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COHORT STUDIES

Disease-modifying drug retention rate according to patient age in patients with early rheumatoid arthritis: analysis of the ESPOIR cohort

S. Mathieu[1] · B. Pereira[2] · A. Saraux[3] · C. Richez[4] · B. Combe[5] · M. Soubrier[1]

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Abstract

Physicians are sometimes hesitant to use disease-modifying antirheumatic drugs (DMARDs) in elderly patients with rheumatoid arthritis (RA), as they are deemed too fragile, although there are no sufficient scientific evidence. We aimed to compare DMARD treatment retention in early RA patients from the ESPOIR cohort, according to age upon inclusion. Overall, treatment retention was evaluated as the percentage of patients whose DMARDs were not stopped, with stratification by age group: < 50, 50–64, and > 65 years. Survival curves were measured using the Kaplan–Meier method. Of the entire ESPOIR cohort ($n = 813$), 7% were > 65 years old. Methotrexate (MTX) was used by 521 patients, and was the sole DMARD for 198 patients. MTX treatment retention appeared better in patients > 65 years old compared to < 50 years old [HR 0.45 (0.25; 0.81); $p = 0.008$, $n = 195/198$] with adjustment on sex, smoking, positive anti-cyclic citrullinated peptide antibodies, positive rheumatoid factor, body mass index, changes in DAS28 and corticosteroid treatment. The proportion of patients using etanercept ($n = 111$), and this drug's retention rate, did not differ according to patient age. The proportion of patients treated with adalimumab ($n = 104$) was significantly higher in patients < 50 years old ($p = 0.003$), and treatment retention was marginally better among younger patients [HR 1.68 (0.88; 3.22), $p = 0.12$]. Within the ESPOIR cohort, DMARD retention did not appear to differ according to age—except for better retention of MTX treatment in patients 50–64 years old, and of adalimumab in patients < 50 years old.

Keywords Rheumatoid arthritis · ESPOIR cohort · Elderly · Drug retention

Introduction

Rheumatoid arthritis (RA) is an inflammatory joint disease that causes structural damage, potentially leading to disability and significant quality-of-life reduction. Such outcomes can be prevented by early initiation of appropriate treatment, with close "tight control" follow-up [1]. Prospects for remission are rising due to the emergence of biotherapies, such as tumor necrosis factor α (TNF-alpha) inhibitors, tocilizumab, abatacept, and rituximab [2]. Corticosteroids can help manage inflammation and disease activity, including among elderly patients [3]. However, oral corticosteroids are associated with increased risks of infections and cardiovascular diseases, even at low daily doses [4]. Thus, disease-modifying antirheumatic drug (DMARD) treatments must be carefully optimized to minimize risk while achieving clinical remission, specifically involving the absence of structural degradation [5].

✉ S. Mathieu
smathieu@chu-clermontferrand.fr

1 Rheumatology Department, CHU Gabriel Montpied, Clermont 1 University, Clermont-Ferrand, France

2 Department of Clinical Research and Innovation (DRCI), University Hospital of Clermont-Ferrand (CHU), Clermont-Ferrand, France

3 Department of Rheumatology, Brest University Hospital, Brest, France

4 Rheumatology Department, CHU Pellegrin, Bordeaux, France

5 Département de Rhumatologie, CHU Montpellier, Université de Montpellier, Montpellier, France

As the general population becomes increasingly older, the population of RA patients is also aging. The number of patients over 75 years of age with RA is growing, and most still lead active lives and want to be able to continue enjoying their hobbies. Most of these patients want their disease to be well managed; therefore, current recommendations advise treating elderly RA patients using the same methods employed in younger sufferers, and setting the same remission objectives [6]. However, it seems that there is less prescription of DMARD and bDMARD in the elderly. This impression is based more on discussion with colleagues or on the experience of rheumatologists than on scientific evidence. The literature is lacking in this subject of area and somewhat contradictory regarding advice for the management or RA in elderly patients [7]. Huscher et al. concluded to a potential treatment deficit in older RA patients in 2013 although Sugihara et al. reported that low disease activity is a realistic goal in elderly RA patients [8]. In their study population of 151 patients, Sugihara et al. applied the "treat-to-target" strategy in 83% of cases at 6 months, and in 75% of cases at 1 year. In 50% of patients, no evolution of structural damage was observed after 1 year [9]. Moreover, several studies have reported that treatment duration and biotherapy efficacy do not differ between elderly and young RA patients [10–12]. However, these findings are not unanimously supported. Payet et al. assessed 1,709 patients from the AutoImmunity and Rituximab (AIR) registry, comparing rituximab efficacy and tolerance across different age groups. The study cohort included 417 patients aged 64–75 years, and 191 patients over 75 years of age. These elderly and very elderly patients received fewer lines of TNF-alpha inhibitor compared to younger patients. Treatment retention duration did not differ across the groups, but the infection rate was higher in the elderly subjects [13]. Similarly, Pers et al. evaluated the effects of tocilizumab in RA patients over and under 65 years old, and found that tolerance and treatment retention were identical in both groups, but clinical efficacy was poorer among patients over 65 years of age [14]. Several studies of the effects of TNF-alpha inhibitors in elderly patients have also concluded that efficacy is poorer in this population [15], while tolerance remains similar to in other age groups [16–19]. Notably, these elderly patients (> 75 years) have different profiles than younger patients, exhibiting more comorbidities (potential renal failure, cardiovascular diseases, etc.) and increased polypharmacy. Thus, physicians are more hesitant to prescribe DMARDs in these elderly patients due to fear of greater risk of adverse effects [20–25]. In such cases, good tolerance to treatment is the priority, and DMARDs are not necessarily optimized for achieving remission [26, 27].

The ESPOIR cohort study, a large national multicenter longitudinal and prospective cohort initiated by the French Society of Rheumatology included patients with undifferentiated arthritis or rheumatoid arthritis, of less than 6 months disease duration. In the present study, our main objective was to compare DMARD treatment retention over the follow-up in the ESPOIR cohort, according to patient age at inclusion and disease activity.

Methods

Study population

We analyzed all 813 patients of the French cohort "Etude et Suivi des Polyarthrites Indifférenciées Récentes (ESPOIR)" [28] and retained only the 698 patients that fulfilled diagnosis ACR/EULAR criteria of rheumatoid arthritis. ESPOIR cohort study initiated by The French Society of Rheumatology initiated is a large national multicenter, longitudinal and prospective cohort, to set up databases to allow various investigations on diagnosis, prognostic markers, epidemiology, pathogenesis and medico-economic factors in the field of early arthritis and rheumatoid arthritis.

Objective and primary endpoint

In this study, our primary objective was to evaluate treatment retention of DMARDs (methotrexate [MTX], hydroxychloroquine, TNF-alpha inhibitors, tocilizumab, abatacept, and rituximab) in the ESPOIR cohort over 5 years of follow-up, with comparisons between different age groups (> 65 years, 50–64 years, and < 50 years). The primary endpoint was treatment retention of DMARD, evaluated at every patient consultation during the 5-year follow-up of the ESPOIR cohort. We decided to analyze only the five first years of follow-up of the 10-year ESPOIR cohort because the number of patients followed after 5 years was too low to draw strong conclusions. We recorded the date of initiation of each DMARD, and then analyzed the DMARDs that were still being received at each follow-up visit.

Retention was defined as the same treatment still being received at the same dosage or at an altered dosage. A temporary suspension of treatment for less than 6 months was not considered as a treatment cessation. On the other hand, beyond 6 months, the treatment was considered stopped and if represcribed, we noted a new start date. Discontinued DMARD was defined as when a treatment was changed, including cessation of the previous treatment. When a treatment was still being administered but in combination with another DMARD (bi- or tritherapy), this was defined as discontinued monotherapy.

Statistical analysis

Statistical analyses for a two-sided type I error at 5% were performed using Stata software (Version 13; StataCorp, College Station, USA). Continuous data were described as mean ± SD or median [interquartile range (IQR)], according to statistical distribution. We evaluated the assumption of normality using the Shapiro–Wilk test. Patient age was first considered as a quantitative criterion, then by category according to clinical relevance: > 65 years, 50–64 years, and < 50 years. These age groups were compared at baseline using ANOVA or Kruskal–Wallis tests if the assumptions of ANOVA were not met for continuous parameters, and with the Chi-squared or Fisher's exact tests for categorical variables. Where appropriate (omnibus p value of < 0.05), post hoc tests were used to account for multiple comparisons: Tukey–Kramer or Dunn after ANOVA, and Kruskal–Wallis and Marascuillo after Chi-squared or Fisher's exact tests. Treatment retention during the 5 years of follow-up of the ESPOIR cohort was defined as the percentage of patients whose treatment was not discontinued or modified, as assessed at each follow-up visit. In analyses, comparing the overall retention of DMARD treatment among the different patient age groups during the 5-year follow-up in the ESPOIR cohort, any treatment discontinuation was considered as right-censored data.

Estimates were calculated using the Kaplan–Meier method. Next, between-group comparisons were performed using the log-rank test for univariate analyses, and Cox proportional-hazards regression for multivariate analyses. The following covariates were fixed according to univariate results and clinical relevance: sex, smoking, positive anticyclic citrullinated peptide antibodies (ACPA), rheumatoid factor, body mass index (BMI), changes in disease activity score (DAS28), and corticosteroid treatment. We studied the proportional-hazard hypothesis using the Schoenfeld test and plotting residuals, and tested the interactions between possible prognostic factors. The results were expressed as hazard ratios (HRs) and 95% confidence intervals. A sensitivity analysis was conducted for the same statistical analysis plan with age considered a continuous variable.

ESPOIR was registered in ClinicalTrials under No. NCT03666091.

Results

Our present analyses included the 698 RA patients in the ESPOIR cohort. The mean age upon inclusion was 48.6 ± 12.1 years. Around half of the population were < 50 years old (335/698, 48%), and 7% (n = 50) were over 65 years of age. Table 1 summarizes the comparison of patient characteristics upon inclusion according to age.

Table 1 Comparison of three age categories according to characteristics upon inclusion

	Under 50 y	50–64 y	Over 65 y	p value
Female	274, 81.8%	229, 73.2%	33, 66.0%	0.006
Smoker	175, 52.2%	151, 48.2%	15, 30.0%	0.013
DAS28	5.12 ± 1.24	5.34 ± 1.21	5.68 ± 1.47	0.005
HAQ	0.97 ± 0.67	1.06 ± 0.67	1.17 ± 0.81	0.096
BMI	24.08 ± 4.65	25.97 ± 4.72	26.04 ± 3.20	< 0.001
ESR	20 [11; 34]	24 [12; 45]	33 [22; 68]	< 0.001
CRP	9 [5; 23]	10 [4; 27]	17 [6; 45]	0.010
Positive RF	236, 70.5%	190, 60.7%	30, 60.0%	0.02
Positive ACPA	174, 51.9%	122, 39.0%	19, 38.0%	0.002
Sharp	1.0 [0.0; 3.3]	2.5 [1.0; 5.0]	4.0 [1.0; 9.5]	< 0.001
Comorbidities	199, 59.8%	221, 71.1%	44, 88.0%	< 0.001

Data are presented as n, % or as mean ± standard deviation

y years old, *DAS28* disease activity score, *HAQ* Health Assessment Questionnaire, *BMI* body mass index, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *RF* rheumatoid factor, *ACR* American College of Rheumatology

Patients over 65 years of age were primarily male, nonsmokers, had a higher BMI, and presented with a higher mean DAS28 score (indicating more significant biological inflammatory syndrome).

Information regarding corticosteroid therapy was available at baseline only for 86 patients. We did not have data at baseline for the other patients and we did not know if information was missing or if the patient did not use corticosteroid. Among the 86 patients on corticosteroid treatment at baseline, 13 (15.1%) were used dose higher or equal to 0.5 mg/kg/day. The mean corticosteroid dose did not statistically differ according to age at baseline (p = 0.96): 19.4 ± 15.6 mg/day in patients < 50 years (n = 40), 18.7 ± 13.7 mg/day in 50–64 years (n = 39) and 17.1 ± 13.2 mg/day in patients > 65 years (n = 7). The mean dose of corticosteroid after 1 year of follow-up in the ESPOIR cohort was already not different in the 3 age groups (p = 0.81) and was lower compared with baseline: 7.8 ± 6.6 mg/day in patients < 50 years (n = 133), 7.6 ± 5.2 mg/day in 50–64 years (n = 147) and 8.3 ± 10.1 mg/day in patients > 65 years (n = 20).

Over the 5-year follow-up, 83 patients did not receive DMARDs. In this group, the mean age upon inclusion was 49.6 ± 13.0 years, 18/83 (22%) were men, 39/83 (47%) were nonsmokers, and the mean DAS28 upon admission was 4.81 ± 1.41. Among these 83 patients, 39 (47%) had erythrocyte sedimentation rates (ESR) of ≥ 20 mm/h, 15 (18%) tested positive for anti-CCP antibodies, 23 (28%) presented rheumatoid factors with titers of > 10, and 36 (43%) had median Sharp scores of > 1 upon inclusion. In this patients group (n = 83), 21 patients were lost to follow-up from the start, and 9 patients were lost after one or two follow-up

visits. In 20 patients, rapid DAS remission was achieved, with no structural progression. Thirty-three patients exhibited Sharp score increases of over 0.5 point, of whom 27 exhibited low disease activity or DAS remission, and the other 6 exhibited moderate or strong disease activity.

Among the patients who received DMARDs, 267 received one DMARD, 173 received two, 103 received three, 36 received four, and 36 received five or more. MTX was taken by 521 patients, and was used as monotherapy in 198. The proportion of patients receiving MTX monotherapy did not significantly differ among the three age groups: 72.7% of patients < 50 years, 76.4% of patients 50–64 years, and 68.4% of patients > 65 years ($p = 0.67$). By the same way, the percentage of patients started on MTX as first DMARD in each group of age was not different (60.5% in patients < 50 years ($n = 296$), 63.3% in 50–64 years ($n = 275$) and 59.5% in patients > 65 years ($n = 42$); $p = 0.76$). Seventy-four percent of the 698 RA patients are still present in the cohort at 5 years. The median time of stopping MTX is 15.5 months [IQR: 5.6–29.5]. MTX treatment retention appeared to be better among the oldest subjects (Fig. 1) ($p = 0.01$). This result was confirmed by multivariable analysis adjusted on sex, smoking, positive ACPA, FR, BMI, changes in DAS28 and corticosteroid treatment. We found no impact on the corticosteroid use on the results of retention rate of MTX. Indeed, we also observed significantly better MTX retention in patients of 50–64 years compared to those < 50 years old [HR 0.45 (0.25; 0.81); $p = 0.008$, $n = 195/198$].

MTX treatment retention decreased with the number of treatments received by the patients (Fig. 2), but remained better among the oldest subjects irrespective of the number of DMARD treatment lines received: [HR = 0.66 (0.50; 0.87), $p = 0.003$, $n = 491/521$] Hydroxychloroquine was taken by 148 patients, and was the only DMARD used by

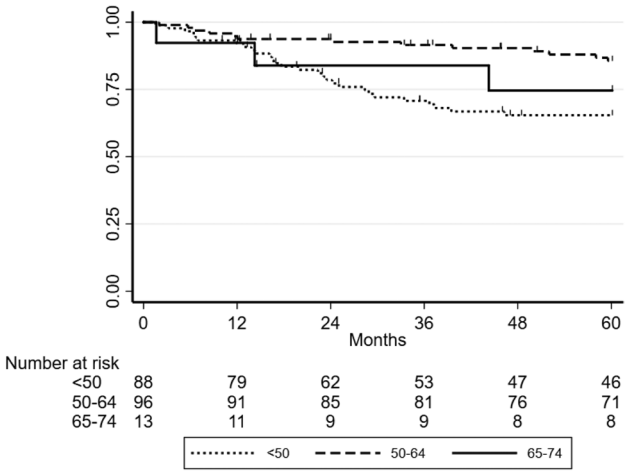

Fig. 1 Methotrexate monotherapy retention according to age

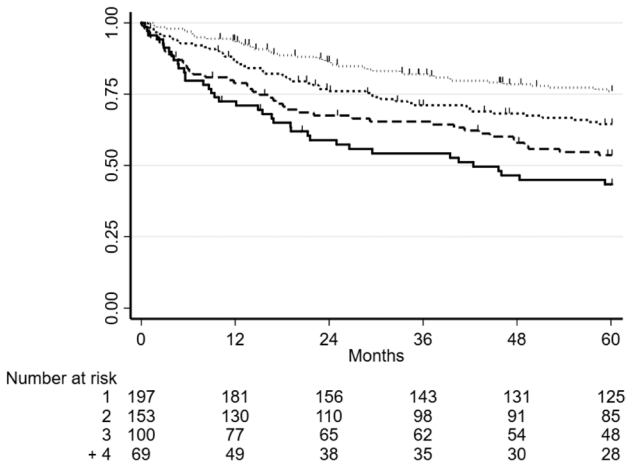

Fig. 2 Methotrexate monotherapy retention according to number of disease-modifying antirheumatic drug lines received

39 patients. Treatment retention among these patients did not differ according to age [multivariable analysis: HR 1.15 (0.71; 1.84), $p = 0.57$ for 50–64 years compared to those < 50 years].

The percentage of patients treated with biologics (TNF-alpha inhibitor, rituximab, tocilizumab, and abatacept) was greater among the youngest subjects: 38% of patients < 50 years old ($n = 113/298$), 28% of patients 50–64 years old ($n = 76/275$), and 24% of patients > 65 years old ($n = 10/42$). In our analyses, we focused on the rates of TNF-alpha inhibitor use because the numbers of patients using the other biotherapies were too low: rituximab, $n = 35$; tocilizumab, $n = 20$; and abatacept, $n = 18$. The proportion of patients using TNF-alpha inhibitors was higher among patients < 50 years old (110/298, 37%) than patients 50–64 years old (70/275, 25%) and patients > 65 years old (9/42, 21%) ($p = 0.005$). TNF-alpha inhibitors' retention rate did not differ according to patient age ($p = 0.38$) (Fig. 3). For etanercept ($n = 111$), the proportion of RA patients using this treatment was not different among inclusion age ($p = 0.61$), and treatment retention for etanercept did not differ according to patient age upon inclusion [multivariable analysis: HR 0.60 (0.26; 1.40), $p = 0.24$ for 50–64 years compared to those < 50 years, $n = 73/111$]. A total of 104 patients were treated with adalimumab, and the rate of adalimumab use was significantly higher among patients < 50 years old (22%, 66//298) than patients of 50–64 years old (12%, 34/275) and patients > 65 years old (10%, 4/42) ($p = 0.003$). Adalimumab treatment retention appeared to be marginally worse among the oldest patients [univariate analysis: HR 1.72 (0.99; 3.02), $p = 0.055$], and this difference remained marginally significant in multivariate analysis [HR 1.68 (0.88; 3.22), $p = 0.12$; $n = 93/104$]. The

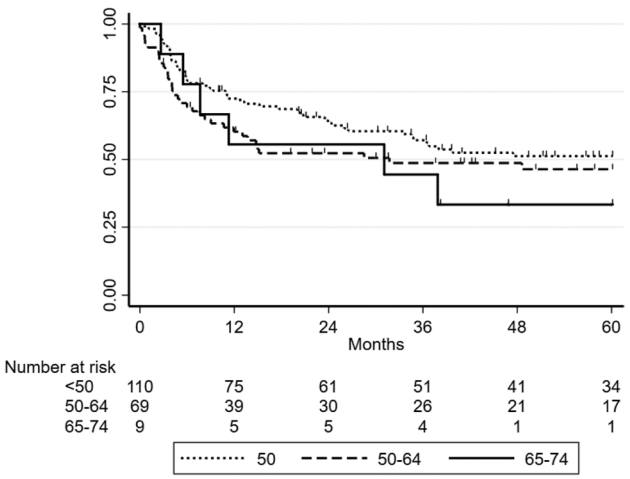

Fig. 3 TNF-alpha inhibitors retention according to age

rates of other TNF-alpha inhibitors could not be effectively analyzed due to low numbers: infliximab, $n = 23$; certolizumab, $n = 11$; and golimumab, $n = 3$.

Sensitivity analysis with age considered as continuous variable found the same results for treatment retention for MTX, etanercept and adalimumab. The conclusions were similarly supported by these results (data not shown).

Discussion

Our present results showed that DMARD treatment retention did not appear to fundamentally differ according to patient age upon inclusion in the ESPOIR cohort—except that MTX retention was better among patients 50–64 years old, and adalimumab retention was better among patients < 50 years old. The ESPOIR cohort included few elderly individuals, with only 59 patients (7%) over 65 years of age. Although those who were ≥ 65 years old upon inclusion were ≥ 75 years of age by the end of the 10-year follow-up. This reflects common practice for elderly patients, yet poses challenges for analysis. As this study examined real-life follow-up and prescription practices, the number of treatment sequences is important, thus, rendering it difficult to draw solid conclusions.

Our analyses of the use and retention of biologics treatments primarily concerned etanercept and adalimumab. We were unable to analyze data for other individual TNF-alpha inhibitors or biotherapies due to the small numbers of samples. This can largely be explained by the fact that some biotherapies (e.g., certolizumab, golimumab, and tocilizumab) had only recently received market approval, and were thus less common 10 years ago compared to other TNF-alpha inhibitors. Moreover, the use of infliximab by only 21 patients was likely because the included patients were mostly younger people, whose lifestyles and professional activities are better served by subcutaneously administered biotherapies. In our sample, nearly identical numbers of patients received etanercept or adalimumab. In the Swedish registry, collated between 2003 and 2011, etanercept was the most commonly prescribed TNF-alpha inhibitor [29], while worldwide prescription rates show adalimumab at the top of the list. It is unfortunate that we were unable to study a larger sample of patients receiving abatacept ($n = 18$), since this treatment is often prioritized in elderly subjects, largely due to its reduced infection risk [30] and good efficacy [6, 11]. Ebina et al. recently described the tolerance of biotherapies and reasons for discontinuation among RA patients > 65 years old, and reported that abatacept presented the best treatment retention in this population based on observed adverse effects and efficacy [31].

We cannot exclude the possibility that MTX treatment retention was better among the elderly population because TNF-alpha inhibitors were less commonly used in this demographic. The results of our present multivariate analysis were inconclusive. The impact of corticosteroid therapy is also crucial, as it is possible that MTX treatment was maintained for a longer duration among elderly patients because they received larger corticosteroid doses, enabling better control of disease activity. However, our analysis showed that the mean corticosteroid dose did not differ according to patient age. Additionally, the percentage of patients whose corticosteroid dosage was halved over time did not differ between the age groups (< 50 years, 50–64 years, and > 65 years). In the Corpus study, RA management was compared between patients over and under 75 years of age, revealing that the elderly patients exhibited less recourse to TNF-alpha inhibitors and received higher doses of corticosteroids [32]. The Corpus study included patients from 2007 to 2009, a time period during which physicians may have been more hesitant to intensify treatment in elderly subjects. This phenomenon may explain why MTX retention was better among elderly patients, especially MTX monotherapy, since TNF-alpha inhibitors were less frequently prescribed. We obtained similar results in the ESPOIR cohort, albeit with more frequent prescription of TNF-alpha inhibitors. The most commonly prescribed was etanercept, which is recognized as offering better tolerance and lower infection risk.

This study had several limitations. One was the upper age limit (< 70 years) at inclusion in the ESPOIR cohort, which did not allow us to analyze patients of > 75 years old. It would have been interesting to observe very elderly patients, as it may be this age group that differs the most from younger populations with regards to DMARD prescriptions. On the other hand, the 10-year follow-up period of the ESPOIR cohort was an advantage, as it enabled us to assess whether patients aged > 65 years upon admission had different follow-ups once they reached > 75 years of age compared

to younger patients. Our analysis revealed no apparent difference in follow-up or prescriptions. Within the entire study cohort of 813 patients with early-stage RA, 138 received no treatment. This number may seem surprising, and raise questions regarding the reliability of the cohort. However, these 138 patients included 39 for whom an RA diagnosis was excluded, and 51 who were lost to follow-up, and the rest of this group had RA that went into remission without requiring treatment. This demonstrates that the cohort results were similar to in common practice and real-life populations, where there is doubt surrounding diagnoses, patients do not show up for consultation, some stop their treatment, and some no longer need drugs because they are in remission.

The presently analyzed data from the ESPOIR cohort appears to validate the recommendation that elderly patients with RA should be treated and followed-up the same as younger patients, with recourse to biotherapies to obtain remission.

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