

VU Research Portal

Clinical implications of immunogenicity

Bartelds, G.M.

2011

document version

Publisher's PDF, also known as Version of record

[Link to publication in VU Research Portal](#)

citation for published version (APA)

Bartelds, G. M. (2011). *Clinical implications of immunogenicity*. [PhD-Thesis – Research external, graduation internal, Vrije Universiteit Amsterdam].

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal

Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

E-mail address:

vuresearchportal.ub@vu.nl

Chapter 9

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

Charlotte Louise Maria Krieckaert
Geertje Margret Bartelds
Willem Frederik Lems
Gerrit Jan Wolbink

Arthritis Res Ther. 2010;12(5):217.

Abstract: Therapeutic monoclonal antibodies have revolutionized treatment of various inflammatory diseases. Immunogenicity against these antibodies has shown to be clinically important: it is associated with shorter response duration due to 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's 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 tumour necrosis factor are powerful modalities in the treatment of various inflammatory diseases, however, 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's serum. The problem of immunogenicity against therapeutic antibodies has been described since TmAbs are on the market for the treatment of various inflammatory diseases and the knowledge regarding anti-TmAb antibodies is increasing. Nevertheless, technical factors, standardisation 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, ATI) and in adalimumab (anti-adalimumab antibodies, AAA). [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 also to the use of concomitant immunosuppressive treatment.

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

Inflammatory disease	ATI (%)	AAA (%)	references
RA	8-52	12-44	2-9
Crohn's disease	14-75	2.6-17	10-17
JIA	NA	17	18
AS	29	31	19, 20
PsA	NA	18	21
Psoriasis	NA	45	22

AAA anti-adalimumab antibodies, AS ankylosing spondylitis, ATI antibodies to infliximab, JIA juvenile idiopathic arthritis, NA not applicable, PsA psoriatic arthritis, RA rheumatoid arthritis

Relevance of anti-TmAb antibodies

In studies where 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 levels leads 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 antibodies to infliximab 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 antibodies to infliximab 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 to 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 Anti Rheumatic Drugs (DMARDs), since effectiveness is increased compared with

monotherapy. [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 co morbidity are of influence. Also, daily practice differs between inflammatory diseases, e.g. in rheumatoid arthritis it is common to prescribe methotrexate together with biological treatment, however in Crohn's disease, the number of patients receiving concomitant immunomodulators are 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 TmAbs treatment. Search terms were: infliximab, adalimumab, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis, Crohn's disease, juvenile idiopathic arthritis, juvenile rheumatoid arthritis, immunogenicity, antibodies, anti-adalimumab antibodies, anti-infliximab antibodies, methotrexate, MTX, 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 was described. CK and MB performed the PubMed search and evaluated all the articles.

Prospective studies

Almost 15 years ago Maini et al investigated whether methotrexate could reduce the immunogenicity of infliximab. [4] They postulated that if methotrexate was added to infliximab in a dosage of 7.5 mg weekly, methotrexate itself would not be effective and toxicity would be minimized, however, it would have an additive benefit on decreasing immunogenicity.

They performed a 26-week, double-blind, placebo-controlled, multicenter trial, in which 101 patients with RA were randomized to 1 of 7 groups, receiving infliximab at 1, 3 or 10 mg/kg or placebo with or without methotrexate 7.5 mg/week, for 14 weeks. The overall incidence of ATI 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 ATI, with incidence rates of 15%, 7% and 0% at the three dose levels. The enzyme immunoassay used to measure the presence of ATI was fully described in the article.

The authors suggest that immunologic tolerance to infliximab was induced by higher dosages of infliximab, probably due to 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's 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 2-2.5 mg/kg, in a second arm 50 patients used concomitant intramuscular or subcutaneous methotrexate 15 mg weekly, whereas in a third arm 59 patients received infliximab monotherapy. Measurements of ATI were performed by Prometheus laboratories before and 4 weeks after each infusion. Again, the concomitant use of immunosuppressive therapy was associated with a lower incidence of ATI compared to patients with

infliximab monotherapy (46% versus 73%, $p < 0.001$). This difference was observed in both the methotrexate (44% ATI, $p = 0.002$) and the azathioprine arm (48% ATI, $p = 0.004$). When trough infliximab levels were stratified according to the presence or absence of ATI, patients with ATI had lower infliximab levels than patients without ATI and these levels were even lower when patients were not taking concomitant immunosuppressive treatment. There was a trend towards significance for the presence of ATI being associated with a shorter duration of response in patients not taking concomitant immunosuppressive treatment compared to patients taking azathioprine or methotrexate. ($p = 0.06$) Strikingly, when no ATI 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

Beside these prospective studies, there are a number of observational cohort studies on the subject of immunogenicity or studies secondary describing 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, anti-adalimumab antibodies were detected in 21/121 (17%) of adalimumab treated RA patients. [7] A radioimmunoassay designed by Sanquin Amsterdam was used to measure the anti-adalimumab antibodies. Patients receiving concomitant methotrexate (mean dosage 19.4 mg/week) had a lower rate of antibody development than patients receiving adalimumab monotherapy (12% versus 38%). EULAR (European League Against Rheumatism) non-responders had AAA significantly more often than good responders (34% versus 5% $p = 0.032$). AAA formation corresponded with lower serum adalimumab concentrations at 28 weeks follow-up.

One-hundred-thirty-three Juvenile Idiopathic Arthritis (JIA) patients were randomly assigned to receive adalimumab or placebo. [18] In total 16% of the patients had at least one positive test for AAA during the study. Five of 85 patients (6%) receiving methotrexate and 22 of 86 patients (26%) not receiving methotrexate developed AAA. Presence of AAA 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 AAA was not described.

In Crohn's disease an anti-immunogenic effect of concomitant immunosuppressive therapy was shown in a cohort study on 125 patients. [10] Patients who were taking immunosuppressive agents had a lower incidence of ATI (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's disease without fistulas) and II (fistulising Crohn's disease) trials, patients received infliximab induction therapy followed by placebo or maintenance therapy up to 54 weeks. [11 12] In the ACCENT I trial, 442 patients were assessed for the presence of ATI. Fourteen percent of patients developed antibodies to infliximab, 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 ATI. 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%) ATI. 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 ATI. In both trials, infusion reactions occurred more often among patients with ATI than in patients without. In the ACCENT I trial as well as in the ACCENT II trial, assays used for the measurement of ATI were not described in the text.

Recently, 508 biological and immunomodulator naive Crohn's 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, ATI were detected in 1/116 (0.9%) of patients receiving combination therapy and in 15/103 (14.6%) patients receiving infliximab alone. Median trough infliximab serum concentrations were higher for patients receiving combination therapy compared to patients receiving infliximab monotherapy (1.6 mcrg/ml versus 3.5 mcrg/ml, $p < 0.001$). The assay used to measure ATI was not described.

A small study on 30 adalimumab treated patients with Crohn's disease assessed whether AAA affect adalimumab treatment outcome. [16] Seventeen percent of patients developed AAA. The presence of AAA was related to non-response to adalimumab (OR 13.1 CI 1.7-99.2, $p = 0.006$). Of the 13 patients using concomitant medication (steroids or immunomodulators), only one patient (7.7%) developed AAA, whereas 20% of patients without concomitant medication developed these antibodies. AAA were detected with the radioimmunoassay developed by CLB Sanquin Amsterdam.

After induction therapy in the CLASSIC I trial, [17] 276 Crohn's Disease patients 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 week 0 and 4 (55) in CLASSIC I, were randomised to receive adalimumab 40 mg every other week (eow), weekly or placebo for 56 weeks. Patients not in remission enrolled in an open-label arm and received adalimumab 40 mg eow. In these four groups 17%-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 (2.6%) patients developed AAA. Eighty-four out of 269 patients received concomitant immunosuppressants and none of them were positive for AAA. Out of the 185 patients who did not receive concomitant immunosuppressive agents 7 patients (3.8%) developed AAA. Assays used for the measurement of anti-adalimumab antibodies were not described.

Unclear or no effect shown

Besides the studies described above, where a beneficial effect of concomitant immunosuppressive therapy on the immunogenicity of TmAbs was described, there are a few studies showing less or no effect of immunomodulators on immunogenicity.

In an observational cohort study on adalimumab therapy for Crohn's 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 with 106 RA patients, among anti-infliximab antibody-positive patients, 40% were treated concomitantly with methotrexate and this frequency did not differ significantly from the patients who were ATI negative (50%). However, those patients who were receiving methotrexate had slightly lower antibody levels than those who were not receiving methotrexate. [2] In another study on 51 RA patients, 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 RA patients was described by Maini et al almost 15 years ago, there has been only one other prospective study on the effect of concomitant medication on the immunogenicity of infliximab. [13] Both studies indicate a clear effect of methotrexate and azathioprine on the formation of ATI in patients with rheumatoid arthritis or Crohn's 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 favourable 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 is harmless. The occurrence of (serious) adverse events ((S)AE) did not increase when immunomodulators are added to TmAbs in Crohn's disease and RA. [28 29] Only the proportion of patients with infusion reactions was lower in patients receiving immunomodulators (12.5%) compared to patients not receiving concomitant immunosuppressants (22.0%). [28] Of 4879 patients treated with adalimumab, 5.3% using at least one concomitant DMARD reported a SAE versus 7.3% of the patients using adalimumab monotherapy. This frequency did not differ between various DMARDs. [29]

The mechanism behind the effect of immunosuppressants on immunogenicity is not 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.

Reference list

- (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, Johanss 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, Ghayeb 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.