**Do low-dose anti-TNF regimens have a role in patients with Ankylosing Spondylitis?**

**Strap line: Evidence suggests they have a place but questions remain as to when and in whom to try them [ A: please feel free to amend]**

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Tumour necrosis factor alpha inhibitors (anti-TNFs) are highly effective in treating the symptoms of Ankylosing spondylitis (AS) and are well established in clinical practice [1]. Unfortunately they are expensive, potentially toxic and have not been shown conclusively to prevent or reduce structural radiographic progression. In the UK, anecdotal experience has shown that many patients choose to reduce the dose of their prescribed drug. It is, therefore, important to consider what place, if any, reduced dose anti-TNF regimes have in the treatment of AS.

Several studies have assessed dose modification strategies for anti-TNF agents in AS; however, there have been no dose reduction studies in non-radiographic axial spondyloarthritis. There are two potential approaches to dose modification: either start low or taper (Table 1). ***Table 1*** *illustrates and summarises the published approaches to dose modification in AS.*

Low dose regimens have only been tested with Remicade (infliximab). The first low dose Remicade (infliximab) (3mg/kg every 8 weeks) regimen was trialled in an open label setting in 22 patients who met NICE eligibility criteria for anti-TNF therapy [2]. They were recruited consecutively and there was no blinding or comparator arm. Of the 22 patients given low dose Remicade (infliximab), 12 met response criteria (50% reduction in BASDAI) at 3 months, 14 patients at 6 months and this was maintained at one year. Overall 19 out of 22 patients continued on 3 mg/kg Remicade (infliximab) [2]. A second open label study assessed the effectiveness of 3mg/kg Remicade (infliximab) in 34 patients. Of these patients, 14 discontinued Remicade (infliximab) six due to lack of efficacy, six due to side effects and two lost to follow-up. Efficacy demonstrable at one year was maintained at four years. Dose escalation to 5 mg/kg was required in five patients only [3]. In a placebo controlled trial of low dose Remicade (infliximab) (3mg/kg) given every 8 weeks, 76 patients were recruited to test the effectiveness of a low dose regimen in controlling the symptoms of AS at 12 weeks [4]. At 12 weeks Remicade (infliximab) 3 mg/kg was effective in 53.8% of participants compared to 30.6% in the control group and this reached statistical significance. Following this, there was an extended open label phase. Those participants who did not reach the response criteria as defined by 50% reduction in BASDAI at week 22 or week 38, had their dose escalated to 5 mg/kg. During this extended period, 68% of participants required an increase in Remicade (infliximab) dose to 5 mg/kg [4].

Tapering strategies have been undertaken with several anti-TNF agents. This can be achieved by either dose reduction or extension of the administration interval after a period of standard dose administration. A study of 23 consecutive patients recruited for an open label study of dose tapering using Remicade (infliximab) was reported in 2013[ A: is this study ref 5? - Yes] [5]. Of the 23 patients screened, 19 were recruited and received Remicade (infliximab) 5mg/kg at 6 weekly intervals for 56 weeks, following which the Remicade (infliximab) dose was reduced to 3mg/kg at 8 weekly intervals [5]. All patients also received 7.5mg of methotrexate per week with the rationale of preventing anti-drug antibodies (although 27% did develop antibodies). Per protocol analysis of data were available for 15 patients. These patients maintained their treatment response and reduced inflammatory markers by the end of the study (2 years) compared to the week 56 time point, concluding that a dose taper regimen was possible in these patients. Four participants withdrew from the trial; three due to loss of efficacy and one lost to follow-up [5].

To date, the studies involving dose reduction of enbrel (etanercept) have been on dose tapering designs and there are five published trials. These include dose reduction (3 studies), extending the dosing interval (1 study), or a combination of these two strategies (1 study).These small studies have revealed that maintenance of clinical remission is possible following a period of standard dosing (ranges of success 52% to 90.5%) [6, 7, 8, 9, 10]. However comparison of results from these studies are hampered by the lack of consistent definitions for remission.

An observation study within the national Czech register (the ATTRA register) was performed using propensity score matching[11]. This method was required since there was no specified and pre-agreed protocol and individual physicians decided on the dose reduction strategy. Therefore, without propensity score matching significant selection bias could be introduced. There were 83 patients treated with standard dose anti-TNF and 53 with a reduced regimen. Of the 83 patients in the standard group: 33 (39.8%) received Remicade (infliximab), 31 (37.3%) received Enbrel (etanercept) and 19 (22.9%) Humira (adalimumab). The dose reduction strategies used were to increase the dosing interval (80.7% of patients), reduce the dose (14%) or a combination (5.3%). Of the patients in the reduced dosing group, 17 received Remicade (infliximab), 25 Enbrel (etanercept) and 11 Humira (adalimumab). There were no significant differences between the groups for either relapse or adverse events at 12 months. In the dose reduction group, the initial anti-TNF dose was a third lower than the standard dose and was half the dose at 1 year. Of the 53 patients in the initial reduced dose group, 21% required a return to standard dosing [11].

The available evidence shows that dose reduction may be feasible in a proportion of patients with AS and that treatment response can be achieved and maintained with lower than licenced doses. Symptom control and wellbeing are the key, rational objectives. The studies are limited as most are of an open label design and record patient-measured outcomes only. Further larger randomised control studies are required to determine the optimum clinical characteristics that should be reached prior to dose-reduction being attempted (clinical remission or inactive disease, duration of these states), whether efficacy can be re-established on reinstating the licenced dose in those whom have lost treatment response, and to calculate the potential cost savings during any period of remission or low disease activity during the dose reduction phase of treatment.

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