Immunogenicity negatively influences the outcome of adalimumab treatment in Crohn's disease

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SUMMARY

Background

Adalimumab is an effective treatment in patients with Crohn's disease; as it is a humanized anti-tumour necrosis factor monoclonal antibody, immunogenicity is thought not to be of any significance.

Aim

To assess whether antibodies to adalimumab (ATAs) affect adalimumab treatment outcome in patients with Crohn's disease previously treated with infliximab.

Methods

A retrospective study was performed. Patients with active Crohn's disease and who had lost response or were intolerant to infliximab were treated with adalimumab. Clinical response and side effects were assessed as were serum ATAs and antibodies to infliximab (ATIs).

Results

In total 30 patients [M/F (7/23)], median age 36 years (range 21–73) were treated with adalimumab for 318 days (median range 83–632). Clinical response was 77% (23/30), a dose escalation was necessary in eight (27%) patients and side effects were observed in 47% (14/30). In five patients (17%) ATAs were detected; of these patients, four were nonresponders. The presence of ATAs was related to nonresponse to adalimumab ($P = 0.006$). ATIs were positive in 57% of patients (17/30) and serum levels were significantly increased in adalimumab nonresponders ($P = 0.01$).

Conclusion

Immunogenicity plays a role in adalimumab treatment because of the development of ATAs.

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INTRODUCTION

The chimeric monoclonal antibody to tumour necrosis factor (TNF-alpha), infliximab, is effective as an induction and maintenance therapy for patients with moderate-to-severe Crohn's disease[1-3] including fistula closure[4, 5] and probably even better in combination with antibiotics.[6] However, its use is associated with the formation of antibodies to infliximab (ATIs), which can lead to infusion reactions, loss of efficacy and delayed hypersensitivity reactions.[7-9]

In contrast to infliximab, adalimumab is a fully humanized IgG1 class anti-TNF antibody that can be administered subcutaneously. Studies have shown that adalimumab is effective in inducing and maintaining clinical remission in patients with moderate-to-severe Crohn's disease naive to anti-TNF therapy and also in patients previously treated with infliximab.[10-12] In addition, adalimumab is also an effective induction therapy in patients who have previously responded to infliximab and then lost response or become intolerant.[13]

As seen in infliximab treatment, the immunogenicity of a biological has important consequences for treatment outcome and therapeutic approach, for example, the use of concomitant immunosuppressive therapy. The role of immunogenicity in adalimumab treatment has not yet been fully elucidated in Crohn's disease. Based on the fully humanized molecular structure of this antibody, adalimumab would presumably be less immunogenic than the chimeric antibody infliximab. However, in rheumatoid arthritis patients, antibodies to adalimumab (ATAs) were associated with lower serum adalimumab concentrations and a nonresponse to adalimumab therapy.[14]

As the role of immunogenicity in adalimumab treatment is not clear in patients with Crohn's disease, this study aimed to assess whether ATAs affect adalimumab treatment outcome in these patients.

MATERIALS AND METHODS

A retrospective study was performed and all patients signed an informed consent for taking extra serum samples. The first patients treated with adalimumab in our centres were included in this study. These patients had active luminal or fistulizing Crohn's disease and had lost response to or were intolerant to infliximab. No primary nonresponders were included in this study. The following subcutaneous regimen was used: 160 mg

at week 0, 80 mg at week 2 and 40 mg every 2 weeks. Clinical response and side effects were assessed. Clinical response for luminal disease was assessed by a physician specialized in treating patients with Crohn's disease. Nonresponse was defined as no improvement in the following clinical symptoms: general wellbeing, abdominal pain, number of liquid or very soft stools, presence of abdominal mass and extra-intestinal manifestations. For fistulizing Crohn's disease, clinical response was defined as a reduction of 50% or more from baseline in the number of draining fistulas. Closure of a perianal fistula was defined as no drainage despite firm finger compression. The physician assessing clinical response was blinded to the presence of ATAs.

Serum was taken from patients prior to adalimumab treatment for the detection of ATIs and during treatment for the detection of ATAs. Serum ATAs levels were only measured when the minimum adalimumab treatment duration was 60 days. Serum ATAs and ATIs levels were detected with a radioimmunoassay as described by Bartelds et al.[14] and Wolbink et al.[15] The cut-off level for a positive signal was set at 12 AU/mL for both assays.

Data were analysed as frequencies and percentages. Differences between responders and nonresponders were assessed using the chi-squared test. The Fisher's exact test was used to assess the relationship between clinical response and the presence of ATAs and ATIs. The antibodies levels are presented as means ± standard error of mean, unless stated otherwise. The differences in the mean serum ATIs levels between responders and nonresponders were assessed using the Student's t-test. Two-sided P-values <0.05 were considered to indicate statistically significant differences. All analyses were performed using SPSS 14.0 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

In total, 30 patients previously treated with infliximab were included in this study. Patient characteristics are described in Table 1. Median adalimumab treatment duration was 318 days (range 83–632). Overall clinical response was 77% (23/30); 81% (18/22) in patients with luminal and 63% (five of eight) in patients with fistulizing disease. A dose escalation to 40 mg weekly was necessary in eight patients (27%) of which six patients finally responded. Side effects were observed in 47% (14/30) of patients leading to withdrawal of

	Patients ($n = 30$)
Gender (M/F)	7/23
Age (years), median (range)	36 (21–73)
Type of Crohn's disease	
Luminal	22
Fistulizing	8
Reason for infliximab discontinuation	
Loss of response	4
Intolerance	23
Unknown	3
Concomitant medication	13
Corticosteroids	4
Any immunosuppressive agent	
Azathioprine	4
Mercaptopurine	1
Methotrexate	4

treatment in six. The main side effects were headache, fever and rash, but no severe side effects occurred.

The median time between initial adalimumab treatment and the assessment of ATAs was 346 days (range 68–671). ATAs were detected in five patients (17%); of these patients, four were nonresponders. The presence of ATAs was related to a nonresponse to adalimumab (OR 13.1, 95% CI: 1.7–99.2, $P = 0.006$; Figure 1).

When patients with luminal and fistulizing disease were assessed separately, no relationship between the
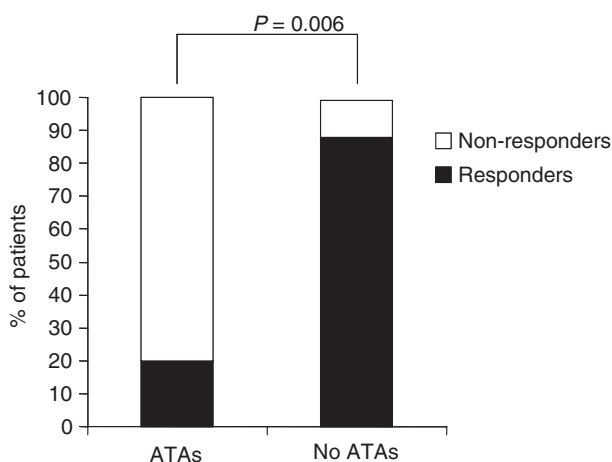

Figure 1. The relationship between the presence of antibodies to adalimumab (ATAs) and response to adalimumab treatment. The presence of ATAs was related to a nonresponse to adalimumab (OR 13.1, CI: 1.7–99.2, $P = 0.006$).

presence of ATAs and clinical response was found in the patients with fistulizing disease. However, for patients with luminal disease, ATAs were detected in 75% (three of four) of the nonresponders compared to 5.6% (one of 17) of the responders. In this subgroup, the presence of ATAs was associated with nonresponse (OR 13.5, 95% CI: 1.9–98.5, $P = 0.01$).

Of the 13 patients using concomitant medication, only one was found to have ATAs (7.7%) while of the 17 patients without immune suppression, four patients developed ATAs (20%). This difference was not significant. Furthermore, of the eight patients requiring a dose escalation, only two were found to have ATAs. There was no relationship between the presence of ATAs and the requirement for dose escalation.

Antibodies to infliximab were found in 57% (17/30) of patients; the mean serum ATIs level was 246.3 ± 75.3 AE/mL. Of the 17 ATIs positive patients, 12 were responders and five nonresponders to adalimumab. No relationship was found between the presence of ATIs and response to adalimumab therapy. However, serum ATIs levels were significantly increased in adalimumab nonresponders (responders vs. nonresponders: 163.0 ± 58.6 vs. 520.4 ± 244.0 AE/mL, $P = 0.01$). No relationship was observed between the presence of ATAs and ATIs.

DISCUSSION

Adalimumab is an effective treatment in patients with Crohn's disease and as it is a humanized anti-TNF monoclonal antibody, immunogenicity is thought not to be of any significance. However, in this study, patients were found to develop ATAs, which negatively influenced response to adalimumab treatment.

To our knowledge, this is the first study in patients with Crohn's disease to find that immunogenicity affects the outcome of adalimumab treatment. Previous studies did not find a correlation between the presence of ATAs and loss of response to adalimumab. The adalimumab induction and continuation trial for maintenance of remission[10, 11] only included infliximab naïve patients. In both studies, a small number of patients developed antibodies, 0.04% (one of 225) and 2.6% (seven of 269) respectively and no relationship was found between clinical response and the presence of ATAs. The difference in occurrence of antibody formation between these trials and our study might be explained by the difference in inclusion criteria; infliximab naïve patients versus those previously

treated with infliximab. Previous infliximab treatment might be an important immunizing factor increasing the rate of adalimumab immunogenicity. In the Gauging Adalimumab Efficacy in Infliximab Nonresponders (GAIN) study, patients with infliximab refractory disease were included, as in our study[13] but none of these patients developed ATAs. However, follow-up was only 4 weeks in the GAIN study.

In the initial studies evaluating the efficacy and safety of adalimumab in patients with rheumatoid arthritis, ATAs were found in patients, but no correlation with clinical response was seen.[16] However, in a more recent study in patients with rheumatoid arthritis, findings similar to those in this study[14] were reported. In a prospective study, Bartelds et al. evaluated adalimumab and adalimumab antibody levels in relation to clinical response in a cohort of 121 rheumatoid arthritis patients up to 28 weeks after initiation of adalimumab treatment. Similar to our results, 17% of the patients tested positive for ATAs, this was also associated with lower serum adalimumab concentrations and nonresponse to adalimumab therapy.

There are two possible explanations for the discrepancy in the incidence and effect of ATAs in the studies mentioned above. First, in some studies, the follow-up time might have been too short to identify all patients with antibodies and to detect an effect on treatment outcome. Secondly, these differences could be because of the use of different assays, as Bartelds et al.[14] discussed in their study. Therefore, assays must be standardized to compare studies and to gain more insight into the effect of antibody formation on therapeutic outcome in patients treated with adalimumab.

In infliximab treatment, immunomodulators are often used as they are thought to suppress the formation of ATIs.[7, 8] The question arises whether this is the case for adalimumab treatment. This is unknown for patients with Crohn's disease. However, in patients with rheumatoid arthritis, the concomitant use of methotrexate during adalimumab treatment reduced the rate of antibody development.[14] In our study, the number of patients was too small to draw conclusions about the role of concomitant therapy and the formation of antibodies. A larger study with a longer follow-up is needed to assess this.

Our results also suggest that patients previously treated with infliximab with high levels of ATIs have a lower response rate to adalimumab than patients with low levels of ATIs. This effect might be explained hypothetically by the cross reactivity of ATIs with adalimumab. Yet, infliximab and adalimumab are different idiotypes which makes this type of cross reactivity unlikely. This is also supported by in vitro observations (G. J. Wolbink, unpublished data).

The immunogenicity of a biological is determined by the immune response of an individual patient. High levels of ATIs that negatively influenced adalimumab treatment outcome in our study would then be an epiphenomenon reflecting the individual immune reaction. Furthermore, rheumatoid arthritis patients with ATIs have increased ATAs levels (G. J. Wolbink, unpublished data). Previous clinical observations suggest that a loss of response to infliximab treatment may affect response to subsequent treatment with adalimumab. The GAIN trial also found that adalimumab was more effective than a placebo in patients with infliximab refractory disease. ATIs did not seem to play a role, but the relationship with ATIs levels was not reported in this study.[13] In addition, the CHARM study found that patients naïve to infliximab had a slightly better response to adalimumab than those who had previously been treated with infliximab, but this difference was not statistically significant.[12] This suggests that patients who lose response to an anti-TNF antibody never regain full response even when treated with a different anti-TNF antibody. Predisposition to antibody formation may be a factor underlying this phenomenon.

The main limitations of this study are a retrospective study design and the small number of patients included. We also did not use an objective measure such as the Crohn's Disease Activity Index to assess clinical response in luminal disease. Nevertheless, clinical response was assessed by experienced physicians using unequivocal criteria for nonresponse thus making these findings reliable. As this is a retrospective study, ATAs were measured at different time points for each of the patients. However, the minimum adalimumab treatment duration of 60 days allowed sufficient time to assess the presence of antibodies. Furthermore, serum trough adalimumab levels were not measured. However, it has been shown previously that the presence of ATAs is associated with low serum trough adalimumab levels.[14] The reduced adalimumab concentration is probably because of increased clearance of adalimumab via the formation of immune complexes between ATAs and adalimumab. Thus our results give a clear indication that ATAs affect adalimumab treatment outcome.

On the basis of our results, we can conclude that immunogenicity negatively influences response to adalimumab treatment in Crohn's disease patients because of the development of ATAs. This means that a group of patients will not respond or eventually lose response to adalimumab treatment because of the formation of antibodies. Future larger prospective studies will have to provide more insights into this group of patients and on what the best treatment strategy is.

ACKNOWLEDGEMENT

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