

Treatment of active ankylosing spondylitis with abatacept: an open-label, 24-week pilot study

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ABSTRACT

Objective To prospectively explore the short-term efficacy and safety of abatacept in patients with ankylosing spondylitis (AS).

Methods In this prospective open-label pilot study, abatacept (10 mg/kg) was administered intravenously on days 1, 15, 29 and every 28 days thereafter up to week 24 in 15 tumour necrosis factor α (TNF α)-inhibitor naive patients (group 1) and 15 patients with inadequate response to TNF α inhibitors (group 2) with active AS. The primary end point was the proportion of patients with 40% improvement according to the Assessment of SpondyloArthritis international Society criteria (ASAS40) in both groups at week 24.

Results At week 24, ASAS40 was reached by 13% of group 1 and 0% of group 2; 20% improvement (ASAS20) was reached by 27% and 20%, respectively. There was no significant change of Bath Ankylosing Spondylitis Disease Activity Index score, patient global assessment or C reactive protein. Overall, abatacept was well tolerated.

Conclusions In this pilot open-label AS study a major response was not observed.

INTRODUCTION

Ankylosing spondylitis (AS) is a chronic rheumatic disease predominantly of the axial skeleton. Only non-steroidal anti-inflammatory drugs (NSAIDs) and tumour necrosis factor α (TNF α) inhibitors are effective for the treatment of predominant axial manifestations of AS.¹ Thus, in contrast to rheumatoid arthritis (RA) and other inflammatory rheumatic diseases, treatment with disease-modifying antirheumatic drugs does not play a role in the management of AS.^{2–3} In patients with AS treated with TNF blockers, about half show a 50% improvement of their disease activity as measured by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).⁴ In patients with no or only suboptimal response to TNF α inhibitors, alternative treatment options are urgently needed.

Histological studies⁵ and MRI studies⁶ suggest that the primary site of inflammation in patients with AS is the cartilage/bone interface. Mononuclear cell infiltrates are mainly found in cartilage and the subchondral bone. In early, active sacroiliitis, T cells and macrophages are dominant in these infiltrates, suggesting a specific cellular immune response.⁷ Furthermore, T cell responses from CD4⁸ and CD8⁹ T cells against proteoglycan have been found circulating in the peripheral blood of patients with AS. Additional evidence for a potentially important role of T cells in the pathogenesis of AS comes from the well known association of AS with the major histocompatibility class I antigen, human leucocyte antigen (HLA)-B27. Based on these considerations,

T cell targeting immunotherapy would be of interest in AS.

Here, we report the results of a study with abatacept (T cell modulator cytotoxic T lymphocyte antigen 4 (CTLA-4)Ig with a modified Fc) which has been shown to selectively modulate the CD80/86:CD28 costimulatory signal required for full T cell activation and which has already been approved for the management of RA.¹⁰

PATIENTS AND METHODS

Study design

In this pilot open-label prospective phase II clinical trial (ClinicalTrials.gov identifier NCT00558506), abatacept was administered intravenously on days 1, 15, 29 and every 28 days thereafter up to week 24 in 15 TNF α -inhibitor-naïve patients (here termed TNF naïve) and 15 patients with inadequate response to TNF α inhibitors (here termed TNF failures) with active AS.

Patients received a fixed dose of abatacept,¹⁰ approximating 10 mg/kg of body weight; patients weighing less than 60 kg received 500 mg of abatacept (n=3), those weighing 60–100 kg received 750 mg (n=23), and those weighing more than 100 kg received 1000 mg (n=4).

The treatment period was followed by a 12-week follow-up period at week 36. The study was approved by an independent ethics committee.

Inclusion and exclusion criteria

All patients had a diagnosis of AS according to the modified New York criteria and had active disease, defined as a BASDAI score of ≥ 4 and a back pain score of ≥ 4 (BASDAI question 2), despite treatment with at least two NSAIDs. Concomitant treatment with glucocorticosteroids (≤ 10 mg prednisone per day), methotrexate or sulfasalazine was permitted, but had to be stable 4 weeks prior to baseline. The main exclusion criteria were uncontrolled concomitant diseases, pregnancy, and clinical and laboratory examinations with abnormal or clinically relevant changes.

Outcome assessments

The primary end point was a 40% improvement in disease activity at week 24 according to the Assessment of SpondyloArthritis international Society criteria (ASAS40) in both subgroups. Secondary outcome parameters were a 20% improvement (ASAS20)¹¹ and partial remission according to the ASAS criteria, 50% improvement of the BASDAI (BASDAI50), and the mean improvement in BASDAI, Bath Ankylosing Spondylitis Functional Index (BASFI), Bath

Ankylosing Spondylitis Metrology Index (BASMI) and C reactive protein level.¹¹ The Ankylosing Spondylitis Disease Activity Score (ASDAS) was assessed as post hoc analysis.¹² In addition to routine laboratory tests the percentages of interferon γ (IFN γ)-positive, interleukin-17 (IL-17)-positive and TNF α -positive CD4 T cells among all CD4 T cells were quantified by flow cytometry after in vitro stimulation with either phorbol myristate acetate ionomycin or staphylococcal enterotoxin B used as a control.¹³

Statistical considerations

The statistical analysis was based on an intention-to-treat approach using the last observation carried forward technique to handle missing values. The Blyth–Still–Casella method was applied to calculate 95% CIs for response rates.¹⁴ Non-parametric Wilcoxon signed rank tests were used to investigate changes in continuous variables. We postulated an ASAS40 response of 30% or larger within both groups. Under this assumption a sample size of $n=15$ per group would be sufficient to show a superiority of abatacept against reported placebo response rates by means of calculated 95% CIs of ASAS40 response within both groups.⁴

RESULTS

Baseline characteristics

A total of 30 patients with AS, 15 classed as TNF naive and 15 classed as TNF failure, were enrolled into the study. Demographic data for the two subgroups are shown in tables 1 and 2. Patients in the TNF-failure group were significantly older (45.3 years vs 38.0 years, $p=0.028$), had a significantly higher BASFI (6.8 vs 5.4, $p=0.047$), higher ASDAS (4.1 vs 3.6, $p=0.041$) and higher BASMI (5.0 vs 2.9, $p=0.013$) compared to the TNF-naive group.

Primary and secondary end points

The response rates for ASAS40, ASAS20 and ASAS partial remission and BASDAI50 at week 24 are shown in more detail in table 2. At week 24, ASAS40 was reached by 13% and 0%, respectively, in the TNF-naive group and the TNF-failure group. And the ASAS20 response rates were 27% and 20%, respectively (table 2). There were no significant changes of the BASDAI or the ASDAS over 24 weeks in any of the groups (table 2 and figure 1).

Peripheral manifestations such as arthritis and enthesitis were not significantly changed as seen in the mean arthritis and enthesitis scores (table 2). The analysis of the follow-up data at week 36 also showed no significant change in most of the assessed parameters including the ASDAS.

We found no change in the percentage of IFN γ -positive, IL-17-positive or TNF α -positive CD4 T cells over the treatment period, regardless of stimulation agent used (see supplementary table 1).

Table 1 Demographic and baseline data of the 30 patients with ankylosing spondylitis included in this study

	TNF α -inhibitor-naive patients (n=15)	TNF α -inhibitor-failure patients (n=15)	p Value*
Age in years, mean ($\pm$ SD)	38.0 ($\pm$ 7.2)	45.3 ($\pm$ 9.8)	0.028
Disease duration in years, mean ($\pm$ SD)	14.5 ($\pm$ 10.3)	20.5 ($\pm$ 10.8)	0.131
Number (%) male patients	9 (60%)	11 (73%)	0.468
Number (%) HLA-B27 positive	15 (100%)	14 (93%)	0.309
BASDAI (0–10), mean ($\pm$ SD)	5.9 ($\pm$ 1.4)	6.8 ($\pm$ 1.2)	0.065
ASDAS, mean ($\pm$ SD)	3.6 ($\pm$ 0.5)	4.1 ($\pm$ 0.8)	0.041

For other outcome parameters at baseline please also see table 2.

*p Value for comparison between TNF-blocker-naive and TNF-blocker-failure patients with AS according to the non-parametric Wilcoxon signed rank test.

AS, ankylosing spondylitis; ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; HLA, human leucocyte antigen; TNF α , tumour necrosis factor α .

Patient disposition

Abatacept was generally well tolerated and there were no new safety signals either in frequency or severity that have not been described previously.¹⁰ There were serious adverse events (SAEs) reported in three TNF-naive group patients (vertigo, gastroenteritis, hospitalisation for treatment optimisation) and in two TNF-failure group patients (neck pain and colitis). Three patients dropped out in the TNF-naive group (one due to a SAE and two due to lack of efficacy) and another three patients in the TNF-failure group (one due to SAE and two due to lack of efficacy). No serious infections, opportunistic infections or malignancies have been reported.

DISCUSSION

This is the first prospective study assessing the efficacy of the T cell costimulation modulator abatacept in AS. The study failed to show a major response. In order to address the question of whether TNF-naive and TNF-failure patients would respond differently to abatacept treatment, 15 TNF-naive and 15 TNF-failure patients with active AS were prospectively studied.

In TNF-naive group patients with AS the primary end point (ASAS40 response at week 24) was reached by only 13.3% (95% CI (2.4% to 38.4%)) which is in the range of an expected placebo response reported in randomised controlled trials.⁴ Nevertheless, because of the small sample size, a possibly clinically interesting ASAS40 true response rate of at least 30% cannot be ruled out in this group since 30% is inside the 95% CI. Similar trends were shown for the ASAS 20 response rate.

In the TNF-failure group, no patient reached the primary end point of ASAS40. As the corresponding 95% CI of the ASAS40 response ranged from 0% to 21.3%, it is unlikely that a 30% response rate could be reached in this group. ASAS 20 was achieved by only 20.0% of the TNF-failure group patients (95% CI (5.7% to 44.9%)). However, because an ASAS20 response reached by 30% of the patients might already be regarded as a success in this group such as response cannot be excluded because the upper limit of the 95% CI was greater than 30%.

Overall safety is consistent with the general safety profile shown in patients with RA with no new signals reported.

A limitation of our trial might be the small number of patients, the treatment duration of not longer than 6 months, no dose comparison and its open-label design. However, some treatment effect should be visible in the first 6 months if such a drug should become a treatment option in daily clinical practise. So far no clear dose differences have been observed in the treatment of RA and AS for TNF blockers, the only biological that is effective in both diseases. But a response at a different abatacept dose cannot be excluded based on our trial. Finally, an open-label design should be of less concern if the results are largely negative and if they can be indirectly compared with open-label results with effective drugs in the same disease.¹⁵

Several case reports have previously described conflicting results on the efficacy of abatacept in a total of nine TNF-failure patients with axial spondyloarthritis after 6–9 months of treatment.^{16–18}

Our study underscores the fact that a drug which is effective in RA, in skin psoriasis and in a psoriatic arthritis study^{19 20} will not necessarily also work in AS despite the fact that T cells might play a role in the pathogenesis of AS.^{7–9} With respect to therapeutic strategies, there are differences in the affected structures: while the synovium is a critical target in RA, it is bone and the entheses which are most likely the target in AS.

Of note, peripheral blood T cell function as measured by stimulated in vitro cytokine expression was not changed during

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Table 2 Outcome measures in the two subgroups (TNF naïve vs TNF failure) at week 24 compared to screening

Primary and secondary outcome parameters	TNF α -inhibitor-naïve patients (n=15)		TNF α -inhibitor-failure patients (n=15)	
	Screening	Week 24	Screening	Week 24
ASAS20, % (number of patients) (95% CIs)	NA	26.7% (4/15) (9.7% to 55.1%)	NA	20.0% (3/15) (5.7% to 44.9%)
ASAS40, % (number of patients) (95% CIs)	NA	13.3% (2/15) (2.4% to 38.4%)	NA	0% (0/15) (0% to 21.3%)
ASAS partial remission, % (number of patients) (95% CIs)	NA	6.7% (1/15) (0.4% to 31.2%)	NA	0% (0/15) (0% to 21.3%)
BASDAI50, % (number of patients) (95% CIs)	NA	6.7% (1/15) (0.3% to 30.2%)	NA	0% (0/15) (0% to 21.3%)
BASDAI (0–10), mean ($\pm$ SD)	5.9 ($\pm$ 1.4)	5.1 ($\pm$ 2.1)	6.8 ($\pm$ 1.2)	6.7 ($\pm$ 1.5)
ASDAS, mean ($\pm$ SD)	3.6 ($\pm$ 0.5)	3.2 ($\pm$ 1.1)	4.1 ($\pm$ 0.8)	4.2 ($\pm$ 0.8)
Patient's global assessment (0–10), mean ($\pm$ SD)	6.6 ($\pm$ 1.7)	6.0 ($\pm$ 2.5)	7.6 ($\pm$ 1.3)	7.6 ($\pm$ 1.5)
BASFI (0–10), mean ($\pm$ SD)	5.4 ($\pm$ 2.0)	4.8 ($\pm$ 2.3)	6.8 ($\pm$ 1.7)	6.7 ($\pm$ 2.0)
BASMI (0–10), mean ($\pm$ SD)	2.9 ($\pm$ 2.4)	3.3 ($\pm$ 2.0)	5.0 ($\pm$ 1.8)	4.8 ($\pm$ 1.7)
Physician global assessment (0–10), mean ($\pm$ SD)	6.1 ($\pm$ 1.6)	5.8 ($\pm$ 2.0)	6.4 ($\pm$ 0.6)	6.7 ($\pm$ 1.9)
Arthritis joint count (0–64), mean ($\pm$ SD)	0.4 ($\pm$ 1.6)	0.5 (1.1)	0.7 ($\pm$ 1.1)	0.1 ($\pm$ 0.5)
Enthesitis score (range 0–17), mean ($\pm$ SD)	0.8 ($\pm$ 1.7)	1.2 ($\pm$ 2.8)	2.9 ($\pm$ 3.8)	2.0 ($\pm$ 3.1)
CRP (reference value 5 mg/litre), mean ($\pm$ SD)	14.6 ($\pm$ 10.9)	13.5 ($\pm$ 10.9)	30.7 ($\pm$ 31.0)	31.3 ($\pm$ 25.1)

ASDAS, Ankylosing Spondylitis Disease Activity Score; ASAS20, 20% improvement according to the Assessment of SpondyloArthritis international Society criteria; ASAS40, 40% improvement according to the ASAS criteria; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Diseases Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; CRP, C reactive protein; NA, not applicable.

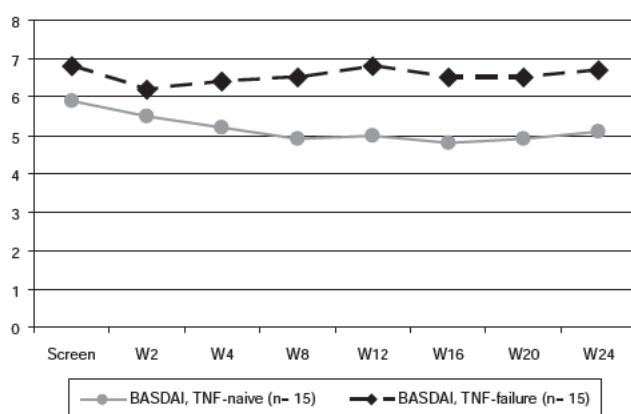


Figure 1 Mean Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) over the period of 24 weeks during treatment with abatacept (10 mg/kg). Data shown the tumour necrosis factor (TNF)-naïve group (n=15) and the TNF-failure group (n=15).

treatment suggesting that T cell suppression may not be a major concern during abatacept treatment.

In summary, a major response from treatment with abatacept in patients with active AS could not be shown in this pilot study.

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Competing interests I-HS and HH: consulting fees or other remuneration from Wyeth/Pfizer Pharmaceuticals, Merck Sharp Dohme/Schering Plough, Abbott Immunology Pharmaceuticals. FH: consulting fees or other remuneration from Merck Sharp Dohme/Schering Plough. MR, JB and JS: Wyeth/Pfizer, Merck Sharp Dohme/Schering Plough, Abbott Immunology Pharmaceuticals, UCB. AW: none.

Ethics approval Approval was obtained from the local ethics committee (Landesamt für Gesundheit und Soziales, Geschäftsstelle der Ethik-Kommission des Landes Berlin, Sächsische Straße 28, 10707 Berlin, Germany).

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