RHEUMATOLOGY

Rheumatology 2016;55:1188–1194
doi:10.1093/rheumatology/kew033
Advance Access publication 21 March 2016

Original article

Anti-TNF discontinuation and tapering strategies in patients with axial spondyloarthritis: a systematic literature review

Victoria Navarro-Compán[1], Chamaida Plasencia-Rodríguez[1], Eugenio de Miguel[1], Alejandro Balsa[2], Emilio Martín-Mola[1], Daniel Seoane-Mato[2] and Juan D. Cañete[3]

Abstract

Objective. The aim was to evaluate whether anti-TNF discontinuation and tapering strategies are efficacious for maintaining remission or low disease activity (LDA) in patients with axial spondyloarthritis.

Methods. A systematic literature review up to September 2014 was performed using Medline, EMBASE and Cochrane databases. Longitudinal studies evaluating the efficacy of discontinuation/tapering of anti-TNF therapy to maintain clinical response achieved after receiving a standard dose of the same drug were included. The results were grouped according to the type of strategy (discontinuation or tapering) evaluated.

Results. Thirteen studies out of 763 retrieved citations were included. Overall, published data are scarce and the level of evidence of the studies is weak. Five studies provided evidence for assessing discontinuation strategy. The frequency of patients developing flare during the follow-up period ranged between 76 and 100%. The median (range) follow-up period was 52 (36–52) weeks and time to flare 16 (6–24) weeks. Additionally, eight studies evaluating tapering strategy were selected. The percentage of patients maintaining LDA or remission was reported in five studies and ranged between 53 and 100%. The remaining three studies reported the mean change in BASDAI and CRP after reducing the anti-TNF dose and did not observe any relevant increase in these parameters.

Conclusion. Published data indicate that a tapering strategy for anti-TNF therapy is successful in maintaining remission or LDA in most patients with axial spondyloarthritis. However, a discontinuation strategy is not recommended because it leads to flare in most cases. Further studies with an appropriate design covering the whole spectrum of the disease are required to confirm these results.

Key words: anti-TNF, axial spondyloarthritis, discontinuation, tapering

CLINICAL SCIENCE

Rheumatology key messages

- Published evidence on discontinuation and tapering strategies in axial spondyloarthritis is scarce and weak.
- Discontinuation of anti-TNF therapy in patients with axial spondyloarthritis leads to flare in most cases.
- Tapering anti-TNF therapy is successful in maintaining low disease activity in most patients with ankylosing spondylitis.

Introduction

The spectrum of the disease axial spondyloarthritis (axSpA) includes patients with AS and patients with non-radiographic axSpA (nr-axSpA). In both types of patients, anti-TNF therapy has proven efficacy for improving signs and symptoms in randomized controlled trials (RCTs) [1–5].

[1]Department of Rheumatology, IdiPaz, University Hospital La Paz, [2]Research Unit, Spanish Society of Rheumatology, Madrid and [3]Department of Rheumatology, Hospital Clinic and IDIBAPS, Barcelona, Spain

Submitted 17 July 2015; revised version accepted 3 February 2016

Correspondence to: Victoria Navarro-Compán, Department of Rheumatology, University Hospital La Paz, Madrid, Spain.
E-mail: mvictoria.navarroc@gmail.com

In contrast, opposite to RA and PsA, anti-TNF therapy has not been shown clearly to inhibit radiographic progression in patients with axSpA. In addition to this, anti-TNF therapy is costly and not exempt from important adverse effects, some of which are dose dependent [6]. Thus, in clinical practice, the question that arises nowadays is whether anti-TNF therapy might be discontinued or tapered in patients with axSpA who achieve the clinical goal without an increase of the disease activity level. The potential benefits of this strategy could be significant, including a substantial reduction of costs and of safety problems. Although some studies have provided some evidence in this regard, this point is still unclear. Based on this, the objective of the present study was to investigate whether discontinuation or tapering strategies of anti-TNF therapy are efficacious for maintaining remission or low disease activity (LDA) in patients with axSpA.

Methods

Research question and search strategy

A systematic literature review (SLR) was performed using Medline, EMBASE and Cochrane databases in collaboration with an epidemiologist with expertise on SLR methodology. The search included studies published in English, Spanish or French up to 4 September 2014. Supplementary data, research strategy section, available at *Rheumatology* Online, shows all the terms used to conduct the search. The research question was formulated according to the Population, Intervention, Comparison, Outcome and Study design (PICOS) method, in which each of the items was defined as specified below. LDA and clinical remission were not pre-defined, but the exact definition used in each study was collected.

The population was patients with axSpA, AS or nr-axSpA, who achieved LDA or clinical remission after receiving a standard dose of anti-TNF therapy.

Two intervention strategies were evaluated: discontinuation of anti-TNF therapy or tapering (dose reduction compared with the standard dose) anti-TNF therapy. Comparison was made with maintaining a standard dose of anti-TNF.

The outcome was flare or change (increase) on disease activity parameters. As there is no accepted definition for flare in axSpA, this was not pre-defined, but the exact definition employed in each study was also collected. Longitudinal studies with at least 6 months of follow-up since the intervention (strategy) started were included.

Selection of studies

First, titles and abstracts of the retrieved citations were screened to select articles for full-text review. Later, based on the full-text reading of the selected articles, two readers (V.N.-C. and C.P.-R.) independently decided whether or not to include a specific study for data extraction and, in instances of disagreement, they discussed until a consensus was reached. Inclusion criteria were based on the PICOS components. Exclusion criteria were non-compliance with the definitions established on the PICOS or insufficient data provided by the article to evaluate the objective of the present study.

Data extraction and data summary

Using a systematic extraction data form developed for this specific purpose, both reviewers independently extracted data for each study, including the following: characteristics of the studies (year of publication, design and follow-up period) and patients (total number of patients, demographics and disease characteristics); definition of LDA or clinical remission used in the study; intervention (anti-TNF therapy and dose regimen); and outcome (definition and percentage of patients who achieved the specific outcome). Furthermore, we also evaluated the quality and potential biases of the studies, assigning an overall quality score per study between 0 and 5 points according to the Oxford level of evidence. To summarize the extracted data, the studies selected for data extraction were classified in two groups based on the type of intervention strategy, namely discontinuation or tapering.

Results

Characteristics of the studies

A detailed flow chart with the results of the literature search is shown in Fig. 1. Out of the 763 citations retrieved by the search, 33 studies were selected for full-text review. In total, 13 studies were included for data extraction [7–19]; discontinuation strategy was assessed in five studies, whereas tapering strategy was evaluated in eight studies. The reasons for excluding the remaining studies are depicted in supplementary Table S1, available at *Rheumatology* Online.

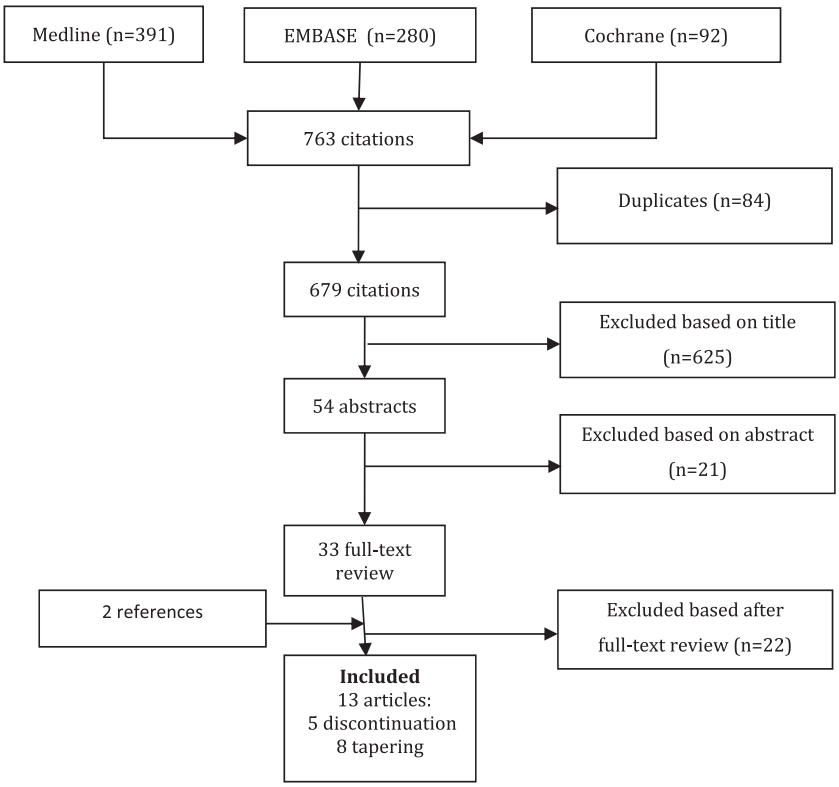
Discontinuation

Five studies [7–11] were included to evaluate the efficacy of an anti-TNF discontinuation strategy for maintaining LDA or remission in patients with axSpA after achieving this state with a standard dose of anti-TNF therapy. Table 1 shows in detail the characteristics and results of these studies. In total, they included 220 patients (84% AS and 16% nr-axSpA). Four of these studies were observational after participation in an RCT, and only one of them was an RCT to evaluate the effect of thalidomide to prevent flare after discontinuation of anti-TNF therapy. The discontinued therapy was etanercept (n = 3), infliximab (n = 1) or adalimumab (n = 1). The median (range) sample size of the studies was 26 (17–111) patients. The median (range) follow-up period after discontinuation was 52 (36–52) weeks. The level of evidence was four in all studies.

Median (range) values for baseline characteristics of patients included in the studies were as follows: age 39 (37–40) years old; 68% (45–77) males; disease duration 8 (3–15) years; 92% (67–100) HLA-B27 positive; and time on anti-TNF therapy before discontinuation 11 (2.5–36) months.

In these studies, patients receiving standard doses of an anti-TNF drug discontinued this therapy and were followed to assess the appearance of flare. The exact

Fig. 1 Flow chart of the studies through review



definition of flare used in each study is depicted in Table 1. In most of them, a flare was defined as BASDAI $\geqslant$ 4 and physician's assessment of disease activity $\geqslant$ 4 or an increase in BASDAI of $\geqslant$2 units. The median (range) percentage of patients developing flare during the follow-up period was 79% (76–100%). Specifically, the percentage and corresponding period for each study were as follows: 100% (within 36 weeks) [7]; 98% (within 48 weeks) [8]; and 76, 79 and 79% (all three within 52 weeks) [9–11]. The median (range) time to flare was 16 (6–24) weeks.

Furthermore, the patients participating in the four observational studies following an RCT were re-treated using the same anti-TNF after flare occurrence. Overall, a similar response to the one achieved at the beginning of the RCT was observed for most clinical parameters of disease activity.

Tapering

Eight studies [12–19] assessed the efficacy of a tapering strategy of anti-TNF therapy after achieving LDA or clinical remission. The characteristics and results of these studies are presented in Table 2. All of them included patients with AS from a single centre, but no study included patients with nr-axSpA. Most of them were observational studies [retrospective (n = 3), prospective (n = 3)] and only two of them were interventional [non-randomized trial (n = 1) and RCT (n = 1)]. The level of evidence was four in all studies except one, in which it was 2b.

Median (range) values for the main characteristics of the studies were as follows: number of patients included in the study 43 (8–136); number of patients on low-dose regimen 21 (8–109); and follow-up period after anti-TNF tapering 12 (6–21) months. The anti-TNF therapy administered was etanercept (n = 5), infliximab (n = 1) or adalimumab/etanercept/infliximab (n = 2). Baseline characteristics of patients included in the studies were as follows: age 41 (35–54) years old; 78% (75–90) males; disease duration 9 (3–13) years; and 89% (75–91) HLA-B27 positive. The time in remission or LDA before reducing the anti-TNF dose was provided in four studies and it was heterogeneous: $<$3 months (n = 1) and at least 3 (n = 1) or 6 (n = 2) months.

In these studies, patients receiving standard doses of anti-TNF therapy who were in remission (usually defined as BASDAI $<$ 2 and normal CRP) or with LDA (usually defined as BASDAI $<$ 4 and normal CRP) reduced anti-TNF therapy dose according to an established protocol (n = 5) or according to the physician's criterion (n = 3). Dose reduction was most frequently done by increasing the interval between drug administration rather than decreasing the dose of the injection/infusion. The percentage of patients maintaining LDA or remission after reduction of the anti-TNF dose was reported in five out of the eight studies. In detail, these were 67% [18], 75% [19], 53–81% (depending on the anti-TNF therapy) [14], 86% [15] and 100% [17]. The remaining three studies reported

Table 1 Characteristics of studies selected for evaluating a discontinuation strategy of anti-TNF therapy in patients with axial spondyloarthritis

Characteristics of the study	Brandt *et al.* [7]	Baraliakos *et al.* [8]	Song *et al.* [9]	Deng *et al.* [10]	Haibel *et al.* [11]
Year	2003	2005	2012	2013	2013
Journal	Arthritis Rheum	Arthritis Res Ther	Ann Rheum Dis	Rheumatol Int	Arthritis Rheum
Design	Prospective, observational after RCT	Prospective, observational after RCT	Prospective, observational after RCT	RCT	Prospective, observational after RCT
Period	2001	2003	2003	–	–
Country	Germany	Germany	International	China	Germany
Number of patients, AS/nr-axSpA	26/0	42/0	6/11	111/0	0/24
Patients who discontinued	26	42	17	111 (thalidomide *vs* SSZ or NSAID)	24
Control group	No	No	No	No	No
Follow-up, weeks	36	52	52	52	52
Characteristics of patients					
Age, years	37	40	34	18–57	38
Male	77	65	71	–	45
Disease duration, years	Mean (S.D.) 14 (9)	Mean (S.D.) 15 (9)	All patients <5 symptom duration	Mean 9	Adalimumab, mean 7; placebo mean 8
HLA-B27+	89	–	94	100	67
Peripheral arthritis	–	–	–	–	30
Synthetic DMARDs	0%	–	–	–	–
Anti-TNF	Etanercept	Infliximab	Etanercept	Etanercept	Adalimumab
Time on anti-TNF, months	3	36	11	2.5	12
Definition to discontinue anti-TNF	⩾20% improvement in BASDAI	All patients (at least, they all had ⩾30% improvement in BASDAI)	ASASpr and remission on MRI	ASAS20 response	ASAS40 response
Outcome					
Flare definition	BASDAI ⩾4 and PhyGV⩾4	BASDAI ⩾4 and PhyGV ⩾4	Increment in BASDAI of 2 units *vs* baseline	Increment in BASDAI of 2 units or 80% of BASDAI prior to treatment	Loss of ASAS40 response *vs* baseline
Number patients with flare	75% at 12 weeks, 100% at 36 weeks	24% at 12 weeks, 98% at 48 weeks	76% at week 52	79% at week 52	79% at week 52
Time to flare, weeks	Mean (S.D.) 6.2 (3.0)	Mean (S.D.) 17 (8)	Mean 24	Mean (S.D.) 14 (9)	Mean (S.D.) 15 (5.5)
Predictor of flare	–	No ASASpr, high BASDAI or high CRP at discontinuation	–	CRP, PtGV, spinal inflammation	Not found
Response after re-treatment	58% BASDAI 50 31% ASAS after 54 weeks	Similar to initial (BASDAI 6.1 at reinfusion *vs* 2.9 after 12 weeks)	Similar to initial except for ASASpr that was less frequently achieved	–	ASAS40 was achieved by 63% after 1 year and 74% after 2 years
Level of evidence					
Oxford level of evidence	4	4	4	4	4

ASASpr: partial response according to Assessment of SpondyloArthritis international Society; nr-axSpA: non-radiographic axial spondyloarthritis; PhyGV: physician's global assessment of disease activity; PtGV: patient's global assessment of disease activity; RCT: randomized controlled trial.

Table 2 Characteristics of studies selected for evaluating tapering strategy of anti-TNF therapy in patients with axial spondyloarthritis

Characteristics of the study	Lee *et al.* [12]	Navarro-Compán *et al.* [13]	Paccou *et al.* [14]	Cantini *et al.* [15]	Mörck *et al.* [16]	Borrás-Blasco *et al.* [17]	De Stefano *et al.* [18]	Závada *et al.* [19]
Year	2010	2011	2012	2013	2013	2014	2014	2016
Journal	Clin Rheumatol	Clin Rheumatol	J Rheumatol	Biologics: Targets and Therapy	Mediators of Inflammation	Expert Opin Biol Ther	Clin Rheumatol	Ann Rheum Dis
Design	Retrospective	Prospective	Retrospective	RCT	Clinical trial	Retrospective	Prospective	Prospective
Period	2004–09	2003–10	2001–10	2005–09	2003–06	2003–06	2007–10	2007–13
Country	Korea	Spain	France	Italy	Sweden	Spain	Italy	Czech Republic
Total number of patients	109	51	65 (49)	43	19	8	21	136
Patients with tapering	109	16	49	22	19	8	21	53
Control group	No	35	No	21	No	–	–	83
Follow-up, months	21	At least 6 mean 26	At least 6 mean 30	21	12	6	9	12
Characteristics of patients								
Age, years	35	43	45	37	40	–	44	41
Male (%)	90	87	79	79	74	–	76	75
Disease duration, years	9	8	14	13	8	–	3	9
HLA-B27 + (%)	91	87	80	–	80	–	87	75
Peripheral arthritis	–	19	–	–	–	–	15	34
Synthetic DMARDs (%)	94	31	10	–	100	–	–	11
Anti-TNF	Etanercept	Etanercept	Adalimumab (5), etanercept (17), infliximab (25)	Etanercept	Infliximab	Etanercept	Etanercept	Adalimumab, etanercept or infliximab
Time on anti-TNF, months		17 (12)			12	32 (13)	3	35
Tapering strategy	Protocol	Physician	Physician	Protocol	Protocol	Protocol	Protocol	Physician
Outcome								
Remision or LDA	–	BASDAI <4 and PCR 0	BASDAI <2, no peripheral symptoms and PCR[a]	BASDAI <4, no peripheral symptoms and CRP[a]	–	BASDAI <2	ASASpr	BASDAI <4
Time in remission after tapering, months	–	>6	⩾3	–	–	–	<3	⩾6, mean 27
Remission maintenance (%)	–	–	At month 12: 80% adalimumab 53% etanercept 81% infliximab	86	–	100	67	75
Most frequent regimen	Increasing interval (25 mg/ 12 days)	25 mg/week	40 mg/3 weeks 25 mg/week 5 mg/kg/9 weeks	50 mg/2 weeks	3 mg/kg/8 weeks	25 mg/week	25 mg/2 weeks	Increasing interval (regimen not specified)
Before tapering								
BASDAI	2.3	1.6	–	–	2.1	2.1	–	–
CRP, mg/l	0.06	1.0	–	–	8	–	–	–
After tapering			–	–			–	–
BASDAI	0.6	1.4	–	–	3.2	2.0	–	–
CRP, mg/l	0.06	1.3	–	–	8	–	–	–
Level of evidence								
Oxford level of evidence	4	4	4	2b	4	4	4	4

[a]Value within normal range. ASASpr: partial response according to Assessment of SpondyloArthritis international Society; RCT: randomized controlled trial.

the mean change in disease activity measures after reducing anti-TNF therapy [12, 13, 16]. The mean BASDAI in these studies before reduction of the anti-TNF dose was 2.3, 1.6 and 2.1, and at the end of the study this was 0.6, 1.4 and 3.2, respectively. Mean CRP (in milligrams per litre) before reduction of the anti-TNF dose was 0.06, 1.0 and 8, and at the end of the study this was 0.06, 1.3 and 8, respectively.

Discussion

This SLR summarizes the published evidence on the use of discontinuation or tapering strategies of anti-TNF therapy in patients with axSpA after achieving clinical remission or LDA with a standard dose of the same drug. The findings for a discontinuation strategy are consistent. Published data indicate that discontinuation of anti-TNF therapy in patients with axSpA leads to the appearance of flare within a few months in most cases. Therefore, despite the possible benefits, the use of this strategy is not recommended. However, if for any specific reason, such as surgery or pregnancy, discontinuation is required in a patient with axSpA, published evidence also indicates that the probability of achieving a similar response after reinitiating anti-TNF therapy is very high.

Furthermore, published data also suggest that a tapering strategy may be efficacious to maintain remission or LDA in most patients with axSpA. Although the comparison with other rheumatic diseases is difficult, the frequency of flare after implementation of a tapering strategy seems to be lower in patients with axSpA than in patients with RA [20]. The implementation of this strategy in clinical practice would have a great impact, such as reducing possible adverse effects related to anti-TNF therapy and, especially, saving costs. Importantly, however, not all patients who switched to a tapering strategy remained at the same disease activity status. The identification of those patients who have less probability of success after implementation of the tapering strategy is therefore essential, but so far no predictors have been clearly identified. Among possible predictors, it seems that the time under remission before tapering anti-TNF therapy as well as the absence of peripheral and extra-articular manifestations are associated with a better outcome. In this sense, the use of concomitant DMARDs could also help to maintain remission after implementation of an anti-TNF tapering strategy, but this possible beneficial effect of adding a DMARD to an anti-TNF therapy in patients with axSpA has not been demonstrated and needs further investigation. In addition to this, the consequences of a tapering strategy on long-term outcomes, such as function, mobility, quality of life and cardiovascular mortality, also need to be evaluated.

To our knowledge, this is the first SLR that has examined the efficacy of discontinuation and tapering of anti-TNF therapy in patients with axSpA to maintain remission or LDA after this has been achieved with a standard dose. Nevertheless, this SLR has important limitations that should be considered when interpreting its results. First, published studies evaluating this topic are limited and included a small sample size of patients, mainly attending a specific centre. Second, the overall quality of the studies included is poor. None of the studies had a proper design (non-inferiority RCT) to provide a clear answer to the research question. Third, no established definition for clinical remission, LDA and flare has been used in patients with axSpA [21]. As a consequence, the definitions used in the studies for these outcomes are heterogeneous, which makes the comparison between studies and the interpretation of the SLR results difficult. In addition, most of the studies included only patients with AS and established disease, and only one of them (evaluating a discontinuation strategy) included patients with nr-axSpA. Also, it is necessary to remark that the inclusion criteria used by most of the studies were the modified New York criteria or the European Spondyloarthropathy Study Group criteria, which may contain patients with predominantly peripheral disease. Therefore, the extrapolation of these results to all patients covered by the whole spectrum of the disease axSpA according to the new Assessment of SpondyloArthritis international Society remains to be established.

Acknowledgements

This SLR was performed as part of the development process of the update of Espoguia [Guidelines to treat patients with spondyloarthritis of the Spanish Society of Rheumatology (SER)]. The SER received funding from Abbvie for the development of Espoguia. The authors also thank Mercedes Guerra and Susana García for their assistance to perform the search.

Funding: This work was supported by the Spanish Society of Rheumatology (Sociedad Española de Reumatología) as part of the development process of the update of Espoguía.

Disclosure statement: A.B. is a consultant for, participated in clinical trials for, member of a speaker bureau for, received research grants from Abbvie, Boehringer, BMS, MSD, Novartis, Pfizer, UCB, MSD and Roche. J.D.C. is a consultant and participated in clinical trials for Abbvie, Boehringer, BMS, Celgene, MSD, Novartis, Novo-Nordisk, Pfizer and UCB. C.P.-R. has received grants from Pfizer. V.N.-C. has received speaking fees or funding for research projects and attending congresses from Abbvie, BMS, MSD, Novartis, Pfizer and Roche. E.M.-M. has been a consultant for, participated in clinical trials for, member of a speaker bureau and received research grants from Abbvie, Amgen, Biogen, BMS, Janssen, Hospira, MSD, Novartis, Pfizer, Roche, Sanofi and UCB. E.dM. has been a consultant for, participated in clinical trials and speaker bureau for and received research grants from Abbvie, MSD, Astra-Zeneca, Novartis, Pfizer, MSD, Celgene and Menarini. The other author has declared no conflicts of interest.

Supplementary data

Supplementary data are available at *Rheumatology* Online.

References

1 van der Heijde D, Dijkmans B, Geusens P *et al*. Efficacy and safety of infliximab in patients with ankylosing spondylitis: results of a randomized, placebo-controlled trial (ASSERT). Arthritis Rheum 2005;52:582–91.

2 Davis JC, van der Heijde DM, Braun J *et al*. Sustained durability and tolerability of etanercept in ankylosing spondylitis for 96 weeks. Ann Rheum Dis 2005;64:1557–62.

3 van der Heijde D, Kivitz A, Schiff MH *et al*. Efficacy and safety of adalimumab in patients with ankylosing spondylitis: results of a multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2006;54:2136–46.

4 Inman RD, Davis JC, Jr, Heijde D *et al*. Efficacy and safety of golimumab in patients with ankylosing spondylitis: results of a randomized, double-blind, placebo-controlled, phase III trial. Arthritis Rheum 2008;58:3402–12.

5 Landewe R, Braun J, Deodhar A *et al*. Efficacy of certolizumab pegol on signs and symptoms of axial spondyloarthritis including ankylosing spondylitis: 24-week results of a double-blind randomised placebo-controlled Phase 3 study. Ann Rheum Dis 2014;73:39–47.

6 Bongartz T, Warren FC, Mines D *et al*. Etanercept therapy in rheumatoid arthritis and the risk of malignancies: a systematic review and individual patient data meta-analysis of randomised controlled trials. Ann Rheum Dis 2009;68:1177–83.

7 Brandt J, Khariouzov A, Listing J *et al*. Six-month results of a double-blind, placebo-controlled trial of etanercept treatment in patients with active ankylosing spondylitis. Arthritis Rheum 2003;48:1667–75.

8 Baraliakos X, Listing J, Brandt J *et al*. Clinical response to discontinuation of anti-TNF therapy in patients with ankylosing spondylitis after 3 years of continuous treatment with infliximab. Arthritis Res Ther 2005;7:R439–44.

9 Song IH, Althoff CE, Haibel H *et al*. Frequency and duration of drug-free remission after 1 year of treatment with etanercept versus sulfasalazine in early axial spondyloarthritis: 2 year data of the ESTHER trial. Ann Rheum Dis 2012;71:1212–5.

10 Deng X, Zhang J, Zhang J, Huang F. Thalidomide reduces recurrence of ankylosing spondylitis in patients following discontinuation of etanercept. Rheumatol Int 2013;33:1409–13.

11 Haibel H, Heldmann F, Braun J *et al*. Long-term efficacy of adalimumab after drug withdrawal and retreatment in patients with active non-radiographically evident axial spondyloarthritis who experience a flare. Arthritis Rheum 2013;65:2211–3.

12 Lee J, Noh JW, Hwang JW *et al*. Extended dosing of etanercept 25 mg can be effective in patients with ankylosing spondylitis: a retrospective analysis. Clin Rheumatol 2010;29:1149–54.

13 Navarro-Compán V, Moreira V, Ariza-Ariza R *et al*. Low doses of etanercept can be effective in ankylosing spondylitis patients who achieve remission of the disease. Clin Rheumatol 2011;30:993–6.

14 Paccou J, Bacle-Boutry MA, Solau-Gervais E, Bele-Philippe P, Flipo RM. Dosage adjustment of anti-tumor necrosis factor-α inhibitor in ankylosing spondylitis is effective in maintaining remission in clinical practice. J Rheumatol 2012;39:1418–23.

15 Cantini F, Niccoli L, Cassarà E, Kaloudi O, Nannini C. Duration of remission after halving of the etanercept dose in patients with ankylosing spondylitis: a randomized, prospective, long-term, follow-up study. Biologics 2013;71–6.

16 Mörck B, Pullerits R, Geijer M, Bremell T, Forsblad-d'Elia H. Infliximab dose reduction sustains the clinical treatment effect in active HLAB27 positive ankylosing spondylitis: a two-year pilot study. Mediators Inflamm 2013;2013289845.

17 Borrás-Blasco J, Gracia-Pérez A, Rosique-Robles JD, Casterá ME, Abad FJ. Clinical and economic impact of the use of etanercept 25 mg once weekly in rheumatoid arthritis, psoriatic arthropathy and ankylosing spondylitis patients. Expert Opin Biol Ther 2014;14:145–50.

18 De Stefano R, Frati E, De Quattro D, Menza L, Manganelli S. Low doses of etanercept can be effective to maintain remission in ankylosing spondylitis patients. Clin Rheumatol 2014;33:707–11.

19 Závada J, Uher M, Sisol K *et al*. A tailored approach to reduce dose of anti-TNF drugs may be equally effective, but substantially less costly than standard dosing in patients with ankylosing spondylitis over 1 year: a propensity score-matched cohort study. Ann Rheum Dis 2016;75:96–102.

20 Fautrel B, Pham T, Alfaiate T *et al*. Step-down strategy of spacing TNF-blocker injections for established rheumatoid arthritis in remission: results of the multicentre non-inferiority randomised open-label controlled trial (STRASS: Spacing of TNF-blocker injections in Rheumatoid ArthritiS Study). Ann Rheum Dis 2016;75:59–67.

21 Kiltz U, Baraliakos X, Braun J, van der Heijde D. Withdrawal of medical therapies in axial spondyloarthritis: what would be the optimal trial design? Clin Exp Rheumatol 2013;31(4 Suppl 78):S47–50.