Worldwide treatment opportunities of rheumatoid arthritis

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CHAPTER 5

Sex-associated treatment differences and their outcomes in rheumatoid arthritis – results from the METEOR register

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ABSTRACT

Objective: To assess differences in initial treatment and treatment response in male and female rheumatoid arthritis (RA) patients in daily clinical practice.
Methods: The proportion of RA-patients starting different antirheumatic treatments (DMARDs) and the response to treatment were compared in the international, observational METEOR register. All visits from start of the first DMARD until the first DMARD switch or the end of follow-up were selected. The effect of gender on time to switch from first to second treatment was calculated using Cox regression. Linear mixed model analyses were performed to assess whether men and women responded differently to treatments, as measured by DAS or HAQ.
Results: Women (n=4,393) more often started treatment with hydroxychloroquine, as monotherapy, or in combination with methotrexate or a glucocorticoid, and men (n=1,142) more often started treatment with methotrexate and/or sulfasalazine. Time to switch DMARDs was shorter for women than for men. Women had a statistically significantly higher DAS over time than men [DAS improvement per year β (95% CI) -0.69 (-0.75; -0.62) for men and -0.58 (-0.62; -0.55) for women]. Subanalyses per DMARD-group showed for the csDMARD combination therapy a slightly greater decrease in DAS over time in men [-0.89 (-1.07; -0.71)] compared to women [-0.59 (-0.67; -0.51)], but these difference between both genders were clinically negligible.
Conclusion: This worldwide observational study suggests that in daily practice men and women with RA are prescribed different initial treatments, but there were no differences in response to treatment between both genders.

INTRODUCTION

The prevalence of rheumatoid arthritis (RA) is higher in women than in men, with at least a 3:1 ratio for women compared to men.[1] Men may have a different RA phenotype than women, with a later age of onset and a higher percentage of autoantibody positivity. [2] Genetic and hormonal differences and behavioural factors (e.g. smoking) have been suggested to underlie these gender differences.[3-6]
In the past, when treatment possibilities were limited, and higher disease activity was common, RA resulted in unfavourable outcomes in many patients, and potential gender differences were considered irrelevant.[7] New treatment options and strategies have optimized treatment outcomes. While women and men appear to have similar disease activity levels at presentation, the outcomes of RA treatment may still differ: men, for instance, are more likely to reach low disease activity and (drug free) remission and women report more pain and worse functional ability.[5, 7-12] Individually tailored ('personalized') treatment should ensure that the treatment in a patient is chosen in such a manner that the best clinical response will be obtained at the earliest possible time resulting in highest benefit. In such a strategy it may be relevant to consider that male and female patients may have different treatment needs. They may, for instance, respond differently to different treatment strategies, but prescribing physicians may also have different perceptions about the urgency of effective treatment in men versus women, and the likelihood of a favourable response to a particular treatment.
Our research question was to investigate whether rheumatologists make different treatment choices in male and female patients, and whether male and female patients respond differently to the prescribed treatment.

MATERIALS AND METHODS

Data selection
Data were derived from METEOR (Measurement of Efficacy of Treatment in the Era of Outcome in Rheumatology), which is an international, observational register capturing daily clinical practice. METEOR is not an inception cohort, but includes data of all RA patients visiting a rheumatologist. Data are entered through upload from existing electronic health record systems or registers or by using the free, online METEOR tool. Since the register contains data collected in daily clinical practice, the number of visits and the frequency of follow-up visits differed between patients. At the first visit, several patient and disease characteristics are entered (e.g. year of birth, gender, rheumatoid factor and anti-citrullinated protein antibodies (ACPA) status) and during follow-up visits data on disease activity, medication and physical functioning are gathered, all according to regular

care. METEOR has been described extensively before.[13] Data in METEOR were gathered anonymously and captured only daily clinical practice; hence medical ethics committee approval was not required. To investigate the response to the first antirheumatic treatment (conventional synthetic Disease Modifying Antirheumatic Drugs (csDMARDs) and/or oral or parenteral glucocorticosteroids), we selected data of all patients who fulfilled the following criteria: symptom duration <5 years, medication start within 3 months after diagnosis of RA according to the treating rheumatologist, baseline Disease Activity Score (DAS) ≥1.6, available data regarding medication use at baseline and follow-up, and at least 1 visit with available composite disease activity measure (e.g. DAS(28), Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI)). All available follow-up visits were selected from the start until the first switch in antirheumatic medication, or until the end of follow-up. A medication switch was defined as either a change in type of drug (e.g. from methotrexate to leflunomide) or the addition of a new drug (e.g. from methotrexate to methotrexate + prednisone), but does not include changes in the dose of the current medication, nor tapering of treatment (e.g. from combination therapy with methotrexate + prednisone to methotrexate monotherapy, or tapering to drug free remission).

Outcome measures

Time-to-switch medication, i.e. the time to decide that the first antirheumatic treatment had failed, was used as an efficacy parameter, which was compared between males and females.

Response to the first antirheumatic treatment was measured by the DAS[14] and the Health Assessment Questionnaire (HAQ).[15] Response to treatment was measured over time, taking all available visits into consideration.

Treatment groups

Initiated medications were first divided into 5 treatment groups: 1) csDMARD monotherapy, 2) csDMARD combination therapy, 3) a single csDMARD with a glucocorticoid, 4) combination therapy with more than one csDMARD and a glucocorticoid, 5) glucocorticoid monotherapy. Additional analyses were performed for individual medication combinations.

Statistical analyses

The proportion of patients starting the different medication strategies across genders was compared at baseline. A Cox regression analysis was performed with the time to switch from the first to the second treatment strategy, as proxy for treatment failure, as outcome. Patients were censored when they switched treatment, or at the end of available follow-up. Gender was added as predictor and analyses were adjusted for potential confounders. We considered age, rheumatoid factor, ACPA, country, year of first visit, symptom duration

at diagnosis, BMI, smoking and disease activity as potential confounders and performed linear regression analyses to assess whether these potential confounders were associated with the predictor gender. Each of these variables that was associated with gender ($p<0.20$) was added as confounder. Next, linear mixed model analyses were performed to assess whether men and women respond differently to treatment over time, as measured by DAS and HAQ. First a general effect of gender on treatment response was calculated for all selected patients, by adding gender, follow-up time and the interaction between gender and follow-up time to the model. In the presence of a significant interaction ($p<0.10$), analyses were stratified by gender. Subsequently, subgroup analyses were performed by treatment group and then by individual medication combinations, for medication combinations that were given to at least 100 patients. In these subgroups, the same analyses with the interaction term between follow-up time and gender were conducted. Analyses were adjusted for potential baseline confounders as described above, except for DAS, since this was the outcome of the analysis. To account for irregular time intervals, random intercept and random slope were added to each model, assuming an 'exchangeable' covariance matrix.

Furthermore, effect modification by country was tested by adding an interaction term between gender, time in follow-up and country and effect modification by age was tested by adding an interaction term between gender, time in follow-up and dichotomized age (age <50 and age ≥50). If these interaction terms were non-significant, analyses were performed for all countries and both age categories together and country and age were only added as potential confounders. P-values <0.05 were considered statistically significant.

Missing data regarding disease activity, HAQ, age, body mass index (BMI), smoking, rheumatoid factor and ACPA were imputed using additional information on gender, time in follow-up, country, medication, symptom duration and year of first visit, using multivariable normal imputation (30 imputations).[16] All analyses were performed using Stata SE version 14 (StataCorp LP).

RESULTS

Baseline characteristics and initial treatment

From the 36,576 patients included in the METEOR database, data of 5,820 patients fulfilled the inclusion criteria of the current study (online supplementary figure 1, grey boxes). Of these, 1,142 men and 4,393 women fulfilled the selection criteria for available data and could thus be included in the current analyses. A flowchart of the selection process and a comparison of baseline characteristics of included and non-included patients are presented in online supplementary figure 1 and online supplementary table 1. Non-

included patients had slightly longer symptom duration at diagnosis, but were otherwise mostly similar to included patients. Baseline characteristics of the included patients are shown in table 1. The median (IQR) time in follow-up was 15.3 (8.1; 31.3)months for men and 15.3 (6.7; 35.7) months for women, with a median (IQR) number of 4 (3; 7) visits for both men and women. On average, women were slightly younger and slightly more often rheumatoid factor and/or ACPA positive, had longer symptom duration and higher disease activity compared to men, and there were fewer female smokers compared to male smokers. Initial medication for men and women is presented in table 2.

Table 1. Baseline characteristics of men and women

	Men (n=1142, 21%)		Women (n=4393, 79%)		
		N		N	P
Age at first visit (*years)*	52.0 (14.9)	1139	46.9 (13.9)	4371	<0.001
Body mass index (kg/m^2)	27.1 (4.8)	730	27.0 (6.6)	2500	0.647
Rheumatoid factor *(% positive)*	70.6	1104	75.5	4270	0.001
ACPA *(% positive)*	66.3	656	70.8	2363	<0.001
Smoking *(%)* Never	62.3	900	88.5	3832	<0.001
Previous smoker	14.2		5.2		
Current smoker	23.0		6.3		
Symptom duration at diagnosis *(months) median (IQR)*	10.3 (3.9-23.9)	1142	12.3 (5.9-34.8)	4393	<0.001
Time to treatment initiation from diagnosis *(days)*	4.3 (14.8)	1142	3.8 (14.0)	4393	0.009
HAQ (0-3)	0.96 (0.69)	897	1.1 (0.68)	3668	<0.001
Disease Activity Score	3.5 (1.1)	753	3.7 (1.0)	2689	<0.001
Disease Activity Score 28	5.5 (1.4)	817	5.8 (1.4)	2933	<0.001
Erythrocyte sedimentation rate (mm/h)	46.2 (32.2)	1017	57.4 (33.7)	3809	<0.001
C-reactive protein (mg/L) *median (IQR)*	24 (11-50)	869	21 (9-45)	3391	<0.001
VAS patient global (0-100)	53.5 (23.0)	896	55.0 (22.0)	3295	0.091
Ritchie Articular Index (0-78)	8.6 (6.4)	1061	10.2 (6.6)	4075	<0.001
Swollen Joint Count (0-44)	7.2 (7.4)	1062	6.5 (6.5)	4079	0.027
Tender Joint Count 28 (0-28)	10.9 (8.7)	1129	12.6 (9.3)	4347	<0.001
Swollen Joint Count 28 (0-28)	6.4 (6.2)	1133	5.8 (5.5)	4368	0.021

Mean (SD) reported unless otherwise specified. ACPA = anti-citrullinated protein antibodies, HAQ = health assessment questionnaire, VAS = visual analogue scale, IQR = inter quartile range.

Table 2. Initial treatment of men and women.

	Men (n=1,142)		Women (n=4,393)	
	N (%)	**DAS mean (SD)**	**N (%)**	**DAS mean (SD)**
csDMARD mono	**421 (36.9%)**	**3.4 (1.1)**	**1804 (41.2%)**	**3.6 (1.0)**
MTX	248 (58.9%)	3.6 (1.2)	983 (54.5%)	3.8 (1.0)
SSZ	83 (19.7%)	3.2 (1.1)	181 (10.0%)	3.3 (0.9)
HCQ	80 (19.0%)	2.8 (0.8)	597 (33.1%)	3.4 (0.9)
Other	10 (2.4%)	--	43 (2.4%)	--
GC mono	**103 (9.0%)**	**3.3 (0.9)**	**252 (5.7%)**	**3.3 (0.9)**
csDMARD combi	**233 (20.4%)**	**3.5 (1.1)**	**947 (21.6%)**	**3.9 (1.0)**
MTX + HCQ	95 (40.8%)	3.3 (1.0)	554 (57.9%)	3.9 (1.0)
MTX + SSZ	70 (30.0%)	3.6 (1.0)	192 (20.1%)	3.7 (1.0)
MTX + SSZ + HCQ	40 (17.2%)	3.1 (0.7)	122 (12.8%)	3.5 (0.9)
SSZ + HCQ	19 (8.2%)	3.3 (0.9)	48 (5.0%)	3.5 (0.9)
MTX + LEF	5 (2.2%)	4.8 (0.7)	24 (2.5%)	3.8 (1.2)
Other	4 (1.7%)	--	7 (0.7%)	--
csDMARD + GC	**271 (23.7%)**	**3.7 (1.2)**	**928 (21.2%)**	**3.6 (1.0)**
MTX + GC	226 (83.4%)	3.7 (1.1)	705 (76.0%)	3.6 (1.0)
HCQ + GC	21 (7.8%)	3.8 (1.7)	136 (14.8%)	3.6 (0.9)
SSZ + GC	17 (6.3%)	3.6 (1.3)	53 (5.7%)	3.8 (1.0)
LEF + GC	4 (1.5%)	3.8 (1.2)	26 (2.8%)	3.4 (1.1)
Other	3 (1.1%)	--	8 (0.9%)	--
Combi csDMARD + GC	**114 (10.0%)**	**3.6 (1.1)**	**452 (10.3%)**	**3.9 (1.0)**
MTX + HCQ + GC	48 (42.1%)	3.5 (1.2)	205 (45.4%)	3.8 (1.0)
MTX + SSZ + GC	26 (22.8%)	3.6 (0.9)	111 (24.6%)	3.9 (1.0)
MTX + SSZ + HCQ + GC	20 (17.5%)	3.4 (0.8)	74 (16.4%)	3.6 (1.0)
SSZ + HCQ + GC	13 (11.4%)	3.4 (0.9)	32 (7.1%)	3.6 (1.0)
MTX + LEF + GC	4 (3.5%)	3.1 (1.2)	9 (2.0%)	4.3 (1.1)
Other	3 (2.6%)	--	21 (4.6%)	--

MTX = methotrexate, SSZ = sulfasalazine, HCQ = hydroxychloroquine, LEF = leflunomide, GC = glucocorticoid. DAS = disease activity score, SD = standard deviation. DAS based on the non-imputed database

Table 3. Evolution of HAQ and DAS over time in men and women[a].

	HAQ **p-value**[b]	**DAS** **p-value**[b]	**DAS** **Men** β (95% CI)	**DAS** **Women** β (95% CI)
All patients			n=1,142	n=4,393
Gender*follow-up time	0.200	0.011	--	--
Follow-up time (years)			-0.69 (-0.75; -0.62)	-0.58 (-0.62; -0.55)
csDMARD combination therapy			n=233	n=947
Gender*follow-up time	0.706	0.014	--	--
Follow-up time (years)			-0.89 (-1.07; -0.71)	-0.59 (-0.67; -0.51)
csdMARD monotherapy			n=421	n=1,804
Gender*follow-up time	0.453	0.178	--	--
GC			n=103	n=252
Gender*follow-up time	0.283	0.462	--	--
csDMARD + GC			n=271	n=928
Gender*follow-up time	0.419	0.263	--	--
csDMARD combination + GC			n=114	n=452
Gender*follow-up time	0.848	0.931	--	--

[a]Results stem from linear multivariable mixed models analyses adjusted for age, rheumatoid factor, ACPA, symptom duration at diagnosis, BMI, smoking and country. Different models were constructed for all patients and then for treatment subgroups. Regression coefficients represent the units of change in the outcome per unit of time, in this case, per year.

[b]p-values are only shown for the interactions between gender and time. In the presence of a statistically significant interaction, results are stratified by gender and the evolution of DAS over time is shown for men and women separately.

In general, men and women were treated with similar strategies according to the 5 treatment groups. But across the treatment groups, women more often than men started a treatment strategy containing hydroxychloroquine (hydroxychloroquine monotherapy, methotrexate + hydroxychloroquine and hydroxychloroquine + glucocorticoid, but not methotrexate + sulfasalazine + hydroxychloroquine). Men more often started a treatment strategy containing sulfasalazine and/or methotrexate (sulfasalazine monotherapy, methotrexate + sulfasalazine and methotrexate + glucocorticoid). Men who started hydroxychloroquine monotherapy had on average a lower baseline DAS than men starting different treatments, and also than women who started hydroxychloroquine. Women who started methotrexate monotherapy on average had a slightly higher baseline DAS

than women starting monotherapy with other csDMARDs. In the group starting with combination therapy of more than one csDMARD and a glucocorticoid, no gender differences were present. In addition, since hydroxychloroquine might be preferentially prescribed to pregnant women or to women with a pregnancy wish, we assessed whether hydroxychloroquine was more often prescribed to women of childbearing age. It was found that women ≥50 years of age were less often prescribed hydroxychloroquine (27.5% compared to 36.8% for women <50 years of age). However, the same was found for men (14.9% for men ≥50 years and 23.8% for men <50 years).
Furthermore, since medication use slightly differed between countries, initial treatment of men and women was shown per country, for countries contributing at least 100 patients (online supplementary file, tables 3 to 10). Specifically, in contrast to the overall findings, women did not receive more often hydroxychloroquine monotherapy in Portugal or in the UK, not more often combination of methotrexate + hydroxychloroquine in the UK and not more often combination of hydroxychloroquine + glucocorticoid in Mexico or in the UK. Lastly, the proportion of patients receiving glucocorticoid monotherapy differed for some countries, with more men in Mexico and Portugal and more women in the Netherlands receiving glucocorticoid monotherapy.

Treatment switch

Time-to-switch medication (i.e. the time to decide that the first treatment step had failed) was shorter in women [median (IQR) 175 (91-384) days (25 (13; 55 weeks), n=2756] than in men [median (IQR) 200 (98; 400) days (29 (14; 57) weeks), n=647]. In total, 2,146 patients (1,637 women, 495 men) did not switch treatment before the end of follow-up and were censored [median (IQR) follow-up time 336 (132; 708) days (48 (19; 101) weeks) for women and 387 (187-733) days (55 (27; 105) weeks) for men]. Cox regression analyses on the effect of gender on time from the initial treatment to a next treatment step confirmed that women were slightly more likely to switch treatment than men [HR (95% CI) 1.22 (1.12; 1.33)]. However, after adjusting for age, rheumatoid factor, ACPA, symptom duration at diagnosis, country, BMI, smoking (all at baseline) and DAS as time-varying co-variate, the effect disappeared [HR (95% CI) 1.02 (0.93; 1.12)].

Treatment response

Analyses on the effects of gender on treatment response revealed that for most treatment groups women had a slightly higher DAS and HAQ already at baseline [β (95% CI) 0.18 (0.13; 0.24) higher for DAS and 0.16 (0.12; 0.19) higher for HAQ for all treatment groups combined, online supplementary table 11]. The interaction term between gender and time was statistically significant for the outcome DAS over time (p=0.011). However, after stratification for gender, differences in improvement in DAS over time proved to be negligible between men [β (95% CI) -0.69 (-0.75; -0.62) per year] and women [β (95% CI)

-0.58 (-0.62; 0.55) per year] and the change in HAQ over time was not different between men and women (p=0.200), table 3.
When analyses were repeated in the subgroups of the different medication strategies, the interaction term between gender and time was statistically significant for the outcome DAS over time only in the csDMARD combination therapy subgroup (p=0.014), but analyses stratified for gender revealed no clinically relevant differences in improvement in DAS over time [β (95% CI) -0.89 (-1.07; -0.71) for men and -0.59 (-0.67; -0.51) for women per year, table 3]. For all other treatment strategies, there were no differences in DAS and HAQ improvement between men and women (table 3). Detailed outcomes for the subgroup analyses on the effect of gender on treatment response are shown in online supplementary file 11. When subanalyses were performed within the strategy subgroups for individual medication combinations, there were no gender differences in treatment response as measured by DAS and HAQ, online supplementary table 13.

DISCUSSION

In this study based on real world clinical data we aimed to assess whether men and women with RA are treated differently and whether the response to various therapies differs between them. Previously, a concern has been raised that women with RA might be treated less aggressively than men. For instance, a study in the NOR-DMARD registry reported lower access to bDMARDs for females in the period 2000 – 2003, but not anymore in more recent time periods (2009 – 2011).[17] Another study in the QUEST-RA database found no significant differences in the proportion of men and women taking prednisone, methotrexate or bDMARDs and showed similar delays of initiation to therapy.[7] In the current study, we found that women had, at the start of treatment, slightly longer symptom duration than men, and more often started treatment with hydroxychloroquine, as monotherapy (33% vs 19% in men) or in combination with methotrexate (41% vs 58% in men) or with a glucocorticoid (15% vs 8% in men), whereas men more often started treatment with methotrexate and/or sulfasalazine. This indeed suggests a slightly less aggressive approach in women compared to men: hydroxychloroquine monotherapy reportedly has only a small effect on reducing the swollen joint count, and its effects on delaying joint damage is smaller compared to sulfasalazine.[18, 19] We found that hydroxychloroquine was prescribed to male patients mostly if they had low disease activity, but women were treated with hydroxychloroquine or other csDMARDs irrespective of disease activity. It has to be said, though, that gender differences in medication use were slightly country-dependent. This could be influenced by political, economic or cultural factors that might differ per country but fall beyond the scope of this article.

We found a slightly worse response to treatment for women than for men, but the difference in this effect was small (decrease in DAS, when extrapolated to a year, differed by 0.1 point), and appeared to be based on a statistically significant difference in DAS improvement only for initial treatment with csDMARD combination therapy. But also this difference between men and women was in clinical terms negligible.

It could be argued that women more often receive hydroxychloroquine since hydroxychloroquine is considered safe during pregnancy, in contrast to for example methotrexate, and might therefore be prescribed to pregnant women or to women with a pregnancy wish.[20] It was indeed observed that women ≤50 years of aged more often received hydroxychloroquine, however, this effect was the same for men and therefore does not seem to be related to (wish for) pregnancy. Moreover, we assessed whether age (<50 years or ≥50 years) was an effect modifier for the association between gender and treatment response, but did not find a different response to treatment for these different age categories.

Previous studies in different registers have reported higher response rates in men as compared to women for several treatment strategies with bDMARDs.[8, 9, 21] However, the selection of patients in these studies differs from the current study, in which initial treatment in newly diagnosed RA patients were compared. An analysis in the BeSt study, a randomized clinical trial, identified male gender as a predictor of methotrexate efficacy, which has not been found in the current study.[22] This might be due to differences in patient selection, such as a 1 point higher DAS at baseline in the BeSt study, or to differences in for example dosing schedules in a trial setting compared to daily clinical practice.

It has been suggested that a higher level of disease activity in women is inherent to the components of disease activity composite scores, rather than to differences in 'specifically rheumatic activity in men and women.[7] For example, usually ESR levels are higher in women than in men, especially in older women,[7, 23] and women often report more symptoms and pain in questionnaires as compared to men.[1, 7] In addition, men may have a tendency to underreport problems, as has been described with regard to the HAQ.[24] This may explain part of the previously found gender differences in response to treatment.

We also found that women had a shorter time to switch medication than men. However, after adjusting for several confounders including disease activity over time, gender did not determine the likelihood to switch medication anymore.

This study has several potential limitations. We compared different treatment combinations, but did not take into account differences in dosing schedules between patients. Although dosing schedules for many drugs are fixed, this may still influence outcomes. Moreover, since this is an observational study, associations between variables should not be interpreted in a causal manner. Furthermore, since the prescription of

medication is not randomized, several known and unknown variables may have influenced the choice of the physician to prescribe certain medication (confounding by indication). Confounding by indication may also have influenced the response to treatment. Since only part of the potential confounders is known and measured, it is always possible that residual (unmeasured) confounding exists.

In conclusion, this study shows that men and women are prescribed different treatments: women more often started hydroxychloroquine, as monotherapy or in combination with methotrexate or a glucocorticoid, whereas men more often started treatment with methotrexate and/or sulfasalazine. Although we found a statistically significantly worse response to treatment (decrease in DAS, but not HAQ) for women compared to men to csDMARD combination therapy, these differences between genders were clinically negligible. In general, although the initial treatments prescribed to men and women may differ, it appears that the clinical response is similar for both genders.

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