Clinical implications of immunogenicity

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Chapter 2

High levels of human anti-human antibodies (HAHAs) to adalimumab in a patient not responding to adalimumab therapy

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Adalimumab is a very effective treatment for rheumatoid arthritis (RA). However, a substantial proportion of RA patients either do not respond or lose their initial response. (1)
We report a patient who initially responded to adalimumab therapy, but disease activity increased as treatment continued. We believe that this lack of response to adalimumab is most likely caused by human anti-human antibodies (HAHA) formation.

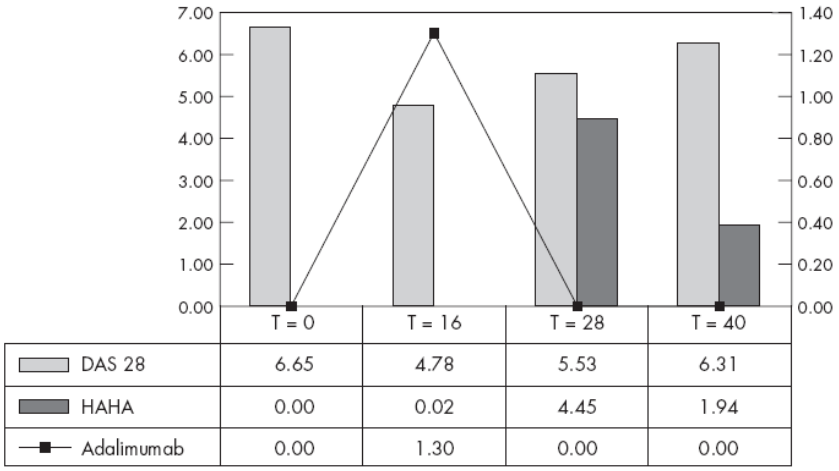
Case report

A 69-year old woman with RA (diagnosed in 1991) and progressive joint destruction had active disease despite treatment with methotrexate 10 mg weekly and prednisone 7.5 mg/day. Therefore, treatment with adalimumab , 40 mg every other week, was started, combined with methotrexate 10 mg weekly.

Table 1 Development of disease activity parameters

Time	*ESR(mm/hr)*	*CRP(mg/l)*	*VAS*	*TJC*	*SJC*	*DAS 28*
T= 0 wk	89	63	98	5	10	6.65
T= 4 wk	58	38	49	1	8	4.88
T= 16 wk	65	26	19	3	5	4.78
T= 28 wk	71	32	85	2	4	5.53
T= 40 wk	91	77	87	5	6	6.31
T= 4 wk (Etanercept)	51	5	37	1	3	4.32

After 16 weeks of adalimumab therapy the patient's DAS 28 score had decreased from 6.65 to 4.78 (table 1). (2) According to the Eular response criteria this qualifies as a (moderate) responder.
At week 20, treatment with adalimumab and methotrexate was stopped for 8 and 4 weeks, respectively, in order to undergo total knee replacement surgery. Despite restarting adalimumab and methotrexate therapy, disease activity remained high for the following weeks. Hence, from week 35 onwards adalimumab 40 mg was administered weekly instead of every other week, but nevertheless disease activity remained high. Therefore adalimumab treatment was switched into etanercept treatment and this change resulted in a substantial improvement of disease activity. Serum trough adalimumab levels were measured by ELISA, similar as described for infliximab elsewhere. (3)(figure 1).
Serum HAHA levels were detected by a newly developed radio-immuno assay, a specific assay measuring high avide antibodies against adalimumab, similar as described for rituximab. (4)



	T = 0	T = 16	T = 28	T = 40
DAS 28	6.65	4.78	5.53	6.31
HAHA	0.00	0.02	4.45	1.94
Adalimumab	0.00	1.30	0.00	0.00

Figure 1 Course of Disease Activity Score (DAS) in relationship to serum adalimumab levels (µg/ml) and serum levels of antibodies (AU/cl). HAHA, human anti-human antibodies.

HAHAs were present after treatment cessation for the planned surgical procedure, and at the same time serum adalimumab levels were undetectable (figure 1). As HAHA levels increased, adalimumab levels dropped, and disease activity increased.

Discussion

Our patient developed HAHAs to adalimumab despite the fact that adalimumab is a human monoclonal antibody. Infliximab is a chimeric antibody and can induce an immunogenic reaction in the form of HACAs. Development of HACAs to infliximab is associated with a reduced response to treatment (5), where as thus far such relationships were not described for adalimumab.

In our patient, the anti-rheumatic drug free period may have influenced the development of HAHAs. The absence of the protective role of methotrexate may have stimulated the formation of HAHAs. Another possibility is that continuous high levels of adalimumab induced immunotolerance and when adalimumab therapy was discontinued, serum levels dropped and HAHAs developed.

A substantial amount of RA patients have persistent disease activity despite treatment with adalimumab. As demonstrated by our case, the formation of HAHAs to adalimumab may be an explanation for failure of adalimumab therapy. Treatment with another TNF blocking agent might be an option in such cases.

Ethics committee approval was secured for the study reported by the Stichting Slotervaartziekenhuis, Medisch Ethische Toetsingscommissie, in Amsterdam.

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