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


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ABSTRACT
Treatment of patients suffering from active ankylosing spondylitis (AS) with TNFα blockers, has been shown to result in clinically significant improvement of signs and symptoms of the disease. Long-term extension studies with these agents have shown sustained clinical efficacy for up to 10 years in patients who continued treatment. However, only a few studies have examined whether reduction of dosage or discontinuation of anti-TNF therapy is possible. In daily clinical practice, prolongation of treatment intervals is frequently tried in patients who are in clinical remission for longer periods of time, but no data on the success of that are available. Discontinuation of treatment is usually needed in patients who want to become pregnant, and in patients with severe infections. This review summarises what is known on the topic of discontinuation of biologic treatment in patients with AS.

Introduction
The established phase of axial spondyloarthritis (axSpA) is called ankylosing spondylitis (AS) and is defined by unequivocal structural changes in the sacroiliac joints, detected on conventional radiographs. Infrequently, structural changes occur earlier in the spinal column. Function and morphology of patients with AS, as usually assessed by Bath AS functional index (BASFI) (1) and the Bath AS metrology index (BASMI) (2), are influenced by both inflammation and structural changes. Pain and stiffness are the main symptoms of inflammation, and these are the major constituents of disease activity which is quantified by the Bath AS disease activity index (BASDAI) (3) and the AS disease activity score (ASDAS) (4). The relationship between inflammation and structural changes is incompletely understood. However, structural changes may occur not only as a consequence of inflammation, but also independently due to other mechanical reasons. Non-steroidal anti-inflammatory drugs (NSAIDs) are recommended by the Assessment of SpondyloArthritis International Society (ASAS) as first choice of therapy in patients with AS (5). High dosages of NSAIDs given continuously appear advantageous in patients with active disease on both a short- and long-term basis, as some evidence indicates that NSAIDs also may inhibit structural damage (6). Patients who experience insufficient responses to NSAIDs often experience significant improvement with agents directed against the proinflammatory cytokine tumour necrosis factor alpha (TNF-α), such as the monoclonal antibodies infliximab, adalimumab, golimumab and certolizumab or the fusion protein etanercept (7-11). These agents resulted in clinically significant improvement of signs and symptoms of AS in several randomised controlled clinical trials (7-11). Long-term extension studies with these agents have shown sustained clinical efficacy in the patients who had remained on anti-TNF treatment. Persistence of clinical response was reported in long-term follow up studies for up to 8 years (12, 13). The clinical improvement in these patients is associated with a significant reduction of inflammation as shown by magnetic resonance imaging (MRI) (14, 15). Only a few studies have been conducted with either discontinuation or reduction of anti-TNF therapy. In daily clinical practice, prolongation of treatment intervals is being considered in patients who are in clinical remission for longer periods of time, while discontinuation of treatment is necessary in patients who want to become pregnant, and patients with severe infections. This review summarises the available evidence on the topic of withdrawal of biologic treatment in patients with established AS.

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J. Sieper has acted as consultant for and has received honoraria and research support from AbbVie, Merck, Pfizer, and UCB; J. Braun has received consultancy fees from AbbVie, Janssen, MSD, Novartis, and Pfizer;
Withdrawal of anti-TNF in established ankylosing spondylitis

In the first (pilot) study ever published on anti-TNF therapy in AS (16), 10 patients were treated with three infusions of infliximab in a dosage of 5 mg/kg at weeks 0, 2 and 6. After the third administration, therapy was discontinued, and all patients flared after a median of 6.5 weeks (range 1–14 weeks). Since this was similar after the 4th and the 5th infusion and since the ‘delayed’ infusion did not seem to have a similar efficacy as the previous three infusions, it was decided to administer infliximab in regular 6-week intervals in a randomised controlled investigator-driven trial (7), which resulted in approval of infliximab for patients with active AS by the European Medicine Association (EMA).

An interesting report on clinical outcomes after withdrawal of treatment with TNF-blockers, with and without methotrexate therapy, after a period of continuous or on-demand anti-TNF therapy was published in 2002 (17). The study included 50 patients with established AS who had active disease at baseline as assessed by BASDAI, (18) using a cut-off ≥30/100 and a serum C-reactive protein (CRP) ≥15 mg/l despite NSAID therapy. Three infusions of infliximab were administered at weeks 0, 2 and 6 before patients were followed up for another 18 weeks. Almost all (n=48) patients completed week 24 of the study; 98% of these patients reported a reduction of the initial pain level by ≥20%, and 94% of patients reached an ASAS-20% response, while 70% patients reached ASAS partial remission (19). A clinical relapse, defined as ≥50% loss of the improvement gained in relation to the pain level at baseline, was observed in 73% of the completers with a median delay of 14 weeks after the last infliximab infusion. After three years of follow-up of the first RCT with infliximab (7) cited above, several clinical outcomes after withdrawal of anti-TNF therapy were assessed before patients were re-treated with infliximab (20). After three years of infliximab therapy, 42 of the initial 69 patients who had been included in the trial (7) discontinued treatment and were then visited regularly. Relapse was defined as an increase of the BASDAI value combined with physician’s global assessment using a cut-off >4. Within the first year after withdrawal, 41/42 patients (97.6%) required re-treatment with infliximab because of clinical relapse. The mean time from infliximab withdrawal to clinical relapse was 17.5±7.9 weeks (range 7–45 weeks): 10 patients (24%) had a relapse within the first 12 weeks while 38 patients (90.5%) relapsed within 36 weeks. At week 52, all but one patient remained in clinical remission without an obvious need for anti-TNF therapy. Predictive factors for longer time to relapse but also for clinical improvement after re-treatment were a status of partial remission according to ASAS (19) and normal CRP levels at the time of withdrawal, while increased BASDAI and elevated CRP were associated with shorter time to relapse.

In a follow-up study after one year of individual re-treatment (21), all 40 re-treated patients responded well to resumption of therapy with infliximab, with clear improvement of signs and symptoms, while BASDAI-50% responses were seen in 25 of 40 completers (63%) and 12 patients were in partial remission (30%). The mean BASDAI improved from 6.0±1.4 at the time of clinical relapse to 2.6±2.0 and the median CRP normalised (from 11.2 to 1.8 mg/l) after one year (both p<0.05). Only 1 patient dropped out of the study one year after re-treatment, due to an increase of local infections. All other patients continued with infliximab in the same dose without signs of loss of efficacy or issues with safety. One patient was still in clinical remission without biological or other medical therapy.

The lower the disease status was at the time point of treatment withdrawal, the longer was the time until relapse and the faster was also the response after retreatment. Patients with lower disease activity status were also more likely to have ongoing benefit of previous therapy for some more months. These findings differ from another study in which young age, high CRP levels, short disease duration and high disease activity were the best predictors for both short- and long-term outcomes after treatment with anti-TNF agents in AS directly after NSAID failure (22). A second, smaller study concerning discontinuation of biologic therapy in established AS was performed in 30 patients who had been treated with etanercept (23). After the initial phase of 6 weeks of active treatment, 57% of the 26 patients who were initially included showed a BASDAI-50% response, versus only 6% of patients who took placebo (p=0.004). Treatment was discontinued after 18 weeks, and patients were followed up clinically for clinical relapse, defined as worsening of the BASDAI ≥2 units compared to the last visit prior to discontinuation. On that basis, 75% of the patients experienced a clinical relapse after a mean of 6 weeks, and the remainder of the patients relapsed only a few weeks later. After re-administration of etanercept (24), a similar efficacy with comparable scores to the time point of withdrawal was seen in most patients. After one year, 88% of patients remained on treatment; 58% of those showed BASDAI-50% improvement, and 31% were in partial remission (23). The largest dataset of AS patients who discontinued anti-TNF therapy has recently been published, but without follow-up data after re-treatment (25). In this prospective longitudinal observational cohort study over 6 years, 220 patients with AS presenting to an outpatient clinic were followed up according to a fixed protocol (n=32 with infliximab, n=137 with etanercept, and n=51 with adalimumab). After 6 months of treatment, 63% of patients showed an ASAS-20, 46% an ASAS-40 and 50% a BASDAI-50% response – similar to previous studies. The retention rate after a median follow-up of 33 months (range 2.4–68.2 months) was 64%. Baseline predictors for treatment discontinuation for any reason were female gender, absence of peripheral arthritis, high BASDAI, and low ESR and CRP levels prior to treatment initiation (25).

It may be that relapse definitions based on an increase in CRP levels and/or a change of MRI findings (for example persistent or newly arising bone mar-
row edema) might provide improved guidance for changes in the therapeutic strategy, beyond a clinical definition. There is an unmet need for a definition of relapse in patients with axSpA, since follow-up data and strategy studies have not been performed so far. However, it is clear that not all patients respond to anti-TNF therapy, not all respond to the same degree and in some there is a dissociation of clinical symptoms from laboratory and MRI findings.

Withdrawal of biologic therapies other than anti-TNF

So far, no other biologic compound has shown clinical efficacy similar to anti-TNF agents in patients with AS in randomised controlled trials. However, in an open pilot study of rituximab 2x1g administered intravenously (i.v.) within 2 weeks combined with 100 mg of methylprednisolone i.v., favourable ASAS response rates were reported for anti-TNF-naive but not for anti-TNF-experienced patients (26). Five patients who had initially responded to the first course were evaluated after having received a second course of rituximab (27). In more detail, patients were classified as responders in case of an ASAS-20 response on at least 2/4 consecutive visits, which were performed at weeks 12, 16, 20 and 24. In a case of clinical relapse, defined as a worsening of the BASDAI of ≥1.5 units as compared to the lowest BASDAI score between weeks 12-24 of the study, patients received a second course of rituximab and were followed for another 48 weeks. After 24 weeks, 9 patients were classified as responders (6 TNF-naive and 3 who had failed anti-TNF-therapy). Five responders relapsed and received a second rituximab course. The mean BASDAI of these (5.7±1.9 at baseline) dropped to 1.6±1.6 after the first course of rituximab. At the time of relapse the BASDAI had increased to 4.2±1.6, but decreased again to 1.7±1.5 at week 48 after the second course of rituximab (insignificant p-values because of low patient numbers). Of interest, ASAS partial remission or BASDAI-50% responses at week 48 after re-treatment were seen only in the two TNF-naive patients. Taken together, there appears a positive signal to perform randomised controlled studies with rituximab in AS. However, no recommendations to use this biologic agent in patients with AS can be given at this moment. It seems likely that studies with biosimilars rather than rituximab will be performed in this indication. In that case, data concerning withdrawal of therapy with the agent that is similar to rituximab should also be presented.

Does immunogenicity play a role in the response to re-treatment after withdrawal of biologic therapy in axial spondyloarthritis?

It is known that immunogenicity of monoclonal antibodies against TNF-α may influence the clinical response of patients treated with these agents – especially infliximab and adalimumab have been reported to give rise to antibody formation (28, 29). However, an association of such antibodies with treatment response rates clearly is not linear (30). The duration of treatment may influence immunogenicity rates (31) and, therefore, also have an influence on the presence and functioning of anti-drug antibodies after discontinuation of biologics.

The role of immunogenicity in the response to re-treatment after withdrawal of biologic therapy was assessed in only one study with infliximab and patients with established AS (21), by measurement of antibodies to infliximab (ATI) after withdrawal and re-treatment (21). Overall, ATIs were detected in only one patient out of a total of 42 patients who were retreated after infliximab discontinuation. This patient was also the only one who dropped out of the study due to repeated local infections during the first year of re-treatment, an observation that appears to argue against a relevant role of anti-drug antibodies. However, these patients, prior to infliximab discontinuation, had already been treated with infliximab for 3 years without any interruption. This may have resulted in a positive selection of patients because patients who had developed ATI had already dropped out of the study. No immunosuppressive co-medication had been allowed in this study. There are data suggesting that co-medication with immunosuppressive agents may reduce the incidence of immunogenicity in patients treated with monoclonal antibodies against TNF-α. Indeed, in studies with patients diagnosed with Crohn’s disease (32, 33) and rheumatoid arthritis (34), co-medication with azathioprine and methotrexate was associated with lower rates of ATI formation and a lower incidence of infusion reactions compared to the absence of such treatment. However, the situation is clearly different in patients with established AS – most probably due to the fact that methotrexate itself is not effective against axial disease in AS (35), and this includes higher dosages given i.v. In the already cited study (35), patients with established AS treated with methotrexate in addition to infliximab in comparison to infliximab monotherapy had similar clinical outcomes and no more adverse events. However, a tendency toward lower incidence of infusion reactions has been reported in one study of AS patients receiving infliximab with concomitant methotrexate (17).

Taken together, there is no evidence that immunosuppressants should be added to anti-TNF agents in patients with established AS and predominant axial symptoms. This may be different in patients with predominant peripheral arthritis. In any case, the number needed to treat should be calculated especially in situations in which reduction of side effects, rather than increased efficacy, is the primary rationale for immunosuppressive medication.

Conclusion

Overall, current data suggest that withdrawal of anti-TNF treatment in patients in established axSpA, e.g. AS, will frequently lead to a clinical relapse resulting in a need for re-treatment. Usually, relapse is seen only a few months after discontinuation of anti-TNF therapy. However, since the clinical response rates after re-treatment are similar to the initial responses, and since the readministration has so far not been associated with relevant safety problems, an attempt of discontinuation of anti-TNF therapy may be performed when it ap-
pears clinically reasonable. However, it remains unclear whether the duration of therapy before discontinuation matters. Predictors for biologic-free periods and good treatment responses after re-administration are a status of partial remission and normal CRP levels at the time of withdrawal (20). Younger age, male gender and high CRP and ESR values are associated with longer treatment periods, i.e. lower likelihood of discontinuation of therapy. By contrast, female gender, no peripheral arthritis, higher BASDAI scores and low ESR and CRP levels prior to treatment initiation are more likely to lead to discontinuation of treatment with anti-TNF agents.

References