Withdrawal of biologic therapy in axial spondyloarthritis: the experience in early disease

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ABSTRACT

Tumour necrosis factor-alpha inhibitors (TNF-blockers) are recommended for the treatment of predominantly axial spondyloarthritis (SpA), after failure of non-steroidal anti-inflammatory drugs (NSAIDs). TNF-blockers are very effective drugs and also show a sustained and stable long-term response in axial SpA. A few trials indicated that withdrawal of TNF-blockers in longstanding ankylosing spondylitis (AS) is not feasible. However, a recent trial in very early axial SpA suggests that reaching a state of biologic-free low disease activity may be a realistic goal in some patients. This review summarises the available data concerning withdrawal of biologic therapies in early axial SpA.

Introduction

The Assessment of SpondyloArthritis international Society (ASAS) classification criteria for axial spondyloarthritis (SpA) covers the whole spectrum of axial SpA, including patients with established ankylosing spondylitis (AS) who fulfill the modified New York criteria, as well as patients with non-radiographic axial SpA (nr-axSpA) who do not (yet) exhibit sacroiliitis on conventional x-ray (1). The ASAS recommendations in predominantly axial SpA include treatment with tumour necrosis factor alpha (TNF-α) inhibitors (here termed TNF-blockers) after failure of at least two non-steroidal anti-inflammatory drugs (NSAIDs) given for a total of at least 4 weeks (2).

TNF-blockers have proven efficacy in treating signs and symptoms of active AS in numerous placebo-controlled randomised controlled trials (RCTs) (3-6). The trials showed that a 50% improvement in the Bath Ankylosing Spondylitis Disease Activity (BASDAI50) or a 40% improvement of the ASAS response criteria (ASAS40) can be achieved in about 45% of patients (3-6). Based on these trials, four TNF-blockers including infliximab, etanercept, adalimumab and golimumab have been approved for the treatment of active AS in Europe, the United States and other many other countries (7-10). Long-term efficacy for several years of TNF-blocker treatment in AS is encouraging as sustained response rates can be observed (11-14).

During recent years, different TNF-blockers including adalimumab, infliximab and etanercept have been evaluated in trials in patients with early axial SpA, including patients with nr-axSpA (15-18). Follow-up data of these three trials addressed the question of drug-(biologic-)-free remission/ low disease activity (19-23). Treatment of patients with early axial SpA consistently indicated very good clinical efficacy, with about 50% of patients reaching ASAS partial remission (15-17). A fifth trial performed as an international placebo-controlled RCT (24) led to the approval of adalimumab for the treatment of nr-axSpA in Europe (9).

In usual clinical care, a question emerges regarding whether TNF-blocker treatment can be stopped while maintaining a state of remission or low disease activity. In clinical trials, flare rates of up to 97–100% were found after about 6 months upon discontinuation of TNF-blocker treatment in longstanding AS with a disease duration of more than 10 years (25, 26). A central question at this time is whether higher rates of TNF-blocker-free remission can be achieved in early axial SpA. This review describes and discusses available evidence of withdrawal of TNF-blockers in early axial SpA.

Withdrawal of TNF-blockers in early axial spondyloarthritis

In early axial SpA so far four studies which have assessed flare rates after discontinuation of TNF-blocker treatment have been performed (15-17).

Table I. Overview of clinical trials with tumour necrosis factor alpha-inhibitors in (early) axial spondyloarthritis which assessed flare rates.

Parameter / Drug	Adalimumab (15, 20)	Infliximab (16, 19, 21)	Etanercept (ESTHER) (17, 22)	Infliximab (INFAST) (18, 23)
Original study design	12-week placebo (PBO)-controlled trial with open extension until W52	16-week PBO-controlled trial with follow-up until W40	48-week trial comparing ETN *vs*. SSZ	28-week PBO-controlled trial with IFX plus NPX *vs*. PBO plus NPX
Number of patients included in original study	46 (22 ADA *vs*. 24 PBO)	40 (20 IFX vs. 20 PBO)	76 (40 ETN *vs*. 36 SSZ)	158 (106 IFX+NPX *vs*. 52 PBO+NPX)
Mean disease duration	7-8 years	15 months	2.9 years	1.8- 1.9 years
%, male / HLA B27 positive	46% / 67%	75% / 100%	58% / 82%	72%/ 86%
%, non-radiographic axial SpA/ AS	100% / 0%	88% / 12%*	49% / 51%	60% / 40%
Duration of induction therapy	at least 40 weeks of ADA treatment	4 IFX infusions (BL - W12) *vs*. PBO	48 weeks of ETN *vs*. SSZ	28 weeks of IFX+NPX *vs*. PBO+NPX
Definition of good response as criterion to interrupt TNF-blocker treatment	ASAS40	NA	ASAS partial remission plus MRI remission#	ASAS partial remission
Good response reached by % (number) of pts	52% (24/46)	NA	33% (13 /40 ETN pts) *vs*. 11% (4/36 SSZ pts)	62% (65/105 IFX+NPX) *vs*. 35% (18/51 PBO+NPX)
Duration of TNF-blocker-free follow-up period to assess flare	52 weeks	24 weeks	48 weeks	24 weeks
Flare definition	Loosing ASAS40 response compared to screening	BASDAI >4	2-point increase of BASDAI compared to BASDAI at W48	BASDAI of ≥3 during 2 consecutive visits within 1–3 weeks
% (number of patients) with flare	79% (19/24)	60% (12/20) of IFX pts *vs*. 89.5% (17/19) of PBO pts	69% (9/13) of ETN pts *vs*. 75% (3/4) of SSZ pts	6% (4/65)***
% (number of pts) with sustained biologic free status of low disease activity (remission)	17% (4/24)	40% (8/20) of IFX pts *vs*. 10.5% (2/19) of PBO pts	23% (3/13) of ETN pts *vs*. 25% (1/4) of SSZ pts	94% (61/65)***
Mean time to flare	14.7 weeks	NA	24.4 weeks for ETN-pts *vs*. 39.6 weeks for SSZ pts	NA
Good response to re-treatment with TNF-blocker?	Yes: After 1 year of re-treatment, ASAS40 reached again in 63.2% (12/19)	Yes: at 5 year follow-up about 80% on TNF-blocker and majority of patients in low disease activity**	Yes: after 48 weeks of re-treatment ASAS remission in 56% (5/9) of ETN pts and 66.7% (2/3) of SSZ pts	NA

ETN: etanercept; ADA: adalimumab; IFX: infliximab; SSZ: sulfasalazine; PBO: placebo; NPX: naproxen; MRI: magnetic resonance imaging; SI-joint: sacroiliac joint; ASAS40: 40% improvement according to the Assessment of SpondyloArthritis Society criteria; NA: not applicable; wk(s): week(s); pts: patients.

*x-ray of sacroiliac joints was performed in 34 of 40 patients; in 4 of 34 patients (12%) modified New York criteria were fulfilled [27];

**this was no systematic follow-up (details please see text);

***a flare was observed in 2.5% (1/40) of patients treated with NPX and 7.5% (3/40) of patients who received no treatment during follow-up (p=0.62); there was is no information available from which initial treatment arm (infliximab plus naproxen or placebo plus naproxen) the four flare patients came from. However, even if all four patients came from the initial infliximab group the corresponding flare rate would only be 6% (4/65) and the corresponding rate of patients in low disease activity would be 94%.

MRI remission in this trial was defined as to be free of active inflammation in the sacroiliac joints and the spine.

The available data are summarised in Table I and Figure 1.

In the first prospective double-blind randomised placebo-controlled trial in nr-axSpA, 22 patients were randomised to adalimumab 40mg s.c. every other week (eow) and 24 patients to placebo (15). There was no limitation in disease duration at entry into this study, and the mean disease duration of patients was 7–8 years. In this study, the only patients included had nr-axSpA, as AS patients who fulfilled the modified New York criteria were excluded. After the 12-week placebo-controlled period all patients were switched to open-label treatment with adalimumab until week 52, and 38 patients continued through week 52. The 24 patients who achieved an ASAS40 response at week 52 were followed up for another year without adalimumab treatment, to recognise a flare (20) defined as loosing ASAS40 at any following visit. After a mean of 14.7 weeks (± 5.5 SD, range 3 to 27 weeks), 79% (19/24) flared after withdrawal of adalimumab treatment. Accordingly, only 17% (4/24) stayed in a state of biologic-free low disease activity during the one year follow-up (one patient was lost to follow-up) (20). A multivariate regression analysis revealed no clear predictors for relapse.

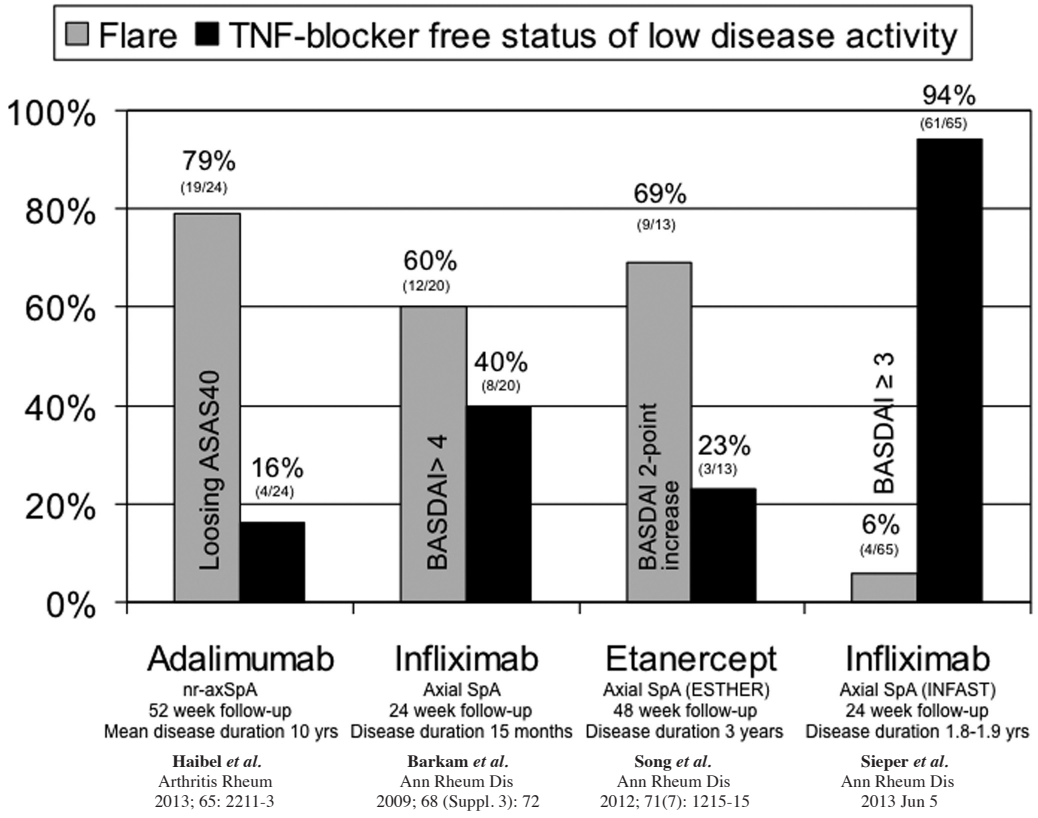

Fig. 1. Percentage (number) of patients with axial spondyloarthritis (SpA) with a flare of disease and corresponding percentage (number) of patients with tumour-necrosis-factor alpha-blocker free status of low disease activity.
ASAS40: 40% improvement according to the Assessment of SpondyloArthritis international Society criteria; BASDAI: Bath Ankylosing Spondylitis Disease Activity; TNF-blocker: tumour necrosis factor alpha-inhibitor; yrs: years; nr-axSpA: non-radiographic axial SpA; axial SpA: referring to patients with axial SpA including ankylosing spondylitis and non-radiographic axial SpA.

The 19 patients who flared were successfully re-treated with adalimumab 40mg s.c. eow (63% ASAS40 and 47% ASAS partial remission after one year of re-treatment, and 74% ASAS40 and 63% ASAS partial remission after two years of re-treatment) (20).

In the second trial, 40 patients with very early axial SpA with a mean duration of only about 15 months were randomised 1:1 to either treatment with infliximab (in total four infusions with 5mg/kg at weeks 0, 2, 6 and 12) or placebo (16). To be included in this trial, all patients had to have a disease duration of less than 3 years, be positive for HLA-B27, and have magnetic resonance imaging (MRI) evidence of active inflammation in the sacroiliac joints (SI-joints) at the beginning of the trial. Only 12% (4/34) of patients for whom radiographs were available had AS, while all other patients had nr-axSpA. The primary outcome measure was a change in the MRI score of the SI-joints, assessed at week 16.

In this study, all available patients including poor responders were followed up until week 40 and assessed for possible high disease activity defined as a BASDAI >4 (19). At week 16, 30% (6/20) of infliximab-treated patients and 63% (12/19) of placebo patients already had a BASDAI >4. During follow-up without active treatment, 60% (12/20) in the infliximab group *vs*. 89.5% (17/19) of the placebo group had active disease during follow-up (p=0.035). Accordingly, 40% (8/20) in the infliximab group *vs*. 10.5% (2/19) in the placebo group remained in a state of (TNF-blocker-free) low disease activity (defined as a BASDAI of ≤4) until week 40.

After a median of 5.3 years, patients who had participated in the original study were invited for a follow-up visit (21). In total, 25 out of 39 patients (64%) could be re-assessed, including 60% (12/20) of the original infliximab group and 68.4% (13/19) of the original placebo group. Of these 25 patients who could be re-assessed, 20 (80%) were being treated with TNF-blockers (8 adalimumab, 9 etanercept, 3 infliximab) and 13 (52%) were taking NSAIDs at follow-up. The majority of patients had low disease activity with a median BASDAI of 0.65 and median BASFI of 0.50; furthermore 88% of patients had CRP <5 mg/L (21). Importantly, only 58% (7/12) of those who originally received infliximab treatment were on TNF-blocker treatment during follow-up compared to 100% (13/13) of those who had received placebo in the original study. Accordingly, 42% (5/12) of the original infliximab group were not on TNF-blocker treatment and 33% (4/12) had minimal or no symptoms after the 5.3 median years of follow-up while only one patient was described to have active disease (BASDAI 4.5) but declined TNF-blocker treatment.

The third trial (ESTHER) was a prospective randomised controlled trial in which patients with axial SpA with a disease duration of <5 years were randomised to treatment with etanercept (n=40) *vs*. sulfasalazine (n=36) (17). Importantly, all patients had active inflammation in the SI-joints and/or the spine on MRI, and reduction of active MRI inflammation at week 48 was the primary outcome in this study.

At week 48, all available patients were assessed as to whether they had reached ASAS partial remission and MRI remission (MRI remission was defined as the

absence of active inflammatory lesions in the spine and the SI-joints as assessed by one blinded radiologist) (22). ASAS partial remission and MRI remission at week 48 were achieved by 33% (13/40) of etanercept-treated patients vs. 11% (4/36) of sulfasalazine-treated patients. After week 48, those patients who had achieved ASAS partial remission and MRI remission were followed for up to one year without study drug, and it was assessed whether the patients experienced a flare of disease activity. Flare in this study was defined as an increase in the BASDAI of 2 points compared to the BASDAI at week 48.

After a mean of 24.4 weeks, 69% (9/13) of etanercept patients showed a flare and after a mean of 39.6 weeks, 75% (3/4) of SSZ patients showed a flare. Correspondingly, 23% (3/13) of etanercept patients and 25% (1/4) of SSZ patients remained in drug-free remission (one patient in the etanercept group was not counted as this patient was falsely classified as a flare patient). Flare patients showed a good clinical response after (re-)introduction of etanercept treatment (22).

While the first three trials mentioned above were performed in patients with axial SpA who had elevated disease activity despite NSAIDs (NSAID-failure patients), a fourth study, INFAST, included patients were either NSAID-naïve or had not been treated with more than two-thirds of the maximal recommended dose of an NSAID, and therefore were potential NSAID-responders (18). In addition, disease duration was limited to ≤3 years at entry into the study. In a double-blind placebo-controlled design 158 patients were randomised 2:1 to either treatment with infliximab plus full-dose naproxen (n=106; infliximab 5mg/kg; 6 infusions between baseline and week 24; naproxen 1000mg daily) or treatment with placebo and naproxen (n= 52; naproxen 1000mg daily) (18). The primary outcome of this study, ASAS partial remission at week 28, was reached significantly more often by patients in the infliximab plus naproxen group (61.9%; 65/105) compared to patients in the placebo plus naproxen group (35.3%; 18/51) (p=0.002).

Patients who had achieved ASAS partial remission at week 28 were offered a 24 week-extension of the trial, in which they were then randomised 1:1 to either maintenance therapy with naproxen (n=41; 1000mg daily or 500mg daily if the higher dose was not tolerated) or placebo (n=41) (23). This second part of the INFAST trial was performed as an open-label and exploratory study. Patients were observed with regard to whether they showed a flare, defined as a BASDAI of ≥3 during 2 consecutive visits within 1–3 weeks of each other between weeks 28 and 52.

During follow-up without infliximab treatment there was a flare rate of only 2.5% (1/40) in the naproxen group and only 7.5% (3/40) in the group receiving no naproxen (p=0.62). The majority of patients (83% to 94%) in both groups maintained a state of low disease activity (BASDAI<3 at all visits).

There was is no information concerning which initial treatment arm (infliximab plus naproxen or placebo plus naproxen) the four flare patients (1+3) came from. However, even if all four patients came from the initial infliximab group the corresponding flare rate would only be 6% (4/65) and the corresponding rate of patients in low disease activity would be 94%.

Discussion

A status of low disease activity (LDA) /remission for up to one year after withdrawal of a TNF-blocker could be achieved in only about 20% (17-23%) of patients with (early) axial SpA who failed previous NSAID treatment and who showed a good response to a one-year induction treatment with adalimumab or etanercept (22, 27).

The percentage of patients who remained in low disease activity during a 24-week follow-up period was higher (40%) in patients treated with infliximab for 12 weeks (16). However, this first trial with infliximab in early axial SpA might not have had the ideal study design to assess flare, as the authors looked at the whole group of patients who were available during follow-up regardless of whether they had responded to initial infliximab treatment (16).

The highest rate of TNF-blocker free remission /low disease activity of up to 94% could be observed during the 24-week follow-up of INFAST patients in whom ASAS partial remission could be achieved after induction therapy with infliximab plus naproxen, or naproxen alone (23). Importantly, in the INFAST trial only potential NSAID-responsive patients were included, and NSAID failure patients were excluded.

A direct comparison of the four trials is difficult, as different definitions for good response and flare were used, and the duration of the induction therapies and follow-up periods (after withdrawal of TNF-blockers) differed among the studies. The strictest criteria for good response (remission) were used in the ESTHER trial in which etanercept was withdrawn only in those who reached ASAS partial remission plus MRI remission. Even by applying this strict criterion, 69% of good responders to etanercept treatment flared and only 23% remained in biologic-free remission for up to one year after withdrawal of the TNF-blocker. Importantly, if the follow-up period in the ESTHER trial would have only been 24 weeks (instead of 48 weeks), the rate of patients in biologic-free remission would have been about 50% instead of only 23% (22) which underlines the importance of the duration of the follow-up period in assessment of medication-free remission.

The data from the INFAST study suggest that a combination therapy of infliximab plus naproxen but also a monotherapy with naproxen could induce remission /low disease activity for at least up to 6 months in axial SpA patients who achieved ASAS partial remission. Indeed, INFAST is the first trial which could demonstrate that a remission-induction approach in patients with very early axial SpA could allow patients to remain in a state of low disease activity, even without NSAIDs.

The review of the available trials in axial SpA which assessed the potency of TNF-blockers to induce biologic-free remission also reveals a lack of a clear definition for flare. While the two infliximab trials used absolute values as the cut-off for flare definition (BASDAI >4 or BASDAI ≥3) (19, 23) the adalimum-

ab and etanercept (ESTHER) trials used relative changes (ASAS40 compared to screening in the adalimumab trial and 2-point BASDAI increase compared to week 48 in the ESTHER trial) (20, 22). Interestingly, only the INFAST trial asked for a certain disease activity at two (and not only one) time points for a flare definition.

It remains unclear which of the available disease activity instruments and which cut-offs might best define a flare. No study so far has applied the Ankylosing Spondylitis Disease Activity Score (ASDAS) which combines both patient reported outcomes and objective disease parameters (represented by CRP) in a flare study design (28). Currently, it is discussed whether an ASDAS cut-off of ≥2.1 could be a good definition for a flare. An ASDAS <2.1 is the cut-off for moderate disease activity; thus an ASDAS of ≥2.1 means that a patient loses moderate disease activity (29).

An argument in favour of using the ASDAS instead of ASAS partial remission could also be that the Bath Ankylosing Spondylitis Functional index (BASFI), which is part of the ASAS partial remission criteria, should not be used to assess remission because it might not be suitable in longstanding disease.

To summarise, the lessons learned from the flare trials in early axial SpA are that TNF-blocker-free remission or low disease activity for up to 6 months is a realistic goal for some patients with shorter symptom duration. However, a longer follow-up of patients should be performed as a substantial proportion of patients showed a flare after 6–12 months.

Similar to a treat-to-target approach in RA (30-32), it would also be of interest whether dose reduction (instead of stopping treatment) would be a better option in patients who achieve remission (33). There is evidence from smaller observational studies that maintaining a state of remission or low disease activity with a reduction of the TNF-blocker dose (for example by increasing intervals between TNF-blocker applications) is feasible in usual clinical care in about 30% of AS patients (34-37).

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