Necessity of TNF-alpha inhibitor discontinuation in rheumatoid arthritis is predicted by smoking and number of previously used biological DMARDs

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Abstract

Objective

Despite the success of TNF-alpha inhibitor (TNFi) treatment in rheumatoid arthritis (RA), a substantial number of patients necessitate discontinuation. Prediction thereof would be clinically relevant and guide the decision whether to start TNFi treatment.

Methods

Data were used from the observational BiOCURA cohort, in which patients initiating biological treatment were enrolled and followed up for one year. In the model development cohort (n=192), a model predicting TNFi discontinuation was built using Cox-regression with backward selection (p<0.05). The parameters of the model were tested again in a model refinement cohort (n=60), for significance (p<0.05) and consistency of effect. In addition, we performed a systematic review to put our study results into perspective.

Results

Of the 252 patients who initiated TNFi treatment, 103 (41%) had to discontinue treatment. Discontinuation was predicted at baseline by female gender, current smoking, high visual analogue scale of general health, and higher number of previously used biological disease-modifying anti-rheumatic drugs (bDMARDs). At refinement, smoking status and number of previously used bDMARDs remained with re-estimated hazard ratios (HRs) in the total cohort of 1.74 (95%-CI 1.15–2.63, p<0.01) and 1.40 (95%-CI 1.1–1.68, p<0.01), respectively. Using these two predictors, we developed a simple score predicting discontinuation (PPV=72.3%). From literature, predictors were pack years of smoking, number of previously used bDMARDs, lack of any concomitant DMARD therapy and in particular lack of concomitant methotrexate (MTX).

Conclusion

TNFi discontinuation is predicted by current smoking and number of previously used bDMARDs, as well as by pack years of smoking and lack of any concomitant DMARD/MTX therapy.

Key words

tumour necrosis factor-alpha, therapy, prognosis, smoking

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Introduction

Rheumatoid arthritis (RA) is a chronic, disabling immune disease predominantly involving synovial joints, affecting 0.5–1% of the population in industrialised countries (1-3). Tumour necrosis factor-alpha inhibitor (TNFi) treatments have dramatically improved the outcome of RA patients. However, a substantial number of RA patients have an unsatisfactory response to these TNFi or experiences adverse effects, necessitating discontinuation of therapy. Treatment success in clinical practice is a matter of balance between drug efficacy and tolerability; which continuously has to be weighed against the possibility of superior success to another treatment. Prediction of discontinuation would give insight in patients at risk for treatment failure, and might indicate relevant factors for physician and patient when contemplating TNFi treatment. Exploratory studies have addressed possible predictors for discontinuation, although these have usually not been validated in a separate cohort. In addition, to our knowledge, no one has ever systemically analysed all reported predictors from literature to investigate whether these are consistent across studies. This abundance in unreplicated predictors that have never jointly been reviewed, leads to a vague idea of what possible predictors could look like in practice, though at the same time results in the absence of any certainties. The aim of the present study was therefore to find predictors for discontinuation and replicate these in a second cohort, and additionally, compare the predictors found in our study with those reported in literature by performing a systematic literature review.

Patients and methods

Patients

Data were used from the "Biologicals and Outcome Compared and predicted Utrecht region in Rheumatoid Arthritis" (BiOCURA) observational cohort, in which the first patient was enrolled in June 2009 and the last in March 2015. In BiOCURA, RA patients eligible for biological treatment according to regular clinical practice in 8 hospitals from the Society for Rheumatology research Utrecht (SRU, see Supplementary Text 1 for participating centres) in the Netherlands were followed up for one year after start of biological treatment, or shorter in case of treatment discontinuation. Re-inclusion after switching to a different biological treatment was possible, at which patients entered again at baseline. We used data of all patients initiating TNFi (adalimumab, etanercept, infliximab, golimumab, and certolizumab pegol). To reflect clinical practice, no patients were excluded.

Data collection

Trained research nurses collected all data at baseline and during follow-up, including patient history, disease activity assessments, concomitant treatment(s), serology status regarding rheumatoid factor (RF) or anti-citrullinated protein antibody (ACPA), body mass index (BMI), smoking status, alcohol use, several questionnaires, and drug survival. Necessity of discontinuation was defined as having to cease the initiated TNFi permanently within one year. Temporarily discontinuation because of certain circumstances (*e.g.* infections, surgery) and complete cessation in case of remission were not considered as necessity of discontinuation. Reasons for discontinuation were categorised as 'inefficacy', 'adverse events' (AEs, including systemic and local allergic reactions, infectious complications, newly diagnosed cancers, and other events that could be related to the treatment), 'combination of AEs and inefficacy', and 'other reasons'. Drug survival was calculated from the first dose of the TNFi until the last dose, for a maximum of one year. The BiOCURA study was approved by the ethical committee of the University Medical Center Utrecht and the institutional review boards of the participating centers. All patients provided written informed consent.

Systematic review

We performed a systematic review of predictors for drug survival of TNFi therapy in RA to compare our findings with current knowledge on reported predictors for continuation or discontinuation. A search was performed on the 15th of July 2015 in PubMed and EMBASE

using a search string including synonyms for RA, TNFi and (dis)continuation (see Supplementary Fig. 1). After removal of duplicates, the articles were screened on title and abstract based on the inclusion criteria. Subsequently, articles were screened for the exclusion criteria after which studies for data-extraction remained (see Supplementary Table I). In order to summarise all studies evaluating the same parameters, we used the same direction of each predictor (*e.g.* methotrexate (MTX) use = "yes") and determined if the predictor was significantly ($p<0.05$) associated with either continuation or discontinuation, or neither of these ($p>0.05$). Predictors were extracted from multivariable models if possible. Given conflicting results of studies, predictors for continuation or discontinuation were considered as "associated with TNFi drug survival" if they met the following two criteria: they had to have been investigated and reported in at least three original publications and they had to have been shown predictive for either continuation or discontinuation in more than a third of the respective studies.

Statistical analyses

We assigned all patients initiating TNFi from June 2009 to October 2012 to a model development cohort (n=192). All subsequent patients initiating TNFi until April 2015 with a year follow-up were assigned to a model refinement cohort (n=60). Because we used for refinement this non-randomly selected cohort, the verification can be considered as in-between internal and external (4). The rationale of this is that a non-random split contributes to differences in baseline characteristics between the model development cohort and the verification cohort, which increases the reliability of predictors if they nevertheless can be replicated. Independent sample *t*-tests and chi-square tests were used to test for statistical differences between the cohorts. Kaplan-Meier curves with Cox-regression were used to compare differences in survival between cohorts and subgroups for different reasons for discontinuation. A multiple imputation process (10 databases) was used to account for missing baseline data, which was present for a maximum of 15% per predictor. In the model development cohort, a univariate pre-selection ($p<0.2$) with Cox-regression was performed to select predictive variables out of 24 clinical parameters (comorbidity, education level, C-reactive protein (CRP), EuroQol 5 dimensions (EQ5D), health assessment questionnaire (HAQ) and all listed in Table I, except the individual TNFis as the choice is usually not at random). The parameters selected via this method were then included in a multivariable Cox-regression model with backward selection ($p<0.05$) to build the development prediction model. This model was re-applied in the model refinement cohort, in which the selected variables were re-tested on significance ($p<0.05$) and consistency of effect (same direction of coefficient), and excluded if either of the two was violated. To develop a simple score for daily clinical practice distinguishing between patients with high and general risk for necessity of discontinuation, the final model was re-applied in the total cohort (n=252). This yielded decimal regression coefficients, not easy to use for a simple prediction score; we therefore converted the coefficients by multiplying these into (nearly) integers. Risk scores for several cut-offs were compared to find a positive predictive value (PPV) for discontinuation

Table I. Baseline characteristics of model development and model refinement cohort.

	Model development cohort (n=192)	Model refinement cohort (n=60)	*p*-value
Gender, female, n (%)	145 (75.5)	43 (71.7)	0.55
Age, mean (SD)	54.0 (±12.3)	57.1 (±10.7)	0.06
Disease duration, median (IQR)	5.0 (2.0-11.8)	6.0 (2.0-15.8)	0.69
Smoking status, current, n (%)	46 (24.0)	21 (35.0)	0.09
Alcohol use, >7 units/week, n (%)	32 (16.8)	10 (16.7)	0.99
BMI, mean (SD)	27.0 (±5.2)	27.6 (±5.9)	0.48
RF, positive, n (%)	125 (65.8)	34 (56.7)	0.20
ACPA, positive, n (%)	134 (71.3)	41 (68.3)	0.66
Baseline DAS28, mean (sd)	4.5 (±1.2)	4.0 (±1.2)	0.02
TJC, median (IQR)	6 (2-12)	5 (2-11)	0.40
SJC, median (IQR)	2 (0*-4)	1 (0*-2)	<0.01
ESR, median (IQR)	19.0 (10-34)	14 (7-34)	0.15
VAS-GH, mean (SD)	55.9 (±24.0)	50 (±21.5)	0.09
No. of previously used bDMARDs, n (%)			0.85
0 (naïve)	119 (62.0)	33 (55.0)	
1	59 (30.7)	20 (33.3)	
2	8 (4.2)	4 (6.7)	
>2	6 (3.1)	3 (5.0)	
Initiated TNFi, n (%)	192 (100.0)	60 (100.0)	0.20
Adalimumab	74 (38.5)	17 (28.3)	
Etanercept	68 (35.4)	29 (48.3)	
Golimumab	28 (14.6)	5 (8.3)	
Infliximab	11 (5.7)	3 (5.0)	
Certolizumab	11 (5.7)	6 (10.0)	
Concomitant MTX, n (%)	137 (71.4)	46 (76.7)	0.42
Concomitant HCQ, n (%)	51 (26.6)	15 (25.0)	0.81
Concomitant SSZ, n (%)	18 (9.4)	4 (6.7)	0.52
Concomitant GC, n (%)	69 (35.9)	21 (35.0)	0.90

All patients in BiOCURA initiating TNFi from June 2009 to October 2012 were assigned to the model development cohort (n=192), and all subsequent patients initiating TNFi until April 2015 to the model refinement cohort (n=60).

The presented clinical characteristics are all before treatment initiation. P-values for comparisons were calculated by means of an independent sample t-test, Mann-Whitney U-test or chi-square based on distribution of the clinical parameter.

ACPA: anti-citrullinated protein antibody; bDMARDs: biological disease-modifying anti-rheumatic drugs; BMI: body mass index; DAS28: disease activity score based on 28 joints; GC: glucocorticoid; HCQ: hydroxychloroquine; MTX: methotrexate; RF: rheumatoid factor; SSZ: sulfasalazine; SJC: swollen joint count; TJC: tender joint count; TNFi: tumour necrosis factor alpha inhibitor; VAS-GH: visual analogue scale general health.

*values for swollen joint count of '0' were usually seen in patients who switched due to side effect and/or had involvement of joints outside 28-joint count.

of at least 70%. All analyses were performed using SPSS (v. 21.0. Released 2012. IBM Corp. Armonk, NY, USA).

Results

Baseline characteristics for patients of the model development and refinement cohorts are shown in Table I. Differences in characteristics were seen due to a non-random split of the cohort, with most importantly a lower baseline DAS28 (mean 4.0 *vs*. 4.5, p=0.02), including a lower swollen joint count (median of 1 *vs*. 2, p<0.01) in the model refinement cohort, compared to model development cohort. Within 1 year of follow-up 103 of the 252 patients (41%) discontinued TNFi treatment, with an incidence rate of 55 per 100 patient years. Patients most frequently discontinued between 10 and 26 weeks after start of treatment (Fig. 1A). The drug survival was not significantly different between the model development and refinement cohort (p=0.38). Inefficacy was the most common reason for discontinuation (62%), followed by AEs (31%) and AEs with inefficacy (6%) (Table II). The least favourable TNFi survival was seen in patients discontinuing because of both AEs and inefficacy (Fig. 1B).

In the model development cohort, nine of the 24 baseline clinical parameters were associated with discontinuation. These parameters were [HR (95%-confidence interval), p-value]: female gender [1.71 (0.94–3.12), p=0.08], current smoking (as opposed to only smoked in the past and never smoked) [1.45 (0.88–2.38), p=0.14], rheumatoid factor positivity [0.72 (0.45–1.15), p=0.17], concomitant use of MTX (0.61 (0.38–0.99), p=0.04], number of previously used biological DMARDs (bDMARDs) (1.42 (1.13–1.77) per biological, p<0.01], baseline DAS28 [1.27 (1.05–1.54), p=0.01], visual analogue scale of general health [VAS-GH, 1.21 (1.09–1.34)/per 10 mm, p<0.01], EQ5D [0.32 (0.15–0.69), p<0.01], and the HAQ, [1.38 (0.95–2.00), p=0.09]. The multivariable prediction model after backward selection is shown in Table III. Discontinuation was predicted by a model including female gender [2.06 (1.12–3.80), p=0.02], current smoking [1.67 (1.00–2.77), p=0.05], higher number of previously used bDMARDs [1.46 (1.15–1.86) per biological, p<0.01], and high VAS-GH score [1.20 (1.08–1.33) per 10 mm, p<0.01]. These four clinical parameters were retested in the model refinement cohort for significance and consistency of effects, resulting in exclusion of VAS-GH score (0.98 (0.84–1.15), p=0.90] and female gender [0.84 (0.34–2.06), p=0.70]. The model that remained contained the predictors current smoking [2.53 (1.14–5.61), p=0.02] and number of previously used bDMARDs [1.43 (1.03–1.99) per biological, p=0.03].

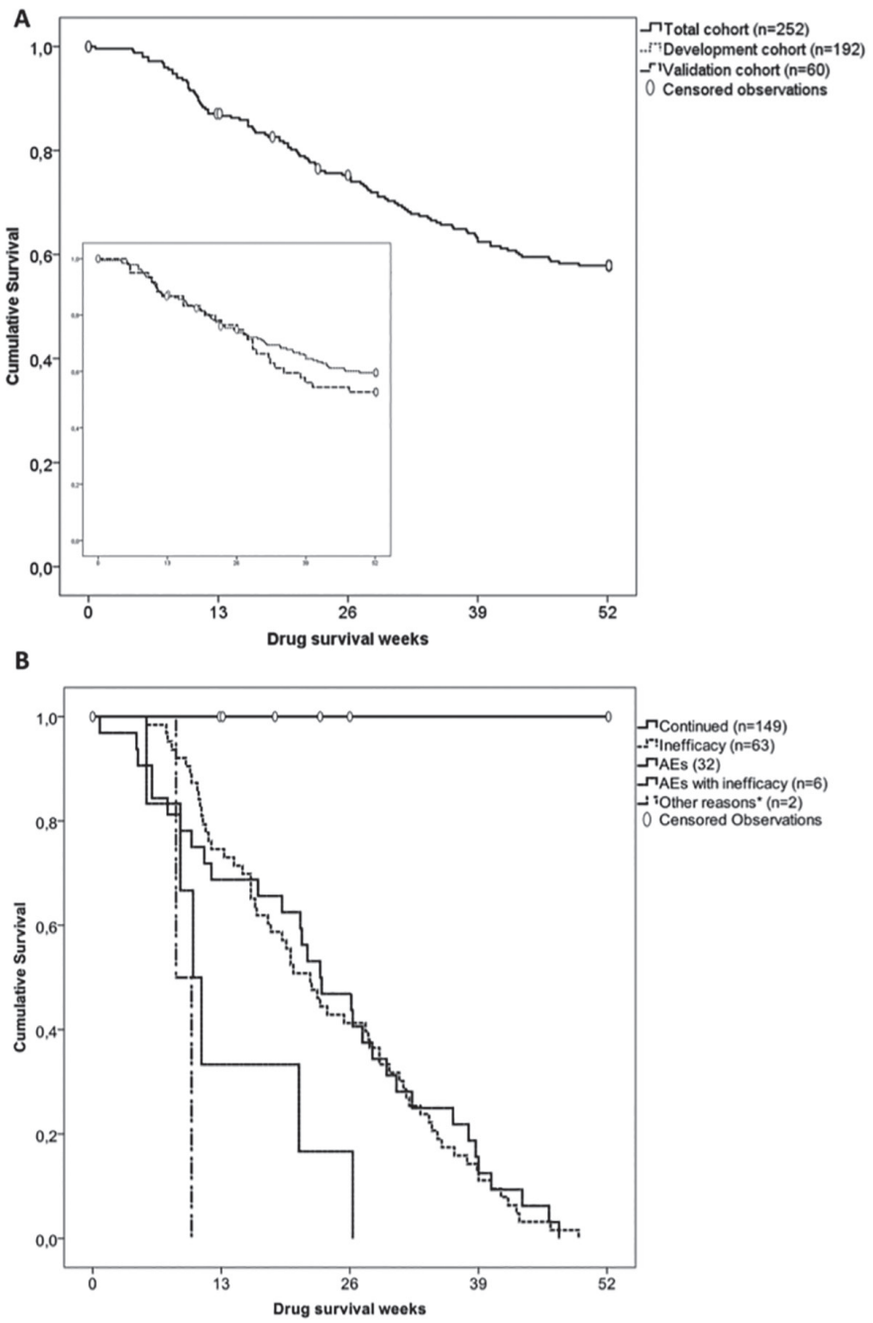

Fig. 1. TNFi drug survival curves. **A**: TNFi drug survival curve for all patients (n=252) and separately for model development (n=192) and model refinement cohorts (n=60). There was no difference in survival between the model development and model refinement cohort (p=0.38, Cox-regression, corrected for age and gender). **B**: TNFi drug survival curves for patients discontinuing for specified reasons. There was no difference in survival between patients discontinuing because of inefficacy and adverse events (AEs) without or with inefficacy (p=0.74, Cox-regression after combining "AEs with inefficacy" with "AEs" to one group (n=38) and compare with inefficacy (n=63), corrected for age and gender).

Table II. Reasons for discontinuation within the first year after TNFi initiation. Shown are the number of discontinuing patients in model development, model refinement and complete cohort.

	Model development cohort (n=192)	Model refinement cohort (n=60)	Total cohort (n=252)
Inefficacy, n (% of total discontinuations)†	48 (64)	15 (54)	63 (61)
AEs, n (% of total discontinuations)	21 (28)	11 (39)	32 (31)
AEs with inefficacy, n (% of total discontinuations)	4 (5)	2 (7)	6 (6)
Other reasons*, n (% of total discontinuations)	2 (3)	0 (0)	2 (2)
Total, n (% of total discontinuations)	75 (100)	28 (100)	103 (100)

*1 patient discontinued because she had a pregnancy wish, 1 patient discontinued for unknown reasons. †Of all 48 patients discontinuing due to inefficacy in the development cohort, n=37 (77.1%) had a primary failure (*i.e.* never experienced a clinical response at all), and n=11 (22.9%) had a secondary failure (*i.e.* lost their initial beneficial response to TNFi treatment). Of all 15 patients discontinuing due to inefficacy in the validation cohort, n=10 (66.7%) had a primary failure and n=5 (33.3%) a secondary failure. AEs: adverse events; TNFi: tumour necrosis factor alpha inhibitor.

Table III. Multivariable Cox model predicting risk of discontinuation.

Development	HR	95%-CI	p-value
Female gender, yes	2.06	(1.12-3.80)	0.02
Current smoking, yes	1.66	(1.00-2.77)	0.05
No. of prev. biologicals, per biological	1.46	(1.15-1.86)	<0.01
VAS-GH, per 10 mm	1.20	(1.08-1.33)	<0.01

The model was built by entering the 9 predictors from univariate pre-selection and performing backward selection (p<0.05) on all patients in the model development cohort (n=192). The categorical variable smoking (current/only in the past/never) was dichotomised in current smoking (yes/no) based on the results of univariate analysis, only showing an effect for current smoking.
CI: confidence interval; HR: hazard ratio; VAS-GH: visual analogue scale general health (0–100, 0=best health).

Table IV. Final prediction model and simple prediction score for use in daily practice.

	HR	95%-CI of HR	p-value	Assigned points*	Score
Current smoking, yes	1.74	(1.15-2.63)	<0.01	5	….
No. of prev. used biologicals, per biological	1.40	(1.16-1.68)	<0.01	3	….
Total score					….

After refinement, the remaining parameters were current smoking and number of previously used bDMARDs. Shown are the estimated predictive values of these remaining parameters in the total cohort (n=252). The regression coefficients of smoking (0.553) and number of previously used biologicals (0.334) were multiplied by 9 to create nearly integers to use as assigned points (5 and 3 respectively). Scores assigned to these predictors have to be summed to get the total score. The cut-off of ≥9 met our criteria of a positive predictive value >0.7, which is scored by 4.4% of the complete cohort. This cut-off is met by non-smokers with 3 or more- and smokers with 2 or more previously used bDMARDs, who have a high risk of having to discontinue the initiated TNFi. CI: confidence interval; HR: hazard ratio.

To create a simple prediction score of use for clinical practice, we first re-estimated the regression coefficients by applying the final model to the complete cohort, which resulted in a HR of 1.74 for current smoking and HR of 1.40 per number of previously used bDMARDs (see Table IV). The subsequently constructed risk score is used by assigning points per patient for the two predictors (5 for smokers, 3 per previously used bDMARD) and summarises these points. For possible cut-offs, the predicted chances on discontinuation were evaluated (Supplementary Table II). The cut-off of ≥9 points predicted an absolute risk of discontinuation (PPV) of 72.3%, and was scored by 11 patients (4.4%) of the total study cohort. This cut-off is met by non-smokers with three or more-, and smokers with two or more previously used bDMARDs.

To put our results in context we performed a systematic literature search. The search resulted in 3311 articles, of which 92 on predicting of continuation or discontinuation remained after screening (Supplementary Fig. 1). After applying the exclusion criteria, 30 full-text articles and 18 congress abstracts remained. Results for the full-text articles and predictors that were studied in ≥3 studies are shown in Table V whereas all investigated predictors and the results including (congress) abstracts are shown in Supplementary Table III. The predictors significantly associated with continuation were concomitant MTX use and any concomitant DMARD use, whereas those associated with discontinuation were number of previously used bDMARDs and pack years smoking. In addition, smoking status was significantly associated with discontinuation in one study and borderline-significant in two other studies (5, 6).

Discussion

Our study shows that TNFi discontinuation can be predicted by smoking status and number of previously used bDMARDs, which is supported by results from other observational studies reported in literature. A simple prediction score was able to predict TNFi discontinuation with accuracy (PPV=72.3%), although was only applicable to a minority of all patients (*i.e.* 4.4%). According to this prediction score, smokers with a history of ≥2 previously used biologicals, and non-smokers with ≥3 biologicals represent a group of RA patients with a low TNFi treatment success. The systematic review also revealed pack years of smoking, lack of any concomitant DMARD therapy and lack of concomitant MTX as predictors for TNFi discontinuation.

Smoking status was investigated in three previous studies (5-7). Although a significant association with TNFi discontinuation was only found in one of these studies (7), the two other studies reported trends in the same direction, with p-values of 0.055 (5) and 0.075 (6). In addition, when our results would be added to the systematic review, current smoking would fulfill the criteria (significant in 2/4 studies). Also of note, in one abstract covering data of 12,000

Table V. Results from systematic review on investigated predictors for TNFi drug survival, reported in three or more studies.

Item	Association with continuation	No association with survival	Association with discontinuation	Conclusion TNFi drug survival
Demographic and clinical parameters				
Age*	0	16	3	-
Female gender	1	16	1	-
Disease-duration	2	10	0	-
Comorbidity[§]	1	7	1	-
RF positivity/levels	0	7	0	-
Current smoking	0	2	1	-
Pack years smoking	0	1	2	†
Assessments				
DAS28*	1	11	3	-
HAQ	0	8	3	-
SJC	0	6	0	-
ESR	1	4	1	-
TJC	0	4	2	-
CRP	1	5	0	-
Treatments				
Concomitant MTX	6	6	2	‡
Concomitant GCs	1	8	1	-
Number of previously used DMARDs*	0	6	2	-
Any concomitant csDMARD	5	0	1	‡
Number previously used bDMARDs*[§]	0	1	4	†
Concomitant SSZ	0	2	1	-

Predictors were drawn from multivariable models if possible and a p-value <0.05 was considered an effect. A predictor from a study was assigned to either one of three categories: associated with continuation, discontinuation or not associated. Per category, the number of studies that mention the particular predictor is shown. The association with survival (*i.e.* conclusion) is based on the consistency of the predictor in predicting the 'same direction' in more than 1/3rd of the studies. The references of all studies per predictor can be found in Supplementary Table III. ANA: anti-nuclear antibodies; bDMARD: biological DMARD; csDMARD: conventional synthetic DMARD; DAS28: disease activity score based on 28 joints; DMARDs: disease-modifying anti-rheumatic drugs; ESR: erythrocyte sedimentation rate; GCs: glucocorticoids; HAQ: Health Assessment Questionnaire; MTX: methotrexate; NSAID: non-steroidal anti-inflammatory drugs; RF: rheumatoid factor; SJC: swollen joint count; SSZ: sulfasalazine; TJC: tender joint count. *combination of numerical and categorical values for this parameter; [§]different categories of parameters per study investigated; [‡]predicting continuation (associated in >1/3rd of studies with continuation); - no association with TNFi drug survival; [†]predicting discontinuation (associated in >1/3rd of studies with discontinuation).

TNFi users, an odds ratio for smoking of 1.20 (1.06–1.36) was found (8). Our results, together with the results from literature therefore indicate that smoking status is a rather moderate, but robust predictor for discontinuation. Smoking is known to increase susceptibility of RA (9-11), is associated with a higher disease activity (12-16) and a reduced clinical response to MTX and TNFi therapy (17-20). Several mechanisms could play a role in the reduced clinical response to treatment. First, in smoking RA patients ACPA levels are higher (14, 17, 21-25), and higher levels are associated with a more severe disease course (26-31). However, when the relationship between smoking and response to therapy is tested, the reduced clinical response seems to be independent from ACPA levels (20); similarly, ACPA positivity was not selected at our univariate pre-selection, but smoking was. These data indicate that smoking is a more robust predictor for discontinuation than ACPA. Second, various serum cytokines and matrix metalloproteinases levels are elevated in smokers which could make smoking patients more resistant to TNFi therapy (17, 32, 33). Third, several pharmacokinetic or dynamic effects could play a role (19, 20). For example, both current smoking and systemic inflammation elevate basal metabolic rate (34), and may reduce the bioavailability of anti-rheumatic drugs in smokers in comparison with non-smokers (24). Fourth, smoking status may also be an indicator of lower socioeconomic status, which is related with a poorer outcome of RA (35). Regardless of the underlying mechanism, it is difficult to use smoking status in clinical decision making, as it seems to negatively affect responsiveness to a range of treatments (17-20), limiting the choice of effective alternatives, although no negative effect of smoking on the efficacy of tocilizumab was found (36). In addition, it has not been proven after quitting of smoking, the effects of TNFis will be better. Nevertheless, because the risk of cardiovascular morbidity and mortality in RA is already increased, even in non-smoking patients (37), smokers should always be encouraged to quit.

The number of previously used biologicals showed a HR of 1.40 (1.16–1.68) in the BiOCURA cohort, and has been reported as a predictor for discontinuation in four out of five studies (38-41) and in all three additional abstracts (42-44). Selection may be the main cause for the predictive ability of this parameter: among non-naïve TNFi patients probably a higher number of TNFi treatment refractory patients was found. It is tempting to speculate that primary refractory patients to TNFi treatment have a type of RA that is probably more dependent on other inflammatory mechanisms than the TNF-alpha pathway, which increases the chance for a second failure to TNFi treatment (38). However, although this makes sense, observations in clinical practice do not support this hypothesis (45). Another explanation for a TNFi refractory RA might be the development of anti-drug antibodies that eliminate the TNFi until subclinical concentrations are reached, leading to a non-response or loss of response. It has been found that patients who developed antibodies to infliximab therapy, are more prone to develop anti-drug antibodies to the next TNFi (adalimumab), compared with infliximab naïve patient that initiate adalimumab (46), which could explain why patients failing a previous TNFi have reduced chances for the next TNFi. However, when all switchers from infliximab to adalimumab were investigated, response to

adalimumab was higher in switchers with detectable anti-infliximab antibodies than in switchers without these antibodies (46, 47), which challenges the hypothesis above.

Lack of any concomitant DMARD and in particular lack of MTX predicted discontinuation of TNFi therapy in literature. In our analysis, concomitant MTX was protective for discontinuation in univariate analysis (HR=0.61), though it was excluded in multivariable analysis. It has been shown that MTX reduces the immunogenicity to TNFi (48). Therefore, even when response to MTX monotherapy is insufficient, continuation of MTX is advised when commencing a bDMARD (49). Female gender and a higher VAS-GH were found to be associated with discontinuation in our model development cohort, however, these predictors could not be replicated in our model refinement cohort. The inability to replicate is in line with the results from literature, which also showed no true association between these predictors and TNFi drug survival (Supplementary Table III).

The limited number of included patients may be considered a limitation of our study. However, our findings are consistent with the results from literature, which reduces the possibility false positive results were shown (type I error). We cannot exclude the possibility though of any predictors not found due to a low power, *i.e.* false negative results (type II error). However, any factor that we have missed due to a low power, would probably have a lesser effect on discontinuation than the predictors we did find, which therefore have less clinical relevance. Also, of all included patients, 31 were re-included for a second treatment course (*i.e.* entered the study twice). In order to analyse if this influenced the results, as a sensitivity analysis the final model was re-applied on the total cohort while excluding all re-inclusions. Only changes in predictive values <10% were observed for smoking status and number of previously used biologicals, demonstrating absence of major bias due to re-inclusion. It should also be noted that model development techniques such as backward selection, increase the chance of model overfitting. It might therefore be possible that the true HRs of the predictors are lower than estimated, or even that any true association with discontinuation is absent. However, the fact that the predictors we found could be validated in literature makes it very unlikely these are false positive results. The systematic literature search was carried out using a broad search string and included many studies and several abstracts. However, the heterogeneity among studies was not taken into account, which might have influenced the categorisation of several factors. The presented data should therefore be regarded as a concise, rather than an exhaustive overview. Also, the limited predictive value in our study and other observational studies could be a result of the subjectivity of the outcome (no strict criteria for discontinuation in practice) and the heterogeneity in the interaction between patients and physicians in clinical decision-making. Moreover, discontinuation is a multidimensional endpoint with many influential parameters, which inhibits the creation of a fully explanatory model containing only several (clinical) parameters. Although future research could add to the identification of better predictors, a relatively wide error margin seems inevitable when using discontinuation as an outcome.

In conclusion, we showed that necessity of TNFi discontinuation is related to smoking status and number of previously used biologicals, which is corroborated by our systemic literature search and also revealed pack years of smoking, lack of any concomitant DMARD therapy and lack of concomitant MTX as predictors. The exact mechanisms of action leading to discontinuation are not always known, and are complicated by the multidimensional complexity that leads to the clinical decision of discontinuation.

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