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Inefficacy of infliximab in ankylosing spondylitis is correlated with antibody formation

M K de Vries, G J Wolbink, S O Stapel, E R de Groot, B A C Dijkmans, L A Aarden, I E van der Horst-Bruinsma

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Tumour necrosis factor blocking agents such as infliximab have proved to be effective in patients with ankylosing spondylitis as up to 60–70% of the patients meet the 20% response criteria of assessment in ankylosing spondylitis (ASAS).[1 2] However, it cannot be explained why 30% of patients fail to respond and develop adverse reactions.

In rheumatoid arthritis, inefficacy to infliximab was associated with low serum trough infliximab levels and the presence of antibodies to infliximab (ATI).[3]

This study was designed to identify whether infliximab levels and ATI predict clinical inefficacy and adverse events in ankylosing spondylitis.

Eight patients with active ankylosing spondylitis (fulfilling the 1984 modified New York Criteria[4]) were treated according to the international ASAS consensus statement,[5] with infliximab 5 mg/kg given intravenously at baseline, weeks 2, 6, and 12, and every 6 weeks thereafter. Sera were collected at 12 and 24 weeks before infusion.

At every visit, questionnaires (eg, Bath Ankylosing Spondylitis Disease Activity Index) to assess ASAS 20% response were obtained and routine laboratory tests were performed. These data were correlated with disease activity (ASAS 20% response), serum trough infliximab levels and antibody levels.

All patients were men, with a median (range) age of 47 (24–52) years, and were human lymphocyte antigen B27 positive, with a median (range) disease duration of 11 (1–28) years (table 1). Patient 1 was concomitantly treated with 15 mg methotrexate weekly and patient 3 was treated with cyclosporine and sulfasalazine.

Most patients responded well to infliximab with a considerable decline in Bath Ankylosing Spondylitis Disease Activity Index, erythrocyte sedimentation rate and C reactive protein, high serum trough levels of infliximab and no development of ATI. However, two non-responders did not show detectable serum trough infliximab levels and developed ATI after, respectively, 12 and 24 weeks. Patient 3 did not respond to treatment at all, whereas patient 5 met the ASAS 20% response criteria but had an increase in erythrocyte sedimentation rate and C reactive protein levels. Both patients developed an infusion reaction to infliximab.

In this study on eight patients with ankylosing spondylitis, a correlation between efficacy of infliximab and high levels of serum trough infliximab was shown. In 25% of these patients

Table 1 Clinical reponse to infliximab in patients with ankylosing spondylitis in relation to infliximab levels and antibodies to infliximab after 24 weeks

Patient	BASDAI week 0 Mean: 5.5 Median: 5.2	BASDAI week 24 Mean: 1.9 Median: 1.8	ESR week 0 Mean: 43 Median: 26.5	ESR week 24 Mean: 11 Median: 8.5	CRP week 0 Mean: 52 Median: 25	CRP week 24 Mean: 8 Median: 5	ASAS 20%	Infliximab level (ng/ml)	ATI (ng/ml)
1	6.4	1.2	88	4	115	4	+	17 800	0
2	4.5	0.7	90	8	120	6	+	10 100	0
3*	†	†	22	26	14	21	†	0	7200
4	7.2	0.0	72	18	104	6	+	20 600	0
5*	4.7	3.1	12	18	7	20	+	0	15 600
6	4.5	1.8	23	9	11	<2.5	+	16 000	0
7	5.2	4.1	10	6	7	<2.5	+	10 300	0
8	6.3	2.1	30	1	36	<2.5	+	16 400	0

ASA, acetylsalicylic acid; ASAS, assessment in ankylosing spondylitis; ATI, antibodies to infliximab; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CRP, C reactive protein; ESR, erythrocyte sedimentation rate.
BASDAI score (scale 0–10), ESR (mm/h), CRP (mg/l), ASAS 20% response.
*Considered as non-responders owing to increase in inflammatory parameters.
†Not done owing to severe visual impairment.

with ankylosing spondylitis ATI developed within 24 weeks in association with undetectable serum trough infliximab levels, inefficacy of infliximab and infusion reactions. The number of patients, however, is too small to draw definite conclusions, but interestingly, these data point in the same direction as described previously in rheumatoid arthritis.[3] Lower serum trough infliximab levels could be explained by enhanced clearance because of immune complex formation between anti-infliximab antibodies and infliximab. To prevent ATI formation that might inhibit the efficacy of infliximab, it might be helpful to increase the dosage of infliximab (as occurs in treatment of rheumatoid arthritis with infliximab), to shorten the interval between infliximab infusions (as is currently the strategy in Crohn's disease) or to provide coadministration of other immunosuppressives (such as methotrexate). These data should be confirmed in a larger group of patients with ankylosing spondylitis to develop a more patient-specific treatment, which might predict the inefficacy of infliximab at an early stage and might prevent adverse reactions.

Authors' affiliations
M K de Vries, Department of Rheumatology, VU University Medical Center, Amsterdam, The Netherlands
G J Wolbink, Sanquin Research, Amsterdam, The Netherlands
S O Stapel, E R de Groot, L A Aarden, Sanquin Research, Amsterdam, The Netherlands
B A C Dijkmans, VU University Medical Center, Amsterdam, The Netherlands
I E van der Horst-Bruinsma, VU University Medical Center, Amsterdam, The Netherlands

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Correspondence to: Dr M K de Vries, Department of Rheumatology, VU University Medical Centre, Room 4A-42, PO Box 7057, 1007 MB Amsterdam, The Netherlands; mk.devries@vumc.nl

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Magnetic resonance imaging in patients with rheumatoid arthritis with complete remission treated with disease-modifying antirheumatic drugs or anti-tumour necrosis factor α agents

M U Martínez-Martínez, E Cuevas-Orta, G Reyes-Vaca, L Baranda, R González-Amaro, C Abud-Mendoza

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Biological treatment, mainly with anti-tumour necrosis factor (TNF)α agents, of patients with rheumatoid arthritis, has been shown to modify their clinical course and progression, and delay or avoid its radiological progression.[1 2] Disease remission in rheumatoid arthritis has been traditionally considered when there is no clinical or biochemical evidence of disease activity.[3]

Magnetic resonance imaging (MRI) has been shown to be more sensitive than clinical and radiological parameters in evaluating the bone erosions and the inflammatory phenomenon that characterise disease activity in patients with rheumatoid arthritis.[4–9] For this reason, the therapeutic response to disease modifying antirheumatic drugs (DMARDs) has been evaluated by MRI.[4–9] However, there are no comparative studies on the therapeutic effectiveness of DMARDs and anti-TNFα agents using this type of imaging studies, mainly when patients have reached clinical remission.

We studied 10 patients with rheumatoid arthritis, who were induced to clinical and laboratory remission with DMARDs alone (n = 5, table 1) or with an anti-TNFα agent with or without DMARDs (n = 5). In both groups, MRI of the hands was performed at least 3 months after disease remission in sagital and coronal projections, and 24 joints were assessed in each patient. In the five patients receiving DMARDs alone, we found MRI evidence of synovitis, with a total count of 24 inflamed joints. By contrast, only two patients receiving anti-TNFα treatment showed MRI evidence of synovitis, with only two inflamed joints (p = 0.001, Fisher's exact test). In addition, we did not find a significant correlation between clinical or laboratory data and MRI results, as has been reported previously.[9 10]

Our results corroborate the fact that MRI imaging is a sensitive parameter for the detection of joint inflammation and destruction in patients with rheumatoid arthritis.[4–9] Our data also show that complete remission in this condition is easily achieved with the addition of anti-TNFα agents, and that treatment with DMARDs alone induces only an apparent remission, defined by clinical and laboratory parameters. We