapy developed human antichimeric antibodies that were associated with a decreased therapeutic response[18,33,34,35]. It has been suggested that fixed time intervals between injections might reduce immunogenicity[22]. In addition, the effect of a simultaneous use of MTX was evaluated on a small number of patients, and the results indicated a reduced immunogenicity and an improvement of the clinical response[36].

It appears that the immunogenicity of TNF-α blockers in PsA has not been thoroughly investigated. To the best of our knowledge, the only study that directly addressed this subject included 22 patients with PsA who were treated with ADA and had an ADAb prevalence of 18% that was associated with a decreased clinical response and low drug level[37]. Kavanaugh, *et al*'s earlier study on 200 patients with PsA (the Infliximab Multinational Psoriatic Arthritis Controlled Trial 2) was a phase III randomized controlled trial that evaluated safety and efficacy in patients with PsA receiving IFX, although it did not specifically evaluate immunogenicity[38]. Their results demonstrated an ADAb prevalence of 15% (26% in patients not taking MTX and 3.6% in patients taking concomitant MTX, not analyzed statistically).

MTX is the main immunomodulatory drug that moderates immunogenicity[18,19,36,39,40,41]. AZA attenuates immunogenicity in IBD similarly to MTX[18,42,43,44], but this has not been reported in rheumatologic conditions such as RA, spondyloarthropathies (SpA), and psoriasis[18]. Moreover, there is insufficient evidence to support the role of other disease-modifying antirheumatic drugs (sulfasalazine, leflunomide, hydroxychloroquine, and cyclosporine A) or prednisolone in moderating ADAb formation[18,39]. The goals of our present study were to evaluate the prevalence of TNF-α blocker immunogenicity in PsA and its correlation to drug levels, disease activity, and the effect of concomitant use of MTX.

MATERIALS AND METHODS

Study design. We conducted a cross-sectional study (transversal analyses) on 93 patients with PsA treated with IFX, ADA, or ETN. The primary endpoint was the prevalence of ADAb to TNF-α blockers in PsA. The secondary endpoints were (1) the correlation between the presence of immunogenicity and drug levels, (2) demographic and clinical features (including disease activity scores), and (3) the effect of concomitant use of MTX. Patients' enrollment was at the trough level of the anti-TNF-α drug, i.e., just before the next administration of the anti-TNF drug. Clinical assessment was performed and blood was drawn at this timepoint.

Study participants. The study was composed of consecutive patients with PsA according to the Classification for Psoriatic Arthritis criteria. They were aged above 18 years, and were undergoing intravenous IFX 5 mg/kg treatment according to the standard protocol, subcutaneous ADA 40 mg every other week, or SC ETN 50 mg/week. Patients who had been treated with IFX, ADA, or ETN for less than 3 months or who were receiving other TNF-α antagonists were excluded from the study.

Demographic data. Clinical data included the pattern of the PsA arthropathy, duration of psoriasis and PsA, comorbid conditions, and current drugs being taken (including MTX) and their dosage. Assessment of disease activity included the 28-joint Disease Activity Score (DAS28), pain evaluation using a visual analog scale (VAS) of 100 mm, the Psoriasis Area and Severity Index (PASI), and the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). Blood was drawn for analyses of the erythrocyte sedimentation rate, anti-TNF-α drug level, and ADAb.

Assessment of drug levels and ADAb. The drug level was measured by ELISA (Promonitor commercial kit of the Progenika Biopharma group) and expressed in microgram per milliliter (μg/ml). The IFX detection threshold was 0.035 μg/ml: levels < 0.035 μg/ml were considered non-detectable, levels 0.035–1.5 μg/ml were considered subtherapeutic, and levels > 1.5 μg/ml were considered therapeutic. Those ranges were derived from clinical studies mainly in RA (and fewer in CD)[44,45], including a study done by means of the Promonitor kit on 78 patients with RA for whom there were 612 blood samples. The detection threshold of ADA was 0.024 μg/ml: levels < 0.024 μg/ml were considered undetectable, levels 0.024–0.8 μg/ml were considered subtherapeutic, and levels > 0.8 μg/ml were considered therapeutic. Those ranges are derived from clinical studies[45], including 1 done by means of the Promonitor kit on 51 patients with RA for whom there were 171 blood samples. The ETN detection threshold was 0.035 μg/ml. There are no therapeutic ranges because of the lack of data: levels < 0.035 μg/ml were considered undetectable and levels > 0.035 μg/ml were considered positive responses.

ADAb and their concentrations were tested by Bridging ELISA (Promonitor). Concentrations were expressed in absorbance units per milliliter (Au/ml). The anti-IFX antibodies detection threshold was 2 Au/ml. We defined a high concentration as the value of the threshold multiplied by 14, i.e., 28 Au/ml. The anti-ADA antibodies detection threshold was 3.5 Au/ml, and a high concentration was defined as a value of the threshold multiplied by 14, i.e., 50 Au/ml. The anti-ETN antibodies detection threshold was 142 Au/ml, and a high concentration was defined as a value of the threshold multiplied by 14, i.e., 2000 Au/ml.

It is noteworthy that high concentration of ADAb ("high" ADAb) is a term mainly used for anti-ADA antibodies. The customary value of a high concentration of antidrug antibodies is above 100 Au/ml for the radioimmunoassay (RIA) test, which is a multiplier of 8.5 from the threshold of positive test, which is 12 Au/ml[19,32]. To date, there is no data known to us that defines high ADAb in the Bridging ELISA test. According to the statistical distribution of ADAb in our study participants, and since the threshold of Bridging ELISA test for positive anti-ADA antibodies is 3.5 Au/ml, we defined high concentration as 50 Au/ml, using a multiplier of 14. We used rougher values with a multiplication by 14 (and not by 8.5) because Bridging ELISA is less accurate than RIA[46,47]. Indeed, these values were arbitrarily determined, but rationally and according to our participants' ADAb levels distribution. A recent paper by Chen, *et al* has shown good concordance between RIA and Bridging ELISA, although again RIA was more accurate[48].

Statistical analysis. Statistical processing was done by Excel (Microsoft Corp.) and SPSS (version 14, IBM Corp.) software. We used the Pearson chi-square test, Fisher's exact test, and Spearman rank correlation coefficient test to obtain correlations between variables. The Student t test and ANOVA were used to compare the means of variables with normal distributions. Medians of variables without normal distribution were tested using the Mann-Whitney U test and Kruskal-Wallis test. A p value < 0.05 was considered statistically significant.

RESULTS

Demographic and clinical characteristics of the participants. Between March 2011 and April 2013, 93 patients with PsA were recruited into our study. Their mean age was 53 years (range 21–83 yrs), and 53% of the subjects were

women. The mean durations of the skin disease and the arthropathy were 21 years and 15 years, respectively. The most common pattern of disease was peripheral polyarthritis (48.5%), followed by combined axial and peripheral (23.5%), oligoarthritis (21.5%), and pure axial (7.5%). Forty-eight patients were taking ADA (51.6%), 24 were taking IFX (25.8%), and 21 were taking ETN (22.6%). About one-fourth of the patients (25.8%) were concomitantly taking MTX at an average weekly dosage of 13.3 mg (Table 1).

Table 2 summarizes the variables of disease activity. The mean DAS28 was 3.4 (moderate disease activity), the mean VAS was 27, the mean BASDAI was 3.95 (moderate to severe), and the mean PASI was 3.5 (mild). Patients receiving ETN presented a significantly milder degree of PsA, while IFX-treated patients had a more severe disease form according to DAS28. Patients treated with ADA had higher levels on the BASDAI. The severity of skin disease (by PASI) was similar for all medication groups.

ADAb prevalence and drug levels. The prevalence of immunogenicity in the whole group was 33.3% (Table 3). One-fifth of the patients had high concentrations of antibodies. None of the members of the ETN group had ADAb. Analysis of the levels of antibodies in the ADA group yielded 2 groups of patients: 54% of the entire group developed ADAb, but only 29% had high ADAb concentrations. ADAb to IFX was found in 21% of the IFX-treated patients, and all of them had high concentrations of antibodies. All of the patients taking ETN demonstrated therapeutic drug levels compared with 79% of the ADA-treated patients and 54% of the IFX-treated patients.

Correlations between immunogenicity and drug levels. The presence of ADAb and high ADAb concentrations significantly correlated with nontherapeutic drug levels: 45% of ADAb-positive patients and 63% of high ADAb patients had nontherapeutic drug levels comparing to only 11% of patients without ADAb. Patients with ADAb (high and low titers) concentrations had a significantly higher DAS28 (3.9 and 4.1, respectively, compared with a score of only 3.2 in patients without ADAb) and a higher VAS (36 and 42, respectively, compared with a score of only 23). There was a trend toward a higher PASI, younger age, and male sex in the ADAb-positive patients; those values did not reach a level of significance (Table 4 and Table 5). The DAS28, VAS, and PASI scores were lower in patients with therapeutic drug levels compared to patients with nontherapeutic drug levels (3.3 vs 3.8, 25 vs 35, and 2.7 vs 6, respectively), but those values did not reach a level of statistical significance.

The effect of MTX on immunogenicity. One-fourth of the study subjects were treated concomitantly with MTX at a mean dosage of 13.3 mg/week. The MTX-treated patients were significantly older (59 yrs vs 51.5 yrs, p = 0.024). The MTX-treated patients had significantly fewer ADAb (i.e., 16.7% vs 39.1%, p = 0.049; Table 6). Moreover, fewer MTX-treated patients had high ADAb concentration (16.7% compared to 21.7% for the non-MTX patients). There was a nonsignificant trend toward a higher proportion of patients with therapeutic drug levels among the MTX-treated patients (92% vs 72.5% for the non-MTX patients). Interestingly, the MTX-treated patients had a higher DAS28 than the non-MTX patients (4 vs 3.2, p = 0.02).

Table 2. Variables of disease activity.

Group	DAS28	VAS	PASI	BASDAI
All patients	3.4	27	3.5	3.95
Infliximab	3.8	32	3.4	4.03
Adalimumab	3.4	30	3.5	4.4
Etanercept	2.9	16	3.5	2.25

DAS28: 28-joint Disease Activity Score; VAS: visual analog scale; PASI: Psoriasis Area and Severity Index; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index.

Table 3. Drug levels and antibodies prevalence. Values are %.

Group	Therapeutic Drug Level	Prevalence of ADAb	Prevalence of High Concentrations of ADAb
All patients	77.4	33.3	20.4
Infliximab	54.2	20.8	20.8
Adalimumab	79.2	54.2	29.2
Etanercept	100	0	0

ADAb: antidrug antibodies.

Table 1. Clinical and demographic data.

Group	Patients, n	Mean Age, Yrs	Female Sex, %	Disease Pattern (poly, oligo, axial, combined, %)	Arthritis Duration, Yrs	Psoriasis Duration, Yrs	MTX, % of Patients (mg/week)
All patients	93	53.4	52.7	48.5, 21.5, 7.5, 22.6	15	20.8	25.8 (13.3)
Infliximab	24	50.9	45.8	50, 8.3, 8.3, 33.3	14	21.6	20.8 (14.5)
Adalimumab	48	53.8	54.2	45.8, 25, 8.3, 20.8	16.5	21.4	33.3 (13.2)
Etanercept	21	55.4	57.1	52.4, 28.6, 4.8, 14.3	12.5	18.4	14.3 (11.7)

Poly: polyarthritis; oligo: oligoarthritis; MTX: methotrexate.

Table 4. Correlation between demographic and clinical data and the presence of antibodies.

Variable	ADAb–negative	ADAb–positive	p
Age, yrs	55	50	0.083
Female sex	59.7%	38.7%	0.08
Therapeutic drug level	88.7%	54.8%	0.0005*
DAS28	3.17	3.9	0.023*
VAS	23	36	0.018*
PASI	2.9	4.6	0.15
BASDAI	4	3.9	0.94
Concomitant MTX	32.3%	12.9%	0.049

* Significant data. ADAb: antidrug antibodies; DAS28: 28-joint Disease Activity Score; VAS: visual analog scale; PASI: Psoriasis Area and Severity Index; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; MTX: methotrexate.

Table 5. Correlation between demographic and clinical data to antibodies concentration levels.

Variable	Negative or Low Concentration of ADAb	High Concentration of ADAb	p
Age, yrs	54.5	49	0.15
Female sex	56%	42%	0.32
Therapeutic drug level	88%	37%	0.0005*
DAS28	3.2	4.1	0.024*
VAS	24	42	0.0005*
PASI	2.9	5.7	0.11
BASDAI	3.7	5	0.37
Concomitant MTX	27%	21%	0.77

* Significant data. ADAb: antidrug antibodies; DAS28: 28-joint Disease Activity Score; VAS: visual analog scale; PASI: Psoriasis Area and Severity Index; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; MTX: methotrexate.

Table 6. Correlations between concomitant MTX use and immunogenicity, and drug level and demographic and clinical data.

Variable	Non-MTX	MTX	p
Patients, n (%)	69 (74)	24 (26)	—
Age, yrs	51.5	59	0.024*
Female sex	49.3%	62.5%	0.34
ADAb-positive	39.1%	16.7%	0.049*
High ADAb concentration	21.7%	16.7%	0.77
Therapeutic drug level	72.5%	91.7%	0.086
DAS28	3.2	4	0.02*
VAS	26	31	0.45
PASI	3.5	3.5	0.99
BASDAI	3.6	6	0.17

* Significant data. MTX: methotrexate; ADAb: antidrug antibodies; DAS28: 28-joint Disease Activity Score; VAS: visual analog scale; PASI: Psoriasis Area and Severity Index; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index.

DISCUSSION

TNF blockers have had an enormous effect on the treatment, course of disease, and prognosis of SpA, including PsA. Indeed, these biologic drugs represent a breakthrough in the management of these conditions. However, the use of these agents has been limited by the phenomenon of immunogenicity, which might induce low drug levels and decreased clinical response in RA, AS, and IBD.

The results of our cross-sectional study have demonstrated that the phenomenon of immunogenicity is limited to IFX and ADA in patients with PsA. The results showed that it reaches a level of up to 50% in ADA-treated patients (29% with high levels), 21% in IFX-treated patients, and none in ETN-treated patients. A clear correlation was found between the presence of immunogenicity, drug levels, and clinical response. The use of MTX significantly decreased the proportion of ADAb.

Our results are similar to the prevalence of immunogenicity in RA[11,22,23]. As others had found in RA[11,12], we observed a correlation between ADAb and low drug levels and decreased clinical response. Interestingly, the effect of immunogenicity in our study was more prominent in active peripheral arthritis, as reflected by DAS28, than in axial arthropathy, as reflected by BASDAI.

Another important finding in our study was the clearly reduced immunogenicity in patients who were also receiving MTX, as had been shown in RA[22,23]. While the concomitant use of MTX with monoclonal antibodies is indicated in RA, there are no similarly clear recommendations in PsA. Our results suggest that the use of MTX should be strongly considered in addition to monoclonal antibodies.

Noteworthy, the patients taking ADA demonstrated an immunogenicity of 54%, but only half of them (29%) showed high concentrations of antibodies. This finding suggests that a variety of levels might be found that might affect the significance of immunogenicity differently among patients producing ADAb.

Most of the known literature about immunogenicity of SpA is in the setting of AS, where its prevalence is about 25%, with correlations between monoclonal ADAb and low drug levels, decreased clinical response, and a high rate of injection-induced hypersensitivity reactions[6,13,31]. A recent trial by Kneepkens, *et al* demonstrated an ADAb prevalence of 27% with a correlation to decreased clinical response in patients treated with ADA[32]. Moreover, those authors found, as we did, a correlation between high ADAb concentrations and decreased clinical response in ADA-treated patients. Studies of immunogenicity in patients with psoriasis demonstrated that ADAb is correlated to IFX and ADA, but not to ETN. Its prevalence was up to one-third, and there was a correlation to decreased drug levels and decreased therapeutic response[33,34,35,42,49]. The concomitant use of MTX reduced ADAb prevalence in SpA and psoriasis, but

unlike RA, it is not clear whether it improved anti-TNF efficacy[18]. On the other hand, attenuating anti-TNF immunogenicity may be even more crucial because there are fewer alternative classes of biologics to use in the event of treatment failure.

Our study has several limitations. It is cross-sectional and based on a relatively small number of patients. The evaluation of ADAb was performed using Bridging ELISA, which is reliable, but considered to be less accurate than RIA[46,47,48]. Likewise, the evaluation of disease activity was based on DAS28, which might not be ideal in PsA.

Similar to RA, the phenomenon of immunogenicity is present in PsA as well, with a prevalence of up to 50%. Immunogenicity clearly affected the therapeutic effect of the monoclonal antibodies and seemed to be attenuated by the concomitant use of MTX. Large-scale studies are warranted to confirm our observations.

REFERENCES

1. Cantini F, Niccoli L, Nannini C, Kaloudi O, Bertoni M, Cassarà E. Psoriatic arthritis: a systemic review. Int J Rheum Dis 2010; 13:300-17.
2. Atteno M, Costa L, Matarese A, Caso F, Del Puente A, Cantarini L, et al. The use of TNF-α blockers in psoriatic arthritis patients with latent tuberculosis infection. Clin Rheumatol 2014;33:543-7.
3. Costa L, Caso F, Atteno M, Giannitti C, Spadaro A, Ramonda R, et al. Long-term safety of anti-TNF-α in PsA patients with concomitant HCV infection: a retrospective observational multicenter study on 15 patients. Clin Rheumatol 2014;33:273-6.
4. Baert F, De Vos M, Louis E, Vermeire S; Belgian IBD Research Group. Immunogenicity of infliximab: how to handle the problem? Acta Gastroenterol Belg 2007;70:163–70.
5. Pendley C, Schantz A, Wagner C. Immunogenicity of therapeutic monoclonal antibodies. Curr Opin Mol Ther 2003;5:172–9.
6. Aybay C, Ozel S, Aybay C. Demonstration of specific antibodies against infliximab induced during treatment of a patient with ankylosing spondylitis. Rheumatol Int 2006;26:473–80.
7. Sethu S, Govindappa K, Alhaidari M, Pirmohamed M, Park K, Sathish J. Immunogenicity to biologics: mechanisms, prediction and reduction. Arch Immunol Ther Exp 2012;60:331-44.
8. Aarden L, Ruuls SR, Wolbink GJ. Immunogenicity of anti-tumor necrosis factor antibodies-toward improved methods of anti-antibody measurement. Curr Opin Immunol 2008;20:431-5.
9. Cheifetz A, Mayer L. Monoclonal antibodies, immunogenicity and associated infusion reactions. Mt Sinai J Med 2005;72:250–6.
10. Baret F, Noman M, Vermeire S, Van Assche G, D'Haens G, Carbonez A, et al. Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. N Engl J Med 2003;348:601-8.
11. Radstake TR, Svenson M, Eijsbouts AM, van den Hoogen FH, Enevold C, van Riel PL, et al. Formation of antibodies against infliximab and adalimumab strongly correlates with functional drug levels and clinical responses in rheumatoid arthritis. Ann Rheum Dis 2009;68:1739-45.
12. Wolbink GJ, Vis M, Lems W, Voskuyl AE, de Groot E, Nurmohamed MT, et al. Development of antiinfliximab antibodies and relationship to clinical response in patients with rheumatoid arthritis. Arthritis Rheum 2006;54:711–5.
13. de Vries MK, Wolbink GJ, Stapel SO, de Vrieze H, van Denderen JC, Dijkmans BA, et al. Decreased clinical response to infliximab in ankylosing spondylitis is correlated with anti-infliximab formation. Ann Rheum Dis 2007;66:1252–4.
14. Bartelds GM, Wolbink GJ, Stapel S, Aarden L, Lems WF, Dijkmans BA, et al. High levels of human anti-human antibodies to adalimumab in a patient not responding to adalimumab treatment. Ann Rheum Dis 2006;65:1249-50.
15. Jamnitski A, Krieckaert CL, Nurmohamed MT, Hart MH, Dijkmans BA, Aarden L, et al. Patients non-responding to etanercept obtain lower etanercept concentrations compared with responding patients. Ann Rheum Dis 2012;71:88-91.
16. Krieckaert CL, Jamnitski A, Nurmohamed MT, Kostense PJ, Boers M, Wolbink G, et al. Comparison of long-term clinical outcome with etanercept treatment and adalimumab treatment of rheumatoid arthritis with respect to immunogenicity. Arthritis Rheum 2012;64:3850-5.
17. de Vries MK, van der Horst-Bruinsma IE, Nurmohamed MT, Aarden LA, Stapel SO, Peters MJ, et al. Immunogenicity does not influence treatment with etanercept in patients with ankylosing spondylitis. Ann Rheum Dis 2009;68:531-5.
18. Jani M, Barton A, Warren RB, Griffiths CE, Chinoy H. The role of DMARDs in reducing the immunogenicity of TNF inhibitors in chronic inflammatory diseases. Rheumatology 2014;53:213-22.
19. Aikawa NE, de Carvalho JF, Almeida Silva CA, Bonfa E. Immunogenicity of anti-TNF agents in autoimmune diseases. Clinic Rev Allerg Immunol 2010;38:82-9.
20. Atzeni F, Talotta R, Salaffi F, Cassinotti A, Varisco V, Battellino M, et al. Immunogenicity and autoimmunity during anti-TNF therapy. Autoimmun Rev 2013;12:703-8.
21. Klareskog L, Gaubitz M, Rodríguez-Valverde V, Malaise M, Dougados M, Wajdula J; Etanercept Study 301 Investigators. Assessment of long-term safety and efficacy of etanercept in a 5-year extension study in patients with rheumatoid arthritis. Clin Exp Rheumatol 2011;29:238-47.
22. Maini RN, Breedveld FC, Kalden JR, Smolen JS, Davis D, Macfarlane JD, et al. Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor alpha monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. Arthritis Rheum 1998;41:1552-63.
23. Bartelds GM, Wijbrandts CA, Nurmohamed MT, Stapel S, Lems WF, Aarden L, et al. Clinical response to adalimumab: relationship to anti-adalimumab antibodies and serum adalimumab concentrations in rheumatoid arthritis. Ann Rheum Dis 2007;66:921-6.
24. Ollendorf DA, Massarotti E, Birbara C, Burgess SM. Frequency, predictors, and economic impact of upward dose adjustment of infliximab in managed care patients with rheumatoid arthritis. J Manag Care Pharm 2005;11:383-93.
25. St Clair EW, Wagner CL, Fasanmade AA, Wang B, Schaible T, Kavanaugh A, et al. The relationship of serum infliximab concentrations to clinical improvement in rheumatoid arthritis: results from ATTRACT, a multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2002;46:1451-9.
26. Pascual-Salcedo D, Plasencia C, Ramiro S, Nuño L, Bonilla G, Nagore D, et al. Influence of immunogenicity on the efficacy of long-term treatment with infliximab in rheumatoid arthritis. Rheumatology 2011;50:1445-52.
27. Cassinotti A, Travis S. Incidence and clinical significance of immunogenicity to infliximab in Crohn's disease: a critical systematic review. Inflamm Bowel Dis 2009;15:1264-75.
28. Sandborn W. Preventing antibodies to infliximab in patients with Crohn's disease: optimize not immunize. Gastroenterology 2003;124:1140–5.
29. Rutgeerts P, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, et al. Comparison of scheduled and episodic treatment strategies of infliximab in Crohn's disease. Gastroenterology 2004;126:202–13.
30. de Vries MK, Wolbink GJ, Stapel SO, de Groot ER, Dijkmans BA,

Aarden LA, et al. Inefficacy of infliximab in ankylosing spondylitis is correlated with antibody formation. Ann Rheum Dis 2007;66:133–4.
31. Ducourau E, Mulleman D, Paintaud G, Miow Lin DC, Lauféron F, Ternant D, et al. Antibodies toward infliximab are associated with low infliximab concentrations at treatment initiation and poor infliximab maintenance in rheumatic diseases. Arthritis Res Ther 2011;13:R105.
32. Kneepkens EL, Wei JC, Nurmohamed MT, Yeo KJ, Chen CY, van der Horst-Bruinsma IE, et al. Immunogenicity, adalimumab levels and clinical response in ankylosing spondylitis patients during 24 weeks of follow up. Ann Rheum Dis 2013 Dec 10 (E-pub ahead of print).
33. Adisen E, Aral A, Aybay C, Gürer MA. Anti-infliximab antibody status and its relation to clinical response in psoriatic patients: a pilot study. J Dermatol 2010;37:708–13.
34. Menter A, Feldman SR, Weinstein GD, Papp K, Evans R, Guzzo C, et al. A randomized comparison of continuous vs. intermittent infliximab maintenance regimens over 1 year in the treatment of moderate-to-severe plaque psoriasis. J Am Acad Dermatol 2007;56:1–15.
35. Cozzani E, Burlando M, Parodi A. Detection of antibodies to anti-TNF agents in psoriatic patients: a preliminary study. G Ital Dermatol Venereol 2013;148:171-4.
36. Lecluse LL, Druesseb RJ, Spuls PI, de Jong EM, Stapel SO, van Doorn MB, et al. Extent and clinical consequences of antibody formation against adalimumab in patients with plaque psoriasis. Arch Dermatol 2010;146:127-32.
37. van Kuijk AW, de Groot M, Stapel SO, Dijkmans BA, Wolbink GJ, Tak PP. Relationship between the clinical response to adalimumab treatment and serum levels of adalimumab and anti-adalimumab antibodies in patients with psoriatic arthritis. Ann Rheum Dis 2010;69:624-5.
38. Kavanaugh A, Krueger GG, Beutler A, Guzzo C, Zhou B, Dooley LT, et al. Infliximab maintains a high degree of clinical response in patients with active psoriatic arthritis through 1 year of treatment: results from the IMPACT 2 trail. Ann Rheum Dis 2007;66:498-505.
39. Bendtzen K, Geborek P, Svenson M, Larsson L, Kapetanovic MC, Saxne T. Individualized monitoring of drug bioavailability and immunogenicity in rheumatoid arthritis patients treated with tumor necrosis factor alpha inhibitor infliximab. Arthritis Rheum 2006;54:3782-9.
40. Krieckaert CL, Nurmohamed MT, Wolbing GJ. Methotrexate reduces immunogenicity in adalimumab treated rheumatoid arthritis. Ann Rheum Dis 2012;71:1914-5.
41. Garces S, Demengeot J, Benito-Garcia E. The immunogenicity of anti-TNF therapy in immune-mediated inflammatory diseases: a systematic review of the literature with a meta-analysis. Ann Rheum Dis 2013;72:1947-55.
42. Maneiro JR, Salgado E, Gomez-Reino JJ. Immunogenicity of monoclonal antibodies against tumor necrosis factor used in chronic immune-mediated inflammatory conditions. JAMA Intern Med 2013;173:1416-28.
43. Vermire S, Noman M, Van Assche G, Baert F, D'Haens G, Rutgeerts P. Effectiveness of concomitant immunosuppressive therapy in suppressing the formation of antibodies to infliximab in Crohn's disease. Gut 2007;56:1226-31.
44. Steenholdt C, Bendtzen K, Brynskov J, Thomsen OØ, Ainsworth MA. Cut-off levels and diagnostic accuracy of infliximab trough levels and anti-infliximab antibodies in Crohn's disease. Scand J Gastroenterol 2011;46:310-8.
45. Llinares-Tello F, de Salazar JR, Gallego JM, Soler GS, Ramírez CS, Heredia ES, et al. Analytical and clinical evaluation of new immunoassay for therapeutic drug monitoring of infliximab and adalimumab. Clin Chem Lab Med 2012;50:1845-7.
46. Svenson M, Geborek P, Saxne T, Bendtzen K. Monitoring patients treated with anti-TNF alpha biopharmaceuticals: assessing serum infliximab and anti-infliximab antibodies. Rheumatology 2007;46:1828-34.
47. Hart MH, De Vrieze H, Wouters D, Wolbink GJ, Aarden LA, Killestein J, et al. Differential effect of drug interference in immunogenicity assays. J Immunol Meth 2011;372:196-203.
48. Chen D-Y, Chen Y-M, Tsai W-C, Tseng J-C, Chen Y-H, Hsieh C-W, et al. Significant associations of antidrug antibody levels with serum drug through and therapeutic response of adalimumab and etanercept treatment in rheumatoid arthritis. Ann Rheum Dis 2014;0:1-9.
49. Menting SP, van Lümig PP, de Vries AC, van den Reek JM, van der Kleij D, de Jong EM. Extent and consequences of antibody formation against adalimumab in patients with psoriasis: one-year follow-up. JAMA Dermatol 2014;150:130-6.