

Decreased clinical response to adalimumab in ankylosing spondylitis is associated with antibody formation

Treatment with anti-tumour necrosis factor (TNF) is very effective in most patients with ankylosing spondylitis (AS), but inefficacy occurs in about 40% of cases.¹ Antibody formation against TNF blocking agents is an increasingly recognised problem;² however, no data have yet been reported on antibody formation against adalimumab (anti-adalimumab) in AS. Lack of response can be explained in two ways: (1) TNF might not be important for disease activity in certain patients; and (2) TNF inhibition might be insufficient. The latter could be caused by excessive production of TNF, low compliance of the patient, insufficient dosing or an enhanced clearance of adalimumab due to antibody formation. Adalimumab is a fully human monoclonal antibody against TNF but, despite this fact, an immune response still can be provoked by the antigen binding site also known as the idiotype. In previous studies we have described the problem of immunogenicity of TNF blocking drugs in patients with rheumatoid arthritis (RA),³ in patients with AS treated with infliximab⁴ and in patients with RA treated with adalimumab,⁵ and concluded that the presence of antibodies against infliximab or adalimumab was associated with low or undetectable serum levels of infliximab or adalimumab and clinical non-response.

The objective of the present study was to investigate the relation between the formation of anti-adalimumab, serum adalimumab levels and clinical response in AS.

Patients with AS⁶ were treated with adalimumab, 40 mg every other week, according to the international ASAS consensus statement.^{7,8} Clinical response was defined as a 50% improvement or an absolute improvement of 2 points on the BASDAI scale (0–10). Serum samples were collected at baseline and after 3 and 6 months of treatment. Serum

Table 1 Baseline characteristics and clinical variables

	Baseline (N = 35)	t = 6 months
Male gender, n (%)	27 (76)	
Mean (SD) age (years)	43 (12)	
Disease duration (years)	9 (3.5–16.5)	
HLA-B27 positive, n (%)	24 (69)	
Presence of IBD, n (%)	4 (12)	
Presence of uveitis, n (%)	15 (46)	
Presence of arthritis, n (%)	11 (32)	
Anti-TNF used before, n (%)	10 (29)	
BASDAI	6.2 (4.9–7.6)	3.0 (1.2–5.3)*
ASAS response (N responders, %)		18 (51%)
Global disease activity	7.2 (5.9–8.0)	2.1 (1.0–5.0)*
ESR	31 (19–44)	7 (3–15)*
CRP	21 (10–35)	<5 (2–6)*

Unless otherwise indicated, values are median (interquartile range).

ASAS, Assessments in Ankylosing Spondylitis (decrease of 50% or >2, global disease activity (0–10 scale)); BASDAI, Bath Ankylosing Spondylitis Disease Activity Index (0–10 scale); CRP, C-reactive protein (normal <10.0 mg/l); ESR, erythrocyte sedimentation rate (normal <15 mm/h); HLA B27, human leucocyte antigen B27; IBD, inflammatory bowel disease.

*p<0.001 compared with baseline.

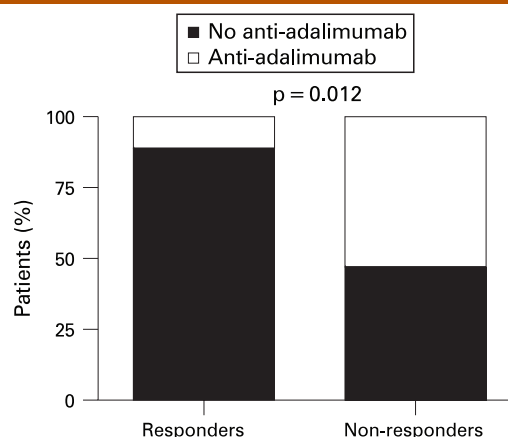


Figure 1 Relation between the presence of anti-adalimumab and response of ankylosing spondylitis to treatment with adalimumab.

adalimumab levels were determined with an ELISA and anti-adalimumab was measured with a validated antigen binding test. The assays used were similar to those described previously for the detection of infliximab levels and antibodies against infliximab.^{4,5}

Thirty-five patients were included. After 6 months of treatment, 18 were ASAS responders (table 1). Within 6 months of treatment, 11 patients developed anti-adalimumab with low or undetectable adalimumab levels, 9 were ASAS non-responders (p=0.012) and 1 had an allergic reaction with flushing, dyspnoea and undetectable serum adalimumab levels (fig 1).

Thus, anti-adalimumab was detected in 31% of the patients after 6 months of treatment and this corresponded with diminished or undetectable serum adalimumab levels in these patients. These preliminary observations will need confirmation in a larger study. In contrast with the treatment of RA, adalimumab is given without methotrexate in the treatment of AS. This might be an explanation for the higher incidence of anti-adalimumab formation in AS. In Crohn's disease and in RA, the concomitant use of immunosuppressive drugs or corticosteroids has been proved to decrease antibody formation against infliximab.^{9,10}

To date, no other papers have reported on immunogenicity in the treatment of AS with adalimumab and no systemic allergic reactions have been described. The detection of antibodies might predict the inefficacy of adalimumab and should be explored further for use in daily clinical practice.

M K de Vries,¹ E Brouwer,⁵ I E van der Horst-Bruinsma,¹ A Spoorenberg,⁶ J C van Denderen,³ A Jamnitski,³ M T Nurmohamed,^{1,3} B A C Dijkmans,^{1,3} L A Aarden,^{2,4} G J Wolbink^{2,3}

¹ VU University Medical Centre, Amsterdam, The Netherlands; ² Sanquin Research, Amsterdam, The Netherlands; ³ Jan van Breemen Institute, Amsterdam, The Netherlands; ⁴ Landsteiner Laboratory Academic Medical Centre, Amsterdam, The Netherlands; ⁵ University Medical Center, Groningen, The Netherlands; ⁶ Medical Center, Leeuwarden, The Netherlands

Correspondence to: Dr I E van der Horst-Bruinsma, VU University Medical Centre, Rheumatology Department, room 3A-64, P O Box 7057, 1007 MB Amsterdam, The Netherlands; ie.vanderhorst@vumc.nl

Acknowledgements: The authors thank Mrs Abrahams and Mrs Bulstra, research nurses, for their support; Mrs van Houten and Mr de Vrieze for determining adalimumab levels and anti-adalimumab; and Mrs Vesters for proof reading this manuscript.

Funding: The clinical part of this study was partially financed by Abbott. This investigation was also facilitated by the Clinical Research Bureau of the Jan van Breemen Institute and received financial support from the Dutch Arthritis Foundation.

Competing interests: None.

Provenance and peer review: Not commissioned; externally peer reviewed.

Accepted 7 February 2009

Ann Rheum Dis 2009;**68**:1787–1788. doi:10.1136/ard.2009.109702

REFERENCES

1. **van der Heijde DM**, Schiff MH, Sieper J, *et al*. Adalimumab effectiveness for the treatment of ankylosing spondylitis is maintained for up to 2 years: long-term results from the ATLAS trial. *Ann Rheum Dis* 2009;**68**:863–7.
2. **Aarden LA**, Ruuls SR, Wolbink GJ. Immunogenicity of anti-tumour necrosis factor antibodies-toward improved methods of anti-antibody measurement. *Curr Opin Immunol* 2008;**20**:431–5.
3. **Wolbink GJ**, Vis M, Lems W, *et al*. Development of anti-infliximab antibodies and relationship to clinical response in patients with rheumatoid arthritis. *Arthritis Rheum* 2006;**54**:711–5.
4. **de Vries MK**, Wolbink GJ, Stapel SO, *et al*. Decreased clinical response to infliximab in ankylosing spondylitis is correlated with anti-infliximab formation. *Ann Rheum Dis* 2007;**66**:1252–4.
5. **Bartelds GM**, Wijbrandts CA, Nurmohamed MT, *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.
6. **van der Linden S**, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. *Arthritis Rheum* 1984;**27**:361–8.
7. **Braun J**, Pham T, Sieper J, *et al*. International ASAS consensus statement for the use of anti-tumour necrosis factor agents in patients with ankylosing spondylitis. *Ann Rheum Dis* 2003;**62**:817–24.
8. **Braun J**, Davis J, Dougados M, *et al*. First update of the international ASAS consensus statement for the use of anti-TNF agents in patients with ankylosing spondylitis. *Ann Rheum Dis* 2006;**65**:316–20.
9. **Baert F**, Noman M, Vermeire S, *et al*. Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. *N Engl J Med* 2003;**348**:601–8.
10. **Maini RN**, Breedveld FC, Kalden JR, *et al*. Therapeutic efficacy of multiple intravenous infusions of anti-tumour necrosis factor alpha monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. *Arthritis Rheum* 1998;**41**:1552–63.

MRSA infections in patients treated with tumour necrosis factor inhibitors

Clinical experience with the three available tumour necrosis factor (TNF) inhibitors (etanercept, infliximab and adalimumab) shows improvement in inflammatory arthritis. Clinical studies have reported serious infections such as reactivation tuberculosis following treatment with TNF inhibitors. Bacterial infections with organisms such as *Staphylococcus aureus* (both methicillin-sensitive (MSSA) and methicillin-resistant (MRSA)), *Streptococcus* and Gram-negative organisms have not been reported to be more frequent or severe. We noticed several severe MRSA infections in patients treated with TNF inhibitors and wondered whether these agents might alter the outcome of these infections. We therefore performed a retrospective analysis of patients treated in our practice.

Between August 2003 and July 2006, 430 patients with inflammatory arthritis (rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis) were treated with anti-TNF agents in our practice. In all instances where infections occurred, bacterial culture results were documented, patients were interviewed and examined and all pertinent hospital and medical records were reviewed. Institutional review board approval for a retrospective chart review was obtained through the Anne Arundel Medical Center (LICJ-0501(E)).

As indicated in table 1, there were 15 severe MRSA infections and 11 severe MSSA infections. The most common infection in both was cellulites. Other infections included osteomyelitis, pneumonia, sinusitis and septic arthritis. There was one case of Fournier's gangrene with MRSA sepsis and one of mastitis. Over half the infections occurred within the first 6 months of treatment. Infections occurred with all TNF agents: infliximab (9), etanercept (10) and adalimumab (6). One patient was a known MRSA carrier.

The average age of the patients was 61 years; 59% were women and 41% were men. Concomitant diseases included diabetes (7), coronary disease (6) and renal insufficiency (3). Prednisone (20) and methotrexate (10) were concomitant treatments in many of these patients.

Most infections were severe and required hospitalisation. Twelve patients with MRSA were hospitalised; 14 required

intravenous antibiotics. Seven patients with MSSA were hospitalised; nine required intravenous antibiotics.

Attempts to restart TNF inhibitors after control of MRSA infection resulted in recurrent MRSA infection in seven patients. Two patients were able to resume TNF inhibitor therapy after the infection was controlled. Two patients were treated with rituxan with no recurrences.

Other infections included Gram-negative bacterial cellulites (4), severe *Clostridium difficile* infections (3) and tuberculosis infection with fatal pneumonia (1). Seventeen other patients had pneumonia (6), diverticulitis (2) and cellulites (9) with no bacterial agent cultured.

In this study, MRSA and MSSA infections were more frequent than any other infection and were more severe than expected. Our patient population was older and had more concomitant diseases such as diabetes than in previous publications. We do not know the MRSA carrier status of most of our patients before initiating treatment with TNF inhibitors. We do know that retreatment of known carriers resulted in recrudescence of MRSA infections in seven patients.

In the USA approximately one-third of patients carry MSSA and 0.8% of patients carry MRSA.^{1 2} A significant number of patients receiving treatment with TNF inhibitors may be at risk for activation of infection.^{3 4}

Several questions arise about treatment with TNF inhibitors:

- ▶ Should known MRSA carriers be treated with TNF agents?
- ▶ Should patients be treated with TNF agents once the infection has subsided?

Table 1 MRSA and MSSA infections in 25 patients treated with anti-TNF agents

	Organism	
	MRSA (n = 15)	MSSA (n = 10)
Cellulitis	6	5
Osteomyelitis	3	1
Pneumonia	1	–
Sinusitis	2	–
Septic arthritis	1	4
Mastitis	1	–
Fournier's gangrene	1	–

MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; TNF, tumour necrosis factor.



Decreased clinical response to adalimumab in ankylosing spondylitis is associated with antibody formation

M K de Vries, E Brouwer, I E van der Horst-Bruinsma, et al.

Ann Rheum Dis 2009 68: 1787-1788

doi: 10.1136/ard.2009.109702

Updated information and services can be found at:

<http://ard.bmj.com/content/68/11/1787.full.html>

These include:

References

This article cites 10 articles, 5 of which can be accessed free at:

<http://ard.bmj.com/content/68/11/1787.full.html#ref-list-1>

Article cited in:

<http://ard.bmj.com/content/68/11/1787.full.html#related-urls>

Email alerting service

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:

<http://group.bmj.com/group/rights-licensing/permissions>

To order reprints go to:

<http://journals.bmj.com/cgi/reprintform>

To subscribe to BMJ go to:

<http://group.bmj.com/subscribe/>