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Concise Report

Real life experience confirms sustained response to long-term biologics and switching in ankylosing spondylitis

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Objective. To investigate the long-term response to biological therapies in AS in a real life clinical setting and to quantify non-response and response to 'switching' therapies in these cases.
Methods. All patients prescribed TNF-blocking therapies for AS between 1999 and 2006 were studied. Response was evaluated using Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI) and CRP results.
Results. A total of 113 patients (84 males: 29 females, mean age 45 yrs, median disease duration 16 yrs, 87% HLA-B27 positive) were identified. At baseline they had a mean BASDAI of 6.57, BASFI 6.57 and CRP of 31 g/dl. At the end of follow-up, these values had reduced to mean BASDAI of 3.12, BASFI 4.16 and CRP of 7 g/dl. Improvements were sustained for 24 months and beyond with no loss of effect. Only nine patients (8%) suffered side-effects leading to cessation or switching of first-line therapy and non-response occurred in 15 patients (13%) in the long term. Fifteen patients (13%) switched to a second drug and 14 of these (93%) had a significant and sustained response. Outcomes were similar regardless of drug used, duration of disease and HLA-B27 status.
Conclusion. Treatment of active AS with TNF blockers according to the British Society of Rheumatology guidelines leads to a sustained response for over 2 yrs with most patients tolerating the drugs well. The rate of non-response is significantly lower than that seen in RA and nearly all of these patients respond well to a second-line agent.

Key words: Ankylosing spondylitis, Biologics, TNF blockers, Treatment, Switching, Non-response.

Introduction

The advent of biological therapies in rheumatology has offered new therapeutic options for patients with AS and the efficacy of TNF blockers has been confirmed in numerous trials [1–4]. However, there is a lack of evidence regarding long-term efficacy of these treatments in a real-life clinical setting.

There has been little previous research into the factors that may influence the outcome of patients who are prescribed biologic therapy. Previous research has shown that HLA-B27 status is associated with higher disease activity and poorer functional outcome in AS [5]. A higher proportion of B27 positive patients meet the guidelines for anti-TNF therapy because of this, but it is not known whether their response to therapy is significantly different.

It has been shown in RA that a significant proportion of patients fail to respond to biological therapies [6]. The mechanisms for this non-response are largely unknown [7], although several types have been defined [8]. Previous research in RA has also shown that switching between different biologic agents may lead to an efficacious response in the case of primary and secondary non-response [9]. However, little is known about the mechanisms of non-response or the effects of switching in AS.

The use of biological therapies in the UK for AS is restricted because of funding issues pending review by the National Institute of Clinical Excellence. However, TNF blockers are used on an individual patient basis in the NHS following guidelines issued by the ASAS/EULAR working group [10] and the British Society of Rheumatology (BSR) [11]. According to these guidelines, TNF blockers should be offered to modified New York criteria AS with active disease [defined as a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) >4 on at least two occasions, 4 weeks apart] who have failed adequate therapeutic trials of at least two NSAIDs. Here, we report on our clinical experience on the use of biological drugs in AS over the last decade.

Methods

A retrospective analysis was conducted of patients with AS treated with TNF-blocking drugs through the Leeds biologics and SpA clinics between 1999 and 2006. All patients who had received treatment for 12 weeks or more and any patients who stopped therapy earlier than 12 weeks due to adverse events were included. Currently, patient selection for biological therapy at Leeds is made based on national and international guidelines as detailed earlier and the clinical judgement of two consultant rheumatologists.

All patients treated in our clinic are invited to be registered in the Leeds SpA and the resistant arthritis databases, which have been approved by the local ethics committee. The vast majority of this cohort have a diagnosis of AS based on the modified New York criteria [12]. However, a minority of patients had a combination of early inflammatory back pain, HLA-B27 positivity and MRI evidence of sacroiliac bone oedema, which has been shown to be associated with a high probability of progressing to AS [13] and were treated as part of a clinical trial. Following informed written consent, clinical and laboratory data are collected prospectively. These include demographics, disease duration, HLA-B27 status, BASDAI, Bath Ankylosing Spondylitis Functional Index (BASFI) and CRP levels. In addition, any reason for discontinuation of therapy is carefully documented. Standard doses of TNF blockers used were: infliximab 5 mg/kg given every six weeks, etanercept 25 mg twice weekly or 50 mg weekly, adalimumab 40 mg fortnightly.

Data are presented as percentage of improvement. Significance testing was done using a one-way analysis of variance test. A P-value of <0.05 was considered as statistically significant.

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TABLE 1. Baseline demographics of the AS cohort prescribed biologic drugs

n	119
M : F ratio	90 : 29
Mean age (yrs)	44.8
Median disease duration (yrs) (range)	16 (12–47)
HLA-B27 positivity (%)	87.8
Associated peripheral arthritis (%)	52
Associated extra-articular conditions (%)	14
Psoriasis	6
IBD	8
Concomitant DMARDs (%)	35.3
MTX	33.6
SSZ	4.2
AZA	0.8
Concomitant NSAIDs (%)	56.3
Etoricoxib	24.4
Indomethacin	10.1
Celecoxib	6.7
Diclofenac	5.0
Others	10.1
Mean BASDAI	6.21
Mean BASFI	6.36
Mean CRP (mg/l)	35.0
Number of biologic drugs prescribed per patient (%)	
1	103
2	16
Drugs used (no. of people prescribed drug)	
Infliximab	60
Etanercept	62
Adalimumab	4

CRP (normal value <10 g/l).

Results

A total of 113 patients receiving 126 biologic drugs were identified (infliximab 60, entanercept 62, adalimumab 4). All of the patients prescribed TNF blockers consented to join the resistant arthritis database and their data was collected prospectively. The demographics of the cohort are typical for an AS population and detailed in Table 1. A relatively high proportion of patients (35%) were receiving concurrent DMARDs in addition to their biologics. Of these, 25 patients had been started on this drug as part of a research treatment protocol [14], the rest had been previously treated with MTX for peripheral arthritis or enthesitis. On average, patients received biologic treatment for 21 months (range 1–88).

Full data on response are available for 108 of these 126 episodes of treatment. The mean BASDAI reduced from 6.57 to 3.12, mean BASFI from 6.45 to 4.16 and the mean CRP reduced from 31 to 7 g/dl. Thirty-three patients (29%) had treatment with one drug for over 24 months with a maintained reduction in BASDAI, BASFI (Fig. 1A) and CRP (reduction of over 20 g/dl maintained).

All patients treated with biologics were assessed for clinical response (based on the opinion of the patient and their physician) and BSR criteria response (reduction in BASDAI of 50% or 2 cm). Data to assess BSR criteria was available for 109 patients and 77 patients (71%) met these criteria. All patients who achieved the BSR criteria also made a subjective clinical response; however, there were also 19 patients deemed to have had a clinical response, but who failed to meet BSR criteria. Although these patients did not achieve a significant reduction in their BASDAI (mean score 5.4 at baseline reducing to 4.6), they showed a significant improvement in the only objective measure available, their CRP levels, with similar reductions to that of BSR responders (failed to meet BSR criteria—mean CRP reduced from 23 g/dl at baseline to 3 g/dl; met BSR criteria—mean CRP reduced from 33 g/dl at baseline to 4 g/dl).

Serious side-effects or allergy requiring cessation or switch of therapy were seen in 8.0% of patients ($n = 9$). One patient restarted infliximab after a long period off treatment and developed a severe reaction to the drug. Primary allergy to adalimumab was seen in one case. Other side-effects seen were neuropathy, depression, fits, rash, raised liver function tests and worsening of uveitis ($n = 2$). All of these resolved on stopping or switching therapy.

At the 12-week assessment, 88% of patients responded to their first drug. Primary non-response was seen in 13 patients (infliximab $n = 10$, etanercept $n = 3$) of whom six refused further biologic drugs. The other seven switched to a second-line agent with six showing good clinical response, all to etanercept. The remaining one patient suffered an allergic reaction to adalimumab and stopped treatment. A further eight patients, who initially responded to their first drug, also switched. This was because of secondary non-response to infliximab ($n = 2$), side-effects ($n = 2$) and availability of drug or patient preference for self-injectable treatment ($n = 4$). All showed a clinical response to their second agent.

The data were further analysed to see if the results differed significantly with different treatments, disease duration or HLA-B27 status. There were no significant differences seen in outcome (reduction in BASDAI, BASFI) between the biologic therapies (Fig. 1B). To investigate disease duration (from time of diagnosis), patients were divided into decades following diagnosis and into short and long durations of disease (<7 or 7+ yrs). There was no significant difference found in either analysis (Fig. 1C). The HLA-B27 status did not alter the baseline BASDAI, BASFI and CRP levels (B27 positive: 6.5, 6.4, 34 and B27 negative: 7.2, 6.8, 26, respectively) or the response to treatment (Fig. 1D). There was no significant difference in the reductions in CRP levels in any of these analyses.

Discussion

The efficacy of biologic therapies in the treatment of AS has been well documented in shorter term trials, although there has been little published work on the outcome of TNF blockers in a clinical setting. Recently, there have been a number of reports looking at the longer term follow-up of open label trial extensions [15–17]. However, little attention has been paid to the drop-out rate seen or the possible reasons for this.

Our data show a very promising view of anti-TNF therapy in AS and confirms previous observations in the context of clinical trials. The overall reductions seen both in subjective and objective measures of disease activity are considerable and maintained over time. The rate of clinical response is high with an impressive rate of response as measured by the BSR criteria.

The incidence of primary and secondary non-response appears to be much lower than that seen in RA with non-response seen in <15% of the patients compared with around 40% reported in RA [6]. The dose of infliximab used in AS is obviously higher than that used in RA, which may account for a difference in response. However, equal doses of etanercept and adalimumab are used in both diseases and the levels of non-response for these drugs seem to be much lower in AS. Furthermore, there is also a better response seen with switching with all but one of our patients responding well to a second agent.

When looking at predictors of response, we found similar rates of response regardless of disease duration, HLA-B27 status or biologic drug used. Interestingly, and in contrast to what has been reported by other groups [18], patients had a similar response rate regardless of their disease duration. This might suggest that treatment should be considered in patients with active disease regardless of their disease duration. It has been shown previously that HLA-B27 is associated with more severe disease and a higher proportion of B27 positive patients meet the BSR criteria for biologic treatment [5]. Analysis of previous trials has suggested that HLA-B27 negativity was a predictor of poor outcome with anti-TNF therapy [19]. However, this was not the case in the present study. Although our population is a selected group of patients with severe disease of whom few were B27 negative, it is

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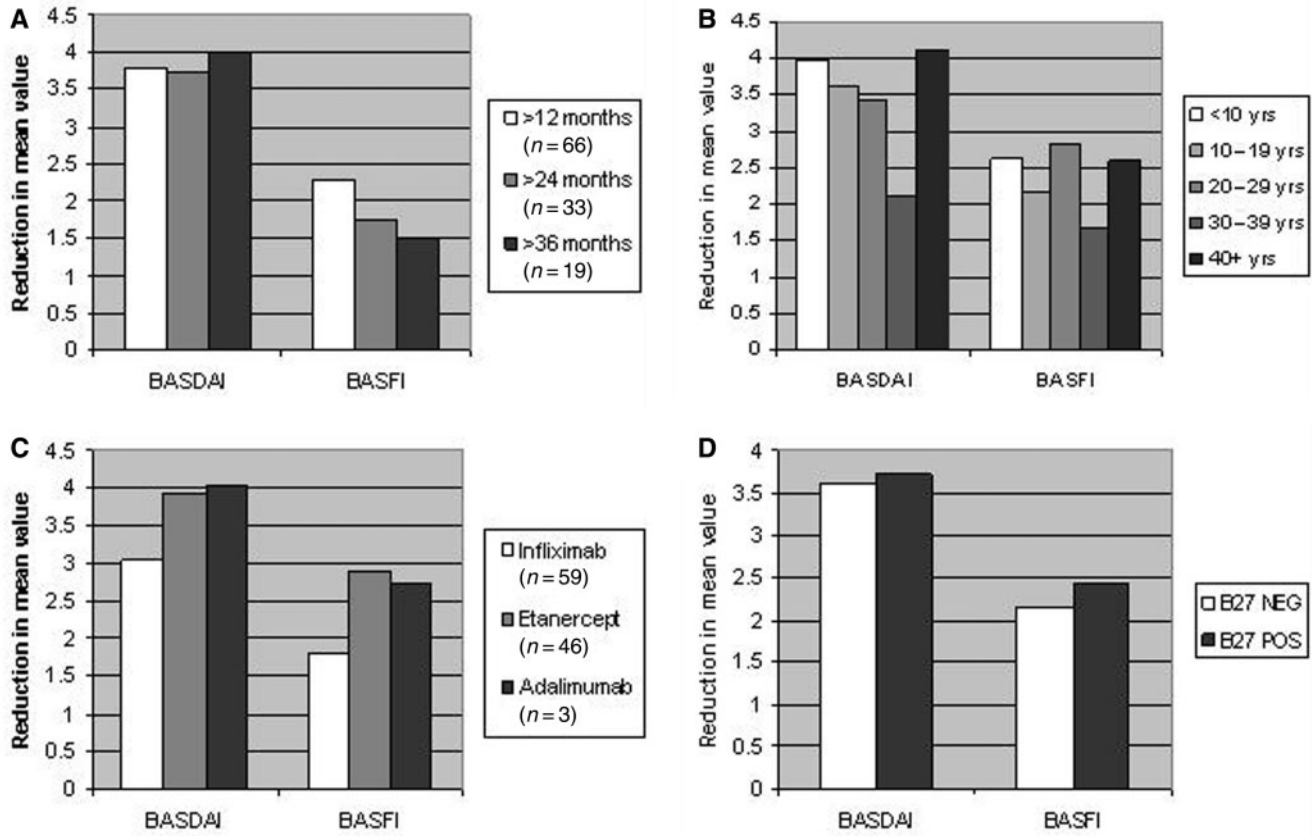

FIG. 1. (**A**) Percentage improvement in response outcome by duration of treatment. (**B**) Percentage improvement in response outcome by biologic agent used. (**C**) Percentage improvement in response outcome by disease duration. (**D**) Percentage improvement in response outcome by HLA-B27 status.

reassuring that this subgroup seemed to respond satisfactorily to treatment.

There are some limitations on interpreting our results, namely that sub-analysis to compare HLA-B27 positive and negative patients and comparison between drugs is difficult due to different group sizes. Additionally, a large proportion of patients received infliximab as the first treatment, introducing a potential bias. Patients on etanercept and adalimumab were more likely to have previously failed TNF therapy, which may increase their chances of a further non-response.

In conclusion, our data show that treatment of active AS with biologic therapy is well tolerated and leads to a prompt and sustained response for over 2 years with the majority of patients responding well to one agent only. Non-response in AS appears to be rare compared with RA. The majority of patients who have non-response will respond to a second drug, so switching should be considered in this cohort. Further research into non-responders may allow the identification of predictors of response.

Rheumatology key messages

- AS patients treated with TNF blockers show a sustained response over time.
- Non-response to these drugs and side-effects are rare in AS.
- Switching between different TNF blockers is effective for the majority of patients.

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