Chapter 7

Discontinuation of infliximab and potential predictors of persistent low disease activity in patients with early rheumatoid arthritis and DAS steered therapy: subanalysis of the BeSt study

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Annals of the Rheumatic Diseases 2011 Aug;70(8):1389-94

ABSTRACT

Objective To describe the disease course after discontinuation of infliximab (IFX) in early rheumatoid arthritis patients with DAS steered treatment and to identify predictors of persistent low disease activity.

Methods In a post hoc analysis of the BeSt study, we observed disease activity and joint damage progression in patients treated with methotrexate (MTX)+IFX, who discontinued IFX after achieving low disease activity (DAS ≤2.4), for 6 months. We identified predictors using Cox regression analysis.

Results 104 patients discontinued IFX, of whom 77 had received IFX+MTX as the initial treatment. Mean DAS at time of IFX discontinuation was 1.3, median symptom duration was 23 months and median Sharp-van der Heijde score was 5.5. The median follow-up was 7.2 years. IFX was reintroduced after loss of low disease activity in 48%, after a median period of 17 months. Joint damage progression rate didn't increase in the year after discontinuation, regardless of flare. After reintroduction of IFX, 84% of these patients again achieved a DAS ≤2.4. In the multivariable model smoking, IFX treatment duration ≥18 months and shared epitope (SE) were independently associated with reintroduction of IFX: 6% of the non-smoking, SE negative patients treated <18 months needed IFX reintroduction.

Conclusion Discontinuation of IFX was successful in 52%, with numerically higher success rates in patients initially treated with IFX. Of the 48% who flared, 84% regained low disease activity. Joint damage progression rate didn't increase in the year after discontinuation. Smoking, long IFX treatment duration and SE were independently associated with reintroduction of IFX.

INTRODUCTION

Current RA treatment strategies are aimed at achieving low disease activity as soon as possible, to improve structural and functional outcome, using frequent treatment adjustments when necessary. Adding a TNF-blocker to methotrexate (MTX) has proved to be an effective way to achieve low disease activity in a short period of time, with less joint damage progression than monotherapy.[1,2]

Treatment with TNF-blockers is expensive and has a possible risk of adverse events. Therefore, discontinuation of TNF-blockers once the treatment goal has been achieved could be beneficial for both society and individual patients. In 25-70% of patients who achieved low disease activity, TNF-blockers can be stopped without losing low disease activity.[3-7] Predicting which patients have a high chance of sustained low disease activity after discontinuation of TNF-blockers is necessary to avoid disease flares and a potentially increased risk of infusion reactions after reintroduction of intravenous TNF- blockers.[8]

In the BeSt study, a study comparing 4 different treatment strategies, infliximab (IFX) was the TNF-blocker used in combination with MTX, either after failure on at least three non-biological DMARD, or as initial treatment. In this post hoc analysis with a median follow-up duration of 7.2 years, we investigated whether and how often low disease activity was sustained after discontinuation of IFX and if predictors for successful discontinuation exist. Secondly, we looked at joint damage progression after IFX discontinuation and we assessed the success and safety of reintroduction.

METHODS

Patients

Between 2000 and 2002, 508 patients were included in the BeSt study, a multi-center randomized single blind clinical trial designed to compare 4 different treatment strategies in DMARD-naïve patients with recent onset, active RA. All patients fulfilled the 1987 ACR inclusion criteria for RA. The ethics committees of all participating centers approved the study protocol and patients gave their written informed consent.

Treatment strategies were initial monotherapy, step-up combination therapy (groups 1 and 2, both starting with MTX), initial combination therapy with MTX, sulfasalazine and prednisolone (group 3) and initial combination therapy with MTX and IFX (group 4). Treatment was adjusted to the next step in the protocol in case of a DAS >2.4 or side effects.

In group 1-3, MTX+IFX were started after patients had failed on 3 treatment steps with non-biological DMARD including prednisolone (groups 2 and 3) or without (group 1). If DAS remained ≤2.4 for at least 6 months, IFX was stopped, after stepwise (10-7.5-6-3)

tapering to 3 mg/kg/8 weeks in those patients who had previously had a dose increase. IFX was immediately restarted if the DAS increased to >2.4. In patients who had also tapered or stopped methotrexate, first MTX was increased to 25 mg/week. Next, IFX was reintroduced if the DAS remained >2.4.The complete study design has been published previously.[9,10]

We analyzed all 104 patients in groups 1-4 who discontinued IFX after the DAS was ≤2.4 for 6 months, who had ≥1 year of follow-up after reaching this point. The median follow-up duration from the moment of IFX discontinuation was 7.2 years (range 14-103 months).

Study endpoints

After discontinuation of IFX, whether patients had to restart IFX due to a DAS >2.4 was monitored. Radiographs of hands and feet were taken at yearly intervals. For the radiograph 'at discontinuation', the radiograph taken closest to the visit at discontinuation was used. For stop-visits in between 2 yearly visits, the yearly visit before discontinuation was chosen. All available radiographs of hands and feet, baseline-1-2-3-4-5 year follow-up were scored blind for patient identity and random in time using the Sharp-van der Heijde score (SHS). Joint damage progression in the year before and after discontinuation was defined as increase of the average score for those years of 2 independent readers. Smokers were defined as patients smoking cigarettes, cigars or pipe at baseline.

Statistical analysis

Baseline and disease characteristics were compared between patients from the initial and the delayed IFX treatment group, using the χ^2, Student's t or Mann-Whitney U test. Joint damage progression and HAQ scores were compared for patients with sustained DAS ≤2.4 and patients who had to restart IFX using the χ^2 and Mann-Whitney U test. To compare damage progression in the years before and after discontinuation and HAQ scores at and after discontinuation, the Wilcoxon signed-rank test was used. To take into account the difference in follow-up after discontinuation between patients, we used Cox regression analyses to identify predictors of successful discontinuation, after verifying that the proportional hazards assumption wasn't violated.[11] The dependent variable was time to reintroduction for patients who restarted IFX, August 1st 2010 for patients with sustained DAS ≤2.4 who were still under follow-up, and time to last follow-up visit for patients lost to follow-up.

We examined the association between baseline characteristics and clinical parameters at the moment IFX was stopped, with successful discontinuation of IFX. Because of the number of variables tested, we considered a $p<0.01$ significant.

To identify independent predictors, variables that showed an association ($p<0.10$) with sustained DAS ≤2.4 in the univariable analyses were entered in a multivariable Cox re-

gression analysis using a stepwise forward selection procedure with a Wald significance <0.05 as inclusion criterion. Subsequently, other variables that were hypothesized to have additional predictive value were added one by one. Model fit was tested using Martingale residuals. Overall goodness-of-fit was examined by adding to the model risk groups, constructed by categorizing the ranked prognostic indices, to test whether this would significantly improve the model likelihood.[11]

RESULTS

Low disease activity

IFX was discontinued after achieving a DAS ≤2.4 for ≥6 months in 104 patients (*figure 1*): 77/120 from the initial IFX treatment group and 27/109 from the delayed treatment group (p<0.001). The mean DAS at time of discontinuation was 1.3 ±0.6 (SD). The median IFX treatment duration was 11 (IQR 9-17) months. Median symptom duration at time of discontinuation was 23 (IQR 15-35) months. In 20 patients the IFX dose had been increased from 3 to 6, mg/kg, to 7.5, in 13 patients and to 10 mg/kg in 5 patients before a DAS ≤2.4 was achieved.

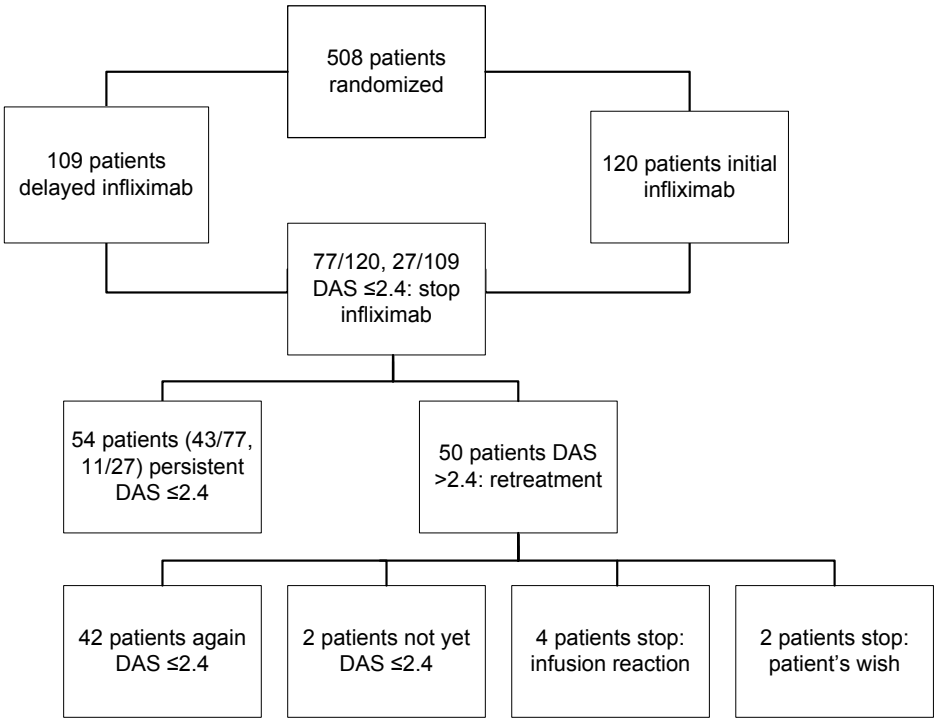

Figure 1: Flowchart of the study

After discontinuation of IFX, the DAS remained ≤2.4 in 43/77 patients (56%) from the initial treatment group and 11/27 (41%) from the delayed treatment group. MTX was then successfully tapered (with 2.5 mg every 4 weeks) to maintenance dose (≤10mg/week) in 34 (62%) patients, without differences between the initial and delayed treatment group (p=0.58). Subsequently, 15 (27%) patients from the initial treatment group achieved drug-free remission. None in the delayed treatment group achieved drug-free remission yet.

Treatment group

In the delayed treatment group, the median (IQR) time from baseline to starting IFX was 14 (11-18) months. Patients in the delayed treatment group had a higher baseline DAS and needed longer IFX treatment before IFX could be discontinued than patients in the initial treatment group. At the time of IFX discontinuation, patients in the delayed treatment group had longer symptom duration and a higher SHS, HAQ and patient's

Table 1: patients' demographic and disease characteristics at inclusion and at discontinuation of IFX in the initial versus delayed IFX treatment group

	All (n=104)	Initial (n=77)	Delayed (n=27)	p-value
Female gender, no. (%)	68 (65)	47 (61)	21 (78)	0.12
Age (years)	56 (46-61)	56 (45-61)	55 (50-62)	0.83
RF positive, no. (%)	68 (65)	45 (58)	23 (85)	0.012
ACPA-positive, no. (%)	76 (73)	56 (73)	20 (74)	0.89
SE positive, no. (%)*	66 (75)	48 (74)	18 (78)	0.67
Smoking +, no. (%)	36 (35)	22 (29)	14 (52)	0.029
BMI kg/m^2	26 (23-28)	26 (23-27)	26 (23-28)	0.59
Symptom duration at discontinuation, months	23 (15-35)	19 (13-27)	44 (33-64)	<0.001
IFX treatment duration at discontinuation, months	11 (9-17)	9 (8-14)	16 (11-23)	<0.001
DAS at inclusion, mean (SD)	4.2 (0.8)	4.1 (0.7)	4.7 (0.9)	<0.001
DAS at discontinuation, mean (SD)	1.3 (0.6)	1.3 (0.6)	1.4 (0.6)	0.50
Remission at discontinuation, no.(%)	69 (66)	51 (66)	18 (69)	0.78
HAQ at inclusion	1.3 (0.9-1.7)	1.3 (0.8-1.8)	1.1 (1.0-1.5)	0.72
HAQ at discontinuation	0.1 (0.00-0.6)	0.2 (0.0-0.5)	0.4 (0.1-0.9)	0.012
SHS at inclusion	3.5 (0.5-10.5)	4.8 (0.5-10.9)	1.5 (0.5-9.0)	0.40
SHS at discontinuation	5.5 (1.0-16.0)	4.8 (0.5-13.9)	13.0 (3.0-30.6)	0.029

RF rheumatoid factor, *ACPA* anti-citrullinated antibodies, *SE* shared epitope, *BMI* body mass index, *IFX* infliximab, *DAS* disease activity score, *HAQ* health assessment questionnaire, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *SHS* Sharp-van der Heijde score, *VAS* visual analogue scale, measured in mm

*SE had missing data for 16 patients

Data are presented as median (IQR), unless stated otherwise.

assessment of disease activity. There were almost twice as many smokers in the delayed treatment group.(*table 1*)

Reintroduction of IFX

In 50/104 patients (48%), IFX was restarted after the DAS had increased to >2.4 in median 17 (IQR 3-47) months. IFX was discontinued for ≥1 year in 29 patients (58%). In 84%, 27/34 from the initial and 15/16 from the delayed IFX treatment group, a DAS ≤2.4 was regained after reintroduction of IFX within median 3 (IQR 2-5) months. In 5 (10%) patients, who had initially had a good response to reintroduction, IFX was later abandoned for another DMARD. Five patients had an infusion reaction after reintroduction of IFX. These infusion reactions were reported as non-serious, but reason for 4 patients to discontinue IFX. In comparison, 8/120 patients from the initial treatment group (group 4) of the BeSt study had an infusion reaction during their first treatment with IFX (p=0.46). Serious infections (requiring hospital admission) occurred in 40/1000 patient-years after reintroduction of IFX, compared to 16/1000 patient-years during the first treatment with IFX and 10/1000 patient-years during discontinuation of IFX.

Joint damage

Radiographs 1 year before, in the year of, and 1 year after IFX discontinuation were available in 90/104 patients. Median damage progression was 0 both for patients who had an increase of the DAS to >2.4 in the first year after discontinuation and patients whose DAS remained ≤2.4 (p=0.56). The average damage progression did not increase in the year after discontinuation compared to the year before discontinuation: 0.0 (IQR 0.0-0.8) vs. 0.0 (IQR 0.0-1.5), p=0.06. Four patients showed radiographic progression >5.(*figure 2*) One of these patients had restarted IFX in that year, the other 3 continued to have a DAS ≤2.4 (mean AUC DAS 2.0 in that year).

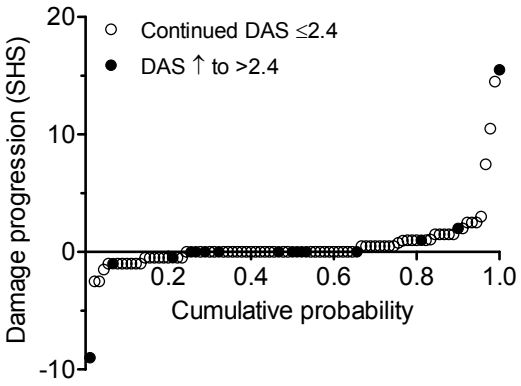

Figure 2: Probability plot of joint damage progression 1 year after discontinuation (90 patients with radiographic data)

Functional ability after discontinuation

HAQ scores at 1 and 3 years after discontinuation were similar to HAQ scores at discontinuation in both restarters and patients with sustained DAS ≤2.4. Five years after discontinuation, restarters had a median HAQ of 0.7, vs 0.3 at discontinuation, p-value=0.02. For patients with sustained DAS ≤2.4, median HAQ remained 0.1. Patients who flared in that year or the year before had higher median HAQ scores than patients who did not flare in those years: 0.4 vs. 0.1 in year 1, 0.5 vs. 0.1 in year 3 and 0.8 vs. 0.4 in year 5, but these differences were not significant.

Predictors

Univariable Cox analyses showed that smoking, longer symptom duration at discontinuation, longer IFX treatment duration, physician's assessment of disease activity, total erosion score at time of IFX discontinuation, and previous yearly change in SHS were associated with reintroduction of IFX.(*table 2*) Treatment timing (delayed vs initial IFX) and positivity for shared epitope (SE) showed a trend. Univariable analyses for the delayed and initial treatment group separately showed similar effect sizes, with the exception of smoking (lower hazard rate) and SE (higher hazard rate) in the delayed treatment group. (*table 2*) The multivariable analyses yielded a model with smoking, SE and treatment duration, adjusted for treatment timing. Treatment duration was dichotomized with 18 months (4th quartile) as cut-off value. The possible interaction between smoking and SE could not be assessed due to small numbers. Smoking (Hazard rate 2.1, 95% CI 1.1;4.2), treatment duration ≥18 months (HR 2.4, 95% CI 1.1;5.4) and presence of SE (HR 3.7, 95% CI 1.3;10.6) were independently associated with reintroduction of IFX.(*table 3*) IFX-free survival was investigated based on the number of predictors present.(*figure 3*) Of the 18% of patients who had no predictors present, 94% didn't need IFX reintroduction. Of the 40% who had 1 predictor present, 42% needed IFX reintroduction, compared to 67% of the patients with ≥2 risk factors. Because SE is rarely known in clinical practice and SE and anti-citrullinated protein antibody(ACPA)-status are highly correlated, we repeated the analyses using ACPA instead of SE. ACPA was not an independent predictor in the original model, or after omitting smoking. However, of the 18 patients who were non-smokers, had short treatment duration and were ACPA-negative, only 2 (11%) needed IFX reintroduction.(*figure 3D*)

Table 2: hazard rates for clinical and demographic parameters and increase of DAS to >2.4 with restart of IFX (univariable analysis)

	Hazard rate (95% CI)	Initial IFX	Delayed IFX
Female gender	1.1 (0.6;2.0)		
Age	1.00 (0.98;1.02)		
RF positive	1.2 (0.6;2.1)		
ACPA-positive	1.5 (0.8;3.1)	1.9 (0.8;4.5)	1.08 (0.3;3.4)
SE positive	3.9 (1.4;11.0)	3.2 (0.97;10.9)	7.0 (0.89;54.2)
Smoking	2.4 (1.4;4.3)	2.9 (1.5;5.8)	1.2 (0.4;3.2)
BMI	1.04 (0.96;1.12)		
IFX delayed	2.0 (1.1;3.7)		
Symptom duration, months	1.02 (1.01;1.03)	1.01 (0.99;1.03)	1.02 (0.995;1.05)
Treatment duration, months	1.05 (1.02;1.07)	1.07 (1.01;1.13)	1.03 (0.999;1.07)
IFX dose increase	1.2 (0.7;2.2)		
DAS	1.1 (0.7;1.9)		
DAS<1.6 vs DAS ≤ 2.4	0.98 (0.5;1.8)		
HAQ	1.5 (0.8;3.0)		
ESR	1.00 (0.98;1.02)		
CRP	0.98 (0.93;1.02)		
Tender joint count	1.08 (0.93;1.27)		
Swollen joint count	0.97 (0.77;1.22)		
Radiographic damage	1.02 (1.00;1.03)		
Erosion score	1.03 (1.01;1.06)	1.03 (0.99;1.07)	1.03 (0.99;1.07)
Joint space narrowing	1.03 (1.00;1.06)	1.03 (0.99;1.07)	1.02 (0.98;1.07)
Yearly change in SHS	1.07 (1.02;1.13)	1.08 (1.01;1.15)	1.06 (0.98;1.15)
Disease activity, VAS	1.01 (0.99;1.02)		
General health, VAS	1.00 (0.99;1.02)		
Morning stiffness, VAS	1.01 (1.00;1.02)		
Pain, VAS	1.01 (1.00;1.03)		
Disease activity, doctor VAS	1.03 (1.01;1.06)	1.03 (1.004;1.06)	1.09 (1.01;1.18)

RF rheumatoid factor, *ACPA* anti-citrullinated antibodies, *SE* shared epitope, *BMI* body mass index, *IFX* infliximab, *DAS* disease activity score, *HAQ* health assessment questionnaire, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *SHS* Sharp-van der Heijde score, *VAS* visual analogue scale, measured in mm

Adjusted for age, gender and, with the exception of "IFX delayed", treatment timing

Table 3: independent predictors of increase of DAS >2.4 with restart of IFX (multivariable model)

	Hazard rate (95% CI)	Hazard rate (95% CI) after adjustment*
Shared epitope +	3.5 (1.2;10.1)	3.7 (1.3;10.6)
Smoking +	2.4 (1.3;4.6)	2.1 (1.1;4.2)
Treatment duration ≥ 18 months	2.8 (1.3;6.1)	2.4 (1.1;5.4)
Delayed treatment IFX	n.a.	1.8 (0.9;3.7)

* Model including treatment timing

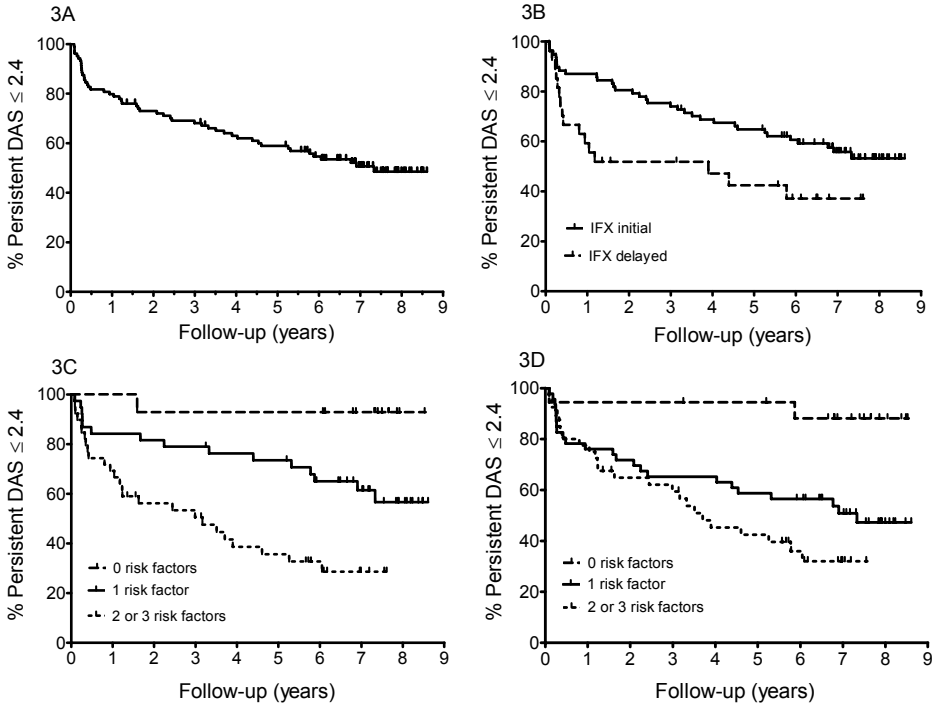

Figure 3: Kaplan Meier plots, showing the percentage of patients with persistent DAS ≤2.4 after discontinuation of IFX over time for all patients (3a), per treatment group (3b) and per number of risk factors with SE (3c) and with ACPA instead of SE (3d)

DISCUSSION

In the Best study, 45% of patients treated with infliximab could discontinue IFX. Eighty percent of these patients could stop for at least 1 year, 52% did not restart during a median follow-up of 7.2 years. In the year after IFX discontinuation, significant joint damage progression was rare, regardless of disease flare. Retreatment with IFX was successful in 84%. Smoking, SE and long IFX treatment duration (≥18 months) were independent predictors for reintroduction of IFX.

Our results are in line with previous reports, although there are differences in patient characteristics, requirements to discontinue or restart TNF-blockers, and duration of follow-up. Quinn *et al.*[7] were the first to report on successful discontinuation of a TNF-blocker (IFX), in 7/10 patients with early RA, regardless of disease activity (which in general was low). Brocq *et al.*[3] reported on 21 patients with advanced RA who were in remission after delayed treatment with a TNF-blocker (6 as monotherapy). Five patients successfully stopped the TNF-blocker for 12 months. The 16 who flared regained remission after retreatment. Saleem *et al.*[6] reported a 40% overall success rate in 2 years in 47 patients who had achieved remission and discontinued TNF-blockers. Remission was maintained in 60% of patients who had the TNF-blocker as initial treatment, compared to 3/20 patients who had had delayed treatment (10 had failed on a previous TNF-blocker). The RRR study by Tanaka *et al.*[4] has a comparable sample size to ours, and IFX was also discontinued if a DAS ≤2.4 was repeatedly achieved. The rate of successful discontinuation of IFX in 1 year was 55%, compared to 80% in 1 year in the BeSt study. This may be due to a high percentage of BeSt patients who had received IFX as initial treatment, whereas in the RRR study, all patients received IFX after failure on various systemic DMARDs. The differences in patient characteristics and follow-up duration may also explain why Tanaka *et al.* found remission at discontinuation to be predictive of maintaining a DAS ≤2.4, whereas we did not.

The percentage of infusion reactions after retreatment was not increased when compared to infusion reactions during initial treatment in group 4 of the BeSt study, so the hypothesis of Takeuchi *et al.*[8] of an increased risk of infusion reactions after reintroduction of IFX was not confirmed. This might be explained by the design of the BeSt protocol: MTX is continued after discontinuation of IFX until sustained remission is achieved on maintenance dose, and in patients in drug-free remission who flare, first methotrexate is reintroduced and increased, before IFX can be restarted. The presence of antibodies to infliximab was not tested.

The rate of serious infections was higher after reintroduction of IFX compared to during the initial treatment-period or the period of IFX-discontinuation. The difference between infection rates during discontinuation and after retreatment may be the result of physicians choosing intravenous over oral antibiotics in patients using a TNF-blocker, longer exposure to IFX or of longer and more active disease duration. The difference in serious infections between first time IFX users and restarters could reflect patient selection, since restarters had longer symptom duration and possibly more severe RA, which is associated with a higher infection risk.[12,13]

To our knowledge, the inverse association between smoking and SE and successful IFX discontinuation has not been previously reported. Both characteristics are associated with more severe disease.[14,15] Smoking, but not SE, might be associated with poor response to TNF-blockers.[15-18] Smoking and SE are associated with increased ACPA levels,[19]

but neither our analysis nor the analysis by Saleem *et al.*[6] showed a strong association between ACPA and successful discontinuation, although this may be due to relatively small numbers. For daily practice this is disappointing, since it is not current routine to test for SE. Our analyses did show that of the non-smoking, ACPA-negative patients with short IFX treatment duration, only 11% needed to restart IFX.

In the BeSt study, tapering and discontinuation of IFX was DAS steered. Therefore, the association between shorter IFX treatment duration and continued DAS ≤2.4 after discontinuation correlated with time to achieve a DAS ≤2.4 for 6 months consecutively while on IFX.

Previously, we reported that patients from the BeSt-study who received infliximab as initial treatment were more likely to achieve a DAS ≤2.4 and discontinue IFX than patients from the delayed treatment group.[20] In the current analysis, an association was found between successful discontinuation and initial treatment. Since patients in groups 1-3 only started MTX+IFX after failing on 3 treatment steps, they had longer symptom duration at time of IFX discontinuation, and probably more difficult to treat RA than the unselected patients who started with initial MTX+IFX. The differences in disease characteristics at baseline between the initial and delayed treatment groups corroborate this.(*table 1*) Despite these differences we combined patients from both groups for the analysis, because we set out to find predictors of successful discontinuation irrespective of treatment timing, and to gain power. In separate analyses for the 2 groups, we found similar effect sizes, with the exception of smoking in the delayed treatment group, possibly due to small numbers and a higher proportion of smokers in this group. Previously, we compared the response to IFX in both treatment groups using propensity scores to adjust for the differences at baseline. Since the current subanalysis compares selected patients from the 2 treatment groups who discontinued IFX because of sustained DAS ≤2.4, this method cannot be applied. The association between treatment timing and successful discontinuation was also described by Saleem *et al*.,[6] but this study had comparable limitations. Thus, the observed association is affected by patient selection based on earlier failure on at least 3 non-biological DMARD treatment steps and initiation of infliximab after a 'delay' of on average 14 months. Of course in daily practice, where TNF-blockers are currently reserved for patients who fail on non-biological DMARD, one must assume that similar selection processes are at work.

A second limitation of this subanalysis is that for 16/104 patients, SE status was not known. We included SE in the multivariable model because of the strong association with successful discontinuation. This resulted in exclusion of the patients with missing SE data.

In conclusion, infliximab can be successfully stopped for at least 1 year in 80% of patients. Joint damage does not increase in this year, regardless of flare. After a median period of 7.2 years, 52% had not restarted IFX. Even temporary discontinuation can benefit both

the individual patient and, given the high costs of TNF-blockers, society as a whole. Non-smoking, SE- or ACPA-negative patients who needed less than 18 months of IFX treatment, very rarely have to restart IFX due to an increase of the DAS to >2.4. However, not all of those who have to restart infliximab regain a DAS ≤2.4, and restarting IFX carries a (small) risk of (mild) infusion reactions. We therefore recommend that in particular for patients with one or more of the above mentioned risk factors, IFX discontinuation has to be carefully considered on an individual basis.

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