Failure in Longterm Treatment is Rare in Actively Treated Patients with Rheumatoid Arthritis, But May Be Predicted by High Health Assessment Score at Baseline and by Residual Disease Activity at 3 and 6 Months: The 5-year Followup Results of the Randomized Clinical NEO-RACo Trial

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ABSTRACT. ***Objective.*** With modern initial aggressive combination treatments with synthetic disease-modifying antirheumatic drugs (sDMARD), most patients with rheumatoid arthritis (RA) achieve remission, have marginal radiographic progression, and sustain normal function. Here we aim to identify the patients failing these targets even after aggressive treatment.

Methods. Ninety-nine patients with early, active RA were treated with a combination of 3 sDMARD and prednisolone (PRD), and either infliximab or placebo infusions during the first 6 months, aiming at strict remission. After 24 months, the treatments became unrestricted. At 60 months, 4 evident clinical features of treatment failure were defined: area under curve (AUC) between 6–60 months for disease activity score assessing 28 joints > 2.6; AUC 6–60 for health assessment questionnaire > 0.5; progression in total Sharp/van der Heijde score 0–60 months > 3 units; and need of PRD or biologic DMARD treatment at 60 months.

Results. A total of 93 patients were followed up for 60 months. Of them, 45 had no features of treatment failure, 30 had 1, 10 had 2, 7 had 3, and 1 patient had all 4 features. Having 2–4 features of treatment failure at 5 years was predicted by the health assessment score at baseline, and by even low residual disease activity at 3 and 6 months.

Conclusions. Only 20% of the patients with RA treated early with combination sDMARD and PRD have more than 1 clinical feature of treatment failure at 60 months. Residual clinical disease activity at 3–6 months was the most important predictor for identifying these patients. The study was registered at www.clintrials.gov (NCT00908089). (J Rheumatol First Release Occt 1 2014; doi:10.3899/jrheum.140267)

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To increase the likelihood of a nonprogressive state of the disease and maintenance of normal function, the current treatment of rheumatoid arthritis (RA) aims at early and sustained remission[1]. Nonetheless, with widely used synthetic disease-modifying antirheumatic drugs (sDMARD) in monotherapy, this goal is achievable only in a minority of patients[2,3]. Yet, with a combination of sDMARD, an increasing number of patients may reach longterm remission[4]. Thus, because idealistic goals have turned into reality for most patients, the next target would be to make them achievable for all. This, however, requires the early recognition of patients not adequately responding to aggressive combination sDMARD treatment.

We have previously shown that in early RA, an intensified initial Finnish Rheumatoid Arthritis Combination Therapy Trial (FIN-RACo) combination treatment [methotrexate (MTX), sulfasalazine (SSZ), hydroxychloroquine (HCQ), and small-dose prednisolone (PRD)] results in very low disease activity in most patients, with 82% of the patients being in 28-joint Disease Activity Score (DAS28) remission (DAS28 < 2.6) at 2 years[5], and up to 87% at 5 years[4], regardless of the concomitant initial infliximab (IFX) treatment for 6 months. However, even though these results are better than in any other previous trial, not all patients achieve remission. Some develop radiographic damage or compromised function, and in some, the maintenance of low disease activity requires treatment with glucocorticoids (GC) or biological DMARD (bDMARD). In this analysis, we studied whether such patients could be identified at an early stage.

MATERIALS AND METHODS

Study design and patients. In our investigator-initiated, multicenter, controlled study, the NEO-RACo trial (The Finnish Rheumatoid Arthritis Combination Therapy Trial with IFX added for 6 mos), 99 patients with early, active RA were treated with an intensified FIN-RACo regimen starting with a combination of MTX up to 25 mg/week (subcutaneous when needed), SSZ up to 2 g/day, HCQ 35 mg/kg/week, and PRD 7.5 mg/day for 2 years, and double-blindly randomized to receive either IFX or placebo (PLA) infusions at weeks 4, 6, 10, 18, and 26. An active use of intraarticular GC injections to all inflamed joints was part of the protocol. At all timepoints, the treatment was targeted to a strict NEO-RACo remission, defined as the absence of swollen (66 joint count) or tender joints (68 joint count), and the presence of 5 out of the 6 following criteria: (1) morning stiffness < 15 min, (2) no fatigue, (3) no joint pain, (4) no tender joints, (5) no swelling in joints or tendons, and (6) the erythrocyte sedimentation rate (ESR) < 30 mm/h in women and < 20 mm/h in men. The patient selection criteria as well as the treatment protocol have been described in detail[5].

Our study was conducted according to the Declaration of Helsinki, and its protocol was approved by the national health authorities and by the ethics committee of the Hospital District of Helsinki and Uusimaa. All patients gave informed written consent. The study has been registered at www.clintrials.gov (NCT00908089).

Followup and treatment. The patients were assessed at weeks 0, 4, 6, 10, 14, 18, 22, and 26, and at months 8, 10, 12, and thereafter every 3 months up to 5 years. If the treatment response was ≥ American College of Rheumatology 50% (ACR), but not strict NEO-RACo remission, the sDMARD could be substituted by others according to a predefined protocol that was also applied in case of intolerability. Nevertheless, during the first 2 years, it was obligatory to use a combination of 3 sDMARD, 1 of which had to be a cytostatic or an immunomodulating agent. If, at any time between 6–24 months, the treatment response was less than ACR50 at 2 consecutive visits[6], the patient was regarded as a treatment failure and the therapy became unrestricted, including the opportunity to use tumor necrosis factor blockers, but the IFX/PLA code was not opened and the patient continued in the study. At 5 years, the patients who had begun taking a bDMARD within 2 years were included, even though they had been excluded from the 2-year analysis. After 24 months, if the patient was in remission, PRD dose was decreased by 2.5 mg/day every 3 months and tapered off if the patient continued to be in remission. In the case of sustained remission without PRD, the sDMARD could also be tapered down according to a predefined protocol, starting with SSZ[4]. In the case of nonremission, the maximum tolerated doses of the combination treatment were continued throughout the followup and the therapies modified according to the judgment of the treating rheumatologist, allowing the use of GC and bDMARD, and aiming at sustained strict NEO-RACo remission.

Outcomes. The clinical assessments included the evaluation of the number of swollen and tender joints (out of 66 and 68 joints, respectively), patient's assessment of pain [10 cm visual analog scale (VAS)], patient's global assessment of disease activity (10 cm VAS), physician's global assessment of disease activity (10 cm VAS), patient's assessment of physical function [Health Assessment Questionnaire (HAQ)][7], and acute-phase reactants (C-reactive protein, ESR) at each visit (recorded to the results at mos 6, 12, 18, 24, 30, 36, 42, 48, 54, and 60). The DAS28 was calculated[8], and the proportions of patients in the strict NEO-RACo remission, as well as in the Boolean ACR/European League Against Rheumatism (EULAR) remission[9], were calculated.

The current medications were elucidated at each visit.

The small joints of the hands and feet were radiographed at baseline and at 2 and 5 years, and scored by an experienced radiologist according to the modified Sharp/van der Heijde method (SvdH)[10].

Definitions of treatment failure. At 60 months, 4 different features of treatment failure were identified: (1) lack of sustained remission: DAS28 the area under the curve (AUC) between 6–60 months > 2.6; (2) lack of restored normal function: HAQ AUC 6–60 > 0.5; (3) continued joint destruction: progression in total SvdH 0–60 months (ΔSvdH) > 3 units; and (4) the need to deviate from the treatment protocol to reach the clinical response: either the need to start a bDMARD before 60 months or the need to use PRD at 60 months. The patient was defined to have true treatment failure if fulfilling 2 of these 4 criteria.

Statistical methods. The data are presented as means with SD, medians with interquartile range, or as counts with percentages. The most important outcomes are given with 95% CI. The linearity across the groups was tested by using bootstrap type analysis of variance with an appropriate contrast, Cochran-Armitage test for trend, or Cuzick test, depending on the distribution of the outcome. When adjusting for baseline age, sex, and seropositivity for rheumatoid factor, bootstrap type analysis of covariance or

logistic regression with probit link function was used. The associations between baseline characteristics and having true treatment failure (yes/no) were investigated by multivariate logistic regression analysis. Receiver-operating characteristic (ROC) curves were used for determining the optimal cutoff point for DAS28 in predicting the 2–4 features of treatment failure, and the respective areas under the curve were calculated. ROC regression was applied to get adjusted areas under the ROC. The optimal cutoff point was defined using the Liu method (maximizes the product of the sensitivity and specificity) with bias-corrected bootstrap CI[11]. Youden's index (sensitivity + specificity –1) and the corresponding diagnostic characteristics of the test sensitivity, specificity, and positive likelihood ratios were calculated. The 95% CI for areas under the ROC and Youden's index were obtained by bias-corrected bootstrapping.

RESULTS

A total of 93 patients (94%) were followed up after 2 years; their main clinical outcomes at 5 years have been presented[4]. Forty-five patients (48%) had no features of treatment failure. Thirty patients (32%) had 1 feature of treatment failure. Most often it was the use of PRD or a bDMARD (18 patients), followed by the ΔSvdH > 3 units (11 patients); only 1 patient had HAQ-AUC 6–60 > 0.5 and none of the patients had the DAS28-AUC 6–60 > 2.6 as the sole feature of treatment failure. Ten patients (11%) had 2 features of treatment failure, most often the combination of the use of PRD or a bDMARD and the ΔSvdH > 3 units (5 patients). Seven patients (8%) had 3, and only 1 (1%) patient all 4 features of treatment failure (Figure 1).

At baseline, only HAQ and physician's global assessment were linearly related to the number of criteria of treatment failure at 5 years (Table 1). In a multivariate ordered regression analysis, only the physician's global assessment had some significance in predicting the subsequent number of features of treatment failure (data not shown). On the other hand, in a multivariate regression analysis, only the HAQ score had some significance in predicting subsequent true treatment failure (Table 2).

All of the clinical outcome measures clearly improved from baseline to 3 months, and further to 6 months. However, both at 3 and 6 months, all of the single clinical measures, the HAQ, and the DAS28 worsened linearly according to the number of criteria of treatment failure and, respectively, the proportions of patients in strict NEO-RACo remission or in the Boolean ACR/EULAR remission diminished (Table 3).

With an ROC curve, the optimal cutoff value for DAS28 at 3 months was 2.25 (95% CI 1.99–3.13; Youden's 0.53, 95% CI 0.28–0.73) and at 6 months 2.24 (95% CI 1.14–2.33; Youden's 0.52, 95% CI 0.27–0.75; Figure 2). It is noteworthy, however, that at 6 months, the cutoff value of DAS28 at 2.24 had a specificity as high as 0.97 to find the patients having a true treatment failure at 5 years (Figure 2).

DISCUSSION

Our study shows that only a minority of patients with RA may be considered to have failed the treatment when an early, remission-targeted treatment with a combination of sDMARD and systemic (supplemented with intraarticular, if needed) GC therapy is applied. Clinical treatment response by 3–6 months is the most important factor for identifying these patients.

The previous results of the NEO-RACo trial have shown that with a targeted approach, frequent control visits, and aggressive initial use of sDMARD as well as systemic and, if needed, intraarticular GC, the treatment results in RA have evolved markedly, setting a new standard for treating RA[4,5]. At 5 years, about 60% of the patients with initially highly active RA were in strict NEO-RACo remission, 87% were in DAS28 remission, 70% had an HAQ value of 0, and the radiographic progression was marginal[4]. Nevertheless, that still leaves some patients with suboptimal outcomes. Because the ultimate aim of RA treatment is to get each and every patient into remission and to a nonprogressive state of disease, early recognition of the patients failing the initial treatment would enable the use of a different approach before any irreversible damage has occurred.

Nonetheless, with the constantly improving treatment strategies for RA, the definition of treatment failure has changed over the years and a unanimous consensus is still lacking[12]. In clinical trials comparing new drugs to placebo, the ACR20/50/70 improvement criteria[6] and the EULAR response criteria are valid instruments[13]. From an updated

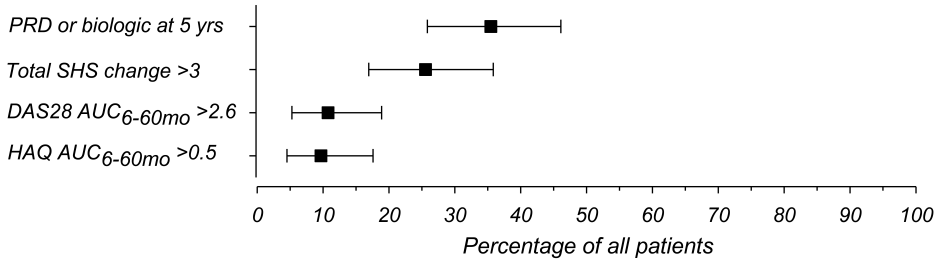

Figure 1. The percentages (95% CI) of initially aggressively treated patients with rheumatoid arthritis fulfilling various criteria of treatment failure after 5 years of treatment. PRD: prednisolone; SHS: Sharp/van der Heijde method; DAS28: 28-joint Disease Activity Score; AUC: area under the curve; HAQ: Health Assessment Questionnaire.

Table 1. Baseline data of the initially aggressively treated patients with early rheumatoid arthritis categorized according to the number of criteria of treatment failure fulfilled at 5 years.

Characteristics	No. Criteria			p*
	0, n = 45	1, n = 30	2–4, n = 18	
Demographic data at baseline				
Female, n (%)	29 (64)	23 (77)	11 (61)	0.93
Age, mean (SD)	47 (11)	44 (9)	47 (11)	0.69
BMI, mean (SD)	27.0 (4.0)	24.1 (3.1)	26.5 (5.5)	0.22
Duration of symptoms, mos, median (IQR)	3 (2–6)	4 (3–6)	4 (3–5)	0.37
Currently smoking, n (%)	12 (27)	9 (30)	7 (39)	0.36
Rheumatoid factor present, n (%)	31 (69)	25 (83)	13 (72)	0.53
Anticitrullinated protein antibodies present, n (%)	32 (71)	26 (87)	11 (61)	0.77
Measures of disease activity at baseline, mean ± SD				
No. swollen joints	15 (6)	14 (6)	17 (9)	0.56
No. tender joints	20 (11)	18 (9)	25 (11)	0.20
C-reactive protein, mg/l	25 (26)	34 (47)	38 (46)	0.17
Erythrocyte sedimentation rate, mm/h	32 (20)	34 (22)	33 (26)	0.90
Patient's global assessment, VAS, mm	47 (23)	46 (27)	60 (26)	0.10
Patient's assessment of pain, VAS, mm	52 (26)	52 (26)	60 (28)	0.36
Physician's global assessment, VAS, mm	47 (20)	53 (19)	60 (20)	0.013
Physical function, HAQ	0.92 (0.66)	0.80 (0.55)	1.42 (0.62)	0.025
Disease Activity Score at 28 joints	5.51 (1.14)	5.51 (1.17)	5.76 (1.44)	0.54
Radiography at baseline, Sharp/van der Heijde score				
Erosion score, mean ± SD	2.3 (7.1)	2.0 (3.3)	0.6 (0.9)	0.21
Narrowing score, mean ± SD	0.3 (1.2)	0.4 (1.3)	0.3 (0.8)	0.68
Total score, mean ± SD	2.5 (8.2)	2.4 (3.7)	0.9 (1.7)	0.33
Erosions in hand or foot radiographs, n (%)	15 (33)	14 (47)	6 (33)	0.75
The initial randomization group, n (%)				0.15
FIN-RACo + placebo	18 (40)	18 (60)	10 (56)	—
FIN-RACo + infliximab	27 (60)	12 (40)	8 (44)	—

*p for linearity. BMI: body mass index; IQR: interquartile range; VAS: visual analog scale; HAQ: Health Assessment Questionnaire; FIN-RACo: The Finnish Rheumatoid Arthritis Combination Therapy Trial.

Table 2. Multivariate logistic regression analysis of the baseline variables for predicting the presence of true treatment failure at 5 years.

Variables at Baseline	OR (95% CI)	p
Male	1.24 (0.33–4.70)	0.75
Age	1.01 (0.95–1.08)	0.71
BMI	1.04 (0.89–1.21)	0.60
Smoking	1.67 (0.42–6.67)	0.46
Duration of symptoms	1.07 (0.80–1.42)	0.65
Anticitrullinated protein antibody positivity	0.48 (0.11–2.15)	0.34
Disease Activity Score, 28 joints	0.46 (0.21–1.01)	0.052
Physician's global assessment, VAS	1.04 (1.00–1.08)	0.076
Physical function, HAQ	4.84 (1.55–15.08)	0.007
Erosions in hand or foot radiographs	0.58 (0.15–2.25)	0.43
Initial randomization group	0.57 (0.16–1.96)	0.37

BMI: body mass index; VAS: visual analog scale; HAQ: Health Assessment Questionnaire.

clinical point of view, however, too many of the patients achieving these responses still have marked residual disease activity and are, in fact, failing treatment[12]. One definition of treatment failure is the failure to reach remission or low disease activity, which in current clinical practice has been set as the treatment goal[1]. Nevertheless, the definitions of remission and of its sustainability vary[14,15,16,17]. In clinical practice, a treatment failure has been defined as a decision to discontinue a specific treatment or to add another to it[18]. Further, the amount of radiographic damage may describe treatment failure. It well describes the cumulative problem of the disease, but interestingly enough, might not always be in concordance with clinical disease activity[19,20]. Additionally, patient-reported outcomes such as functional capacity may perform better than the conventional clinical ones in classifying treatment responses[21]. However, no clear-cut limits for defining treatment failure exist for either radiographic progression or functional capacity.

With all the evolving treatment strategies, the single, old outcomes may not be as relevant as before, and a composite measure to define treatment failure might be needed. In this respect, we were inspired by the 5-year extension of the PREMIER study, where comprehensive disease remission was defined by a set of criteria, including DAS28 remission, HAQ ≤ 0.5, and radiographic nonprogression (ΔSvdH ≤ 0.5)[22]. However, because RA is a chronic and dynamic disease, we found it more relevant to study the clinical outcomes during the whole followup period and not only at

Table 3. Measures of disease activity at 3 and 6 months of the initially aggressively treated patients with early rheumatoid arthritis sorted according to the number of criteria of treatment failure fulfilled at 5 years. For statistical significance, the crude value and the value adjusted by baseline age, sex, and seropositivity for rheumatoid factor are presented. Values are mean (± SD) unless otherwise specified.

Characteristics	No. Criteria			p*	
	0, n = 45	1, n = 30	2–4, n = 18	Crude	Adjusted
Measures of disease activity at 3 mos					
No. swollen joints	1 (2)	1 (2)	4 (4)	0.007	0.004
No. tender joints	2 (4)	3 (3)	6 (5)	0.015	0.007
C-reactive protein, mg/l	5 (11)	3 (3)	11 (14)	0.25	0.20
Erythrocyte sedimentation rate, mm/h	10 (13)	6 (4)	12 (15)	0.79	0.65
Patient's global assessment, VAS, mm	7 (9)	8 (13)	22 (23)	0.006	0.006
Patient's assessment of pain, VAS, mm	6 (9)	6 (9)	25 (26)	0.005	0.004
Physician's global assessment, VAS, mm	5 (8)	7 (8)	19 (16)	0.001	< 0.001
Physical function, HAQ	0.07 (0.14)	0.05 (0.19)	0.36 (0.36)	0.002	0.001
Disease Activity Score at 28 joints at 3 mos	1.77 (1.02)	1.82 (0.82)	2.78 (1.06)	0.001	< 0.001
Patients in strict NEO-RACo remission, n (%)	18 (40)	12 (40)	1 (6)	0.016	0.014
Patients in ACR/EULAR Boolean remission, n (%)	25 (56)	14 (47)	1 (6)	< 0.001	< 0.001
Measures of disease activity at 6 mos					
No. swollen joints	0 (0)	0 (0)	1 (2)	0.006	0.005
No. tender joints	1 (2)	1 (1)	3 (4)	0.026	0.020
C-reactive protein, mg/l	4 (5)	4 (3)	6 (7)	0.17	0.20
Erythrocyte sedimentation rate, mm/h	8 (11)	5 (3)	11 (12)	0.51	0.49
Patient's global assessment, VAS, mm	5 (13)	4 (7)	19 (22)	0.029	0.026
Patient's assessment of pain, VAS, mm	6 (14)	3 (5)	18 (24)	0.073	0.068
Physician's global assessment, VAS, mm	2 (5)	2 (3)	10 (12)	0.008	0.007
Physical function, HAQ	0.04 (0.11)	0.01 (0.03)	0.28 (0.33)	0.006	0.006
DAS28 at 6 mos	1.33 (1.75)	1.21 (0.55)	2.25 (1.37)	0.014	0.009
Patients in strict NEO-RACo remission, n (%)	30 (67)	17 (57)	3 (17)	< 0.001	0.001
Patients in ACR/EULAR Boolean remission, n (%)	33 (73)	23 (77)	5 (28)	0.004	0.007

*p for linearity. VAS: visual analog scale; HAQ: Health Assessment Questionnaire; NEO-RACo: The Finnish Rheumatoid Arthritis Combination Therapy Trial with infliximab added for 6 months; ACR: American College of Rheumatology; EULAR: European League Against Rheumatism; DAS28: 28-joint Disease Activity Score.

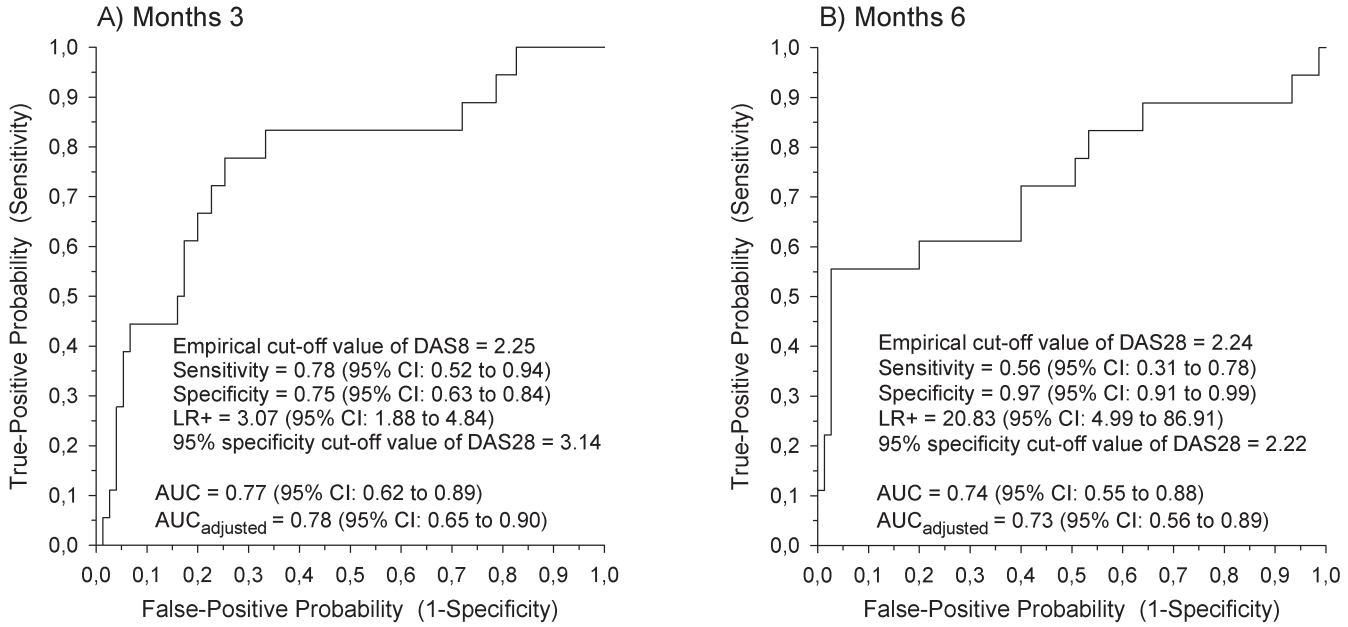

Figure 2. ROC for the probability of consequent treatment failure after 5 years of rheumatoid arthritis for DAS28 at (A) 3 months, and (B) 6 months. AUC was adjusted for baseline age, sex, and seropositivity for rheumatoid factor. ROC: receiver-operated curve; DAS28: 28-joint Disease Activity Score; AUC: area under the curve.

a seemingly random cross-sectional timepoint of 5 years. Therefore, to represent the sustainability of the DAS28 remission and the HAQ ≤ 0.5, we used the AUC 6–60 with the same limits for these 2 variables. As for the radiographic criterion, we found ΔSvdH ≤ 0.5 to be clinically an irrelevant limit to represent the true watershed of radiographic progression[23]. Therefore, we set the limit at ΔSvdH > 3 during 5 years, which we found to best differentiate the patients with progressive damage from those without. As the fourth criterion, we included a clinically relevant approach, the need to intensify the treatment, and here in particular the need to start a bDMARD or the failure to taper down or the need to reinstitute systemic GC.

We consider these 4 criteria of treatment failure relevant and rather strict, but realistic to overcome with aggressive treatment. Therefore, it was reassuring to ascertain that almost half of our patients had no features, and only one-fifth had 2 or more. Even though the criteria are not identical, our results are better than those of the 5-year extension of the PREMIER study, where 35% of the patients treated initially with a combination of MTX and adalimumab, and after 2 years with adalimumab and optional MTX, met their criteria of comprehensive disease remission at 5 years[22].

In our further analyses, we set the limit of true treatment failure at fulfilling 2 or more of the criteria. Even with the most effective treatments of RA, we are still pursuing the induction and maintenance of remission, not "curing" the disease. Consequently, if the treatment needs to be modified because of increased disease activity, and this is done appropriately enough to induce remission and to prevent radiographic damage or compromised function, the strategy can be considered successful. Accordingly, in our current study, the most common single feature of treatment failure was the need for treatment intensification, and no patient had the DAS28-AUC 6–60 above the remission limit as the sole feature of treatment failure.

When studying the predictive factors for identifying such patients, none of the baseline factors performed well. This is in accordance with the clinical experience, as well as with the results of other investigators[24]. Nevertheless, the HAQ score at baseline significantly predicted the consequent true treatment failure, underlining the role of feasible, patient-reported outcomes even at the time of the diagnosis. Further, the physician's assessment tended to have predictive value as well. This clinical experience is, however, hard to objectively define and time-consuming to tutor and learn. Still, at 3 and 6 months, all the clinical outcome measures were worse in the patients having subsequent true treatment failure than in the patients having no or just 1 such feature. These findings are in accordance with those of others, even though our criteria of treatment failure are much stricter[25]. Still, notably, all measures of disease activity were very low, and even our patients with true treatment failure at 5 years had the mean DAS28 at 6 months below the remission limit.

Unfortunately, we were unable to provide infallible cutoff values with a definite sensitivity and specificity for the prediction of the patients failing the intensified FIN-RACo regimen. Thus, the recognition of these patients remains on the dependence on the early clinical intuition of the treating rheumatologist, and on the unsatisfactory treatment response by 3, and at the latest by 6, months. A rough conclusion could be that patients having more than 1 swollen joint and all the VAS assessments above 20 mm at 3 months are likely to subsequently fail the treatment, while the patients in strict NEO-RACo remission at that point can be considered protected. Undeniably, for patients having the DAS28 > 2.24 at 6 months, another treatment approach should be considered.

In our trial, the initial IFX treatment did not improve clinical outcomes[4] or further reduce the low risk of longterm treatment failure. In that respect, the sometimes suggested use of bDMARD as first-line treatment is not justified, especially because our study proves that no certain features of poor prognosis may be identified at baseline. Also, others have shown that initial IFX is not superior to intravenous GC combined with MTX[26]. However, it remains to be solved by future trials whether some patients now failing the treatment would benefit from other sDMARD, an available initial bDMARD treatment other than IFX, or new emerging therapies. To date, because of the lack of biomarkers, early clinical treatment response is our best tool to find the patients in whom another approach should be tested. It is to be hoped that some day, biomarker-based, tailored therapies will become a reality[27,28].

The main limitation of our trial was the small study population size. However, 94% of the patients continued in the followup for 5 years, which increased the credibility of our results markedly. Another common contemporary limitation was that the study patients have more severe disease and fewer comorbidities than the real-life patients in the clinic[29]. Therefore, it is possible that the aggressive treatment in this trial is seldom necessary for patients with a "milder" RA, emphasizing especially the protracted use of systemic GC.

Our study proved that only 20% of the initially aggressively treated patients with RA fail the treatment in the long term, even though very strict definitions for treatment failure are used. Moderate residual disease activity at 3 and 6 months helps identify these patients so that in clinical practice, a modified treatment strategy may be applied to them.

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