arthritis research&therapy

REVIEW

# The effect of immunomodulators on the immunogenicity of TNF-blocking therapeutic monoclonal antibodies: a review

Charlotte Louise Maria Krieckaert*[1], Geertje Margret Bartelds[1], Willem Frederik Lems[2] and Gerrit Jan Wolbink[1]

**Abstract**

Therapeutic monoclonal antibodies have revolutionized the treatment of various inflammatory diseases. Immunogenicity against these antibodies has been shown to be clinically important: it is associated with shorter response duration because of diminishing concentrations in the blood and with infusion reactions. Concomitant immunomodulators in the form of methotrexate or azathioprine reduced the immunogenicity of therapeutic antibodies in rheumatoid arthritis, Crohn disease, and juvenile idiopathic arthritis. The occurrence of adverse events does not increase when immunomodulators are added to therapeutic antibodies. The mechanism whereby methotrexate and azathioprine influence immunogenicity remains unclear. Evidence-based consensus on prescribing concomitant immunomodulators is needed.

## Immunogenicity of biologicals

Therapeutic monoclonal antibodies (TmAbs) that block tumor necrosis factor are powerful modalities in the treatment of various inflammatory diseases, but both chimeric and human TmAbs can induce anti-TmAb antibodies. Immunogenicity can change the pharmacokinetics of biological therapeutics, resulting in suboptimal therapeutic levels of the drug in patient serum. The problem of immunogenicity against therapeutic antibodies has been described since TmAbs have been on the market for the treatment of various inflammatory diseases, and knowledge regarding anti-TmAb antibodies is increasing. Nevertheless, technical factors, standardization of the assays used to measure anti-TmAb antibodies, and the timing of the measurements make immunogenicity a complex subject to investigate. Several studies in various inflammatory diseases demonstrate the presence of anti-TmAb antibodies [1]. Table 1 gives an overview of the reported frequency of anti-TmAb antibodies in infliximab (antibodies to infliximab, or ATIs) and in adalimumab (anti-adalimumab antibodies, or AAAs) [2-22]. The large variation in the percentages of anti-TmAb antibodies measured could be related to the differences in assays, duration of treatment, and the use of concomitant immunosuppressive treatment.

### Relevance of anti-TmAb antibodies

In studies in which trough serum adalimumab or infliximab concentrations were measured, the presence of anti-TmAb antibodies was associated with decreased serum drug levels and a diminished response [2,5-7,10,11,13,14]. Furthermore, anti-TmAb antibodies in the presence of TmAb concentrations in patients serum lead to the formation of immune complexes [23]. The continuous presence of immune complexes in the serum could lead to adverse events. Little is known about the safety of TmAb and anti-TmAb antibody immune complexes. The presence of ATIs and of immune complexes of various sizes might be associated with infusion-related hypersensitivity reactions [2,6,10,23,24]. In one study, higher concentrations of ATIs predicted a higher risk of infusion reactions [10]. Concomitant immunosuppressive therapy, in the form of methotrexate or azathioprine, was shown to be associated with a lower frequency of anti-TmAb antibodies compared with TmAb monotherapy in multiple studies [4,7,10-13,15,16,18,25]. The administration of concomitant immunosuppressive therapy could be an opportunity to bypass the detrimental effect of immunogenicity on the efficacy of biological therapeutics and possible immune complex-related adverse events. In rheumatoid arthritis (RA), biological therapeutics are preferably prescribed with concomitant disease-modifying antirheumatic drugs (DMARDs) since effectiveness is increased compared with monotherapy

*Correspondence: c.krieckaert@janvanbreemen.nl
[1]Department of Rheumatology, Jan van Breemen Institute, Dr Jan van Breemenstraat 2, 1056 AB Amsterdam, The Netherlands
Full list of author information is available at the end of the article

**Table 1. Frequency of reported antibodies to infliximab and adalimumab in various inflammatory diseases**

| Inflammatory disease | ATIs, percentage | AAAs, percentage | References |
|---|---|---|---|
| Rheumatoid arthritis | 8-52 | 12-44 | [2-9] |
| Crohn disease | 14-75 | 2.6-17 | [10-17] |
| Juvenile idiopathic arthritis | NA | 17 | [18] |
| Ankylosing spondylitis | 29 | 31 | [19,20] |
| Psoriatic arthritis | NA | 18 | [21] |
| Psoriasis | NA | 45 | [22] |

AAA, anti-adalimumab antibody; ATI, antibody to infliximab; NA, not applicable.

[26]. It is unclear whether this effect is related to a synergistic or an anti-immunogenic effect. However, in clinical practice, the decision to prescribe concomitant immunosuppressive treatment is determined by many factors: adverse events or intolerance, patient's preference, rheumatologist's preference, effectiveness of immunosuppressant monotherapy, and comorbidity. Also, daily practice differs among inflammatory diseases; for example, in RA, it is common to prescribe methotrexate together with biological treatment, but in Crohn disease, the number of patients receiving concomitant immunomodulators is lower [13]. In psoriasis, methotrexate treatment is often discontinued before the start with biological treatment, and in ankylosing spondylitis, effective therapeutic options (DMARDs) are lacking [22,27]. Furthermore, there are no clear guidelines on prescribing concomitant immunosuppressants.

## Current knowledge

We performed a systematic PubMed search of articles on the subject of concomitant immunosuppressive therapy with TmAb treatment. Search terms were infliximab, adalimumab, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis, Crohn disease, juvenile idiopathic arthritis, juvenile rheumatoid arthritis, immunogenicity, antibodies, anti-adalimumab antibodies, anti-infliximab antibodies, methotrexate, MTX, and immunomodulators. Articles were selected if a full text was available and if the formation of antibodies against adalimumab/infliximab and the possible effect of immunomodulators on immunogenicity were described. CLMK and GMB performed the PubMed search and evaluated all of the articles.

### Prospective studies

Almost 15 years ago, Maini and colleagues [4] investigated whether methotrexate could reduce the immunogenicity of infliximab. The authors postulated that, if added to infliximab in a dosage of 7.5 mg weekly, methotrexate itself would not be effective and toxicity would be minimized, but it would have an additive benefit on decreasing immunogenicity, and toxicity would be minimized. They performed a 26-week, double-blind, placebo-controlled, multicenter trial in which 101 patients with RA were randomly assigned to one of seven groups, receiving infliximab at 1, 3, or 10 mg/kg or placebo with or without methotrexate 7.5 mg per week for 14 weeks. The overall incidence of ATIs after 26 weeks was 17.4%. The development of antibodies was inversely associated with the infliximab dose: 53%, 21%, and 7% in patients receiving 1, 3, and 10 mg/kg monotherapy, respectively. The use of concomitant methotrexate greatly diminished the appearance of ATIs, with incidence rates of 15%, 7%, and 0% at the three dose levels. The enzyme immunoassay used to measure the presence of ATIs was fully described in the article. The authors suggest that immunologic tolerance to infliximab was induced by higher dosages of infliximab, probably because of the maintenance of circulating levels of infliximab, and that this tolerance was potentiated by the simultaneous administration of methotrexate at a dose of 7.5 mg per week.

In a prospective proof-of-concept study in patients with Crohn disease, the concomitant use of immunosuppressive therapy was compared with infliximab monotherapy in 174 patients [13]. In one study arm, 65 patients used concomitant azathioprine 2 to 2.5 mg/kg; in a second arm, 50 patients used concomitant intramuscular or subcutaneous methotrexate 15 mg weekly; and in a third arm, 59 patients received infliximab monotherapy. Measurements of ATIs were performed by Prometheus Laboratories (San Diego, CA, USA) before and 4 weeks after each infusion. Again, the concomitant use of immunosuppressive therapy was associated with a lower incidence of ATIs compared with patients with infliximab monotherapy (46% versus 73%, $P$ <0.001). This difference was observed in both the methotrexate arm (44% ATIs, $P$ = 0.002) and the azathioprine arm (48% ATIs, $P$ = 0.004). When trough infliximab levels were stratified according to the presence or absence of ATIs, patients with ATIs had lower infliximab levels than patients without ATIs and these levels were even lower when patients were not taking concomitant immunosuppressive treatment. There was a trend toward

significance for the presence of ATIs being associated with a shorter duration of response in patients not taking concomitant immunosuppressive treatment compared with patients taking azathioprine or methotrexate ($P$ = 0.06). Strikingly, when no ATIs were present, the duration of response was not influenced by immunosuppressive co-treatment. This suggests that the anti-immunogenic effect was more important than a possible synergistic effect.

#### Descriptive studies

Besides these prospective studies, a number of observational cohort studies on the subject of immunogenicity and studies with immunogenicity as secondary objective describe the postulated effect of immunosuppressive agents on immunogenicity of TmAbs [4,7,10-13,15,16,18,25]. These studies and the two studies described above are summarized in Table 2.

During a 28-week cohort study, AAAs were detected in 21/121 of adalimumab-treated RA patients (17%) [7]. A radioimmunoassay designed by Sanquin (Amsterdam, The Netherlands) was used to measure the AAAs. Patients receiving concomitant methotrexate (mean dosage of 19.4 mg per week) had a lower rate of antibody development than patients receiving adalimumab monotherapy (12% versus 38%). EULAR (European League Against Rheumatism) non-responders had AAAs significantly more often than good responders did (34% versus 5%, $P$ = 0.032). AAA formation corresponded with lower serum adalimumab concentrations at 28-week follow-up.

One hundred thirty-three patients with juvenile idiopathic arthritis (JIA) were randomly assigned to receive adalimumab or placebo [18]. In total, 16% of the patients had at least one positive test for AAAs during the study. Five of 85 patients (6%) receiving methotrexate and 22 of 86 patients (26%) not receiving methotrexate developed AAAs. The presence of AAAs did not lead to a greater rate of discontinuation of adalimumab and did not increase the incidence of serious adverse events. The assay used to measure AAAs was not described.

In Crohn disease, an anti-immunogenic effect of concomitant immunosuppressive therapy was shown in a cohort study of 125 patients [10]. Patients who were taking immunosuppressive agents had a lower incidence of ATIs (43%) and higher infliximab concentrations than patients who were not taking immunosuppressive agents (75%, $P$ <0.01). Tests were performed by Prometheus Laboratories. The incidence of infusion reactions was reduced and the duration of response increased in patients taking immunosuppressive agents. There was a negative relation between the ATI concentration and the duration of response to infliximab ($P$ <0.001).

In the ACCENT I (Crohn disease without fistulas) and II (fistulizing Crohn disease) trials, patients received infliximab induction therapy followed by placebo or maintenance therapy for up to 54 weeks [11,12]. In the ACCENT I trial, 442 patients were assessed for the presence of ATIs. Fourteen percent of patients developed ATIs, and 46% had an inconclusive result. Six percent of the patients receiving concomitant steroids and immunomodulators, 17% of the patients receiving concomitant steroids alone, 10% of the patients receiving concomitant immunomodulators alone, and 18% using infliximab monotherapy developed ATIs. Median infliximab concentration in patients positive for antibodies was lower than in patients who had negative or inconclusive results. In the ACCENT II trial (n = 306 patients), response rates were similar among patients with (32%) or without (31%) ATIs. In this study, antibody status and efficacy of infliximab were not related. Four percent of patients receiving concomitant steroids and immunomodulators, 13% of patients receiving concomitant steroids alone, 11% of patients receiving concomitant immunomodulators alone, and 24% using infliximab monotherapy developed ATIs. In both trials, infusion reactions occurred more often among patients with ATIs than among those without ATIs. In the ACCENT I trial as well as in the ACCENT II trial, assays used for the measurement of ATIs were not described in the text.

Recently, 508 biological and immunomodulator-naive Crohn disease patients were randomly assigned to receive azathioprine 2.5 mg/kg, infliximab 5 mg/kg, or combination therapy with azathioprine and infliximab for up to 26 weeks [25]. At 30 weeks, ATIs were detected in 1/116 patients (0.9%) receiving combination therapy and in 15/103 patients (14.6%) receiving infliximab alone. Median trough infliximab serum concentrations were higher for patients receiving combination therapy compared with patients receiving infliximab monotherapy (1.6 versus 3.5 μg/mL, $P$ <0.001). The assay used to measure ATIs was not described.

A small study of 30 adalimumab-treated patients with Crohn disease assessed whether AAAs affect adalimumab treatment outcome [16]. Seventeen percent of patients developed AAAs. The presence of AAAs was related to non-response to adalimumab (odds ratio 13.1, confidence interval 1.7 to 99.2, $P$ = 0.006). Of the 13 patients using concomitant medication (steroids or immunomodulators), only one patient (7.7%) developed AAAs, whereas 20% of patients without concomitant medication developed these antibodies. AAAs were detected with the radioimmunoassay developed by Landsteiner Laboratory Sanquin Research (Amsterdam, The Netherlands).

After induction therapy in the CLASSIC I trial [17], 276 patients with Crohn disease enrolled in the CLASSIC II trial and received open-label adalimumab 40 mg at weeks 0 and 2 [15]. Patients who were in remission at weeks 0 and 4 (55) in CLASSIC I were randomly assigned

**Table 2. The effect of methotrexate or azathioprine on the formation of antibodies against adalimumab or infliximab**

| Study | Disease | TmAbs | IS used | % AAAs or ATIs | IS + % AAAs or ATIs | IS – % AAAs or ATIs | *P* value | Assay |
|---|---|---|---|---|---|---|---|---|
| Maini et al. [4] | RA | IFX | MTX | 17.4% | 0%-15% | 7%-53% | NA | LoBuglio et al. [30] |
| Vermeire et al. [13] | Crohn | IFX | AZA MTX | 55% | 46% | 73% | *P* <0.001 | Prometheus Laboratories (San Diego, CA, USA) |
| Baert et al. [10] | Crohn | IFX | MTX | 61% | 43% | 75% | *P* <0.01 | Prometheus Laboratories |
| ACCENT I [11] | Crohn | IFX | MTX | 14% | 10% | 18% | NA | NA |
| ACCENT II [12] | Crohn | IFX | MTX | 32% | 11% | 24% | NA | NA |
| Colombel et al. [25] | Crohn | IFX | AZA | NA | 0.9% | 14.6% | NA | NA |
| Bartelds et al. [7] | RA | ADA | MTX | 17% | 12% | 38% | NA | Sanquin (Amsterdam, The Netherlands) |
| Lovell et al. [18] | JIA | ADA | MTX | 16% | 6% | 26% | NA | NA |
| West et al. [16] | Crohn | ADA | MTX | 17% | 7.7% | 20% | NA | Sanquin |
| CLASSIC II [15] | Crohn | ADA | MTX | 2.6% | 0% | 3.8% | NA | NA |

AAA, anti-adalimumab antibody; ACCENT, A Crohn's Disease Clinical Trial Evaluating Infliximab in a New Long-term Treatment Regimen in Patients With Fistulizing Crohn's Disease; ADA, adalimumab; ATI, antibody to infliximab; AZA, azathioprine; CLASSIC, Clinical Assessment of Adalimumab Safety and Efficacy Studied as Induction Therapy in Crohn's Disease; IFX, infliximab; IS, immunosuppressive treatment; JIA, juvenile idiopathic arthritis; MTX, methotrexate; NA, not applicable; RA, rheumatoid arthritis; TmAb, therapeutic monoclonal antibody.

to receive adalimumab 40 mg every other week or weekly or placebo for 56 weeks. Patients not in remission enrolled in an open-label arm and received adalimumab 40 mg every other week. In these four groups, 17% to 33% of the patients were treated with concomitant immunosuppressive agents. Remission rates did not differ between patients treated with or without concomitant immunosuppressants. Blood samples were collected for 269 out of 276 patients. Seven patients (2.6%) developed AAAs. Eighty-four out of 269 patients received concomitant immunosuppressants and none of them was positive for AAAs. Out of the 185 patients who did not receive concomitant immunosuppressive agents, 7 patients (3.8%) developed AAAs. Assays used for the measurement of AAAs were not described.

### Unclear or no effect shown

Besides the studies described above (in which a beneficial effect of concomitant immunosuppressive therapy on the immunogenicity of TmAbs was described), a few studies show less or no effect of immunomodulators on immunogenicity. In an observational cohort study on adalimumab therapy for Crohn disease (n = 168), concomitant immunomodulator therapy at baseline did not affect treatment outcome, trough serum concentration, or the development of antibodies against adalimumab and had no negative impact on serious adverse events. Only time to dose escalation was longer in patients who were treated with immunomodulators [14].

In a study of 106 patients with RA, 40% of anti-infliximab antibody-positive patients were treated concomitantly with methotrexate and this frequency did not differ significantly from that of patients who were ATI-negative (50%). However, patients who were receiving methotrexate had antibody levels that were slightly lower than those of patients who were not receiving methotrexate [2]. In another study of 51 patients with RA, only three patients were not taking concomitant immunosuppressants. Antibodies were detected in two of these three patients [6].

## Perspective

Since the effect of methotrexate on the immunogenicity of infliximab in patients with RA was described by Maini and colleagues [4] almost 15 years ago, there has been only one other prospective study on the effect of concomitant medication on the immunogenicity of infliximab. Both studies indicate a clear effect of methotrexate and azathioprine on the formation of ATIs in patients with RA or Crohn disease. Although no prospective studies of adalimumab on this subject have been performed, other cohort studies describing the effect of immunomodulator co-treatment on the immunogenicity of adalimumab show similar results. Therefore, we conclude that there appears to be a favorable effect of immunosuppressive co-treatment on the immunogenicity of adalimumab and infliximab.

Few data are available on the occurrence of adverse events associated with concomitant immunosuppressants, but even fewer data are available on the safety of anti-TmAb antibodies. The lack of known clinical manifestations associated with anti-drug antibodies does not imply that the continuous stimulation of the immune system and the development of immune complexes are harmless.

The occurrence of (serious) adverse events, or (S)AEs, did not increase when immunomodulators were added to TmAbs in Crohn disease and RA [28,29]. Only the

proportion of patients with infusion reactions was lower in patients receiving immunomodulators (12.5%) compared with patients not receiving concomitant immunosuppressants (22.0%) [28]. Of 4,879 patients treated with adalimumab, 5.3% using at least one concomitant DMARD reported an SAE versus 7.3% of the patients using adalimumab monotherapy. This frequency did not differ among various DMARDs [29].

The mechanism behind the effect of immunosuppressants on immunogenicity has not been elucidated. We hypothesize that by adding immunomodulators to the TmAbs, the immune response will be suppressed, leading to a decrease in antibody formation. In other words, methotrexate or azathioprine could block the expansion of the immune reactive cells, whereby the formation of anti-TmAb antibodies is reduced in quantity.

Optimization of treatment response should be the main goal when prescribing costly biological therapeutics. Especially in those inflammatory diseases in which it is not common to prescribe concomitant immunomodulating therapy, great benefits in lowering the incidence of anti-TmAb antibodies could be achieved by the use of concomitant immunosuppressants, resulting in an increased portion of patients with therapeutic concentrations of TmAbs in their blood.

The concomitant use of immunosuppressants has not been associated with a higher incidence of (S)AEs; however, to minimize the risk of toxicity/intolerance, the minimal sufficient dose of immunosuppressants to decrease the immunogenicity of TmAbs should be assessed. To facilitate an evidence-based consensus on prescribing concomitant immunosuppressive therapy in various inflammatory diseases, a prospective, controlled, dose-finding trial is warranted.

**Abbreviations**

AAA, anti-adalimumab antibody; ACCENT, A Crohn's Disease Clinical Trial Evaluating Infliximab in a New Long-term Treatment Regimen in Patients With Fistulizing Crohn's Disease; ATI, antibody to infliximab; CLASSIC, Clinical Assessment of Adalimumab Safety and Efficacy Studied as Induction Therapy in Crohn's Disease; DMARD, disease-modifying antirheumatic drug; RA, rheumatoid arthritis; (S)AE, (serious) adverse event; TmAb, therapeutic monoclonal antibody.

**Competing interests**

The authors declare that they have no competing interests.

**Author details**

[1]Department of Rheumatology, Jan van Breemen Institute, Dr Jan van Breemenstraat 2, 1056 AB Amsterdam, The Netherlands. [2]Department of Rheumatology, VU Medical Center, PO Box 7057, 1007 MB Amsterdam, The Netherlands.

Published: 20 October 2010

**References**

1. Emi AN, de Carvalho JF, Artur Almeida SC, Bonfa E: **Immunogenicity of anti-TNF-alpha agents in autoimmune diseases.** *Clin Rev Allergy Immunol* 2010, **38:**82-89.
2. 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 the tumor necrosis factor alpha inhibitor infliximab.** *Arthritis Rheum* 2006, **54:**3782-3789.
3. Lipsky PE, van der Heijde DM, St Clair EW, Furst DE, Breedveld FC, Kalden JR, Smolen JS, Weisman M, Emery P, Feldmann M, Harriman GR, Maini RN: **Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group.** *N Engl J Med* 2000, **343:**1594-1602.
4. Maini RN, Breedveld FC, Kalden JR, Smolen JS, Davis D, Macfarlane JD, Antoni C, Leeb B, Elliott MJ, Woody JN, Schaible TF, Feldmann M: **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:**1552-1563.
5. Radstake TR, Svenson M, Eijsbouts AM, van den Hoogen FH, Enevold C, van Riel PL, Bendtzen K: **Formation of antibodies against infliximab and adalimumab strongly correlates with functional drug levels and clinical responses in rheumatoid arthritis.** *Ann Rheum Dis* 2009, **68:**1739-1745.
6. Wolbink GJ, Vis M, Lems W, Voskuyl AE, de Groot E, Nurmohamed MT, Stapel S, Tak PP, Aarden L, Dijkmans B: **Development of antiinfliximab antibodies and relationship to clinical response in patients with rheumatoid arthritis.** *Arthritis Rheum* 2006, **54:**711-715.
7. Bartelds GM, Wijbrandts CA, Nurmohamed MT, Stapel S, Lems WF, Aarden L, Dijkmans BA, Tak PP, Wolbink GJ: **Clinical response to adalimumab: relationship to anti-adalimumab antibodies and serum adalimumab concentrations in rheumatoid arthritis.** *Ann Rheum Dis* 2007, **66:**921-926.
8. Miyasaka N: **Clinical investigation in highly disease-affected rheumatoid arthritis patients in Japan with adalimumab applying standard and general evaluation: the CHANGE study.** *Mod Rheumatol* 2008, **18:**252-262.
9. van de Putte LB, Atkins C, Malaise M, Sany J, Russell AS, van Riel PL, Settas L, Bijlsma JW, Todesco S, Dougados M, Nash P, Emery P, Walter N, Kaul M, Fischkoff S, Kupper H: **Efficacy and safety of adalimumab as monotherapy in patients with rheumatoid arthritis for whom previous disease modifying antirheumatic drug treatment has failed.** *Ann Rheum Dis* 2004, **63:**508-516.
10. Baert F, Noman M, Vermeire S, Van Assche G, D'Haens G, Carbonez A, Rutgeerts P: **Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease.** *N Engl J Med* 2003, **348:**601-608.
11. Hanauer SB, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, Rachmilewitz D, Wolf DC, Olson A, Bao W, Rutgeerts P: **Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial.** *Lancet* 2002, **359:**1541-1549.
12. Sands BE, Anderson FH, Bernstein CN, Chey WY, Feagan BG, Fedorak RN, Kamm MA, Korzenik JR, Lashner BA, Onken JE, Rachmilewitz D, Rutgeerts P, Wild G, Wolf DC, Marsters PA, Travers SB, Blank MA, van Deventer SJ: **Infliximab maintenance therapy for fistulizing Crohn's disease.** *N Engl J Med* 2004, **350:**876-885.
13. Vermeire 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:**1226-1231.
14. Karmiris K, Paintaud G, Noman M, Magdelaine-Beuzelin C, Ferrante M, Degenne D, Claes K, Coopman T, Van Schuerbeek N, Van Assche G, Vermeire S, Rutgeerts P: **Influence of trough serum levels and immunogenicity on long-term outcome of adalimumab therapy in Crohn's disease.** *Gastroenterology* 2009, **137:**1628-1640.
15. Sandborn WJ, Hanauer SB, Rutgeerts P, Fedorak RN, Lukas M, MacIntosh DG, Panaccione R, Wolf D, Kent JD, Bittle B, Li J, Pollack PF: **Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial.** *Gut* 2007, **56:**1232-1239.
16. West RL, Zelinkova Z, Wolbink GJ, Kuipers EJ, Stokkers PC, van der Woude CJ: **Immunogenicity negatively influences the outcome of adalimumab treatment in Crohn's disease.** *Aliment Pharmacol Ther* 2008, **28:**1122-1126.
17. Hanauer SB, Sandborn WJ, Rutgeerts P, Fedorak RN, Lukas M, MacIntosh D, Panaccione R, Wolf D, Pollack P: **Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial.** *Gastroenterology* 2006, **130:**323-333.
18. Lovell DJ, Ruperto N, Goodman S, Reiff A, Jung L, Jarosova K, Nemcova D, Mouy R, Sandborg C, Bohnsack J, Elewaut D, Foeldvari I, Gerloni V, Rovensky J, Minden K, Vehe RK, Weiner LW, Horneff G, Huppertz HI, Olson NY, Medich JR, Carcereri-De-Prati R, McIlraith MJ, Giannini EH, Martini A: **Adalimumab with or without methotrexate in juvenile rheumatoid arthritis.** *N Engl J Med* 2008, **359:**810-820.

19. de Vries MK, Wolbink GJ, Stapel SO, de Vrieze H, van Denderen JC, Dijkmans BA, Aarden LA, van der Horst-Bruinsma IE: **Decreased clinical response to infliximab in ankylosing spondylitis is correlated with anti-infliximab formation.** *Ann Rheum Dis* 2007, **66:**1252-1254.
20. de Vries MK, Brouwer E, van der Horst-Bruinsma IE, Spoorenberg A, van Denderen JC, Jamnitski A, Nurmohamed MT, Dijkmans BA, Aarden LA, Wolbink GJ: **Decreased clinical response to adalimumab in ankylosing spondylitis is associated with antibody formation.** *Ann Rheum Dis* 2009, **68:**1787-1788.
21. 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:**624-625.
22. Lecluse LL, Driessen RJ, Spuls PI, de Jong EM, Stapel SO, van Doorn MB, Bos JD, Wolbink GJ: **Extent and clinical consequences of antibody formation against adalimumab in patients with plaque psoriasis.** *Arch Dermatol* 2010, **146:**127-132.
23. van der Laken CJ, Voskuyl AE, Roos JC, Stigter vW, de Groot ER, Wolbink G, Dijkmans BA, Aarden LA: **Imaging and serum analysis of immune complex formation of radiolabelled infliximab and anti-infliximab in responders and non-responders to therapy for rheumatoid arthritis.** *Ann Rheum Dis* 2007, **66:**253-256.
24. Vultaggio A, Matucci A, Nencini F, Pratesi S, Parronchi P, Rossi O, Romagnani S, Maggi E: **Anti-infliximab IgE and non-IgE antibodies and induction of infusion-related severe anaphylactic reactions.** *Allergy* 2010, **65:**657-661.
25. Colombel JF, Sandborn WJ, Reinisch W, Mantzaris GJ, Kornbluth A, Rachmilewitz D, Lichtiger S, D'Haens G, Diamond RH, Broussard DL, Tang KL, van der Woude CJ, Rutgeerts P: **Infliximab, azathioprine, or combination therapy for Crohn's disease.** *N Engl J Med* 2010, **362:**1383-1395.
26. Heiberg MS, Rodevand E, Mikkelsen K, Kaufmann C, Didriksen A, Mowinckel P, Kvien TK: **Adalimumab and methotrexate is more effective than adalimumab alone in patients with established rheumatoid arthritis: results from a 6-month longitudinal, observational, multicentre study.** *Ann Rheum Dis* 2006, **65:**1379-1383.
27. Goh L, Samanta A: **A systematic medline analysis of therapeutic approaches in ankylosing spondylitis.** *Rheumatol Int* 2009, **29:**1123-1135.
28. Lichtenstein GR, Diamond RH, Wagner CL, Fasanmade AA, Olson AD, Marano CW, Johanns J, Lang Y, Sandborn WJ: **Clinical trial: benefits and risks of immunomodulators and maintenance infliximab for IBD-subgroup analyses across four randomized trials.** *Aliment Pharmacol Ther* 2009, **30:**210-226.
29. Burmester GR, Mariette X, Montecucco C, Monteagudo-Saez I, Malaise M, Tzioufas AG, Bijlsma JW, Unnebrink K, Kary S, Kupper H: **Adalimumab alone and in combination with disease-modifying antirheumatic drugs for the treatment of rheumatoid arthritis in clinical practice: the Research in Active Rheumatoid Arthritis (ReAct) trial.** *Ann Rheum Dis* 2007, **66:**732-739.
30. LoBuglio AF, Wheeler RH, Trang J, Haynes A, Rogers K, Harvey EB, Sun L, Ghrayeb J, Khazaeli MB: **Mouse/human chimeric monoclonal antibody in man: kinetics and immune response.** *Proc Natl Acad Sci U S A* 1989, **86:**4220-4224.

doi:10.1186/ar3147
**Cite this article as**: Krieckaert CLM, *et al.*: The effect of immunomodulators on the immunogenicity of TNF-blocking therapeutic monoclonal antibodies: a review. *Arthritis Research & Therapy* 2010, **12:**217.