
The BeSt way of withdrawing biologic agents

C.F. Allaart¹, W.F. Lems², T.W.J. Huizinga¹

¹Department of Rheumatology, Leiden University Medical Center, Leiden;

²Department of Rheumatology, Free University Medical Center, Amsterdam, the Netherlands.

Cornelia F. Allaart, MD, PhD

Willems F. Lems, MD

Tom W.J. Huizinga, MD, PhD

Please address correspondence to:

C.F. Allaart, MD, PhD,

Department of Rheumatology,
Leiden University Medical Center,
PO Box 9600,

2300 RC Leiden, The Netherlands.

E-mail: c.f.allaart@lumc.nl

Received on August 5, 2013; accepted in revised form on August 23, 2013.

Clin Exp Rheumatol 2013; 31 (Suppl. 78): S14-S18.

© Copyright CLINICAL AND EXPERIMENTAL RHEUMATOLOGY 2013.

Key words: biological agents, withdrawal, BeSt study

ABSTRACT

Objectives. Treat-to-target strategies in the management of patients with rheumatoid arthritis (RA) involve intensifying medication as long as low disease activity or remission is not achieved. Our aim was to discuss reasons and opportunities for tapering and discontinuing medication when the target is achieved, in particular of biological agents.

Methods. Data from the *Behandel Strategieën (BeSt)* study are presented, a multicentre randomised clinical trial comparing 4 treatment strategies in patients with recent onset active RA (1987 criteria): 1. Sequential monotherapy, 2. Step up to combination therapy (both starting with methotrexate (MTX) monotherapy), 3. Initial combination therapy with MTX, sulfasalazine and prednisone and 4. Initial combination therapy with MTX and infliximab. Treatment adjustments involving dose increases, drug changes or expansion to combination therapy occurred based on three-monthly calculations of the Disease Activity Score (DAS), with a target of ≤ 2.4 . If this was achieved for 2 consecutive evaluations, treatment was tapered (combinations to monotherapy, monotherapy to maintenance dose). Prednisone and infliximab (either as part of initial treatment or as delayed treatment after failure on earlier therapies in arms 1, 2 and -for infliximab- 3) were always tapered and discontinued before other drugs. The outcomes of discontinuation of infliximab are presented.

Results. 77/120 (64%) of patients who started initial infliximab were able to discontinue infliximab, whereas 27/109 (25%) of patients who started delayed infliximab in arms 1–3 could discontinue infliximab. Discontinuation was independent of previous dose increases in order to achieve low DAS.

After discontinuation of infliximab, 16 of 27 patients (59%) in arms 1–3 and 34 of 77 patients (44%) in arm 4 suffered a DAS flare >2.4 and had to re-

start treatment. Median time without infliximab treatment was 17 (IQR 3–47) months, and 29 of the 61 patients (58%) who needed to restart had been at least 1 year without infliximab. Restarting infliximab resulted in DAS ≤ 2.4 in all patients, and there was no progression of radiological damage. Presence of shared epitope, smoking, and a long treatment with infliximab were independent predictors of infliximab restart.

Conclusion. Data on infliximab discontinuation in the BeSt study suggest that this possible in 1 in 4 patients, or more if infliximab was the initial treatment, who have had at least 6 consecutive months of low disease activity. While MTX is continued, about 50% of patients can permanently stop infliximab without radiological damage progression, the others regain low disease activity after restarting infliximab. Treat to target strategies using biologic agents should include strategies for discontinuation.

Introduction

Biologic agents have revolutionised the treatment and outcomes of treatment of patients with rheumatoid arthritis (RA). Initially, treatment with biologic agents occurred in patients who had incomplete or no responses to multiple synthetic DMARDs, and provided clinical relief and discontinuation of radiographic progression. More recently, biologic agents have been used earlier in disease course, resulting in more and more patients on active treatment with these drugs. In some patients complete remission appears to be achieved. This success, combined with the potential side effects and high drug-costs of continued biologic treatment, has prompted consideration of drug discontinuation in such patients. A study in 10 early RA patients showed that after discontinuation of infliximab disease activity could still remain low (1). The BeSt study introduced discontinuation of infliximab as a fixed ele-

Competing interests: none declared.

ment of a treatment protocol guided by disease activity. The background and results of this approach are discussed below.

Background and design of the BeSt study

In the late 1990s, Dutch rheumatologists from 20 hospitals in the south-western region who worked together in rheumatology research designed a clinical trial to investigate which was the best way to use the then available anti-rheumatic drugs in patients with a new diagnosis of rheumatoid arthritis (RA). Although the COBRA trial (2) had already documented that initial combination therapy with methotrexate, sulfasalazine and a tapered initially high dose of prednisone led to more rapid clinical improvement than sulfasalazine alone, at that time it was still common practice to initiate treatment with a single synthetic DMARD, followed by other single synthetic DMARDs if clinical improvement was found to be insufficient. Combination therapy could follow later if necessary, either with prednisone, or with infliximab. This TNF-inhibitor had just arrived on the market when the study, called BeSt (acronym for *Behandel-Strategieën*, Dutch for treatment strategies), was on the verge of initiation. Infliximab in daily practice was available only for patients with active RA who had experienced incomplete responses or failed to respond to methotrexate and at least one other synthetic DMARD. Since infliximab in combination with MTX had been shown to be very effective in halting joint damage progression in patients with advanced RA (3-5), it was hypothesised that using infliximab as initial treatment might prevent damage from developing at all in early RA.

It was, however, expected that methotrexate, in daily practice rapidly replacing sulfasalazine as preferred initial DMARD in RA, would be so effective in the majority of patients that many patients in one treatment arm (the 4th), who were randomised to initial treatment with methotrexate and infliximab, might be overtreated. Thus, it was decided that after a good response was achieved, infliximab would be discon-

Sequential monotherapy	Step up to combination therapy	Initial combo including prednisone	Initial combo including infliximab
MTX 15 mg/wk	MTX 15 mg/wk	MTX+SSA+pred 60 to 7.5mg	MTX+IFX 3mg/kg
↓	↓	↓	↓
25 mg/wk	25 mg/wk	MTX+CSA+pred	↓
SSA	MTX+SSA	↓	↓
↓	↓	↓	↓
Leflunomide	MTX+SSA+HCQ	MTX+IFX 3mg/kg	MTX+IFX 10mg/kg
↓	↓	↓	↓
MTX+IFX 3mg/kg	MTX+SSA+HCQ +pred	↓	SSA
↓	↓	↓	↓
↓	↓	MTX+IFX 10mg/kg	
↓	↓	↓	
MTX+IFX 10mg/kg	MTX+IFX 10mg/kg	Leflunomide	Leflunomide
↓	↓	↓	↓
<i>Other steps</i>	<i>Other steps</i>	<i>Other steps</i>	<i>Other steps</i>

Fig. 1. Treatment strategies in the BeSt trial.

tinued, to reveal which patients could continue to do well with methotrexate alone. A similar tapering down of initial combination therapy to monotherapy was planned in the 3rd treatment arm, in which the COBRA scheme was to be tapered down to sulfasalazine monotherapy.

In arms 1 and 2, on the other hand, patients with insufficient response to initial monotherapy with methotrexate would ultimately be treated with combination therapy involving infliximab. But if low disease activity was achieved and maintained, these patients also would discontinue infliximab. In all arms, infliximab dosage (begun at 3 mg/kg/8 weeks) could be increased first to 6, then 7.5 and ultimately 10 mg/kg/8 weeks if necessary to achieve low disease activity (DAS ≤ 2.4). However, once this level was achieved for at least 6 consecutive months, the doses would be reduced and ultimately infliximab would be stopped if DAS was ≤ 2.4 for ≥ 4 months.

Results

Between March 2000 and August 2002, 508 patients with RA (1987 ACR classification criteria, symptom duration < 2 years, at least 6 inflamed joints and ESR > 20 mm/hr) were included in the trial and randomised: 126 to arm 1 and 121 to arm 2, starting with methotrexate monotherapy 15 mg/week; 133 to arm 3, starting with methotrexate 7.5 mg/week, sulfasalazine and prednisone; and 128 to arm 4, starting with

methotrexate 25 mg/week and infliximab 3 mg/kg.

After the first 3 months, 17% in arm 1, 19% in arm 2, 55% in arm 3 and 47% in arm 4 had achieved a DAS ≤ 2.4 . (6). In these patients, the treatment remained stable until the next DAS calculation 3 months later. With persistent DAS ≤ 2.4 , MTX monotherapy would be tapered per 2 weeks with 2.5 mg/week in arms 1 and 2; prednisone (already tapered in the first 7 weeks from 60 mg/day to 7.5 mg/day) would be stopped, followed at week 40 by methotrexate, in arm 3; and in arm 4 infliximab would be stopped while methotrexate continued, to be tapered to 10 mg/week if the DAS remained ≤ 2.4 at subsequent evaluations.

If DAS was > 2.4 , medication in each treatment arm was changed or intensified. Infliximab plus methotrexate was initiated (and if necessary, eventually increased) in arms 1 and 2 after three synthetic DMARDs had been unsuccessfully tried (with low dose prednisone in arm 2), and in arm 3 when, after the initial combination, also methotrexate with cyclosporine had not resulted in DAS ≤ 2.4 . Thus, 109/380 (29%) of patients in arms 1-3 started infliximab. As in arms 1-3, in arm 4 the dose of infliximab was to be increased from 3 to 6 to 7.5 and finally to 10 mg/kg/8 weeks in case of persistent DAS > 2.4 .

Because of selection bias due to previous treatment failures in arms 1-3, success and failure rates of infliximab dis-

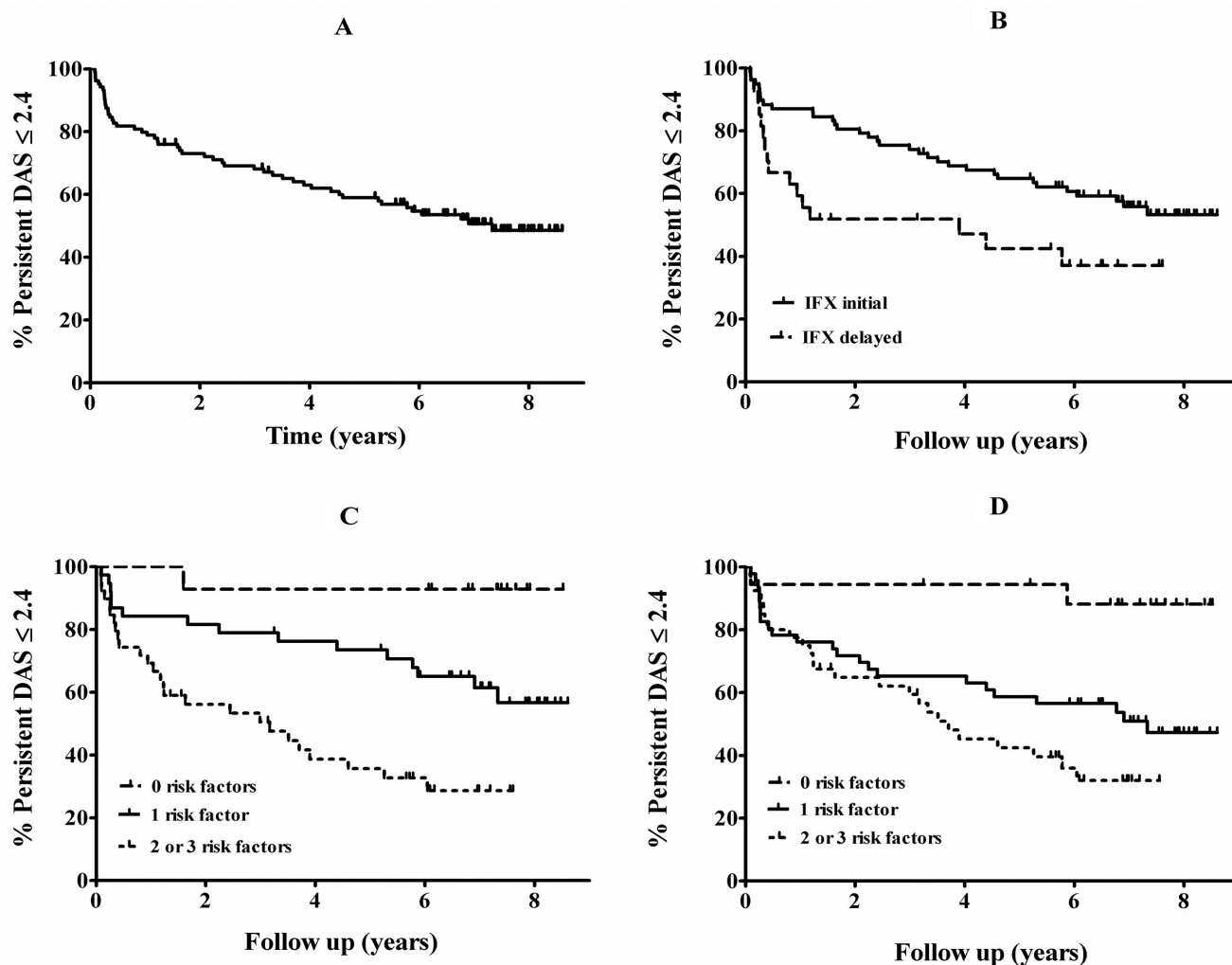


Fig. 2. Kaplan Meier plots showing infliximab-free survival (A) in all patients, (B) in patients treated with early or delayed infliximab, and (C and D) in patients with independent risk factors (positive history of smoking, being shared epitope positive and longer disease duration) for disease flare and need to restart infliximab.

continuation in these and arm 4 cannot be optimally compared. After propensity scoring to avoid at least the influence of differences between groups at baseline, we found that patients treated with initial infliximab plus methotrexate benefitted more from that treatment than patients treated with delayed infliximab plus methotrexate, showing more improvement in functional ability and less radiographic damage progression, while being able to discontinue infliximab more often (8).

In arm 4, 77/120 (64%) of the patients who started infliximab plus methotrexate achieved a persistent (as defined on more than 6 months) DAS ≤ 2.4 and discontinued infliximab. In arms 1–3, 27/109 (25%) of the patients who started infliximab with methotrexate could discontinue infliximab after achieving

persistent DAS ≤ 2.4 . In 38 (49%) patients who could discontinue, the dose of infliximab first had been increased because of initial insufficient response (8). After discontinuation of infliximab in arm 4, it appeared that more patients (53% at $t=2$ years) could remain on methotrexate monotherapy because of persistent DAS ≤ 2.4 , than patients who had initially started with methotrexate monotherapy (32% at $t=2$ years).

Among patients who discontinued infliximab, 16 of 27 patients (59%) in arms 1–3 and 34 of 77 patients (44%) in arm 4 suffered a DAS flare >2.4 and had to restart treatment. We found presence of shared epitope, smoking, and a prior treatment with infliximab for more than 18 months to be independent predictors of a DAS flare and infliximab restart. Because of small num-

bers, a potential interaction between smoking and shared epitope could not be investigated. Patients who had all three risk factors were at greatest risk for DAS flare after infliximab discontinuation (9). Median time without infliximab treatment was 17 (IQR 3–47) months, and 29 of the 61 patients (58%) who needed to restart had been at least 1 year without infliximab.

Patients who discontinued infliximab had similar (low) radiographic progression in the following year as in the year before discontinuing. Functional ability did not deteriorate after discontinuation of infliximab in those who remained in low disease activity (median HAQ 0.1); however, the restarters had slightly higher HAQ 5 years after discontinuation than just before discontinuation (0.7 vs. 0.2, $p=0.02$). Restarting

infliximab resulted in DAS ≤ 2.4 in all patients, although 10 patients wished to discontinue again because of (mild) infusion reactions or other reasons (9).

Discussion

In the BeSt study, a treat to target strategy included DMARD dose intensifications and drug changes until a DAS ≤ 2.4 was achieved. For the first time in a clinical trial, the BeSt study protocol also required drug tapering and drug discontinuation if the target of low disease activity was achieved and maintained. The BeSt study showed that, at a group level the best treatment strategy for patients with newly diagnosed active RA is initial combination therapy with either infliximab or prednisone. The study also demonstrated that joint damage progression and functional deterioration can be prevented with continued targeted treatment. Finally, the BeSt study also shows that a targeted treatment strategy can include tapering and discontinuation of a biologic agent. Early treatment, preferably during the so-called 'window of opportunity,' is generally recommended for the management of RA, and has the potential of halting or reversing the inflammatory and joint-damaging disease process. In that line, it is tempting to think that early use of the most effective therapies currently available, biologic agents, may be more efficacious than using them only when synthetic DMARDs have proven to be ineffective.

In the BeSt study we investigated if such a benefit of early over late biologic therapy can be identified. As in daily practice, the comparison of early versus late infliximab was complicated by the fact that patients who receive early infliximab represent an unselected patient group, whereas those who receive late infliximab are selected on the basis of having failed on previous DMARDs: in those patients the next treatment is already less likely to be successful. Nonetheless, we have previously shown that, having incomplete or no response to initial methotrexate monotherapy, more patients in arms 1 and 2 achieved DAS ≤ 2.4 on fourth line infliximab than on second line (monotherapy or add-on) sulfasalazine, third line leflunomide, or a combination of methotrexate, sulfasalazine and hydroxychloroquine (10). Next, we showed that patients in arm 4 who started treatment with infliximab plus methotrexate improved more in functional ability and suffered less joint damage progression than patients in arms 1-3 who received delayed infliximab plus methotrexate (10).

Why discontinue infliximab if it yields such good results?

Why discontinue infliximab if it yields such good results?

In particular for patients who received early infliximab plus methotrexate, we had two reasons. First, we suspected that many patients would have benefitted equally from initial methotrexate monotherapy. However, our initial optimism about the efficacy of initial methotrexate monotherapy was dampened by our finding that after 6 months of treatment, only 44% of patients thus treated had achieved a DAS ≤ 2.4 , and after 2 years, only 32% were still successfully treated with methotrexate monotherapy, while the others had needed to progress to other treatment steps. In arm 4, 47% of patients had achieved DAS ≤ 2.4 already after 3 months, 62% of patients had achieved DAS ≤ 2.4 after 6 months, and 72% of patients remained in the initial treatment step until $t=2$ years, 53% having discontinued infliximab and remaining on methotrexate alone (8). Radiological damage progression in arms 1 and 2 was statistically significant more than in arm 4 but with the very low levels of joint damage achieved with a treat to target strategy like BeSt the clinical relevance is probably doubtful. This suggests that fewer patients than expected have sufficient suppression of disease activity on methotrexate monotherapy, and that initial infliximab has helped to alter the disease process so that a persistently good response to methotrexate monotherapy is more often achieved.

Second, because early infliximab plus methotrexate may indeed help to alter the disease process, continuing infliximab may be unnecessary and possibly undesirable. If disease activity remains low, stopping infliximab reduces treatment costs, as we demonstrated in the first 2 years of the BeSt study (11), and

may avoid infectious complications (12).

Stopping infliximab when used as 'rescue' medication if synthetic DMARDs have failed may be more difficult, but not impossible, as was also demonstrated in the RRR study (13). We found that 25% percent of delayed infliximab starters could discontinue infliximab later, compared to 64% of those treated with initial infliximab.

Stopping medication means risking a disease flare. If we stopped infliximab in the BeSt trial, it was only after DAS ≤ 2.4 for at least two consecutive 3-monthly evaluations, while methotrexate in the highest tolerated dose was maintained and only gradually tapered if disease activity remained low in subsequent months. Sixty-five percent of patients who discontinued initial infliximab and 41% of those who discontinued delayed infliximab did not suffer a flare and remained without infliximab. Shared epitope (or ACPA) positive patients, patients who smoke and patients with prolonged disease activity prior to start of infliximab were found more likely to flare and needed to restart infliximab more often than other patients. Those patients did enjoy a drug holiday, with a median duration of 17 months, although a need to restart infliximab was seen. After reintroduction of infliximab, some mild infusion reactions occurred, causing 5 patients to ask for discontinuation of the treatment again, but this did not occur more often than during treatment with initial infliximab, and generally appears to be a low rate (14). Joint damage did not increase after infliximab discontinuation, and functional ability remained stable. Again, this may possibly be explained by continued use of methotrexate.

In conclusion, by integrating drug tapering and discontinuation with treatment intensification in a treat to target approach, the BeSt study is the first to present data on the possibility and success rate of discontinuation of infliximab, either started as initial treatment or after failure on multiple synthetic DMARDs. Early treatment with infliximab plus methotrexate appears to result in the best outcomes, but provided that co-medication is continued while

tight control and treatment adjustments steered by DAS ≤ 2.4 are maintained, all patients with persistent low disease activity should be offered the chance to have a temporary or perpetual drug holiday.

References

- QUINN MA, CONAGHAN PG, O'CONNOR PJ *et al.*: Very early treatment with infliximab in addition to methotrexate in early, poor-prognosis rheumatoid arthritis reduces magnetic resonance imaging evidence of synovitis and damage, with sustained benefit after infliximab withdrawal: results from a twelve-month randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2005; 52: 27-35.
- BOERS M, VERHOEVEN AC, MARKUSSE HM, VAN DE LAAR MA *et al.*: Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. *Lancet* 1997; 350: 309-18.
- LIPSKY PE, VAN DER HEIJDE DM, ST CLAIR EW *et al.*: ANTI-TUMOR NECROSIS FACTOR TRIAL IN RHEUMATOID ARTHRITIS WITH CONCOMITANT THERAPY STUDY GROUP: Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. *N Engl J Med* 2000; 343: 1594-602.
- MAINI RN, BREEDVELD FC, KALDEN JR *et al.*: Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group: Sustained improvement over two years in physical function, structural damage, and signs and symptoms among patients with rheumatoid arthritis treated with infliximab and methotrexate. *Arthritis Rheum* 2004; 50: 1051-65.
- SMOLEN JS, HAN C, BALAM *et al.*: ATTRACT Study Group: Evidence of radiographic benefit of treatment with infliximab plus methotrexate in rheumatoid arthritis patients who had no clinical improvement: a detailed subanalysis of data from the anti-tumor necrosis factor trial in rheumatoid arthritis with concomitant therapy study. *Arthritis Rheum* 2005; 52: 1020-30.
- GOEKOOP-RUITERMAN YP, DE VRIES-BOUWSTRA JK, ALLAART CF *et al.*: Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. *Arthritis Rheum* 2005; 52: 3381-90.
- VAN DER BIJLAE, GOEKOOP-RUITERMAN YP, DE VRIES-BOUWSTRA JK *et al.*: Infliximab and methotrexate as induction therapy in patients with early rheumatoid arthritis. *Arthritis Rheum* 2007; 56: 2129-34.
- VAN DER KOOIJ SM, LE CESSIE S, GOEKOOP-RUITERMAN YP *et al.*: Clinical and radiological efficacy of initial vs delayed treatment with infliximab plus methotrexate in patients with early rheumatoid arthritis. *Ann Rheum Dis* 2009; 68: 1153-8.
- van den BROEK M, KLARENBEK NB, DIRVEN L *et al.*: Discontinuation of infliximab and potential predictors of persistent low disease activity in patients with early rheumatoid arthritis and disease activity score-steered therapy: subanalysis of the BeSt study. *Ann Rheum Dis* 2011; 70: 1389-94.
- VAN DER KOOIJ SM, DE VRIES-BOUWSTRA JK, GOEKOOP-RUITERMAN YP *et al.*: Limited efficacy of conventional DMARDs after initial methotrexate failure in patients with recent onset rheumatoid arthritis treated according to the disease activity score. *Ann Rheum Dis* 2007; 66: 1356-62.
- VAN DEN HOUT WB, GOEKOOP-RUITERMAN YP, ALLAART CF *et al.*: Cost-utility analysis of treatment strategies in patients with recent-onset rheumatoid arthritis. *Arthritis Rheum* 2009; 61: 291-9.
- GALLOWAY JB, HYRICH KL, MERCER LK *et al.*: BSRBR CONTROL CENTRE CONSORTIUM; BRITISH SOCIETY FOR RHEUMATOLOGY BIOLOGICS REGISTER: Anti-TNF therapy is associated with an increased risk of serious infections in patients with rheumatoid arthritis especially in the first 6 months of treatment: updated results from the British Society for Rheumatology Biologics Register with special emphasis on risks in the elderly. *Rheumatology* (Oxford) 2011; 50: 124-31.
- TANAKA Y, TAKEUCHI T, MIMORI T *et al.*: RRR STUDY INVESTIGATORS: Discontinuation of infliximab after attaining low disease activity in patients with rheumatoid arthritis: RRR (remission induction by Remicade in RA) study. *Ann Rheum Dis* 2010; 69: 1286-91.
- HELDMANN F, BRANDT J, VAN DER HORST-BRUIJNSMA IE *et al.*: The European ankylosing spondylitis infliximab cohort (EASIC): a European multicentre study of long term outcomes in patients with ankylosing spondylitis treated with infliximab. *Clin Exp Rheumatol* 2011; 29: 672-80.