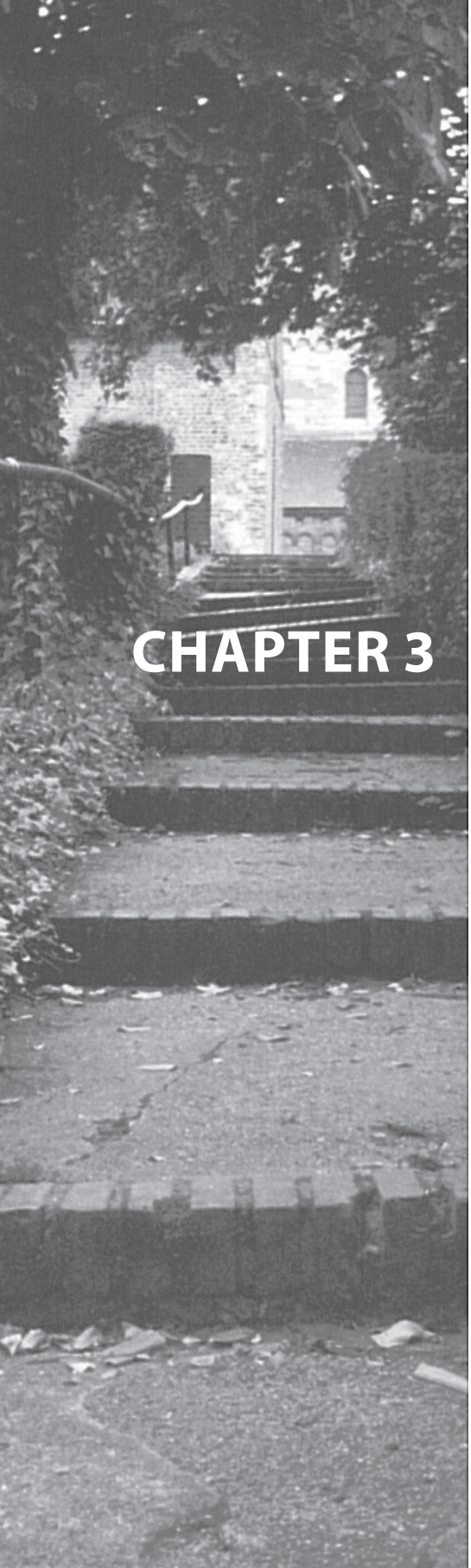

CHAPTER 3

Remission Induction Therapy with Methotrexate and Prednisone in patients with Early Rheumatoid and Undifferentiated Arthritis (the IMPROVED study)

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ABSTRACT

Objective

Classifying more patients as rheumatoid arthritis (2010 ACR/EULAR criteria for RA) may improve treatment outcomes but may cause overtreatment in daily practice. We determined the efficacy of initial methotrexate (MTX) plus prednisone treatment in patients with 1987 or 2010 classified RA and undifferentiated arthritis (UA).

Methods

Six-hundred-ten patients with recent onset RA or UA started with MTX 25 mg/week and prednisone 60 mg/day tapered to 7.5 mg/day in 7 weeks. Percentages remission after 4 months were compared between RA (1987 or 2010 criteria) and UA. Predictors for remission were identified.

Results

With the 2010 criteria 19% more patients were classified as RA than with the 1987 criteria, but similar remission rates were achieved: 291/479 (61%) 2010 classified RA and 211/365 (58%) 1987 classified RA patients ($p=0.52$), and 79/122 (65%) UA ($p=0.46$). ACPA positive RA patients achieved more remission (66%) than ACPA negative RA patients (51%, $p=0.001$), but also had a lower mean baseline DAS (3.2 versus 3.6, $p<0.001$). ACPA negative RA patients who achieved remission had a shorter median symptom duration. Independent predictors for remission were male sex, low joint counts, DAS and HAQ, low Body Mass Index (BMI) and ACPA positivity.

Conclusions

Initial treatment with MTX and a tapered high dose of prednisone results in similarly high remission percentages after four months (about 60%) in RA patients, regardless of fulfilling the 1987 or 2010 criteria, and UA patients. Independent predictors indicate that initiating treatment while disease activity is relatively low results in more remission.

INTRODUCTION

Starting treatment earlier in the disease course of Rheumatoid Arthritis (RA) has improved functional and radiological outcome as compared to delayed treatment.[1-6] New RA classification criteria support this trend,[7] but have triggered concerns that some patients may now be misclassified and overtreated as a result.[8]

Remission has increasingly become a treatment goal in clinical trials, resulting in remission rates that vary between 26% and 42%.[9]

It is hypothesized that starting treatment already in the phase of Undifferentiated Arthritis (UA) may prevent progression to classified RA and increase permanent remission rates. However, methotrexate (MTX) monotherapy for patients with probable RA postponed but did not prevent progression to RA. Similar drug free remission rates (about 25%) were achieved in the MTX group and the placebo group.[10]

Since in RA initial combination treatment with prednisone leads to a more rapid clinical improvement and less radiological progression of joint damage than disease modifying anti-rheumatic drugs (DMARD) monotherapy,[3,11-14] treatment with combination possibly in the phase of UA may increase remission and drug free remission rates, as well as improve short-term functional outcome and long-term joint damage progression.

To investigate this, we designed the IMPROVED (Induction therapy with Methotrexate and Prednisone in Rheumatoid Or Very Early arthritic Disease) study, the first clinical trial in patients with UA and early RA, with an induction phase with MTX and a tapered high dose of prednisone, aimed at achieving remission. This trial allowed us to evaluate the effect of classifying patient groups according to the old and the new RA classification criteria and to identify predictors of remission.

METHODS

Study design

The IMPROVED-study is a multicenter, clinical trial in recent onset RA and UA patients. All patients were initially treated for four months with MTX 25 mg/week and a tapered high dose of prednisone, starting with 60 mg/day, tapered in 7 weeks to 7.5 mg/day, continued in this dose up to four months. Later, this introduction phase will be followed by a single blind randomized controlled trial, where those patients who did not achieve remission will be treated according to two treatment strategies; one starting with a combination of MTX, sulfasalazine, hydroxychloroquine and low dose prednisone, the other with a combination of MTX with adalimumab.

Rheumatologists participating in the Foundation for Applied Rheumatology Research (FARR) designed and conducted the study. Patients were recruited between March 2007 and

September 2010 in 12 hospitals in the Western part of the Netherlands. The Medical Ethics Committee of each participating centre approved the study protocol and all patients gave written informed consent. The IMPROVED trial was registered in the ISRCTN Register (number 11916566) and the EudraCT (number 2006-006186-16).

Patients

Patients with RA classified according to the 1987 American College of Rheumatology (ACR) criteria [15] with a symptom duration of < 2 years and UA, defined as likely to have early RA according to the treating rheumatologist, with at least one arthritic joint and one other painful joint, regardless of symptom duration, were included in the trial. All patients had a disease activity score (DAS) ≥1.6.[16]

Exclusion criteria included previous therapy with DMARDs or corticosteroids, pregnancy or pregnancy wish during the study, malignancy within the last five years, bone marrow hypoplasia, elevated liver enzyme levels (alanine transaminase (AST) and/or aspartate transaminase (ALT) >3 times normal value), serum creatinine level >150 umol/l or estimated creatinine clearance of <75%, uncontrolled diabetes mellitus, uncontrolled hypertension, heart failure (NYHA class III/IV), alcohol or drug abuse, serious infections in the previous 3 months or chronic infectious disease, opportunistic infections within previous 2 months, active or latent hepatitis B infection, documented HIV infection or AIDS, lymphoproliferative disease and multiple sclerosis. All patients with active tuberculosis (TB) were excluded, as well as UA patients with latent TB. RA patients with latent TB could be included if they started adequate anti-tuberculous therapy (according to local TB specialists) prior to initiation of high dose prednisone.

Reclassification according to the 2010 ACR/EULAR classification criteria

After inclusion was complete the new classification criteria were published. Unless specified otherwise (by adding the year of classification criteria between brackets), 'RA' in the text denotes RA classified according to the 2010 criteria, and 'UA' denotes not fulfilling the 2010 criteria.

Outcomes

Primary outcomes after four months were percentage clinical remission, defined as a DAS <1.6,[16] disease activity measured by DAS, functional ability measured by the Health Assessment Questionnaire (HAQ)[17] and radiological progression using the Sharp/van der Heijde scoring method (SHS).[18]

Radiological damage was assessed by two independent readers using SHS, blinded for patient identity and time order of the radiographs.[18] Progression was defined as an increase in SHS score of ≥0.5 points. Due to the small distribution of SHS scores, caused by a large proportion of patients without progression, the inter-observer and intra-observer intraclass

correlation coefficients (ICC) were not suitable for measuring reliability.[19] In 91.5% of patients both readers scored the same progression. In the others, the median (IQR) difference in progression score between readers was 2 (2-3). A consensus score was reached for radiographs with inter-reader differences ≥ median difference in progression score (n=41).

Percentages remission according to ACR/EULAR preliminary definition [20] were compared with percentages remission based on the DAS.

Statistical analysis

All outcomes were calculated according to the intention-to-treat (ITT) principle. Percentages remission in the RA and the UA group were compared using Chi-square test. Categorical variables were compared between groups using Chi-square test, normally distributed outcome measures using Independent Samples t-test and skewed outcome measures using Mann-Whitney U-test.

Independent predictors for remission were identified using univariate followed by multivariate logistic regression with achieving or not achieving remission as binominal dependent variable. All available clinical variables were entered in a univariate regression analysis. Using a P-value <0.10, significant variables were then entered in the multivariate regression analysis.

RESULTS

Study profile

Between March, 2007 and September, 2010, 730 patients signed informed consent and were screened for inclusion.(figure 1) We included 610 patients; 364 RA patients (1987 classification criteria) or 479 RA patients (2010 classification criteria) and 122 UA patients (i.e. not fulfilling the 2010 classification criteria).(table 1)

During 4 months 12 patients left the trial: 2 patients because of a revised diagnosis (1 osteoarthritis, 1 lupus), 2 because of comorbidity, 6 withdrew consent and 2 died.(figure 1)

Table 1: Classification of patients according to the 1987 ACR and the 2010 ACR/EULAR criteria for RA.

Inclusion 1987 criteria, no (%)	RA (1987): 364 (60%)	UA: 246 (40%)
Reclassification 2010 criteria, no (%)*	RA (2010): 479 (79%)	UA (2010): 122 (20%)
	RA (2010)	UA (2010)
RA (1987), no (%)	324/364 (89%)	34/364 (9%)
UA, no (%)	155/246 (63%)	88/246 (36%)

*9 patients could not be classified because of insufficient data.
no, number; RA (1987), RA according to the 1987 classification criteria for RA; UA, at least one swollen and one painful joint, at risk for developing RA according to the rheumatologist; RA (2010), included in trial as RA (1987) or UA, reclassified as RA according to the 2010 classification criteria for RA; UA (2010), included in trial as RA (1987) or UA, not fulfilling the 2010 classification criteria for RA.

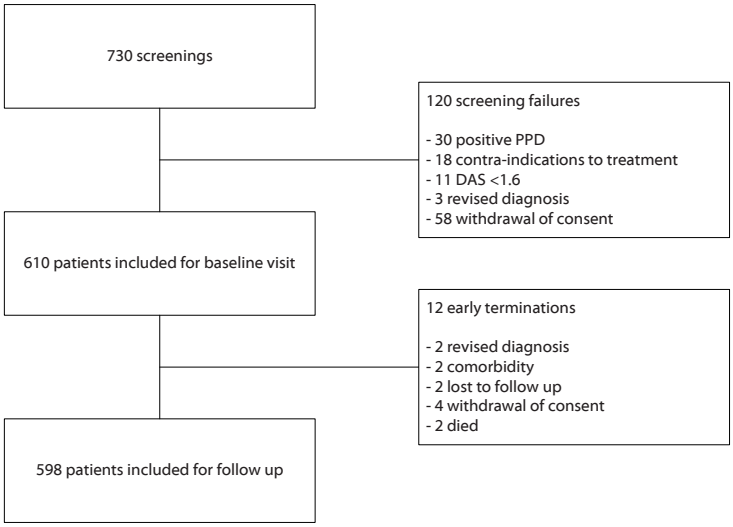

Figure 1: Flow chart of screenings failure and early terminations
PPD, purified protein derivative; DAS, disease activity score.

Baseline characteristics

RA (1987) patients had a higher mean DAS based on more affected joints, higher erythrocyte sedimentation rate (ESR) and higher serum C-reactive protein (CRP) than RA (2010) patients. UA patients included fewer females, were less often RF and ACPA positive, had lower disease activity and HAQ. There was no significant difference between RA (1987 or 2010 classified) and UA patients in baseline damage scores or erosiveness.(table 2)

After four months, DAS <1.6 was achieved in 58% of the RA (1987), 61% of the RA (2010) (p=0.52) and 65% of the UA patients (p=0.46 compared to RA 2010).

DAS improved more in the RA (2010) group than in the UA group and similar as in the RA (1987) group, resulting in comparable mean (SD) DAS levels after 4 months: 1.4 (0.9) in UA, 1.6 (0.9) in RA (1987) and 1.5 (0.9) in RA (2010) patients. Also HAQ improved more in the RA patients than the UA patients, resulting in HAQ levels of 0.44 both in UA and RA patients (p=0.96) after 4 months.

Baseline and 4 months radiographs of hands and feet were available for 546 patients. After four months, 61 patients (10%) showed radiological progression, without a difference between UA and RA patients. In those with progression the median (IQR) SHS progression was 1(1-1) points.

Patients who did not achieve remission after 4 months treatment had a higher baseline DAS, and higher DAS components, and were more often ACPA negative than patients who did achieve remission (table 3). Of the ACPA positive RA patients, 66% achieved remission compared to 51% of the ACPA negative RA patients (p=0.001). ACPA positive RA patients had

Table 2: Baseline characteristics and clinical outcomes after 4 months of patients classified as rheumatoid arthritis either by 1987 or 2010 criteria and of patients with undifferentiated arthritis.

	RA (1987)	**RA (2010)**		**UA**	
Baseline	N= 364	N= 479	P-value	N= 122	P-value*
Age, years (mean, SD)	53.5 (14)	52 (13)	0.08	52 (16)	0.90
Female, no (%)	256 (70)	333 (70)	0.8	74 (61)	0.06
Symptom duration, weeks (median, IQR)	17 (8-32)	18 (9-34)	0.25	16 (8-28)	0.14
RF positive, no (%)	245 (67)	330 (69)	0.59	5 (4)	<0.001
ACPA positive, no (%)	228 (63)	324 (68)	0.15	4 (3)	<0.001
ESR mm/hr (median, IQR)	29 (15-45)	26 (12-41)	0.04	16 (9-38)	0.01
CRP mg/l (median, IQR)	13 (6-35.5)	11 (5-28)	0.046	10 (4-24)	0.25
DAS (mean, SD)	3.50 (0.9)	3.34 (0.9)	0.02	2.70 (0.65)	<0.001
Swollen Joint Count (median, IQR)	8 (4-12)	7 (3-11)	0.02	3 (2-6)	<0.001
Tender Joint Count (median, IQR)	7 (5-11)	7 (4-10)	0.18	5 (3-8)	<0.001
HAQ (mean, SD)	1.26 (0.65)	1.19 (0.67)	0.11	1.03 (0.62)	0.02
BMI (mean, SD)	25.5 (4.1)	25.9 (4.5)	0.18	25.8 (4.0)	0.88
Total SHS (median, IQR)	0 (0-1)	0 (0-0.5)	0.33	0 (0-0.4)	0.98
Erosive, no (%)	49 (13)	60 (13)	0.62	12 (9)	0.46
4 months follow up					
DAS (mean, SD)	1.56 (0.89)	1.52 (0.89)	0.56	1.43 (0.85)	0.30
HAQ (mean, SD)	0.45 (0.51)	0.44 (0.53)	0.81	0.44 (0.51)	0.96
Improvement DAS (mean, SD)	1.93 (1.04)	1.82 (1.04)	0.11	1.26 (0.88)	<0.001
Improvement HAQ (mean, SD)	0.80 (0.64)	0.74 (0.66)	0.16	0.59 (0.61)	0.03
Total SHS (median, IQR)	0 (0-1)	0 (0-0.5)	0.37	0 (0-0)	0.85
Erosive, no (%)	48 (13)	64 (13)	0.98	11 (9)	0.22
SHS progression (median, IQR)	0 (0-0)	0 (0-0)	0.75	0 (0-0)	0.93
Remission (DAS <1.6), no (%)	211 (58)	291 (61)	0.52	79 (65)	0.46

* P-value based on difference between RA (2010) and UA (2010)

ACPA, anti-citrullinated protein antibodies; BMI, body mass index; CRP, C-reactive protein; DAS, disease activity score; erosive, defined as having ≥1 erosions; ESR, erythrocyte sedimentation rate; HAQ, health assessment questionnaire; IQR, inter quartile range; no, number; RA (1987), RA according to the 1987 classification criteria for RA; RA (2010), RA according to the 2010 classification criteria for RA; RF, rheumatoid factor; SD, standard deviation; SHS, Sharp-van der Heijde Score; UA, undifferentiated arthritis.

a lower baseline DAS (mean (SD) 3.19 (0.89)) than ACPA negative RA patients (mean (SD) 3.64 (0.94), p<0.001). ACPA negative RA patients who achieved remission had a shorter median (IQR) symptom duration (12 weeks (8-26)) than those who did not (20 weeks (10-31), p=0.02). In the whole study population, there was a trend for more remission in patients with shorter symptom duration.

The distribution of joints was different in patients with RA and UA. All RA patients had involvement of small joints (wrists, hands and feet), compared to 94% of the UA patients

Table 3: Baseline characteristics and clinical characteristics after 4 months of patients achieving remission versus patients not achieving remission.

	Remission	**No remission**	
Baseline	N=375	N=221	P-value
DAS (mean, SD)	2.99 (0.85)	3.57 (0.92)	<0.001
Swollen joint count	5 (2-9)	7 (3-12)	0.001
Tender joint count	5 (3-8)	8 (6-14)	<0.001
VAS global health, mm (mean, SD)	42 (24)	52 (21)	<0.001
ESR mm/hr (median, IQR)	23 (10-38)	25 (13-41)	0.20
HAQ (mean, SD)	1.03 (0.65)	1.37 (0.62)	<0.001
Small joints* (median, IQR)	8 (4-13)	12 (7-18)	<0.001
Large joints** (median, IQR)	1 (0-2)	2 (1-4)	<0.001
Age, years (mean, SD)	52 (14)	51 (14)	0.54
Symptom duration, weeks (median, IQR)	16 (9-30)	21 (9-37)	0.08
Female no (%)	231 (62)	172 (78)	<0.001
RF positive no (%)	219 (58)	111 (50)	0.09
ACPA positive no (%)	220 (59)	106 (48)	0.007
Diagnosis RA(2010) no (%)	291 (78)	177 (80)	0.46
BMI	25.4 (3.9)	26.6 (5.1)	0.001
4 months follow up			
DAS (mean, SD)	0.94 (0.36)	2.45 (0.65)	<0.001
Swollen joint count	0 (0-0)	1 (0-4)	<0.001
Tender joint count	0 (0-1)	4 (3-8)	<0.001
VAS global health, mm (mean, SD)	13 (14)	36 (21)	<0.001
ESR mm/hr (median, IQR)	6 (3-13)	11 (6-22)	<0.001
HAQ (mean, SD)	0.23 (0.33)	0.82 (0.59)	<0.001

*number of swollen and/or tender small joints (metacarpophalangeal joints, proximal interphalangeal joints, thumb interphalangeal joints, wrists, second through fifth metacarpophalangeal joints)
** number of swollen and/or tender large joints (shoulders, elbows, hips, knees, ankles)
ACPA, anti-citrullinated protein antibodies; BMI, body mass index; DAS, disease activity score; ESR, erythrocyte sedimentation rate; HAQ, health assessment questionnaire; IQR, inter quartile range; no, number; RF, rheumatoid factor; RA (2010), RA according to the 2010 classification criteria for RA; SD, standard deviation; VAS, visual analogue scale.

(p<0.001). Large joint (all other joints) involvement was found in similar percentages of RA and UA patients (73% versus 68%, p=0.22). Patients with large joint involvement had more affected small joints (median (IQR) 10 (6-17) versus 7 (4-11), p<0.001) and achieved less often remission than patients without large joint involvement (57% versus 76%, p<0.001).

Predictors for remission

Significant univariate clinical predictors for achieving remission in the total study population were baseline DAS, HAQ, symptom duration, male sex, ACPA positivity, number of affected

Table 4a: Univariate logistic regression analyses with remission after 4 months (yes/no) as dependent variable.

Univariate regression	Odds ratio	95% CI
Classified RA (2010)	0.85	0.56 - 1.30
Baseline DAS	0.49	0.40 - 0.60
Baseline HAQ	0.43	0.33 - 0.57
Small joints*	0.93	0.90 - 0.95
Large joints**	0.72	0.65 - 0.79
Symptom duration (weeks)	0.99	0.99 - 1.00
ACPA positivity	1.59	1.14 - 2.23
Age (years)	1.00	0.99 - 1.02
Male sex	2.19	1.50 - 3.20
BMI (kg/m^2)	0.94	0.90 - 0.98

*number of swollen and/or tender small joints (metacarpophalangeal joints, proximal interphalangeal joints, thumb interphalangeal joints, wrists, second through fifth metacarpophalangeal joints)
** number of swollen and/or tender large joints (shoulders, elbows, hips, knees, ankles)
BMI, body mass index; CI, confidence interval; DAS, disease activity score; HAQ, health assessment questionnaire; RA (2010), RA according to the 2010 ACR/EULAR classification criteria.

Table 4b: Multivariate logistic regression analyses with remission after 4 months (yes/no) as dependent variable.

Multivariate regression	Analysis with DAS		Analysis with small and large joints	
	Odds ratio	95% CI	Odds ratio	95% CI
Baseline DAS	0.61	0.47-0.78	-	-
Small joints*	-	-	0.96	0.93-0.99
Large joints**	-	-	0.81	0.72-0.90
Baseline HAQ	0.66	0.46-0.94	0.63	0.46-0.88
Symptom duration (weeks)	0.99	0.98-0.997	0.99	0.98-0.997
ACPA positivity	1.59	1.09-2.33	1.44	0.98-2.12
Male sex	2.03	1.34-3.08	2.01	1.32-3.07
BMI (kg/m^2)	0.94	0.90-0.98	0.94	0.90-0.98

*number of swollen and/or tender small joints (metacarpophalangeal joints, proximal interphalangeal joints, thumb interphalangeal joints, wrists, second through fifth metacarpophalangeal joints)
** number of swollen and/or tender large joints (shoulders, elbows, hips, knees, ankles)
ACPA, anti-citrullinated protein antibodies; BMI, body mass index; CI, confidence interval; DAS, disease activity score; HAQ, health assessment questionnaire.

small joints, number of affected large joints and body mass index (BMI).(table 4) Fulfilling the 1987 or 2010 classification criteria for RA was not a predictor of remission. In a multivariate regression analysis including baseline DAS and excluding number of affected small and large joints, independent predictors were baseline DAS, HAQ, symptom duration, ACPA positivity, male sex and BMI. In a model including the baseline numbers of affected small and large

joints instead of the DAS, the number of affected small and large joints were both predictive, independently of each other. In this analysis, ACPA positivity was not an independent predictor.(table 4)

ACR/EULAR preliminary definition of remission

According to the preliminary ACR/EULAR definition [20] 157/610 (26%) of the patients achieved remission after four months (34 patients could not be defined because of missing data), without a difference between UA and RA patients (29/122 (24%) versus 126/479 (26%), p=0.45).

Mean (SD) DAS after four months of patients in ACR/EULAR remission is 0.82 (0.41).

206/610 (34%) patients did achieve DAS remission but were not in ACR/EULAR remission. They had a median (IQR) TJC of 0 (0-1), a median (IQR) SJC of 0 (0-0), a median (IQR) CRP of 5 (3-9) and a mean (SD) VAS general health of 21(14).

Table 5: Numbers of adverse events reported during 4 months of treatment with MTX and a tapered high dose of prednisone.

Numbers of adverse events	
Gastro-intestinal symptoms	98
Nausea	47/98
Liver enzyme elevations	45
Infectious	80
Upper airway tract	26/80
Gastro-intestinal	18/80
Skin/mucosa infection	8/80
Pneumonia	9/80
Urinary tract infection	7/80
Influenza/fever	7/80
Skin/mucosa	75
Hair loss	19/75
Rash	16/75
Stomatitis	9/75
Central Nervous System	73
Headache	18/73
Dizziness	11/73
Mood disorders	21/73
Cardiovascular	45
Hypertension	20/45
Metabolic	21
Pulmonary	21
Urogenital	8
Hematologic	5

152/610 (25%) patients achieved remission by both criteria, 201/610 (33%) did not achieve remission according to either and 5/610 (0.8%) patients were in ACR/EULAR remission but not DAS remission, based on arthritis in the feet (not included in the ACR/EULAR remission definition).

The data suggest that the ACR/EULAR definition of remission is more stringent than DAS-remission, resulting in lower remission percentages. Clinical and radiological follow-up is needed to show which definition is most adequate.

Adverse events

During 4 months of treatment 341/610 (56%) of the patients reported one or more adverse events (table 5). There were 16 serious adverse events in 16 (3%) of 610 patients (8 per 100 patient years). Two patients died: a 70 year old female from a myocardial infarction later found to be caused by giant cell arteriitis (incorrect inclusion due to alternative diagnosis), and an 85 year old female after refusing treatment for pneumonia. Fourteen hospital admissions were reported for patients with bacterial coxarthritis, Pneumocystis Carinii Pneumonia (a patient with pre-existing Non-Specific Interstitial Pneumonia), other pneumonia (3 patients), viral pneumonitis, urothelial cell carcinoma, surgery for carcinoma of the cecum, diverticulitis, bleeding from a benign intestinal polyp, supraventricular tachycardia, hypertension, peripheral arterial occlusion and pulmonary embolism.

DISCUSSION

Initial treatment with MTX and a tapered high dose of prednisone results in similar remission rates in 2010 classified and 1987 classified RA patients and in UA patients after four months. The majority (90%) of the patients showed no radiological progression after four months. Independent predictors for remission were low baseline DAS, low numbers of affected large and small joints, ACPA positivity, male sex and BMI.

The early remission rate of 61% is higher than previously reported in cohorts such as Combinatietherapie Bij Reumatoide Artritis (COBRA) and Behandel Strategieën (BeSt), where patients also received MTX and a tapered high dose of prednisone, combined with sulfasalazine.[3,11] This is most likely explained by our intentional inclusion of patients with milder disease activity and not (yet) fulfilling the classification criteria for RA. Also, our patients had on average a shorter symptom duration. Thus, the higher remission rate in this study would support the window of opportunity theory. However, earlier inclusion may have over classified patients who possibly had self-limiting disease.[8] Other possible explanations are the initial dose of methotrexate (25 mg/week compared to 7.5 mg/week in the other cohorts) and the absence of sulfasalazine in the initial drug combination.

The 2010 ACR/EULAR classification criteria were formulated to classify patients earlier in disease course.[7] In this study however, the symptom duration of patients classified as RA according to the 1987 or the 2010 criteria is comparable, which might explain why we found no difference in clinical response and remission rates between the groups, even though the 2010 criteria classified 19% more patients.

Also, we found no difference in remission rates between RA and UA patients, although we hypothesized that UA patients, as presumably very early RA, would benefit more from early combination therapy, and despite the facts that UA patients had a lower mean baseline disease activity and were predominantly male. This may be explained by the comparable symptom duration in UA and RA patients. Of the UA patients 64% had a symptom duration >12 weeks, thus possibly missing the so called window of opportunity.[21] Also, only a few UA patients were ACPA positive, compared to 68% in the RA group, and ACPA positivity in the total study population was found to be a predictor of achieving remission. ACPA negative RA and ACPA negative UA both may represent or include illnesses that do not sufficiently respond to combination therapy with MTX and prednisone and require different treatments.[22] Previously, in the PRObable rheumatoid arthritis: Methotrexate versus Placebo Treatment (PROMPT) study ACPA negative UA patients did not benefit from treatment with methotrexate monotherapy.[10]

The baseline characteristics in this study population suggest that classifying patients as RA by the new classification criteria rests predominantly on numbers of (small) joints involved and ACPA positivity, with UA patients having less joints involved and almost all UA patients being ACPA negative. ACPA negative patients who were still classified as RA had a higher disease activity and a longer symptom duration than ACPA positive RA patients. These characteristics may explain why ACPA negative RA patients achieve less remission than ACPA positive RA patients. It is possible that they might have benefited more from treatment if they were treated earlier.

As shown in previous studies, male patients achieve more remission than female patients.[23] Our results show that male sex is an independent predictor of remission and not associated with a lower pain score or tender joint count. Also a lower body mass index (BMI) was found to be an independent predictor of remission, which may be related to relative under dosing of patients with a high BMI.

The early and intensive treatment with a high dose of methotrexate and a tapered high dose of prednisone in this study was accompanied by adverse events in more than half (56%) of the patients. Although most adverse events were mild, serious adverse events were reported in 3% of patients. Two elderly patients died, one from pneumonia that may have been treatment related and on the patient's request remained untreated, one of a vasculitis related cardiac event. This patient thus was misdiagnosed, and, since the lethal event occurred during treatment with the tapered dose of prednisone, possibly under dosed.

In conclusion, initial therapy with MTX and a tapered high dose of prednisone results in high remission percentages (about 60%) both in early RA patients (regardless of classification according to the 1987 or 2010 criteria) and in UA patients after four months of treatment. Independent predictors for remission, besides male sex and low BMI, indicate that initiation of treatment while disease activity is relatively low results in more remission, regardless of whether patients fulfil the classification criteria for RA. ACPA negative patients may benefit from early treatment, but on the whole achieve less remission on MTX with prednisone than ACPA positive patients. This may indicate that this subgroup of patients represents a different disease, for which the optimal treatment remains to be determined.

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