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Original article

Phenotype and treatment of elderly onset compared with younger onset rheumatoid arthritis patients in international daily practice

Johanna M. Maassen [1], Sytske Anne Bergstra [1], Arvind Chopra[2], Nimmisha Govind[3], Elizabeth A. Murphy[4], David Vega-Morales[5], Tom W. J. Huizinga[1] and Cornelia F. Allaart[1]

Abstract

Objective. To identify possible differences in baseline characteristics, initial treatment and treatment response between RA patient subgroups based on age at disease onset.

Methods. Daily practice data from the worldwide METEOR registry were used. Patients (7912) were stratified into three age-groups (age at disease diagnosis <45 years, 45–65 years, >65 years). Initial treatment was compared between the different age-groups. With Cox regression analyses the effect of age-group on time-to-switch from first to second treatment was investigated, and with linear mixed models differences in response to treatment (DAS and HAQ) between the age-groups were assessed, after correction for potential confounders.

Results. The >65 years age-group included more men, and more seronegative RA with somewhat higher inflammatory markers. Initial treatment choices differed only slightly between the age-groups, and the time-to-switch from initial treatment to the next was similar. DAS and HAQ improvement were dependent on the age-group, reflected by a significant interaction between age-group and outcome. The stratified analysis showed a difference of −0.02 and −0.05 DAS points and, −0.01 and 0.02 HAQ points per month in the <45 and 45–65 years age-groups as compared with the >65 year age group, a difference that did not seem clinically relevant.

Conclusion. In this international study on worldwide clinical practice, patients with RA onset >65 years include more men and seronegative arthritis, and were initially treated slightly differently than younger patients. We observed no clinically relevant differences in timing of a next treatment step, or response to treatment measured by DAS and HAQ.

Key words: rheumatoid arthritis, elderly, treatment, disease phenotype, epidemiology

Rheumatology key messages

- RA diagnosed at elderly age may be a different phenotype than that in younger patients.
- Elderly onset RA patients have a different phenotype, and rheumatologists treat them slightly differently.
- Clinical improvement measured by DAS and HAQ was similar in elderly and younger patients.

Introduction

It has been recognized that treatment of RA should ideally be personalized, as there appear to be subtypes of RA, and because individual RA patients are different. In particular, older patients have different prognostic concerns, potentially different needs, and in general have more comorbidities (including OA, which may influence clinical presentation and diagnosis), co-medications and limitations to use of antirheumatic drugs than younger patients [1–3]. In accordance, it has been postulated that there is a specific age-related RA phenotype, 'elderly onset RA', in patients with disease onset above the age of 60–65 years [4, 5]. In these patients the female predominance is found to be less marked, and RF and ACPA positivity are found less frequently; however, at disease onset markers of

[1]Department of Rheumatology, Leiden University Medical Center, Leiden, The Netherlands, [2]Center for Rheumatic Diseases, Pune, India, [3]Division of Rheumatology, University of the Witwatersrand, Johannesburg, South Africa, [4]University Hospital Wishaw, Wishaw, UK and [5]Rheumatology, Hospital Universitario 'Dr. José Eleuterio González', Monterrey, Mexico

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Correspondence to: Johanna M. Maassen, Department of Rheumatology, Leiden University Medical Center, PO Box 9600, Leiden 2300 RC, The Netherlands. E-mail: j.m.maassen@lumc.nl

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inflammation and scores for disease activity and functional disability are higher [6–9].

Best practice in treating elderly RA patients is unknown. Current treatment guidelines do not provide recommendations regarding treatment of elderly patients [10, 11], and clinical trials often exclude elderly patients [12]. It has been shown that this might result in older patients receiving less aggressive treatment [5, 13]. Miscellaneous reports on the safety of effective antirheumatic drugs in elderly and/or comorbid patients may have contributed to different treatment choices in different age groups [14]. However, only limited studies have evaluated the treatment response in daily practice in elderly compared with younger RA patients. It is also unknown whether any age-related difference in RA phenotype, treatment and treatment response are continuous with increasing age, or whether there is a group of patients with disease onset at intermediate age that is quite different from the younger as well as the older patients.

Therefore, the aims of this study were to evaluate the 'age at onset' distribution in RA patients using worldwide data, to identify possible subgroup characteristics, to assess if rheumatologists make different treatment choices in elderly RA patients in daily clinical practice and to evaluate whether elderly RA patients respond differently to the prescribed treatment.

Methods

Data selection

Data from the Measurement of Efficacy of Treatment in the Era of Outcome in Rheumatology (METEOR) (described elsewhere [15]), an international registry recording real life clinical data in RA patients, were used. Recorded data included patient and disease characteristics, disease activity, medication use, and physical functioning at baseline and during follow-up. Medical ethics committee approval was not required since data capture in METEOR is anonymous and include observational data only, with visits and measurements scheduled and performed according to daily clinical practice. Patient consent was not required.

Data (recorded between July 2000 and January 2019) were selected for all patients who fulfilled the following criteria: age at diagnosis $>$16 years; symptom duration $\leq$5 years; DMARD naïve (as defined by first medication initiated within 3 months after RA diagnosis); baseline DAS $\geq$1.6; initial medication non-biological DMARD; at minimum two follow-up visits with available data on composite disease activity measure (i.e. DAS, DAS-28, Simplified Disease Activity Index or Clinical Simplified Disease Activity Index, or Routine Assessment of Patient Index Data3); and available data on date of birth and medication use. Follow-up visits were selected from presentation until the first medication switch, or the end of the available follow-up. A 'switch' was defined by a new DMARD, for this analysis encompassing conventional synthetic (csDMARD) and biologic DMARDs as well as oral glucocorticosteroids (GC) being introduced, instead of or in addition to the initial DMARD or DMARD combination. Dose changes in a DMARD, reduction of the number of DMARDs in a prescribed DMARD combination or tapering of a single DMARD were not considered a switch.

Stratification groups

Because of differences in the age at diagnosis distribution between countries, countries were divided over two 'country subgroups', one with a mean age at disease diagnosis lower, and one with a mean age at diagnosis higher than that in the whole study population. Thereafter, patients were stratified into 'age-groups' based on their individual age at disease diagnosis; young age-group: $<$45 years; middle age-group: 45–65 years; elderly age-group: $>$65 years.

Treatment groups

Initiated medication was divided into five treatment groups: (i) csDMARD monotherapy; (ii) GC monotherapy; (iii) csDMARD monotherapy + GC; (iv) csDMARD combination therapy; and (v) csDMARD combination therapy + GC. Analyses were performed for medication groups, combinations and individual medications separately.

Outcome measures

Time-to-switch medication (i.e. the time to decide that the first antirheumatic treatment had failed) was used as a proxy for treatment failure and physicians willingness to escalate treatment, which was compared between the different age-groups. Response to the first antirheumatic treatment was measured by the DAS and the HAQ [16, 17]. Response to treatment, measured by DAS and HAQ, was evaluated over-time until 6 months or until the first medication switch, whichever came first.

Statistical analysis

Baseline characteristics were compared between the different age-groups. The proportion of patients starting different initial treatment strategies were compared between the age-groups using the χ^2 test. Cox regression analyses were performed with the time-to-switch from initial to a next treatment as outcome, and the age-group as predictor. Patients were censored when they switched treatment, or at the end of available follow-up. The analyses were adjusted for potential confounders based on clinical reasoning; sex, BMI, RF and/or ACPA presence, smoking status, symptom duration at baseline, year of first visit and country of origin.

Linear mixed model analyses were performed to evaluate the possible differences in response to the initial treatment, measured by DAS and HAQ, over time in the first 6 months. Linear mixed model analyses were performed because these models can deal with (unequal numbers of) repeated measures within individuals over time, and include both fixed (e.g. sex, auto-antibody positivity, BMI) and random effects (e.g. random intercept for each individual). First a general effect of

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age-group on treatment response was calculated for all patients (per country subgroup), by adding age-group, follow-up time and an interaction term between age-group and follow-up time to the model. The interaction term was added to evaluate whether the age-group should be considered as an effect modifier in the relationship between age at disease diagnosis and treatment response. In case of a significant interaction ($P < 0.10$), analyses were stratified by age-group. Subsequently, similar analyses were performed by treatment group, combination and individual medication (if >100 patients received this treatment). We adjusted for the confounders described above. To account for irregular time intervals, random intercept and random slope were added to each model. All analyses were performed for the 'countries with a high age at disease diagnosis' and 'countries with a low age at disease diagnosis' separately.

Missing data on gender, BMI, smoking, disease activity scores, HAQ, ACPA and RF were considered missing at random and were imputed by multiple variable imputation with chained equations by predictive mean matching (five nearest neighbours) for 30 imputation cycles, using additional information on age at disease diagnosis, time in follow-up, country, symptom duration at diagnosis and year of first visit. All analyses were performed using Stata SE version 16 (StataCorp, College Station, TX, USA). *P*-values <0.05 were considered statistically significant.

Results

Baseline characteristics

From all 47 557 patients included in the METEOR database at 17 January 2019, 11 431 patients were eligible for the current study, after applying the eligibility criteria. Thereafter, 3519 patients were excluded because of insufficient follow-up (<3 months), missing data on date of birth or missing data on composite disease activity measures. A flowchart of the selection procedure can be found in supplementary Fig. S1, available at *Rheumatology* online. Baseline characteristics for the 7912 included and 3519 excluded patients were tabulated and were comparable between the groups (supplementary Table S1, available at *Rheumatology* online). Country subgroup stratification resulted in 5549 patients (70.1%) being classified as originating from a country with low mean age at disease diagnosis and 2363 patients (29.9%) from a country with high mean age at disease diagnosis (see supplementary Table S2, available at *Rheumatology* online, for the distribution of the countries over the country subgroups). Symptom duration was longer, and DAS and percentage of patients with positive autoantibodies were higher in countries with low mean age at disease diagnosis (supplementary Table S3, available at *Rheumatology* online).

Next, patients were stratified into three age-groups: young (<45 years); middle age (45–65 years) and elderly (>65 years). Baseline characteristics for the separate age-groups are presented in Table 1. In the countries with high mean age at disease diagnosis, the elderly age-group had the highest percentage of male patients, more smokers, fewer patients who were positive for both RF and ACPA, and ESR and CRP were high, whereas symptom duration was shorter compared with the other age-groups. In the middle age-group, more patients were positive for RF and ACPA compared with the young age-group, without further significant differences in baseline characteristics between the young and middle age-groups. Also, in the countries with low age at disease diagnosis the elderly age-group had the highest percentage of male patients, but there were no differences in auto-antibody positivity or symptom duration. The HAQ and visual analogue scale for patient global health were highest in the elderly age-group.

Initial treatment

In the countries with a high age at disease diagnosis, patients in the elderly age-group were more often treated with a combination of csDMARDs, and less often with one or more csDMARD(s) and GC. Patients in the young and middle age-groups were treated similarly. There was also a trend for patients in the elderly age-group starting more often with GC monotherapy. Elderly patients treated with GC as monotherapy or in combination with a csDMARD had slightly higher DAS than other patients. Across the different treatment groups, MTX was initiated less and SSZ more often in the young (fertile) age-group when compared with the middle and elderly age-groups. Patients in the middle and elderly age-group were more often treated with MTX with HCQ, but MTX with SSZ was more often used in the young age-group. The combination of MTX with HCQ and GC was used less in elderly patients; instead MTX with SSZ and GC was used more often (Table 2). In the countries with a low age at disease diagnosis, patients in the elderly age-group were less often treated with csDMARD monotherapy but more often with a one or more csDMARD with GC, compared with patients in the young and middle age-groups (Table 3). Differences in initial treatment were less pronounced between the age-groups of the individual countries (supplementary Tables S4A–F and S5A and B, available at *Rheumatology* online).

Time-to-switch initial treatment

In countries with a high age at disease diagnosis 1346/2363 (57%) patients never switched treatment within the available follow-up and were censored after a median [interquartile range (IQR)] follow-up time of 15.8 (IQR 11.2–26.4) months [<45 years: 345 patients, median (IQR) 17.2 (11.3–28.0) months; 45–65 years: 679 patients, median (IQR) 15.6 (11.3–27.5) months; >65 years: 322 patients, median (IQR) 15.2 (11.0–24.7) months]. For patients who switched, the time-to-switch increased with increasing age at disease diagnosis [<45 years:

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Table 1 Baseline characteristics

	Countries with high age at disease diagnosis						Countries with low age at disease diagnosis					
	N	<45 years	*N*	45–65 years	*N*	>65 years	*N*	<45 years	*N*	45–65 years	*N*	>65 years
Percentage within subgroup, %	630	27	1220	51	513	22	2737	49	2620	47	192	4
Age at diagnosis, mean (s.d.), years	630	33.4 (7.7)	1220	55.0 (5.8)	513	73.3 (5.4)	2737	33.9 (6.3)	2620	52.6 (5.7)	192	70.9 (4.3)
Age at symptom onset, mean (s.d.), years	630	32.6 (7.7)	1220	54.0 (5.9)	513	72.6 (5.5)	2737	31.9 (6.8)	2620	50.4 (5.9)	192	68.7 (4.7)
Female, %	623	80	1214	74	505	66	2733	86	2619	84	192	64
RF-positive, %	585	67	1163	75	480	58	2729	80	2609	80	185	77
ACPA-positive, %	415	68	930	73	216	54	1556	79	1421	80	99	81
BMI, mean (s.d.), kg/m^2	349	26.9 (6.8)	710	28.4 (6.1)	333	26.8 (4.9)	1445	25.2 (6.2)	1290	27.4 (6.1)	93	26.5 (6.7)
Smokers, %	471	12	912	19	373	26	2576	–	2546	<1	183	–
Symptom duration, median (IQR), months	630	7.4 (3.6–15.6)	1220	7.6 (3.6–18.3)	513	5.0 (2.6–12.0)	2737	23.9 (9.8–35.9)	2620	23.9 (12.0–35.9)	192	23.9 (11.7–42.5)
HAQ, mean (s.d.)	416	1.3 (0.7)	796	1.3 (0.8)	323	1.2 (0.8)	2548	0.9 (0.6)	2449	1.0 (0.6)	175	1.1 (0.6)
DAS, mean (s.d.)	378	3.3 (1.1)	758	3.3 (1.0)	347	3.3 (0.9)	1969	3.9 (1.0)	1868	4.0 (0.9)	140	4.0 (1.1)
ESR, mean (s.d.), mm/h	556	32.4 (25.9)	1106	35.5 (26.5)	471	44.9 (28.1)	2499	67.2 (31.9)	2382	74.2 (32.6)	181	75.6 (34.4)
CRP, mean (s.d.), mg/L	469	10 (4–26)	860	12 (5–30)	323	18 (7–37)	2393	23 (1–48)	2297	26 (13–53)	171	33 (15–64)
VAS patient global, mean (s.d.), 0–100	512	58.7 (25.6)	1007	58.5 (24.9)	417	56.7 (25.2)	2168	52.2 (18.1)	2073	54.2 (18.4)	160	57.3 (20.1)
Ritchie articular index, median (IQR), 0–78	516	6 (3–9)	987	6 (3–8)	442	5 (3–8)	2686	12 (6–17)	2569	13 (7–18)	178	12 (7–17)
Swollen Joint Count, median (IQR), 0–44	517	5 (2–10)	987	5 (2–10)	443	6 (3–11)	2689	4 (1–9)	2569	4 (2–9)	178	4 (1–12)

Baseline characteristics are reported as mean (s.d.), median (IQR) or percentage (%) when appropriate. VAS: visual analogue scale; IQR: interquartile range.

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Table 2 Initial medication for all patients in countries with high age at disease diagnosis—stratified by age-group

	<45 years, *N* = 630		45–65 years, *N* = 1220		>65 years, *N* = 513		*P*-value[b]
	n (%)	Baseline DAS[a], mean (S.D.)	*n* (%)	Baseline DAS[a], mean (S.D.)	*n* (%)	Baseline DAS[a], mean (S.D.)	
csDMARD monotherapy	**246 (39.1)**	**3.0 (1.0)**	**422 (34.6)**	**3.3 (0.9)**	**198 (38.6)**	**3.3 (0.9)**	**0.10**
MTX	128 (52.0)	3.1 (1.0)	283 (67.0)	3.3 (0.9)	127 (64.1)	3.3 (0.9)	
SSZ	74 (30.1)	2.8 (0.9)	70 (16.6)	3.5 (1.1)	39 (19.7)	3.3 (0.9)	
HCQ	40 (16.3)	3.1 (1.1)	56 (13.3)	2.8 (0.9)	27 (13.7)	3.2 (0.7)	
Other	4 (1.6)	–	13 (3.1)	–	5 (2.5)	–	
GC monotherapy	**32 (5.1)**	**3.1 (1.1)**	**78 (6.4)**	**3.4 (0.9)**	**44 (8.6)**	**3.8 (1.0)**	**0.06**
csDMARD + GC	**239 (37.9)**	**3.6 (1.2)**	**450 (36.9)**	**3.3 (1.0)**	**147 (28.7)**	**3.6 (1.0)**	**<0.01**
MTX + GC	209 (87.5)	3.7 (1.2)	419 (93.1)	3.3 (1.0)	129 (87.8)	3.5 (1.0)	
SSZ + GC	11 (4.6)	3.3 (0.9)	9 (2.0)	4.0 (1.1)	8 (5.4)	4.0 (1.0)	
HCQ + GC	15 (6.3)	3.5 (0.7)	16 (3.6)	2.7 (0.5)	7 (4.8)	3.9 (0.8)	
LEF + GC	3 (1.3)	3.2 (1.7)	–	–	1 (<1.0)	4.6 (–)	
Other	1 (<1.0)	–	6 (1.3)	3.7 (1.1)	2 (1.4)	–	
csDMARD combination therapy	**73 (11.6)**	**3.2 (0.9)**	**167 (13.7)**	**3.1 (0.9)**	**100 (19.5)**	**3.1 (0.8)**	**<0.01**
MTX + HCQ	21 (28.8)	3.4 (1.0)	68 (40.7)	3.3 (1.1)	46 (46.0)	2.9 (0.8)	
MTX + SSZ	11 (15.0)	3.0 (0.7)	12 (7.2)	2.9 (0.7)	10 (10.0)	2.8 (0.7)	
MTX + SSZ + HCQ	26 (35.6)	3.1 (0.7)	54 (32.3)	3.0 (0.5)	30 (30.0)	3.2 (0.8)	
SSZ + HCQ	10 (13.7)	3.1 (1.0)	24 (14.4)	2.9 (0.8)	9 (9.0)	3.6 (0.7)	
MTX + LEF	1 (1.4)	–	3 (1.8)	3.7 (–)	1 (1.0)	2.2 (–)	
Other	4 (5.5)	–	6 (3.6)	–	4 (4.0)	–	
Combination csDMARD + GC	**40 (6.3)**	**3.4 (1.3)**	**103 (8.4)**	**3.3 (1.0)**	**24 (4.6)**	**3.3 (0.7)**	**0.01**
MTX + SSZ + GC	2 (5.0)	4.0 (0.8)	8 (7.7)	3.1 (0.4)	7 (29.2)	3.6 (0.6)	
MTX + HCQ + GC	22 (55.0)	4.0 (1.6)	61 (59.2)	3.3 (1.2)	11 (45.8)	3.2 (1.0)	
MTX + SSZ + HCQ + GC	9 (22.5)	2.6 (0.4)	25 (24.3)	3.1 (0.6)	6 (25.0)	3.2 (0.4)	
SSZ + HCQ + GC	4 (10.0)	2.1 (–)	5 (4.9)	3.3 (1.4)	–	–	
MTX + LEF + GC	–	–	1 (1.0)	4.9 (–)	–	–	
Other	3 (7.5)	–	3 (2.9)	2.9 (0.4)	–	–	

The number and corresponding percentage of patients using a specific medication or medication combination are described for the medication subgroups and each medication combination separately. Data on medication subgroups are displayed in bold versus the seperate medication combinations being displayed in regular font. [a]Mean (S.D.) DAS values are based on the non-imputed data. [b]*P*-value of χ^2 test for difference between the initial medication prescribed to the different age-groups. csDMARD: conventional synthetic DMARD; GC: glucocorticoid.

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Table 3 Initial medication for all patients in countries with low age at disease diagnosis—stratified by age-group

	<45 years, *N* = 2737		45–65 years, *N* = 2620		>65 years, *N* = 192		*P*-value[b]
	n (%)	Baseline DAS[a], mean (s.d.)	*n* (%)	Baseline DAS[a], mean (s.d.)	*n* (%)	Baseline DAS[a], mean (s.d.)	
csDMARD monotherapy	**1442 (52.7)**	**3.7 (0.96)**	**1263 (48.2)**	**3.9 (0.96)**	**78 (40.6)**	**3.9 (1.0)**	**<0.01**
MTX	748 (51.9)	4.1 (0.9)	714 (56.5)	4.1 (0.9)	34 (43.6)	4.3 (1.1)	
SSZ	97 (6.7)	3.7 (0.9)	80 (6.3)	3.4 (0.9)	6 (7.7)	4.2 (0.9)	
HCQ	582 (40.4)	3.3 (0.9)	444 (35.2)	3.5 (0.9)	36 (46.1)	3.6 (0.9)	
Other	15 (1.0)	–	25 (2.0)	–	2 (2.6)	–	
GC monotherapy	**28 (1.0)**	**3.9 (1.0)**	**18 (<1.0)**	**4.3 (0.7)**	**2 (1.0)**	**4.2 (0.4)**	**0.40**
csDMARD + GC	**292 (10.7)**	**4.0 (1.0)**	**341 (13.0)**	**4.0 (1.0)**	**42 (21.9)**	**4.1 (1.2)**	**<0.01**
MTX + GC	181 (62.0)	4.1 (0.9)	216 (63.3)	4.1 (0.9)	27 (64.3)	4.3 (1.2)	
SSZ + GC	26 (8.9)	3.7 (1.0)	28 (8.2)	4.2 (1.5)	4 (9.5)	4.6 (0.3)	
HCQ + GC	77 (26.4)	3.7 (1.0)	75 (22.0)	3.8 (1.1)	11 (26.2)	3.7 (1.3)	
LEF + GC	8 (2.7)	3.2 (–)	21 (6.2)	3.4 (0.9)	–	–	
Other	–	–	1 (<1.0)	–	–	–	
csDMARD combination therapy	**689 (25.2)**	**4.0 (0.9)**	**652 (24.9)**	**4.1 (0.9)**	**39 (20.3)**	**4.1 (1.2)**	**0.32**
MTX + HCQ	370 (53.7)	4.1 (0.9)	369 (56.6)	4.1 (0.8)	20 (51.2)	4.3 (1.2)	
MTX + SSZ	191 (27.7)	4.0 (0.9)	171 (26.2)	4.2 (1.0)	9 (23.1)	4.4 (1.2)	
MTX + SSZ + HCQ	64 (9.3)	4.1 (0.9)	33 (5.0)	4.3 (0.9)	1 (2.6)	3.7 (–)	
SSZ + HCQ	53 (7.7)	3.8 (1.0)	35 (5.4)	4.2 (1.0)	5 (12.8)	4.0 (0.4)	
MTX + LEF	8 (1.2)	4.9 (0.7)	29 (4.5)	3.8 (1.0)	3 (7.7)	3.8 (0.3)	
Other	3 (<1.0)	–	15 (2.3)	–	1 (2.6)	–	
Combination csDMARD + GC	**286 (10.4)**	**4.1 (1.0)**	**346 (13.2)**	**4.2 (0.9)**	**31 (16.2)**	**4.3 (1.1)**	**<0.01**
MTX + SSZ + GC	97 (33.9)	4.1 (0.9)	131 (37.9)	4.3 (0.9)	3 (9.7)	4.1 (–)	
MTX + HCQ + GC	125 (43.7)	4.1 (0.9)	133 (38.4)	4.2 (0.9)	13 (41.9)	4.3 (1.3)	
MTX + SSZ + HCQ + GC	31 (10.8)	4.1 (0.9)	47 (13.6)	4.1 (0.8)	3 (9.7)	4.7 (2.0)	
SSZ + HCQ + GC	17 (6.0)	4.0 (1.0)	8 (2.3)	4.2 (1.5)	4 (12.9)	4.5 (0.8)	
MTX + LEF + GC	8 (2.8)	5.0 (0.8)	15 (4.3)	3.8 (0.7)	5 (16.1)	3.9 (0.7)	
Other	8 (2.8)	4.2 (2.5)	12 (3.5)	4.0 (1.0)	3 (9.7)	4.3 (0.3)	

The number and corresponding percentage of patients using a specific medication or medication combination are described for the medication subgroups and each medication combination separately. Data on medication subgroups are displayed in bold versus the seperate medication combinations being displayed in regular font. [a]Mean (s.d.) DAS values are based on the non-imputed data. [b]P-value of χ^2 test for difference between the initial medication prescribed to the different age-groups. csDMARD: conventional synthetic DMARD; GC: glucocorticoid.

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285 patients, median (IQR) 7.6 (3.7–13.6) months; 45–65 years: 541 patients, median (IQR) 8.0 (3.5–14.7) months; >65 years: 191 patients, median (IQR) 8.6 (3.0–13.5) months]. This relation with age at diagnosis was not seen in the countries with a low age at disease diagnosis [<45 years: 1918 patients, median (IQR) 6.2 (3.1–15.0) months; 45–65 years: 1761 patients, median (IQR) 6.6 (3.3–15.4) months; >65 years: 116 patients, median (IQR) 6.1 (3.4–14.0) months]. In this country subgroup, 1754/5549 (32%) patients never switched treatment within the available follow-up and were censored after a median (IQR) follow-up time of 11.7 (5.8–25.0) months [<45 years: 819 patients, median (IQR) 11.8 (6.0–25.2) months; 45–65 years: 859 patients, median (IQR) 11.7 (5.7–25.2) months; >65 years: 76 patients, median (IQR) 10.1 (5.1–17.4) months].

Cox regression analyses did not show an association between age-group and time-to-switch treatment in either of the high/low age at disease diagnosis groups. After adjusting for sex, BMI, smoking, RF, ACPA, symptom duration at baseline, year of first visit and country, similar hazard ratios' and corresponding CIs were found (Table 4).

Treatment response

Linear mixed model analysis on the effect of age-group on treatment response, measured by DAS and HAQ, showed that both for countries with a high and low age at disease diagnosis and for almost all treatment groups, patients in the young and middle age-groups had lower baseline DAS and HAQ compared with patients in the elderly age-group (supplementary Tables S6 and S7, available at *Rheumatology* online). However, these differences are small and unlikely to be clinically meaningful.

In the pooled analyses in the high age at disease diagnosis group, improvement in DAS and HAQ per month was dependent on age-group [significant interaction term age-group × follow-up time for both DAS ($P < 0.01$), middle age-group *vs* elderly age-group; and HAQ ($P = 0.05$), middle age-group *vs* elderly age-group]. However, after stratification the predicted DAS improvement per month was –0.24 (95% CI −0.26, −0.21) for patients <45 years and −0.21 (95% CI −0.23, −0.20) for patients 45–65 years, compared with –0.26 (95% CI 0.29, −0.23) in the eldest age group (>65 years), reflecting only a difference between −0.02 and −0.05 DAS points per month. Differences in HAQ improvement were also minimal between the age-groups, and were predicted between −0.02 and −0.01 HAQ points per month compared with the eldest age-group (Table 5). In subgroup analyses for the different treatment groups DAS improvement was dependent on age-group for the csDMARD with GC treatment group (driven by the group of patients treated with MTX + GC). Nevertheless, stratified analysis by age-group showed only minor differences in improvement between the age-groups (Table 5).

In the countries with low age at disease diagnosis, improvement in DAS over time was not dependent on age-group, and in general comparable improvement of DAS per month was seen for the different treatment groups. In the pooled analysis including all treatment groups HAQ over time was dependent on age-group (interaction term age-group × follow-up time $P = 0.07$ for the young age-group; and $P = 0.02$ for the middle age-group *vs* elderly age-group). After stratification, a trend towards less HAQ improvement in the elderly age-group was seen, however the predicted difference in HAQ improvement per month was only –0.01 in the age groups <45 years and 45–65 years compared with the eldest age-group (Table 5). Similar results were found for the treatment group MTX monotherapy (Table 5).

Table 4 Result from Cox-regression analysis on time-to-switch the initial treatment

	Adjusted[a]		Unadjusted	
	HR	95% CI	HR	95% CI
Countries with high age at disease diagnosis				
<45 years	1.19	0.98, 1.44	1.19	0.99, 1.43
45–65 years	1.07	0.90, 1.27	1.14	0.97, 1.35
>65 years	Ref.		Ref.	
Countries with low age at disease diagnosis				
<45 years	1.07	0.89, 1.30	1.08	0.89, 1.30
45–65 years	1.01	0.83, 1.23	1.02	0.84, 1.23
>65 years	Ref.		Ref.	

[a]Adjusted for sex, BMI, RF, ACPA, smoking status, symptom duration at baseline, year of first visit and country of origin of the data. HR: hazard ratio; Ref.: reference category.

Discussion

It has been suggested that depending on the patient's age at disease onset, RA is more than one type of disease, possibly requiring different treatment approaches. Using real-world clinical data from the METEOR registry, we aimed to evaluate the variance in patient characteristics, initial treatment and response to treatment between RA patients diagnosed at different ages in countries worldwide. We indeed observed some variation in characteristics between the age-groups. The female predominance was less marked in the elderly age-groups. Furthermore, elderly patients had higher levels of acute-phase reactants, and were less often RF or ACPA positive, which is in accordance with previous reports [6, 7, 18]. We observed this only in countries with high age at disease diagnosis, where 19% of patients (compared with 3% in the other countries) had disease diagnosis at age >65 years, and only 27% (compared with 49%) of patients had disease diagnosis at age <45 years. The differences in age-at-diagnosis distribution between countries are possibly related to differences in life

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Table 5 Linear mixed model analyses on DAS and HAQ evolution over time—stratified by age-group

Variable	*P*[a]	Stratified analyses		
		β[c] (95% CI)		
		<45 years	45–65 years	>65 years
DAS, countries with high age at disease diagnosis				
All patients, *n*		630	1220	513
<45 years age-group × follow-up time interaction	0.12			
45-65 years age-group × follow-up time interaction	**<0.01**			
>65 years age-group × follow-up time interaction	Ref.			
Follow-up time, month		−0.24 (−0.26, −0.21)	−0.21 (−0.23, 0.20)	−0.26 (−0.29, −0.23)
csDMARD + GC, *n*		239	450	147
<45 years age-group × follow-up time interaction	0.26			
45–65 years age-group × follow-up time interaction	**<0.01**			
>65 years age-group × follow-up time interaction	Ref.			
Follow-up time, month		−0.27 (−0.31, −0.23)	−0.21 (−0.24, −0.19)	−0.30 (−0.35, −0.25)
MTX + GC, *n*		209	419	129
<45 years age-group × follow-up time interaction	0.51			
45–65 years age-group × follow-up time interaction	**<0.01**			
>65 years age-group × follow-up time interaction	Ref.			
Follow-up time, month		−0.27 (−0.31, −0.23)	−0.21 (−0.24, −0.19)	−0.28 (−0.33, −0.23)
HAQ, countries with high age at disease diagnosis				
All patients, *n*		630	1220	513
<45 years age-group × follow-up time interaction	0.20			
45–65 years age-group × follow-up time interaction	**0.05**			
>65 years age-group × follow-up time interaction	Ref.			
Follow-up time, month		−0.09 (−0.10, −0.07)	−0.08 (−0.09, 0.07)	−0.10 (−0.12, −0.08)
HAQ, countries with low age at disease diagnosis				
All patients, *n*		2737	2620	192
<45 years age-group × follow-up time interaction	**0.07**			
45–65 years age-group × follow-up time interaction	**0.02**			
>65 years age-group × follow-up time interaction	Ref.			
Follow-up time, month		−0.07 (−0.08, −0.07)	−0.08 (−0.09, −0.07)	−0.06 (−0.08, −0.04)
MTX monotherapy, *n*		748	714	34
<45 years age-group × follow-up time interaction	**0.06**			
45–65 years age-group × follow-up time interaction	**0.03**			
>65 years age-group × follow-up time interaction	Ref.			
Follow-up time, month		−0.07 (−0.08, −0.05)	−0.07 (−0.08, −0.06)	−0.03 (−0.09, 0.02)

Analyses were adjusted for gender, RF, ACPA, BMI, smoking status, year of diagnosis, symptom duration and country of origin of the data. [a]The *P*-values are shown for the interaction terms between the age-groups <45 years/45–65 years and follow-up time. Only when one of the interaction terms was statistically significant (p <0.10, displayed in bold) analyses were stratified for age-group and the resulting coefficients were reported. [c]The regression coefficients are the result from a stratified analysis per age-group and represent the change in DAS or HAQ per month. csDMARD: conventional synthetic DMARD; GC: glucocorticoids.

expectancy, population health, access to care and environmental factors [19]. In addition, we indicate that our data in the low age at diagnosis countries are mainly derived from India, and that age-related RA data from this and other low-income countries for reference are scarce.

Earlier reports are contradicting on the use of DMARDs in RA patients with a higher age at disease onset [1, 9]. Active arthritis in the elderly may cause severe disability in daily life, but there is a concern that these patients may receive less aggressive treatment, motivated by the fact that concurrent illnesses and

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therefore polypharmacy and the risk of treatment-related toxicity are more common in this group of RA patients [3, 20, 21]. In the cross-sectional Consortium Of Rheumatology Research Of North America study in the USA it was found that with similar disease activity and HAQ scores in patients >60 years old were less often treated with multiple csDMARDs or a biologic DMARD [2]. Others have also reported on the lower use of csDMARDs in elderly patients with early-stage disease and lower incidence of biological initiation in elderly with established RA [6, 22]. Although we did observe some differences in the initial treatment between patients diagnosed at different ages, the suggestion that elderly RA patients receive less intensive treatment, at least at treatment initiation, was not fully supported by our data, and some findings seem contradicting. CS monotherapy seemed more often prescribed, but also combinations of multiple csDMARDs without CS, whereas combinations of one or more csDMARDs with a CS were less often prescribed to patients in the elderly age-group unless disease activity was high, at least in countries with high age at disease diagnosis. In countries with low age at disease diagnosis, CS are in general less often prescribed, potentially for fear of infectious complications, although for patients with the highest DAS, and in particular for the elderly patients, a combination of CS with one or more csDMARDs was more often prescribed. We speculate that in the elderly, side effects of CS are more feared than in the younger and middle aged-patients, but that monotherapy in the elderly patients is sometimes prescribed for very active RA or the PMR-like phenotype with high inflammatory parameters and proximal joint involvement seen more often in elderly onset RA [23, 24].

Other parameters that could reflect the tendency of physicians to be less aggressive in treating the elderly RA patient are the delay in initiating the first treatment, and the time between treatment initiation and evaluation of the first treatment response. Symptom duration at the start of treatment in this study was similar between the young and middle age-groups, but shorter in the elderly age-group, suggesting that disease onset may be less insidious and more acute in elderly patients, prompting earlier treatment [23, 24]. On the other hand, time-to-switch treatment was not influenced by the age at diagnosis. Our results suggest a slightly better DAS and HAQ response to treatment in the elderly patients in the countries with high age at disease diagnosis, but the differences were small and not clinically relevant (<0.1 points decrease in DAS per month, and <0.05 point decrease in HAQ per month). Others looking at efficacy in csDMARD-treated patients also suggest a similar response to treatment specifically reported for MTX and LEF [25–28].

Some potential limitations of our study need to be mentioned. The method of patient selection from METEOR, based on the available follow-up, could have introduced some selection bias, excluding patients with a different disease profile. However, differences in the observed baseline characteristics were small, and therefore we regard this bias as limited in our study. Furthermore, research on observational data is subject to possible confounding by indication, meaning that the prescribed treatment is not assigned at random but based on several patient characteristics. This might have had an impact on our results in prescribed treatments as well as on the response to treatment. We adjusted for this bias with measured confounders as much as possible in our analyses, but it is possible that to some extent (unmeasured) residual confounding is still present. The METEOR registry does not provide insight into a possible relation between medication use and comorbidities, nor could treatment-related toxicity be assessed. Elderly patients in general have more comorbidities and this may also be the case in the METEOR registry, although differences in comorbidities could not be compared between the age-groups. Potential comorbidity difference, if present, did not result in rheumatologists choosing what might be considered less aggressive treatment in elderly patients, as depicted by our results. In particular, in the countries with a low age at diagnosis, functional impairment was higher in the elderly patients, and rheumatologists may have aimed treatment choices at rapid improvement to restore of self-sufficiency.

Overall, we conclude that patients with elderly onset RA have somewhat different characteristics than younger patients, and that there are slight differences in how they are treated. However, we found no indication that patients with elderly onset RA are treated less aggressively in terms of choice of treatment or time-to-switch to the next treatment step, resulting in the same clinical improvement.

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Data availability statement

The datasets used and/or analysed during the current study are available upon reasonable request.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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