Response to lower dose TNF inhibitors in axial spondylarthritis; a “real world” multicentre observational study.

Liz Van Rossen1, Antoni Chan2, Annie Gilbert3, Karl Gaffney4, Claire Harris5, Pedro M Machado5,6, Liliana R Santos6, Raj Sengupta7, Paul Basset8, Andrew Keat5

1Department of Research and Development, East Kent Hospital University Foundation Trust, Canterbury, Kent, UK
2Department of Rheumatology, Royal Berkshire Hospital, Reading, UK
3AK Gilbert Ltd, Brighton, UK
4Department of Rheumatology, Norfolk and Norwich University Foundation Trust, Norfolk, UK
5Department of Rheumatology, Northwick Park Hospital, London North West University Healthcare NHS trust, London, UK
6Department of Rheumatology & Queen Square Centre for Neuromuscular Diseases, University College London Hospitals NHS Foundation Trust, London, UK
7Department of Rheumatology, Royal united Hospitals Trust, Bath, UK
8Statsconsultancy Ltd, Amersham. UK

Correspondence to: Liz Van Rossen, 30 Ham Shades Lane, Whitstable, Kent, CT51NX, liz.vanrossen@nhs.net
Abstract

Objective: Dose optimisation of TNF inhibitors in axial spondyloarthritis (axSpA) is attractive but it is unclear for which patients this approach might be appropriate.

Methods: Seventy-one patients, from 6 UK centres, with axSpA who had reduced their dose of TNFi, after being considered to be stable responders were identified. All completed a questionnaire concerning their approach to and experience of dose reduction. Data on patient characteristics, metrology and CRP were retrieved retrospectively from patient records.

Results: Over two years of observation, 60 (84.5%) remained (REM) on reduced-dose medication and 11 (15.5%) reverted (REV) to the original dose. Overall mean dose reduction was 39% and 44% for REM and REV patients respectively. Both groups responded similarly to treatment initially, but the data showed a trend that younger women were more likely to revert. Neither BMI nor smoking was associated with continued low-dose responsiveness. Eight of the 11 REV patients reverted by 6 months. None reached criteria of secondary drug failure and all regained control after increasing back to the original dose. Most patients in both groups reached the decision to dose-reduce jointly with clinicians. Preference for taking the reduced dose was not associated with low dose drug survival.

Conclusion: Many patients with axSpA remain well symptomatically after stepping down the dose of TNFi but young women are less likely to do well on a reduced dose. Dose-reduction should be one element of the management of patient with axSpA.

Keywords: Axial Spondyloarthritis, Biologic therapies, Dose reduction, TNFi treatment, Outcome measures

Key messages:

84.5% stable responders to TNFi remained on a mean 39% reduced-dose medication over two years of observation

Younger AS patients and females were associated with risk of reversion to full -dose treatment

Dose-reduction in AS should be part of dose optimisation strategies
Introduction:

Several studies have shown that withdrawal of tumour necrosis factor inhibitor (TNFi) after good response in patients with axial spondyloarthritis (axSpA) results in relapse in the majority of patients\textsuperscript{1-3}. However, clinical experience indicates that some patients with axSpA respond initially to lower-dose treatment\textsuperscript{4-6} and some of those who respond well to full-dose TNFi treatment are able to reduce the dose and remain symptomatically well with or without concurrent methotrexate\textsuperscript{7-10}. Dose optimisation is attractive on cost and safety, but a number of important unresolved questions prevent its recommendation. Chief of these is whether the potential benefits of TNFi treatment, besides symptom control, prevention of long-term structural damage and long-term functional impairment, can be maintained at lower doses. Of equal importance is the identification of patients who are likely to do well on reduced-dose treatment, or even treatment withdrawal, and those in whom such an approach is highly likely to fail. Dose reduction carries the risk of disease flare; this may reflect incidental secondary failure of TNFi treatment\textsuperscript{11,12} but experience of restarting full-dose treatment after treatment dose-reduction suggests that restoration of response is usual.

In the absence of clear data to support such dose reduction strategies, dose reduction has occurred largely on an \textit{ad hoc} basis. Some patients have simply chosen to use the minimum dose because of personal preference whilst some rheumatology units in the UK have allowed dose reduction where patients have expressed a preference. These changes need to be seen in the context of limited compliance with TNFi dosing reported in rheumatoid arthritis and psoriasis, ranging from 40% to above 80% \textsuperscript{13,14}. Such \textit{ad hoc} changes only allow limited conclusions to be drawn about the pros and cons of dose reduction, but they may help to identify individuals in whom such strategies may be successful. While complex therapeutic trials may eventually help to resolve these issues, “real world” observational studies can help to provide some guidance to clinicians and patients who need it now.

At six rheumatology units within the UK, patients with axSpA who were noted to have reduced the dose of TNFi medication after good response were investigated. The study sought to explore patient- and disease-associated factors predictive of long-term success and failure of reducing the doses of TNFi medication over a two-year period.
Methods

Seventy one patients, from 6 UK centres, with a diagnosis of axSpA and fulfilling classification criteria for ankylosing spondylitis (AS, modified New York criteria\textsuperscript{15}) or axSpA (ASAS criteria\textsuperscript{16}) and who had reduced their dose of TNFi, were identified. All were considered to be stable responders to TNFi; their responses fulfilled NICE criteria and were maintained for at least six months by the time of dose reduction. Each was observed for two years after dose reduction, the outcome of interest being the time to reversion back to the standard dose. No planned dose reduction regime was used; patients either decided for themselves or were advised on an \textit{ad hoc} basis by their treating clinicians.

After obtaining ethical approval, all patients, whether now on reduced-dose treatment or having reverted to full-dose treatment, were asked to complete a questionnaire. This asked about ethnicity, the way dose-reduction decisions were taken, including the input of healthcare professionals, the confidence with which patients took or accepted the decision, perceived effects of dose-reduction on symptoms, lifestyle, work and sleep, effects on any associated conditions and any changes in concurrent medication. All patients were also asked to quantify cigarette smoking, past and present.

Data on age, height, weight and body mass index (BMI), disease duration, duration and doses of TNFi treatment and responses as measured by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI) and Bath Ankylosing Spondylitis Metrology Index (BASMI) over time were collected from departmental clinical records. Each patient was assigned a random number so that, after linkage of the two datasets, analysis was carried out on anonymised data.

Thirty-seven patients were treated with adalimumab, 20 with etanercept, 7 with infliximab and 7 with golimumab. All patients started treatment on standard recommended doses and frequency of administration. All patients were taking originator drugs at the time of the study; none was receiving a biosimilar. The proportion of dose reduction was calculated as a percentage, in mg per month, of the original, standard dose. For patients receiving Infliximab, the percentage dose reduction was calculated from mg/kg administered and the interval between infusions. All patients completed BASDAI and BASFI questionnaires at each visit with
annual BASMI measurement. C-reactive protein (CRP) levels were measured frequently. Individuals who continued to take reduced-dose treatment throughout the observation period were designated “Remainers” (REM) and those who reverted to full-dose treatment during it were designated “Reverters” (REV). For REV patients the duration of reduced-dose treatment was recorded. Mean dose reduction for each of the 4 agents was Adalimumab 39%, Etanercept 39%, Golimumab 26%, and Infliximab 46%. Overall mean dose reduction was 39% and 44% for REM and REV patients respectively.

Data were collected at 6 timepoints (tp):

1. immediately before starting TNFi therapy;
2. at the point of dose reduction;
3. at the point of reversion to full-dose treatment (REV only);
4. 6 months after dose reduction;
5. 12 months after dose reduction;
6. 24 months after dose reduction.

Timepoint 3 was notional since reversion could occur at any point over the observation period.

The analysis of the time to reverting to the standard dose was performed using survival analysis methods. The length of follow-up was only recorded up to 24-months, so that only patients reverting within the first 24-months were considered; those who reverted after 24-months were considered not to have reverted. Kaplan-Meier methods were used to graph the proportion remaining on the low-dose over time, and also to quantify the proportion at key timepoints in the follow-up. Patient factors associated with the time to reverting were analysed using Cox regression.

Results

Of the 71 participants, 56 (78.9%) were male, aged 28 – 71 (mean 51.1) years and 15 (21.1%) female aged 24 –71 (mean 49.9) years. Sixty one were white, 8 were of South Asian origin and 2 were of other ethnicity. Within the 24 month period, 60 (84.5%) patients were REM and 11 (15.5%) were REV. Mean disease duration in these two subgroups was 19.4 and 22.2 years.
respectively. REM patients had taken TNFi for a mean of 3.6 years compared with REV patients’ 1.8 years prior to dose reduction. Nine (16.1%) patients had diagnosed inflammatory bowel disease (IBD), 11 (19.6%) had psoriasis and 11 (19.6%) had previously had episodes of uveitis. Eight (11.3%) were current smokers and 38 (53.5%) others had smoked at some time (“ever-smokers”); 25 (35.2%) had never smoked. Fifty-four (76.1%) patients were employed or self-employed, 3 (4.2%) were work-disabled and 13 (18.3%) were retired.

Demographics, including work and associated comorbidities of the whole group, REM and REV patients are demonstrated in table 1. It can be seen that REM and REV patients have broadly similar demographics. Further analysis of age, gender, baseline BASDAI and CRP are presented in table 2.

Age was also associated with reversion (p=0.05) but data suggest that there was not a consistent trend with increasing age. Thus, to best fit the data, it was necessary to include both linear and squared terms for age; the results being best interpreted graphically. Figure 1 shows how the hazard ratio for age changes with time. The risk of reverting to the low dose is presented relative to a person of average age (age 50).

The graph suggests that the highest risk of reverting was for the youngest subjects. The risk decreased with increasing age up to around aged 50. For subjects aged over 60 there was an increased risk in reverting with further increase in age.

The results also suggest a significant association between gender and the time to reverting. Females were found to have a significantly increased risk of reverting than males. The hazard (or risk) of reverting at any time was over 3 times higher in females than males.

A graphical illustration of the results for the total number of patients is shown in supplementary figure S1, available at Rheumatology Advances in Practice online, and Figure 2. Statistical analysis shows no evidence that either of the BASDAI or CRP measures were associated with the time to revert to the original dose.
Two REM patients reported worsening of comorbidity symptoms (one IBD, one psoriasis) but this did not lead to reversion. No REV patients reported worsening of comorbidity symptoms. The proportion of patients remaining on the original dose over the study period is shown in the Kaplan-Meier plot: Supplementary Figure S1, available at *Rheumatology Advances in Practice* online.

It can be seen that 8 of the 11 patients reverted by 6 months and that 84% of patients remained on the low dose at 24-months.

Analyses of factors associated with time to revert to standard dose indicate that females were found to have a significantly increased risk of reverting than males, the risk of reverting at any time being over 3 times higher (p=0.04). This is illustrated in figure 2.

Neither baseline BASDAI score nor CRP levels at the initiation of TNFi treatment were associated with reversion. It can be seen in figure 3 that both groups responded equally to treatment and scored similarly in all measures at dose reduction and six months.

Figure 3 also shows that REM patients’ scores then remained stable or fell over the observation period from dose reduction, with mean BASDAI scores reduced from 2.4 to 2.0 (20.8%), mean BASFI scores reduced from 2.4 to 1.9 (16.6%), mean BASMI scores reduced from 3.5 to 3.3 (5.7%) and mean CRP scores decreased from 3.4 to 1.9mg/dl (87.2%). REV patients’ mean BASDAI scores from dose reduction to dose reversion decreased from 1.6 to 1.2 (25%) but over this period mean BASFI scores increased from 2.2 to 2.5 (13.6%), mean BASMI scores increased from 3.5 to 4.3 (22.8%) and mean CRP scores also increased modestly from 3.4 to 4.4 mg/dl (29.4%).

**Effect of dose reduction on work, convenience, sleep and concomitant medication**

It can be seen in table 3 that most patients in both groups reached the decision jointly with clinicians. 51 (85%) REM patients either preferred or were indifferent about the decision to reduce the dose but 6 (10%) REM and 7 (63.6%) REV patients did not prefer reducing the dose. Preference for taking the reduced dose was associated with success of the low dose regime REV patients were more likely to increase pain medication including NSAIDs.
Discussion

Despite small numbers, these findings suggest signals worthy of further data-collection and analysis. Principally, it suggests that, amongst these selected patients with axSpA, 84% continued to respond well to TNFi treatment over 24 months in spite of a mean 38% dose reduction but that age and gender are associated with drug survival of reduced-dose TNFi regimes. There are grounds for cautiously predicting that older male patients with raised pre-treatment levels of CRP who have achieved NICE response to TNFi treatment for six months are likely to remain symptomatically controlled after dose reduction of approximately 39%. It might be that reducing the dose after a longer period of stable response, perhaps 12 months, would greatly reduce the risk of reversion. It appears likely that patients who are confident with the reduced-dose approach, whose decision has been shared with the clinical team and for whom the opportunity to revert is readily available are more likely to remain well on reduced-dose treatment.

The patients in this study were typical of UK hospital axSpA populations though the low prevalence of women may reflect the lower proportion of patients with non-radiographic axSpA receiving TNFi treatment at the time of recruitment.

Notably, at the point of reversion, REV patients did not reach BASDAI levels indicative of secondary drug failure and all of the REV patients regained control after dose reversion. This was preceded by modest rises in BASDAI, BASFI, BASMI and CRP levels; the worsening of symptoms but maintenance of low CRP levels raises questions as to the mechanisms underpinning dose-reversion. Lower CRP levels have been reported in women with axSpA\(^\text{17}\) though the explanation is unclear. Unsurprisingly, REV patients took more analgesia than REM patients after dose-reduction, commensurate with worse symptoms.

In this small sample, 8 of the 11 REV patients reverted within 6 months. REV patients had taken biologic treatment for less time than REM patients, suggesting that dose-reversion is more likely early in TNFi treatment and soon after dose-reduction. It may be significant that all responded symptomatically to increasing the dose. No clear influence of smoking has been shown, with approximately half the patients in each group being “ever smokers” and only a
few being current smokers. The lack of effect of smoking may be due to the small sample size but it consistent with the findings that smoking does not influence response to TNFi in axSpA\textsuperscript{18}.

The patient’s view of dose reduction is clearly relevant to the success of dose optimization; although this study is small, some important issues have been identified. Most patients in both groups made the dose-reduction decision jointly with clinicians. More REV patients, however, expressed concern about the dose reduction than REM patients, suggesting that illness with dose-reduction might have influenced survival of low-dose treatment in this group. Holmes and colleagues\textsuperscript{19} reported that most patients are interested in reducing the dose of TNFi but that fear of flare and inability to access expert advice tempered this enthusiasm. Hewlett and colleagues\textsuperscript{20} also found that patients with axSpA express anxiety about dose-reduction but that clear rationale, shared decision-making and control over the dose they take improved confidence. Our findings would support these views.

In this study, the process of shared decision-making was not structured nor formalized and the decision to dose-revert was deliberately based on patient choice. In further studies it would be helpful to draw up clear criteria for both dose-reduction and for dose-reversion. It would also be critical to record the nature of symptoms leading to dose-reversion precisely so that typical spondylitic symptoms could be separated from fibromyalgic features, peripheral joint symptoms and other symptoms which might be unrelated to the primary disease. Similarly, it would be useful to categorise patients prior to dose-reduction with regard to such features as anxiety which might influence readiness to dose-revert and to agree to set the decision in the context of objective measures including BASDAI and CRP. This might help to establish whether the desire to dose-revert reflected disease activity or other factors. Ultimately, patient choice may still be a sound basis for dose changes in patients with axSpA receiving biologic therapies. However it is critical that the patient is informed in a precise and standardised way, that the symptoms and measures of disease activity are precisely recorded at the time of dose-change decisions and that there is a justified relationship of trust between patient and condition.

In the treatment of axSpA, the treat to target approach\textsuperscript{21,22}, with its uncertain targets but
implication of careful choice of first drug, dose escalation and drug switching, is appealing but only part of the problem of optimized treatment\textsuperscript{23}. Keeping the target in mind but maintaining it with minimal treatment is an integral part of the approach. In rheumatoid arthritis (RA) dose-reduction strategies are frequently successful\textsuperscript{24} and advocated in its treatment\textsuperscript{25,26} though this is not currently the case with axSpA\textsuperscript{27}.

In axSpA, therefore, it is important to define and understand both flare and relapse; both may reflect symptom change either caused by increased inflammatory activity or non-inflammatory mechanisms. It is of interest that none of the REV patients reached criteria for secondary drug failure. We agree with Edwards and colleagues\textsuperscript{28} that there is also a need to define the targets of not only induction-phase full-dose remission (or low disease activity – LDA) but also maintenance phase remission LDA in patients with axSpA.

Expenditure on medication and drug delivery was not assessed in this study and absolute figures would now be heavily influenced by the introduction of biosimilars. However, it is worthy of comment that of the 60 REM patients, the mean dose reduction was 39\%, offering a substantial saving on medication costs. This is clearly important in countries where drug costs are borne by health services or insurers but may be critically so in those where drug costs, and hence access to treatment, are borne by the patients themselves.

In this study, any individuals who explicitly did not wish to take reduced-dose treatment were excluded. Clearly, extended follow-up will be necessary and the likelihood of regaining LDA after dose reversion needs to be clarified though, in this study, all REV patients regained symptom control, and none switched to an alternative biologic agent. It will be pertinent to consider further step-down approaches and to develop further predictors of their success for both TNFi and other biologic agents.

\textbf{Figure legend}

\textbf{Figure 1: Risk of reverting to original dose by age}

The results also suggest a significant association between gender and the time to reverting. Females were found to have a significantly increased risk of reverting than males. The hazard (or risk) of reverting at any time was over 3 times higher in females than males.
A graphical illustration of the results for the total number of patients is shown in Supplementary Figure S1, available at Rheumatology Advances in Practice online and 2.

Statistical analysis shows no evidence that either of the BASDAI or CRP measures were associated with the time to revert to the original dose.

Two REM patients reported worsening of comorbidity symptoms (one IBD, one psoriasis) but this did not lead to reversion. No REV patients reported worsening of comorbidity symptoms.

The proportion of patients remaining on the original dose over the study period is shown in the Kaplan-Meier plot: Supplementary Figure S1, available at Rheumatology Advances in Practice online.

**Figure 2: Kaplan-Meier plot of time to reverting to original dose by gender**

Neither baseline BASDAI score nor CRP levels at the initiation of TNFi treatment were associated with reversion. It can be seen in figure 4 that both groups responded equally to treatment and scored similarly in all measures at dose reduction and six months.

**Figure 3: BASDAI, BASFI, BASMI and CRP levels from the time of dose-reduction (tp1) to 24 months (tp2).**

Figure 3 also shows that REM patients’ scores then remained stable or fell over the observation period from dose reduction, with mean BASDAI scores reduced from 2.4 to 2.0 (20.8%), mean BASFI scores reduced from 2.4 to 1.9 (16.6%), mean BASMI scores reduced from 3.5 to 3.3 (5.7%) and mean CRP scores decreased from 3.4 to 1.9 mg/dl (87.2%). REV patients’ mean BASDAI scores from dose reduction to dose reversion decreased from 1.6 to 1.2 (25%) but over this period mean BASFI scores increased from 2.2 to 2.5 (13.6%), mean BASMI scores increased from 3.5 to 4.3 (22.8%) and mean CRP scores also increased modestly from 3.4 to 4.4 mg/dl (29.4%).

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Table 1. Patient characteristics

|                        | Total (n=71) | REM (n=60) | REV (n=11) |
|------------------------|-------------|-----------|------------|
| Female, n (%)          | 15 (21.1)   | 10 (16.6) | 5 (45.5)   |
| Age, mean (range) (yrs)| 50.5 (24 – 72) | 51.2 (26 - 71) | 46.8 (24-72) |
| BMI, mean (range) (yrs)| 26.8 (19 - 37) | 26.6 (19 - 37) | 27.6 (24 - 35) |
| Duration of disease, mean (range: yrs) | 19.9 (6-41) | 19.4 (6-41) | 22.2 (15-31) |
| Duration of TNFi at dose-reduction, mean (range: yrs) | 3.9 (0.3-10.9) | 3.6 (0.3 - 10.9) | 1.8 (1.9 - 9.3) |
| Baseline BASDAI        | -           | 6.2       | 5.7        |
| Baseline CRP           | -           | 14.5      | 9.4        |
| Ethnicity:             |             |           |            |
| Caucasian, n (%)       | 61 (85.9%)  | 52 (86.7%)| 9 (81.8%)  |
| South Asian, n (%)     | 8 (11.3%)   | 6 (10%)   | 2 (18.2%)  |
| Other, n(%)            | 2 (2.8%)    | 2 (3%)    | 0 (0%)     |
| Comorbidities:         |             |           |            |
| Uveitis, n (%)         | 11 (19.6%)  | 9 (15%)   | 2 (18.2%)  |
| Psoriasis, n (%)       | 11 (19.6%)  | 8 (13.3%) | 3 (27.3%)  |
| IBD, n (%)             | 9 (16.1%)   | 9 (15%)   | 0 (0%)     |
| Work status*:          |             |           |            |
| Employed, n (%)        | 35 (50%)    | 28 (46.7%)| 7 (63.6%)  |
| Self-employed, n (%)   | 19 (27.1%)  | 17 (28.3%)| 2 (18.2%)  |
| Not working, n (%)     | 16 (22.9%)  | 14 (23.3%)| 2 (18.2%)  |
| Smoking status:        |             |           |            |
| Current smoker, n (%)  | 8 (11.3%)   | 8 (13.3%) | 0 (0%)     |
| Ever-smoker, n (%)     | 38 (53.5%)  | 33 (55%)  | 5 (45.5%)  |
| Never-smoker, n (%)    | 25 (35.2%)  | 19 (31.7%)| 6 (44.5%)  |

*Data missing from 1 patient

IBD: Inflammatory Bowel Disease

Table 2: Regression analyses examining factors associated with time to revert to standard dose

| Variable              | Category / term | Hazard Ratio (95% CI) | p-value |
|-----------------------|-----------------|-----------------------|---------|
| Age (*)               | Linear term     | 0.94 (0.58, 1.48)     | 0.05    |
|                       | Squared term    | 1.38 (1.00, 1.91)     |         |
| Gender                | Male            | 1                     | 0.04    |
|                       | Female          | 3.44 (1.05, 11.3)     |         |
| BASDAI (baseline)     | -               | 0.72 (0.43, 1.19)     | 0.20    |
| CRP (baseline)        | -               | 1.02 (0.79, 1.31)     | 0.89    |

(*) Hazard ratio given for a 10-year increase in age
Table 3 Patient aspects of dose reduction

| Variable                        | Category               | REM 60       | REV 11       |
|---------------------------------|------------------------|--------------|--------------|
| Decision to reduce dose         | Jointly with clinician | 40 (66.6%)   | 8 (72.7%)    |
|                                 | Patient decision       | 11 (18.3%)   | 1 (9.1%)     |
|                                 | Health professional    | 7 (11.7%)    | 1 (9.1%)     |
| Preference for lower dose       | Preferred              | 36 (60.0%)   | 2 (18.2%)    |
|                                 | No difference          | 15 (25.0%)   | 1 (9.1%)     |
|                                 | Did not prefer         | 6 (10.0%)    | 7 (63.6%)    |
| Undisturbed sleep (hours)       |                        | 5.9          | 6.1          |
| Dose of pain meds since reduction | Less                  | 6 (10.0%)    | 1 (9.1%)     |
|                                 | No change              | 41 (68.3%)   | 1 (9.1%)     |
|                                 | More                   | 9 (15.0%)    | 8 (72.7%)    |
Supplementary figure legend

Supplementary Figure S1: Kaplan-Meier plot of time to reverting to original dose (reduced y-axis) It can be seen that 8 of the 11 patients reverted by 6 months and that 84% of patients remained on the low dose at 24-months.

Analyses of factors associated with time to revert to standard dose indicate that females were found to have a significantly increased risk of reverting than males, the risk of reverting at any time being over 3 times higher (p=0.04). This is illustrated in figure 2.
