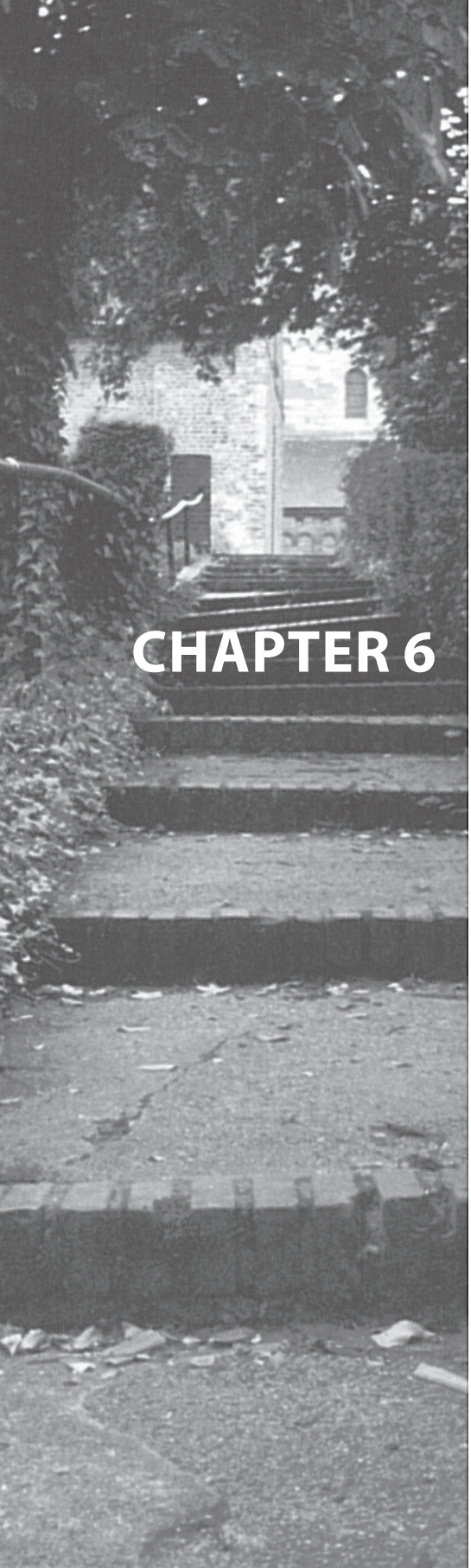

CHAPTER 6

Determinants of drug free remission in patients with early rheumatoid or undifferentiated arthritis after one year of remission steered treatment

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Submitted

ABSTRACT

Objective

To assess if baseline characteristics in patients with undifferentiated or early rheumatoid arthritis affect the possibility to achieve drug free remission after one year (DFR_{1year}) of early remission induction therapy.

Methods

We included 375 patients participating in the IMPROVED study, who achieved remission (DAS<1.6) after four months (early remission) and were by protocol able to achieve DFR_{1year}. Having started with methotrexate (MTX) plus prednisone, patients tapered prednisone to zero after 4 months. After 8 months, those still in remission tapered MTX to zero, while those not restarted prednisone. Characteristics of patients achieving and not achieving DFR_{1year} were compared. Logistic regression was performed to identify predictors of DFR_{1year}.

Results

After one year, 119 patients (32%) were in DFR. Presence of Rheumatoid Factor (RF), fulfilling the 2010 criteria for RA and a low tender joint count were associated with achieving $DFR_{1year,}$ whereas presence of ACPA was not. None of the baseline characteristics were independently associated with $DFR_{1year.}$ DFR_{1year} was sustained for 4 months in 65% patients. ACPA positive patients less often had sustained DFR than ACPA negative patients (58% versus 80%, p=0.013).

Conclusions

After 1 year of remission steered treatment, 32% of the patients who had achieved early remission after 4 months, were able to taper medication and achieved DFR. Neither presence of ACPA nor other baseline characteristics were independently associated with achieving DFR after 1 year but in ACPA positive patients DFR was less often sustained.

INTRODUCTION

With the current treatment strategies, remission has become a realistic goal in patients with rheumatoid arthritis (RA).[1-3] It remains to be seen whether achieving drug free remission (DFR) after tapering medication is also a realistic goal. In recent cohort studies and clinical trials in patients with RA, DFR rates vary between 17 and 29% [4-6] and DFR was sustained for 1-4 years in 9-16%.[4-7] Previously reported independent predictors for sustained DFR are absence of Anti-Citrullinated Protein Antibodies (ACPA), Rheumatoid Factor (RF) and shared epitope, short symptom duration and low disease activity until remission.[6,7]

In the IMPROVED study, patients with recent onset RA or undifferentiated arthritis (UA) clinically suspected for RA received initial treatment with a combination of MTX and a tapered high dose of prednisone. If remission (DAS <1.6) was achieved after 4 months, medication was stepwise tapered until DFR could be achieved already after 1 year (DFR_{1year}).

We previously reported that 61% of the patients achieved early remission after 4 months. Surprisingly, these patients were more often ACPA positive than the patients who did not achieve early remission.[8] Here, we aimed to assess whether ACPA status also influenced the likelihood to achieve DFR_{1year} and to identify possible other determinants of achieving DFR_{1year}.

METHODS

Patients, study design and outcomes

IMPROVED is a multi-center clinical trial in 122 patients with undifferentiated arthritis (UA) and 479 patients with recent onset rheumatoid arthritis (RA, 2010 criteria), treated according to a tight controlled, remission (DAS <1.6[9]) steered protocol. Details on in- and exclusion criteria were previously published.[10] Initially, all patients were treated with MTX 25 mg/week plus prednisone 60 mg/day tapered in 7 weeks to 7.5 mg/day, continued up to 4 months. Patients not in remission after 4 months by protocol could not achieve DFR_{1year} because they had to take additional treatment steps before tapering was possible, and thus were left out of the current analysis. Patients who achieved remission after 4 months (early remission) first tapered prednisone to zero in 4 weeks and, if still in remission after 8 months, also tapered MTX to zero in 2 months. Patients who lost remission while still on MTX restarted prednisone and patients who already discontinued MTX restarted MTX. DFR_{1year} was defined as having a DAS<1.6 from 4 months to 1 year while both prednisone and methotrexate (MTX) were subsequently tapered and stopped. Because DFR_{1year} was only achieved about 2 months before the end of year 1, we included 16 months follow up data to see if DFR could be sustained. Details on study protocol and scoring methods were previously published.[11]

Statistical analysis

Clinical, radiological and laboratory variables during the first year were compared between patients achieving and not achieving DFR_{1year} using the students T test, Mann Whitney U test and Chi Square test. All available baseline clinical, demographic and laboratory characteristics were entered as covariates in univariate logistic regression analyses, with DFR_{1year} as binomial dependent variable. Using a significance level of 0.10, univariate significant variables were entered in a multivariate model to identify independent predictors.

RESULTS

After 4 months, 375 (61%) patients achieved early remission, of which 291 (78%) fulfilled the 2010 classification criteria for RA. Compared to patients not in early remission, patients in early remission had lower mean baseline DAS and HAQ levels, more were ACPA positive and fewer were female.[8] After one year, 119 (32%) patients were in DFR and 245 (65%) were not, although 138 (56%) of those were in remission but on medication. Eleven patients had insufficient data. Whether patients fulfilled the 1987 [12] and/or the 2010 classification criteria for RA [10] did not significantly affect the DFR_{1year} rate (DFR_{1year} was achieved by 51 (28%) patients who fulfilled both classification criteria, 33 (34%) who fulfilled the 2010 but not the 1987 criteria and 21 (37%) who fulfilled neither (p=0.4)). Similar proportions of patients in DFR_{1year} and not in DFR_{1year} were ACPA positive (66 (55%) versus 150 (61%) respectively, p=0.2). There were no differences in baseline DAS, symptom duration and percentage of females between patients in and not in $DFR_{1year.}$ Patients in DFR_{1year} were more often RF negative, and after 4 months as well as after 1 year, they had lower mean DAS and HAQ values than patients not in $DFR_{1year.}$ (table 1)

Results of the univariate regression analyses are shown in table 2. Baseline DAS and HAQ values, ACPA status, age, male sex and symptom duration were not associated with achieving DFR_{1year}. RF positivity, high baseline TJC and fulfilling the 2010 criteria for RA were predictive for less often achieving DFR_{1year}. In a multivariate regression model none of these variables were independently predictive for less often achieving DFR_{1year} (adjusted OR (95%CI) RF positivity 0.6 (0.4-1.1), baseline TJC 0.9 (0.9-1.0), fulfilling the 2010 criteria for RA 0.9 (0.5-1.8)). After leaving out the least significant variable, fulfilling the 2010 criteria for RA (p=0.8), odds ratio's did not change importantly, although RF positivity adjusted for TJC was significantly predictive for less often achieving DFR_{1year} (data not shown).

Seventy seven (65%) patients in DFR_{1year} were still in DFR after 16 months (DFR_{16mo}), 36 (30%) were not and 6 patients had missing data. Those who lost remission were more often ACPA positive than those who sustained DFR (26 (72%) versus 36 (47%), p=0.01), and ACPA positive patients less often sustained remission than ACPA negative patients (36 (58%) versus 40 (80%), p=0.013). Regardless of achieving DFR_{1year}, 107 (29%) patients achieved DFR_{16mo}. Patients in DFR_{16mo} were less often ACPA positive than those not in DFR_{16mo} (47 (44%) versus 159 (67%), p<0.001).(figure 1)

Table 1: Baseline characteristics and clinical outcomes of patients who are and are not in drug free remission after one year.

	DFR_{1year} N= 119	No DFR_{1year} N= 245	p-value
Baseline			
DAS	2.9±0.9	3.0±0.8	0.3
Swollen joint count	4 (2-10)	5 (3-9)	0.2
Tender joint count	5 (3-8)	6 (4-8)	0.1
VAS global health, mm	41±25	43±24	0.3
ESR mm/hr	21 (11-36)	24 (10-38)	0.5
HAQ	1.0±0.7	1.0±0.6	0.5
Age, years	52±13	51±14	0.5
Symptom duration, weeks	16 (8-30)	17 (9-32)	0.4
Female	67 (56)	158 (64)	0.1
RF positive	60 (50)	152 (62)	0.03
ACPA positive	66 (55)	150 (61)	0.2
Diagnosis RA(2010)	87 (74)	196 (80)	0.1
Diagnosis RA(1987)	61 (51)	138 (56)	0.4
SHS total score	0 (0-1)	0 (0-0)	0.08
Erosive	20 (17)	31 (13)	0.3
4 months follow up			
DAS	0.8±0.4	1.0±0.4	<0.001
Swollen joint count	0 (0-0)	0 (0-0)	0.3
Tender joint count	0 (0-1)	0 (0-1)	0.07
VAS global health, mm	12±14	15±13	0.1
ESR mm/hr	6 (2-11)	7 (4-13)	0.08
HAQ	0.2±0.3	0.3±0.3	0.006
ACR/EULAR remission	57 (48)	86 (35)	0.006
1 year follow up			
DAS	0.9±0.4	1.5±0.8	<0.001
Swollen joint count	0 (0-0)	0 (0-2)	<0.001
Tender joint count	0 (0-0.5)	1 (0-3)	<0.001
VAS global health, mm	12±15	25±22	<0.001
ESR mm/hr	6 (3-11)	9 (4-18)	0.01
HAQ	0.2±0.3	0.5±0.5	<0.001
DAS-remission	119 (100)	138 (56)	<0.001
ACR/EULAR remission	64 (54)	54 (22)	<0.001

Data are presented as means ± standard deviations (SD), medians and interquartile ranges (IQR), or numbers and percentages (%) when appropriate. Eleven patients had missing data after 1 year.
ACPA, anti-citrullinated protein antibodies; ACR/EULAR remission, remission according to the Boolean based ACR/EULAR provisional remission definition, based on 44 joint counts; $DFR_{1year,}$ drug free remission defined as DAS<1.6 and all medication tapered after 1 year; DAS, disease activity score; Erosive, number of patients having one or more erosions; DAS-remission, defined as a DAS<1.6; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; RA(2010), Rheumatoid Arthritis according to the 2010 ACR/EULAR classification criteria, RA(1987), RA according to the 1987 ACR classification criteria; SHS harp-van der Heijde score; RF, rheumatoid factor;VAS, visual analogue scale.

Table 2: Univariate logistic regression analyses with drug free remission after 1 year (yes/no) as dependent variable.

Baseline characteristics	Crude OR	95%CI	p-value
Age, years	1.0	0.99-1.0	0.3
Male sex	1.4	0.9-2.2	0.13
DAS	0.8	0.6-1.0	0.10
HAQ	0.9	0.6-1.2	0.5
TJC	0.9	0.9-1.0	0.08
SJC	0.99	0.95-1.0	0.6
ESR, mm/hr	0.996	0.99-1.0	0.4
Symptom duration, weeks	0.997	0.99-1.0	0.6
ACPA positivity	0.7	0.5-1.2	0.2
RF positivity	0.6	0.4-0.96	0.03
Diagnosis RA(2010)	0.6	0.4-1.1	0.099

ACPA, anti-citrullinated protein antibodies; 95% CI, 95% confidence interval; DAS, baseline disease activity score; ESR, baseline erythrocyte sedimentation rate (mm/hr); HAQ, baseline health assessment questionnaire; OR, odds ratio; RA(2010), rheumatoid arthritis according to the 2010 ACR/EULAR classification criteria; RF, rheumatoid factor; SJC, baseline swollen joint count; TJC, baseline tender joint count.

DISCUSSION

In the IMPROVED study, 32% of the early arthritis patients who had achieved remission after 4 months, were able to maintain remission and taper all medication to drug free remission after 1 year (DFR_{1year}), regardless of fulfilling the 1987 and/or 2010 classification criteria for RA at study entrance. Baseline characteristics in the past associated with chronic and/or progressive disease, such as a positive RF and fulfilling criteria for RA, were associated with less often achieving DFR_{1year}, although not independently of each other. Also a high tender joint count at baseline was, non-independently, associated with less often achieving DFR_{1year}. ACPA status and symptom duration were not associated with DFR_{1year}. In 65% of patients in DFR_{1year}, DFR was sustained for 4 more months. Although DFR was achieved in ACPA positive patients as often as in ACPA negative patients, ACPA positive patients less often sustained in DFR than ACPA negative patients.

To our knowledge, IMPROVED is the first study in which DFR was a treatment goal. A DFR rate of 32% after 1 year is probably high, although 29% of the total IMPROVED population did not achieve early remission after 4 months and by protocol were not able to achieve DFR already after 1 year.

Given the fact that we included both RA and UA patients, clinically suspected to have RA but not fulfilling the criteria, we may have included and treated patients who might have remitted spontaneously. This was a reason why we introduced a rapid drug tapering scheme in our protocol. However, if the 32% mainly represented non-chronic types of arthritis, one

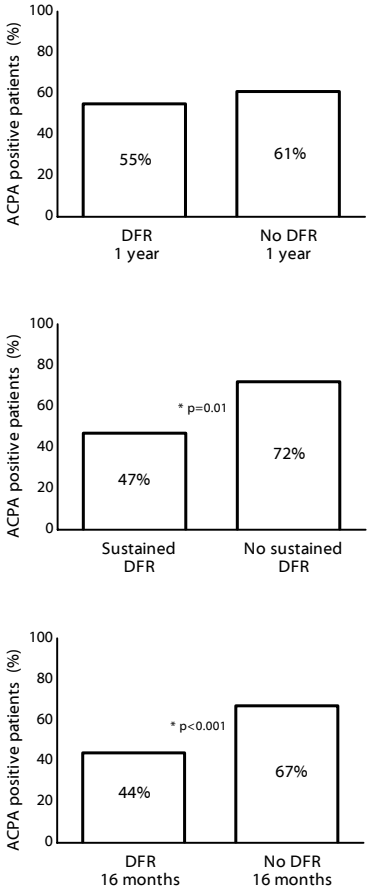

Figure 1: Percentages ACPA positive patients achieving drug free remission after 1 year versus not, sustaining drug free remission up to 16 months versus not and achieving drug free remission after 16 months versus not.
ACPA, anti-citrullinated protein antibodies; DFR 1 year, drug free remission after 1 year; DFR 16 months, patients in DFR after 16 months, regardless of being in DFR after 1 year; Sustained DFR, patients in DFR after 1 year and after 16 months.

would expect that these patients more often were auto-antibody negative, possibly had shorter disease duration or less often fulfilled the criteria sets for RA than patients not achieving DFR, which was not the case.

Interestingly, presence of ACPA was not associated with less DFR_{1year}. Previously we reported that presence of ACPA was associated with achieving more remission after 4 months in the IMPROVED study,[8] which was in contrast with previous data indicating that presence of ACPA is associated with a less favorable disease course.[13,14] In a study comparing DFR in the Leiden Early Arthritis Clinic and the BeSt study, absence rather than presence of ACPA was an independent predictor of sustained DFR.[7] That ACPA positive patients achieve DFR_{1year} in

similar numbers as ACPA negative patients may be explained both by the initial combination with MTX and prednisone and the early remission steered treatment in the IMPROVED study.

However, after treatment was stopped 30% of patients lost remission and had to restart medication within 4 months after achieving DFR, and ACPA positive patients more often lost DFR than ACPA negative patients. This suggests that compared to ACPA negative patients, ACPA positive patients have a similar likelihood of achieving and maintaining remission, even while medication is tapered. But after having successfully tapered and discontinued medication, ACPA positive patients show more relapses in disease activity in the next 4 months, and this may even increase with follow up. Reasons why sustained DFR was achieved less often in ACPA positive patients may be that we have tapered medication too soon or too fast or have not used the optimal initial treatment within the optimal time frame. In the future we will also be able to see which patients who did not achieved early remission after 4 months, may achieve late DFR in the randomization arms and whether this is sustained over time.

In conclusion, 32% of patients with early arthritis who achieved remission after 4 months of initial combination therapy can taper medication until DFR is achieved after one year. Achieving DFR is possible regardless of ACPA status or other baseline disease characteristics, but DFR is sustained less often in ACPA positive than in ACPA negative patients.

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