# Clinical review

## Recent developments in the use of biologics in psoriasis and autoimmune disorders. The role of autoantibodies

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Treatment of autoimmune disorders such as psoriasis, rheumatoid arthritis, and Crohn's disease with so called biologics (selective immunomodulatory drugs) has become a standard way to treat severe or recalcitrant forms of these diseases. In particular, antagonists of tumour necrosis factor α (TNF-α) have been proved to be highly efficacious. In this review we summarise the current knowledge on problems associated with treatment with biologics, with particular emphasis on TNF-α inhibitors and autoantibody development. We also discuss the possible increased risk of lymphoma.

### Summary points

- Immunomodulatory biologic drugs are increasingly being used in the treatment of chronic autoimmune disorders such as psoriasis, rheumatoid arthritis, and Crohn's disease
- The clinical efficacy and tolerability of these new agents has proved to be favourable
- The use of biologics is associated with the development of antibodies against the substance (and/or of autoantibodies) with varying incidence
- Concomitant treatment with immunosuppressive agents such as methotrexate seems to lower the incidence of autoantibody formation
- The clinical relevance of antibodies to the biologics or of autoantibodies remains unclear

### Background

Monoclonal antibodies and fusion proteins have become an important group of drugs (known as biologic drugs) for treatment of chronic autoimmune disorders.[w1] Advances in antibody engineering and new techniques have allowed the generation of fusion proteins and chimeric, humanised, and fully humanised monoclonal antibodies. Fourteen biologic drugs have already been approved in the United States (by the US Food and Drug Administration (FDA)) and in other countries; over 70 are in late stage clinical trials (at least phase II) and over 1000 in preclinical development.[w2]

Treatment with these agents is well established for patients with rheumatoid arthritis and Crohn's disease, and in recent years a major focus of research into new biologics was psoriasis, an inflammatory T cell mediated skin disease. In particular, inhibitors of TNF-α were found to be very effective in the treatment of chronic plaque-type psoriasis, pustular psoriasis, and psoriatic arthritis.[w3-w5] The mechanism of action of these drugs is either binding free TNF-α to the soluble receptor-like fusion protein etanercept (Enbrel) or direct inhibition of TNF-α bioactivity with the monoclonal antibodies infliximab (chimeric, Remicade) or adalimumab (fully human, Humira).[1–5 w6] Other biologics targeting activated T cells and/or their migration into the skin are alefacept (Amevive) and efalizumab (Raptiva). Alefacept is a dimeric fusion protein consisting of a CD2-binding portion of human leukocyte function antigen-3 (LFA-3) linked to the Fc portion of human IgG1; it has been approved by the FDA for treating psoriasis. Efalizumab is a humanised monoclonal antibody directed against the CD11a subunit of leukocyte function antigen-1 (LFA-1) approved by the FDA as well as in European countries.[6 7 w7]

Many patients receiving these new therapies often respond rapidly to them and get a lot of clinical benefit. An increasing number of reports are focusing on side effects and problems of long term safety that require further examination (box 1). One of the major problems during treatment with anti-TNF-α agents has been the reactivation of tuberculosis and the possible development of other opportunistic infections.[w8-w11] Infusion and injection reactions are the most frequently reported side effects during treatment[2 8 w12] and cause about 15% of treatment discontinuations.[w13 w14] Malignancies such as lymphoma and other haematological disorders have also been reported, as well as demyelinating diseases or worsening of congenital heart failure.[9–11 w15-w18]

Two other important problems associated with biologics are their immunogenic potential and the risk of autoimmune reactions. Autoantibodies after treatment with TNF-α inhibitors have often been observed, although their clinical relevance remains unclear.[2 3 12–15] The formation of antibodies against the drugs themselves has also been noted and may effect the

*Extra references (w1-w40) are on bmj.com*

**Box 1: Side effects of anti-TNF-α treatment**

- Infections (tuberculosis (especially extrapulmonary and miliary tuberculosis); other opportunistic infections (histoplasmosis, listeriosis, aspergillosis, pneumocystosis); sepsis)
- Malignancies (lymphoma)
- Other haematological disorders (aplastic anaemia, pancytopenia)
- Demyelinating disorders/neuropathy (multiple sclerosis, optical neuritis)
- Worsening of congestive heart failure
- Occurrence of autoantibodies and autoimmunity (human anti-chimeric antibodies, antinuclear antibodies, anti-doublestranded DNA antibodies, anti-phospholipid antibodies, lupus or lupus-like syndrome)
- Infusion/injection and hypersensitivity reactions

**Box 2: Relation between antibody formation and treatment**

- Lower doses of therapeutic antibodies are more immunogenic than higher doses[18 19]
- Single or episodic administration leads to a higher incidence of antibody formation[18]
- Patients with Crohn's disease who received infusions every eight weeks during the ACCENT 1 trial showed significantly higher treatment responses and remission rates and a lower incidence of antibodies to infliximab compared with those who received only a single infusion[19]
- A greater number of infusions and a higher total dose of infliximab may be associated with the development of new autoantibodies[w22]

safety and pharmacokinetics of the respective treatment.[16–19]

Long term data for the use of alefacept or efalizumab are lacking, but during clinical trials efalizumab was associated with a low incidence of serious adverse events (few cases of immune mediated thrombocytopenia), and no increased risk of serious infections or malignancies compared with placebo was observed.[7] For alefacept the incidence of malignancies during clinical trials was slightly increased compared with placebo, as was the incidence of serious infections (www.rxlist.com).

We review here the latest safety data of etanercept, infliximab, adalimumab, with a specific focus on antibody formation and development of autoimmune disorders and lymphoma. We also review the published literature on the safety of alefacept and efalizumab in the treatment of psoriasis.

## Sources and selection criteria

We searched Medline and obtained original articles through the library service. We also used relevant pages found through an internet search using Google and included data from the Annual European Congress of Rheumatology held in Berlin in June 2004.

## Induction of antibodies against biologics

### Incidence of antibody formation

Immune responses to biological products have been reported for many approved therapeutics.[w19] The formation of antibodies against infliximab is an emerging issue in the treatment of patients with Crohn's disease and rheumatoid arthritis (box 2). Whether these antibodies can attenuate the efficacy of treatment or whether they have no detectable effect on the activity of the product is unclear. Further clinical trials are needed to investigate the possible relation between these antibodies and the long term efficacy of infliximab.[17–19 w20 w21]

Baert et al identified antibodies against infliximab in 61% of their patients with Crohn's disease.[17] A concentration of ≥ 8.0 μg/ml was associated with a shorter duration of response and a higher risk of infusion reactions, which were generally mild to moderate. In other trials, antibodies to infliximab were reported in up to 44% (table 1), and infusion reactions as well as the loss of an initial response were found to be strongly related to the amount of antibodies detected.[18 19 w20 w21]. These antibodies seemed to be specific for infliximab and did not crossreact with other therapeutic antibodies.[w23]

### Mechanisms of antibody induction

Several reasons could account for the different rates of autoantibodies found in clinical trials. Concomitant treatment with hydrocortisone significantly reduced the frequency and serum levels of antibodies against infliximab.[18] Other immunosuppressive agents like methotrexate and azathioprine also seem to prevent the formation of antibodies against infliximab.[17 18] Controversial results have been published, however, and controlled trials will have to assess which immunosuppressive agent provides the best protection against the development of these antibodies.[w21 w24]

Most of the patients with rheumatoid arthritis were treated with concomitant immunosuppressants, whereas less than half of the patients with Crohn's dis-

**Table 1** Studies showing incidence of antibodies to infliximab

| | Patient cohort | Incidence of antibodies to infliximab |
|---|---|---|
| Baert et al[17] | 125 patients with Crohn's disease | 61% after fifth infusion (43% *v* 75% with or without concomitant immunosuppressants respectively); >40% after first infusion |
| Farrell et al[18] | 53 patients with Crohn's disease | 36% (24% *v* 63% with or without concomitant immunosuppressants respectively) |
| Hanauer et al[19] | 233 patients with Crohn's disease at week 54 | 27% (38%, 11%, 8% respectively for episodic treatment; scheduled (every 8 weeks) dose of 5 mg/kg; scheduled (every 8 weeks) dose of 10 mg/kg |
| Maini et al[w24] | 428 patients with rheumatoid arthritis treated with methotrexate | 8% |
| Wolbink et al[w21] | 50 patients with rheumatoid arthritis (44 taking concomitant methotrexate) | 44% |

ease were given additional treatment with these agents. Therefore, the dosing regimen and concomitant medication is often difficult to compare between different cohorts of patients and might account for the varying incidence of antibody formation reported.

Immune responses to therapeutic antibodies are also influenced by the construct type (murine, chimeric, humanised, or human).[w25] There are no standardised assays for measuring the amount of antibodies, and the sensitivity and specificity of the assays used are often not fully reported.[w25] Analysis can be performed only in samples in which no infliximab is present because the drug interferes with the measurement and leads to a lower rate of antibodies detected.[w26] Antibody measurement during the above mentioned studies was performed with a commercial assay from Prometheus Laboratories or with a non-commercial Centocor assay. To date, no studies have compared both assay characteristics.

Humanised monoclonal antibodies such as efalizumab and fully human therapeutic molecules such as etanercept and alefacept or adalimumab have to be further investigated in relation to the induction of antibody formation. Recent studies suggest that antibodies against etanercept occur in about 16% of cases (leaflet in etanercept package). The overall incidence of antibodies against adalimumab during three clinical trials was about 5% but differed remarkably according to the concomitant medication used (leaflet in adalimumab package).[16] Under monotherapy with adalimumab 12% of the patients tested positive for antibodies against the drug[16] whereas in the trials where additional methotrexate was used[2 20] only 1% of the patients developed these antibodies. However, in the latter trials one of the patients treated with placebo also tested positive for anti-adalimumab antibodies, which may point to problems with detection and sensitivity of the assay system, thus possibly affecting the validity of the data.

In the combined safety database of the two biologics approved for the treatment of psoriasis vulgaris only, an overall incidence of antibodies against alefacept was seen in about 3% of cases, and development of antibodies against efalizumab occurred in about 6.3%. Antibody development did not correlate with a worse outcome or significant changes in the incidence of adverse events (www.rxlist.com).

## Autoimmunity

The development of antinuclear antibodies and autoimmune disorders has been observed after treatment with TNF-α inhibitors (box 3, table 2).[12 15] To our knowledge, no autoimmunity related phenomena after treatment with alefacept or efalizumab have been reported. Besides its important role as a proinflammatory cytokine, TNF-α also causes serious immunosuppressive effects by regulating antigen-presenting cell functions and apoptosis of potentially autoreactive T cells.[w27] Therefore, antagonising TNF-α and its suppressive effects may lead to the development or unmasking of autoimmune diseases.[21 22] It remains unclear whether the detection of anti-doublestranded DNA antibodies is predictive of an increased risk of developing lupus-like syndrome or systemic lupus erythematosus. Box 4 gives details of trials of autoimmunity during treatment with TNF-α inhibitors.

**Box 3: Autoimmune diseases and autoantibodies that may occur during treatment with TNF-α inhibitors**

- Lupus-like syndrome
- Leukocytoclastic vasculitis
- Systemic lupus erythematosus
- Antinuclear antibodies
- Anti-doublestranded DNA

Case reports of drug induced lupus after treatment with infliximab and etanercept have been published[22 w28-w31] and a French national survey found 12 cases of systemic lupus erythematosus after anti-TNF-α therapy (in about 7000 patients treated) for inflammatory arthritis.[23] Despite the relatively high incidence of anti-doublestranded DNA antibodies, the frequency of clinical lupus related to anti-TNF-α treatment is very low. No evidence exists that patients who develop new autoantibodies are at significantly increased risk of developing drug induced lupus, but the long term impact remains unclear.[21 24] The risk of developing self limiting autoimmune syndromes seems in most cases to be small compared with the impressive clinical benefit the patients experience with these drugs. Nevertheless these findings underline the need for further monitoring of autoantibody production in patients treated with TNF-α antagonists over longer periods. Physicians therefore need to look for signs and symptoms of autoimmune disorders when using TNF-α antagonists.

## Risk of lymphoma development

Another problem that has been noted after treatment with TNF-α antagonists is the development of

**Table 2** Autoimmunity associated with TNF-α inhibitors

| Study | Cohort | Incidence (%) | | No of patients with lupus-like syndrome or systemic lupus erythematosus |
|---|---|---|---|---|
| | | New positive antinuclear antibodies | Anti-doublestranded DNA antibodies | |
| **Infliximab** | | | | |
| Vermeire et al[12] | 125 patients with Crohn's disease | 49.6 | 32.5 | 2 |
| Charles et al[13] | 156 patients with rheumatoid arthritis | 24 | 14 | 1 |
| Bobbio-Pallavicini et al[14] | 30 patients with rheumatoid arthritis | 30 | 16.7 | 0 |
| De Rycke et al[15] | 97 patients with rheumatoid arthritis or spondylarthropathy | 45.3 | 13.4 | 0 |
| **Adalimumab** | | | | |
| Weinblatt et al[2] | 271 patients with rheumatoid arthritis | 11 | 3.9 | 0 |
| Furst et al[3] | 636 patients with rheumatoid arthritis | 26.5 | 12.5 | 0 |

malignancies such as lymphoma (box 5). Several population studies during the past 20 years have shown an increased rate of lymphoproliferative disorders—particularly non-Hodgkin's lymphoma—in patients with rheumatoid arthritis (and to a lesser degree in patients with Crohn's disease and psoriasis) compared with the general population.[w32-w35] There is a known relation between the use of immunosuppressive treatments and the development of lymphoproliferative malignancies,[w36] and concern about an increased risk of lymphoma after treatment with TNF-α antagonists has been raised.[w37 w38] An FDA meeting in March 2003 about the safety of new drugs for rheumatoid arthritis, examined data of patients with rheumatoid arthritis being treated with infliximab, etanercept, and adalimumab (controlled clinical trials and post-marketing experience) and estimated the risk of lymphoma and neoplasia development among those patients (www.rheumatology.org/publications/hotline/0303TNFL.asp?aud=mem). This examination found an increased risk of lymphoma (standard incidence ratio 2.3 to 6.4). Interdrug comparison was impossible owing to different trial designs and patient characteristics. As a result of this evaluation, a warning concerning malignancy has been added to the labelling for all therapeutic anti-TNF-α agents (letter from Centocor, October 2004).

The possibility that TNF-α inhibitors may accelerate the development of lymphomas in patients receiving long term immunosuppressive treatment with ciclosporin or methotrexate (agents often used as first or second line treatment) has also been discussed.[w39] How safe TNF-α inhibitors are when used long term is unclear, but patients should be monitored closely for development of lymphoma (especially as lymphoma can present with an atypical clinical picture[w40]) until the potential risk is better understood.

**Box 4: Studies on autoimmunity during treatment with TNF-α inhibitors**

**Prospective clinical study of autoimmunity in 125 patients with Crohn's disease treated with infliximab[12]**

- The cumulative prevalence of antinuclear antibodies was 56.8% (71 patients) after a follow up of 24 months, compared with 7.2% (nine patients) at baseline
- In most patients the antibodies emerged shortly after the first infusion; these antibodies were associated with the development of butterfly or papulosquamous skin rashes
- Fourteen of the antinuclear antibody-positive patients developed skin manifestations, compared with only two in the group of patients without development of autoantibodies

**Assessment of the incidence of anti-doublestranded DNA antibodies after infliximab treatment with or without concomitant methotrexate in a placebo controlled trial with 156 patients with rheumatoid arthritis[13]**

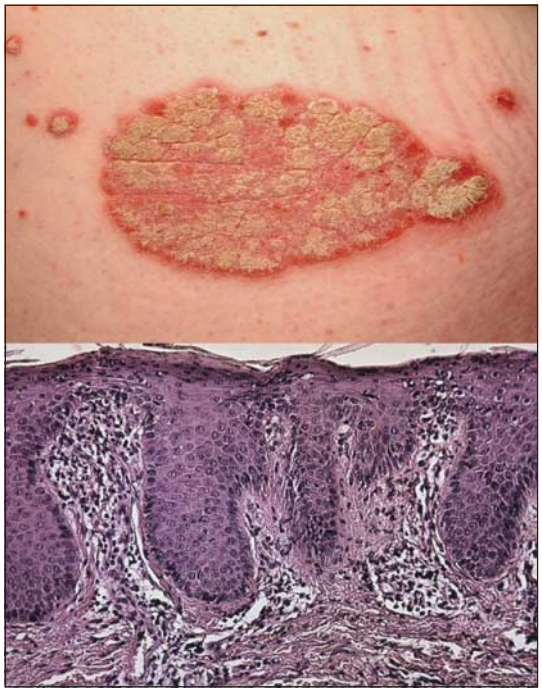
- The incidence of positive antinuclear antibody titres increased from 29% to 53%
- Anti-doublestranded DNA antibodies occurred in 14% of the patients treated with infliximab (0% at baseline); one of the patients developed a reversible lupus-like syndrome
- None of the patients receiving placebo treatment tested positive for anti-doublestranded DNA antibodies
- Concomitant methotrexate did not significantly change the incidence of anti-doublestranded DNA antibodies

**Two large clinical trials with adalimumab in rheumatoid arthritis patients[2 3]**

- These showed a higher rate for new antinuclear antibodies in patients treated with adalimumab than in those treated with placebo (3.9% *v* zero)
- New anti-doublestranded DNA antibodies were detected in 12.5% of patients in the adalimumab group and in 1% of the placebo group

**Box 5: Risk of malignancies after treatment with TNF-α inhibitors**

- Until 2002, 26 cases of malignancy after treatment with TNF-α inhibitors had been reported to the FDA, of which 18 were after treatment with etanercept (19 per 100 000 people treated with etanercept) and eight after treatment with infliximab (6.6 per 100 000 people treated with infliximab)[9]; 14 cases occurred within two months of treatment
- In randomised controlled clinical trials with adalimumab, 10 cases of lymphoma had been identified by March 2003 (www.rxlist.com).
- A few cases of lymphoma after treatment with alefacept and efalizumab have also been reported (www.rxlist.com).



Psoriasis vulgaris: Top: typical erythemato-squamous plaque. Bottom: microscopic cross sectional view of plaque, showing elongated epidermal rete ridges and a dense inflammatory infiltrate

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**Additional educational resources**

**Websites**

MedWatch (www.fda.gov/medwatch/index.html)—The Food and Drug Administration's programme for safety information and for reporting adverse events

Pharmacy Benefits Management Strategic Healthcare Group (www.vapbm.org/PBM/drugmonograph.htm)—Drug monographs and recommendations for practitioners based on current medical evidence and expert opinion from clinicians

Internet drug index (www.rxlist.com)—Information for both consumers and medical professionals about, for example, side effects, precautions, contraindications

**Reviews**

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*One hundred years ago*

## The Japanese art of Ju-jitsu

A most interesting exhibition of Ju-jitsu was given at Chelsea Barracks on January 27th. The programme included demonstrations in the art of falling, of how to upset an opponent by disturbing his balance, of how to throw an opponent, and concluded by bouts between the Japanese teachers and some young soldiers trained in wrestling.

So little is known in this country of the art of Ju-jitsu, the Japanese method of physical training, that this practical demonstration could not fail to be of deep interest. In England, Ju-jitsu is commonly believed to be wrestling pure and simple. In reality, although its literal meaning is "muscle-breaking," it is the art of defeating brute strength by stratagem—an art which enables the smallest and lightest weight men or women to protect themselves from an opponent possessing twice or three times their strength, provided he is ignorant of this science of self-defence. The Japanese have studied the problem of defeating brute strength by art for some hundreds of years. To save one's own strength, to defend oneself by sleight of body while drawing from one's opponent all his strength: this is the art of Ju-jitsu. (*BMJ* 1905;i:259)