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Original article

Effectiveness and safety of abatacept in elderly patients with rheumatoid arthritis enrolled in the French Society of Rheumatology's ORA registry

Clément Lahaye[1], Martin Soubrier[2], Aurélien Mulliez[3], Thomas Bardin[4], Alain Cantagrel[5], Bernard Combe[6], Maxime Dougados[7,8], René-Marc Flipo[9], Xavier Le Loët[10], Thierry Shaeverbeke[11], Philippe Ravaud[12], Xavier Mariette[13] and Jacques-Eric Gottenberg[14] on behalf of the French Society of Rheumatology

Abstract

Objective. To study the effect of age on the risk–benefit balance of abatacept in RA.

Methods. Data from the French orencia and RA registry, including a 2-year follow-up, were used to compare the effectiveness and safety of abatacept according to age.

Results. Among the 1017 patients, 103 were very elderly (⩾75 years), 215 elderly (65–74), 406 intermediate aged (50–64) and 293 very young (<50). At baseline, elderly and very elderly patients had longer disease duration, higher CRP levels and higher disease activity. These age groups showed a lower incidence of previous anti-TNF therapy and less common concomitant use of DMARDs, but a similar use of corticosteroid therapy. After adjusting for disease duration, RF/ACPA positivity, use of DMARDs or corticosteroids and previous anti-TNF treatment, the EULAR response (good or moderate) and the remission rate were not significantly different between the four age groups. At 6 months, the very elderly had a significantly lower likelihood of a good response than the very young (odds ratio = 0.15, 95% CI: 0.03, 0.68). The decrease in DAS28-ESR over the 24-month follow-up period did not differ by age. Increasing age was associated with a higher rate of discontinuation for adverse events, especially severe infections (per 100 patient-years: 1.73 in very young, 4.65 in intermediates, 5.90 in elderly, 10.38 in very elderly; $P < 0.001$).

Conclusion. The effectiveness of abatacept is not affected by age, but the increased rate of side effects, especially infections, in the elderly must be taken into account.

Key words: abatacept, effectiveness, elderly, management, rheumatoid arthritis, safety.

CLINICAL SCIENCE

Rheumatology key messages

- In the ORA registry, age did not affect the effectiveness of abatacept in RA.
- Elderly RA patients treated with abatacept were particularly prone to infections.
- For elderly RA patients, abatacept remains an interesting alternative to anti-TNF drugs, especially when faced with harmful corticosteroids.

[1]Department of Internal Medicine, Hôpital Estaing, [2]Department of Rheumatology, Hôpital Gabriel Montpied, [3]Biostatistics Unit, La Délégation Recherche Clinique et Innovation, CHU de Clermont-Ferrand, Clermont-Ferrand, [4]Department of Rheumatology, Hôpital Lariboisière, Assistance Publique, Hôpitaux de Paris, Paris, [5]Department of Rheumatology, Purpan Hospital, Toulouse, [6]Department of Rheumatology, Hôpital Lapeyronie, Montpellier, Université Montpellier I, Montpellier, [7]Department of Rheumatology, Hôpital Cochin, Assistance Publique Hôpitaux de Paris, Paris, [8]INSERM (U1153), Clinical Epidemiology and Biostatistics, PRES Sorbonne Paris-Cité, Paris, [9]Department of Rheumatology, Lille Teaching Hospital, Lille, [10]Department of Rheumatology, Rouen Teaching Hospital, Rouen, [11]Department of Rheumatology, Bordeaux Teaching Hospital, Bordeaux, [12]Centre d'Epidémiologie Clinique, Hotel Dieu, Assistance Publique, Hôpitaux de Paris, [13]Department of Rheumatology, Hôpital Bicêtre, Assistance Publique, Hôpitaux de Paris and [14]Department of Rheumatology, Strasbourg Teaching Hospital, Strasbourg, France

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Correspondence to: Martin Soubrier, CHU Clermont-Ferrand, Department of Rheumatology, Hôpital Gabriel Montpied, 58 rue Montalembert, Clermont-Ferrand, 63003, France.
E-mail: msoubrier@chu-clermontferrand.fr

Introduction

Among inflammatory rheumatisms, RA particularly affects the elderly [1]. People aged over 60 years account for nearly one-third of all RA patients. Given the high prevalence of RA and the ageing of the population, the already high number of patients with elderly-onset RA is rapidly increasing [2]. This epidemiological challenge comes on top of specific difficulties concerning diagnosis and treatment [3].

Maintenance treatment, traditionally based on conventional synthetic DMARDs, with MTX being the treatment of choice, has been supplemented by the arrival of biologic originator DMARDs (boDMARDs) over the last 15 years. This therapeutic breakthrough, combined with a more intensive, tighter control strategy, has led to dramatic improvements in patient outcomes. Although the goals of RA treatment (to achieve remission as rapidly as possible and to prevent structural damage so as to preserve function and quality of life over the long term) and the benefits of treatment remain similar to those of younger patients, management of elderly-onset RA tends to be less aggressive [4]. Therefore, boDMARDs, combinations of DMARDs and sufficiently high MTX doses tend to be used less frequently [5, 6]. Reluctance to use modern management in the elderly paradoxically means that these patients are more exposed to symptomatic but harmful drugs such as glucocorticoids and NSAIDs [7–9]. Fear of side effects and doubts concerning the efficacy of boDMARDs (which persist because of the paucity of specific studies in the elderly) are major obstacles to their use.

Multiple randomized controlled trials have assessed acceptable efficacy and safety outcomes of abatacept as first- or second-line therapy, even in comorbid RA patients [10–13]. A cohort of RA patients with previous anti-TNF exposure also demonstrated similar response and remission rates among those who switched to another anti-TNF and those who initiated abatacept [14]. However, little is known about the use of abatacept in elderly RA patients. This study aims to evaluate the effectiveness and safety of abatacept in elderly *vs* younger patients using data from the French National Orencia and RA (ORA) Registry of RA patients treated with abatacept.

Materials and methods

The ORA registry is a French nationwide, multicentre, prospective cohort for investigating the effectiveness and safety of first treatment by abatacept in patients with RA after failure or contraindication of anti-TNF therapy. This real-world database was designed by the French Society of Rheumatology (FSR) and the French Rheumatism and Inflammation Club. The registry data are the exclusive property of the FSR, who was the promoter of the registry. The methodology of the registry has been previously reported [15]. The registry was approved by the French authorities (Comite Consultatif sur le Traitement de l'Information en Matière de Recherche dans le Domaine de la Sante and Commission Nationale de l'Informatique et des Libertes).

French rheumatologists are able to prescribe abatacept in combination with MTX (in the absence of contraindications) to any patient with moderate to severe RA, following an inadequate response to previous treatment with one or more DMARDs including MTX or an anti-TNF drug. This treatment is fully reimbursed by social security in cases of severe active RA.

All French hospital and community-based rheumatology units were invited to participate. All consecutive eligible patients (patients receiving abatacept for RA) identified in the 82 participating centres were recruited from June 2008 to April 2010, after having given their written informed consent. Patients were followed prospectively for 5 years after the initial infusion of abatacept. For each patient, available laboratory and clinical data were collected at baseline and then every 6 months. The mean follow-up period for this study was 2 years and analysis concerning the database was frozen in January 2013. Our longitudinal study, based on this registry, was approved by the scientific committee of FSR. Patients were divided into four groups according to their age: <50 years (very young), 50–65 (intermediate-aged), 65–74 (elderly) and $\geqslant 75$ (very elderly). The first two groups together are referred to as young (<65), and the last two groups as aged (>65).

Safety was assessed according to the percentage of patients who discontinued treatment because of adverse events, which included infusion-related reactions to abatacept (anaphylactic shock, skin rash, infusion reactions occurring between the start of infusion and the following 24 h), severe infection (SI), cancer and death. SI was defined as an infection requiring hospitalization and/or intravenous antibiotics and/or resulting in death. The effectiveness of abatacept was assessed by the percentage of EULAR responses (good, moderate, none or remission), the rate of maintenance therapy and the change in DAS28 and/or its parameters, including inflammatory syndrome.

Statistical analysis

The statistical analysis was performed using Stata software (version 12, StataCorp, College Station, USA). Tests were two-sided, with a type I error set at $\alpha = 0.05$. Each analysis was performed for age groups categorized into two classes (>65 and <65) or four modalities ($\geqslant 75$, 65–74, 50–65 and <50). The baseline characteristics of the study population (safety data, DAS, ESR and CRP) were reported as mean (S.D.) or median and interquartile range according to statistical distribution for quantitative variables and as frequencies (associated percentages) for categorical parameters. Comparisons between age groups were made using a chi-squared test (or Fisher's exact test when appropriate) for categorical variables and the analysis of variance (ANOVA) or Kruskal–Wallis test when ANOVA conditions were not verified (normality was assessed with the Shapiro–Wilk test and equality of variance with the Levene test) for quantitative variables. Further tests were used to consider the ordered nature of the age classes: the chi-squared trend test and Kendall's tau coefficient for qualitative and quantitative variables,

respectively. For simplification, only trend P-values are presented in results and tables, because standard P-values provided no additional information with our data. Remission rates at 6, 12 and 24 months were compared between age groups by logistic regression. An adjusted analysis taking into account disease duration, RF/ACPA positivity, presence of co-medication (DMARD or oral corticosteroids) and previous anti-TNF treatment was also carried out for remission rates and EULAR response rates. The EULAR response rates (good, moderate, no response) at 6, 12 and 24 months were compared between age groups by multinomial regression. To take into account the repeated measures over time, we completed these analyses with generalized linear mixed models to study the fixed effects of age group, time-point evaluation and all other (statistically and clinically) relevant covariates, taking into account between- and within-subject variability. Results are reported in terms of odds ratios with 95% CIs. We carried out analyses of treatment discontinuation (for adverse event and inefficacy) using survival methods, to take into account the time to event. Univariate analysis was performed using Kaplan–Meier methods and Log-Rank tests. For multivariate analysis, we constructed a Cox proportional hazard model, adjusted on all relevant covariates. Results of these analyses are shown as hazard ratios (HRs) and their 95% CIs. In cases of drug discontinuation because of lack of effectiveness, the patient was considered a non-responder. In cases of drug discontinuation for another reason before the evaluation date, the response on the day of discontinuation was taken into account. Longitudinal changes in the DAS score and its components were also analysed by random-effects models, taking into account the interaction between age groups and time-point evaluation. A sensitivity analysis was performed to study and characterize the statistical nature of missing data.

Results

Population characteristics

A total of 1017 patients were enrolled in the study: 293 very young (<50 years), 406 intermediate (50–64 years), 215 elderly (65–74 years), and 103 very elderly (>75 years) (mean age 58.2 years) (Table 1). At baseline, there were no statistically significant differences between the groups in terms of sex or presence of RF or ACCP. Median (interquartile range) disease duration in years was significantly longer with age. Disease severity increased with age, in terms of disease activity (mean DAS28-ESR) and inflammatory syndrome. Patients in the listed age groups were treated with abatacept because of failure (respectively, 91.5, 87, 85.6 and 82.4%, P = 0.01) or contraindication to anti-TNF agents. Combination therapy with DMARDs was less common with age.

Effectiveness of abatacept

With regard to good or moderate (*vs* no) EULAR responses after adjustment (for disease duration, RF/ACCP positivity, use of DMARDs, use of corticosteroids and previous anti-TNF treatment), good responses were not significantly more common in younger patients than in patients >65 years at 6 months [odds ratio (OR) = 1.36, 95% CI: 0.75, 2.44], 12 months (OR = 0.78, 95% CI: 0.42, 1.47) or 24 months (OR = 0.83, 95% CI: 0.38, 1.84) follow-up, and neither were moderate responses at

Table 1 Demographic and disease characteristics of RA patients at baseline (n = 1017)

Characteristics	Missing data, n (%)	<50 years, n = 293	50–64 years, n = 406	65–74 years, n = 215	⩾75 years, n = 103	P-values (trend[a])
Age, mean (s.d.), years	0 (0)	41 (7.9)	57.3 (4)	70 (2.8)	79.3 (3)	<0.001
Female, n (%)	0 (0)	248 (84.6)	302 (74.4)	170 (79.1)	87 (84.5)	0.65
Disease duration, median (IQR), years	14 (1.4)	14 (10–22)	16 (11–23)	20 (14–29)	19 (11–26)	<0.001
DMARDs, n (%)	14 (1.4)	203 (69.5)	265 (66.3)	130 (61.9)	61 (60.4)	0.04
Corticosteroids, n (%)	18 (1.8)	217 (74.6)	304 (76)	161 (77.8)	77 (76.2)	0.51
Previous treatment with anti-TNF, n (%)	1 (0.1)	268 (91.5)	353 (87)	184 (85.6)	84 (82.4)	0.01
DAS28, mean (s.d.)	165 (16.2)	5.2 (1.3)	5.3 (1.3)	5.3 (1.4)	5.8 (1.1)	0.001
DAS CRP, mean (s.d.)	315 (31)	4.9 (1.2)	5 (1.3)	5.1 (1.3)	5.3 (1)	0.04
CRP, median (IQR), mg/l	264 (26)	10 (4–23)	13.5 (5–30)	15 (6–37)	17.8 (8–42)	<0.001
ESR, median (IQR), mm	336 (33)	24 (11–40)	27.5 (14–49)	34 (18–52)	43 (25–71.5)	<0.001
RF positivity, n (%)	181 (17.8)	164 (67.5)	236 (71.1)	130 (76.5)	66 (72.5)	0.12
RF titre, median (IQR), IU/ml	597 (58.7)	106 (41–256)	144 (64–320)	118 (46–267)	109 (40–256)	0.94
ACCP antibody positivity, n (%)	737 (27.5)	153 (69.2)	191 (67.3)	123 (78.9)	48 (63.2)	0.66
ACCP antibody titre, median (IQR)	668 (65.7)	212 (102–369)	250 (82–340)	239 (63–340)	250 (110–800)	0.93
Gammaglobulin, median (IQR)	501 (49.3)	10.9 (9.3–13.9)	10.3 (8.4–12.9)	9.6 (7.6–12.7)	10.1 (8.2–13.7)	0.006
IgG, median (IQR), g/l	672 (66.1)	12.5 (10.1–14)	10.9 (8–13.9)	10.3 (7.1–12.8)	9.5 (7.4–12.8)	<0.001
IgM, median (IQR), g/l	675 (66.4)	1.4 (0.8–1.9)	1.1 (0.7–1.6)	1.1 (0.6–1.8)	0.9 (0.6–1.4)	0.002
IgA, median (IQR), g/l	677 (66.6)	2.4 (1.8–3.4)	2.9 (2–4)	2.4 (1.8–3.6)	3.3 (2.1–4.9)	0.17

[a]Taking into account the ordered nature of age groups. IQR: interquartile range; n: number; S.D.: standard deviation.

6 months (OR = 0.72, 95% CI: 0.46, 1.10), 12 months (OR = 0.76, 95% CI: 0.45, 1.30) or 24 months (OR = 1.15, 95% CI: 0.55, 2.37) (Table 2). Comparison of each age group with the three other age groups showed no statistically significant difference in moderate response rate (*vs* no response), regardless of follow-up time (Fig. 1). However, at 6 months, the ⩾75 age group had a statistically significant lower likelihood of a good response (*vs* no response) than the <50 age group (OR = 0.15, 95% CI: 0.03, 0.68). This difference was no longer statistically significant at 12 months (OR = 0.35, 95% CI: 0.06, 1.94) or 24 months (OR = 0.75, 95% CI: 0.13, 4.26).

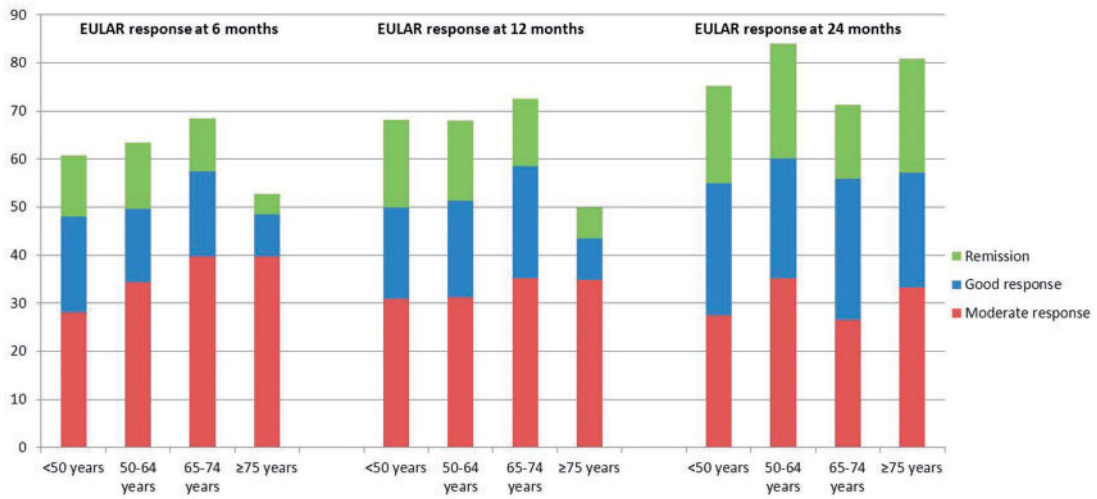
A statistically significant decrease in the DAS28-ESR score (Fig. 2) and its components (ESR, number of swollen joints, number of tender joints, disease activity) was already observed at 6 months of treatment and became more pronounced over the 24-month follow-up in all four age groups. The extent of the DAS28 improvement is similar in the four age groups. At baseline, the very elderly had a higher DAS score than the three other groups [5.81 *vs* (respectively) 5.33 in the elderly (P = 0.04), 5.33 in the intermediate-aged (P = 0.02), 5.17 in the very young (P = 0.001)] and higher ESR values [50 *vs* (respectively) 34 in the intermediate-aged (P < 0.001) and 30.2 in the

Table 2 Response to treatment with abatacept in elderly and young patients with RA

6-month follow-up	Elderly patients ⩾65 years n = 236	Young patients <65 years n = 563	Crude analysis		Adjusted analysis[a]	
			OR (95% CI)	P-value	OR (95% CI)	P-value
Remission, n (%)	21 (8.9)	75 (13.3)	1.57 (0.95, 2.62)	0.08	1.54 (0.79, 3.03)	0.21
EULAR response	n = 214	n = 512				
None, n (%)	97 (45.3)	261 (51)	1		1	
Moderate, n (%)	85 (39.7)	163 (31.8)	0.71 (0.50, 1.01)	0.06	0.72 (0.46, 1.10)	0.13
Good, n (%)	32 (15)	88 (17.2)	1.02 (0.64, 1.63)	0.93	1.36 (0.75, 2.44)	0.31
12-month follow-up	n = 175	n = 419				
Remission, n (%)	21 (12)	72 (17.2)	1.52 (0.90, 2.56)	0.12	0.91 (0.45, 1.85)	0.80
EULAR response	n = 157	n = 376				
None, n (%)	72 (45.9)	185 (49.2)	1		1	
Moderate, n (%)	55 (35)	117 (31.1)	0.83 (0.54, 1.26)	0.38	0.76 (0.45, 1.30)	0.32
Good, n (%)	30 (19.1)	74 (19.7)	0.96 (0.54, 1.59)	0.87	0.78 (0.42, 1.47)	0.45
24-month follow-up	n = 99	n = 232				
Remission, n (%)	17 (17.2)	52 (22.4)	1.39 (0.76, 2.56)	0.28	0.94 (0.40, 2.24)	0.89
EULAR response	n = 89	n = 208				
None, n (%)	39 (43.8)	87 (41.8)	1		1	
Moderate, n (%)	25 (28.1)	67 (32.2)	1.20 (0.66, 2.18)	0.55	1.15 (0.55, 2.37)	0.72
Good, n (%)	25 (28.1)	54 (26)	0.97 (0.53, 1.78)	0.92	0.83 (0.38, 1.84)	0.65

[a]Analyses were adjusted for concomitant DMARDs, use of corticosteroids, previous treatment with anti-TNF drugs, disease duration, disease activity, presence of anti-CCP antibodies and presence of RF. n: number; OR: odd ratio.

Fig. 1 EULAR response at 6, 12 and 24 months according to age, in percent



very young ($P < 0.001$)]. These differences were no longer statistically significant from 12 months for the DAS score and from 18 months for the ESR values. Among the others items of the DAS28-ESR, the reduction in the number of swollen joints, tender joints and Visual Analogue Scale disease activity did not significantly differ according to age.

The remission rate in young patients did not significantly differ from that of patients aged >65 at 6 months (OR = 1.54, 95% CI: 0.79, 3.03), 12 months (OR = 0.91, 95% CI: 0.45, 1.85) or 24 months (OR = 0.94, 95% CI: 0.40, 2.24) (Table 2). Even taking into account the four age groups, there was no statistically significant tendency concerning the remission rate at 6 months (respectively 12.6, 13.8, 10.9 and 4.2%, P = 0.09), 12 months (respectively 18.1, 16.6, 14.1 and 6.4%, P = 0.06) and 24 months (respectively 20.2, 23.8, 15.4 and 23.8%, P = 0.70) (Fig. 1).

At baseline, the four age groups had been equally exposed to corticosteroids (respectively 74.6, 76, 77.8 and 76.2%, P = 0.51). The 6-, 12-, 18- and 24-month follow-ups showed a significant decrease in both the proportion of patients taking corticosteroids (71.1, 66.9, 60.4 and 53.4%, $P < 0.001$) and the dosage of corticosteroids (5.9, 4.9, 4.1 and 3.9 mg, $P < 0.001$).

In multivariable analysis, ACCP positivity was a factor predictive of good or moderate EULAR response for patients under 50 (OR = 3.18, 95% CI: 1.24, 8.15, P = 0.02), between 50 and 64 (OR = 2.12, 95% CI: 0.96, 4.70, P = 0.06) and between 65 and 74 (OR= 3.95, 95% CI: 1.80, 8.66, P = 0.001), but not for very elderly patients (OR = 1.30, 95% CI: 0.30, 5.65, P = 0.73). In contrast, RF positivity was not a predictive factor for good or moderate EULAR response.

Adverse events during the study treatment period

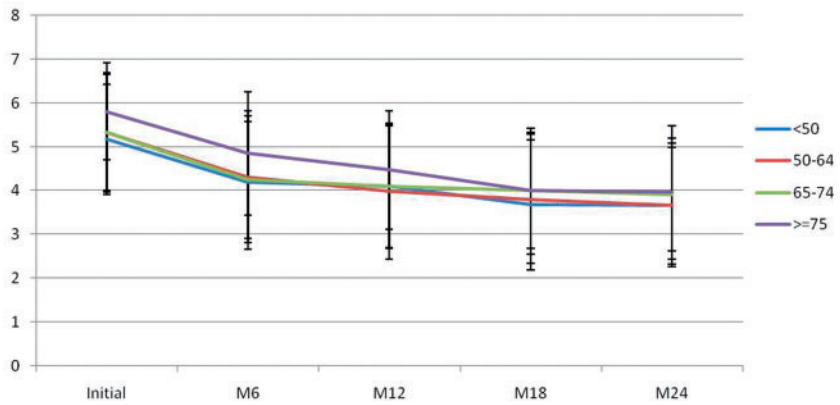
Three-quarters of patients stopped their treatment during follow-up at least once, with no age-related differences (73.1% under 50, 69.8% between 50 and 64, 75.6% between 65 and 74 and 73.3% after 75, P = 0.61) (Table 3). The median retention period in months before one discontinuation did not significantly differ according to age [respectively 11.5 (6.4–21), 12.9 (6.7–23.6), 14.9 (7.1–26.6), 9.7 (6.2–17.9), P = 0.31]. Although the major cause of treatment discontinuation was lack of effectiveness (more often secondary than primary), the reasons differed significantly according to age. The first discontinuation for lack of effectiveness was more frequent among young patients (respectively 72.8, 68.7, 57.1 and 55.4%, $P < 0.001$). In parallel, first discontinuation for adverse events increased with age (respectively 7.8, 14.6, 21.7 and 20.3%, $P < 0.001$).

All the components of adverse events (SI, cancer or death) increased with age. The elderly presented more SIs (per 100 patient-years: 1.73, 4.65, 5.90 and 10.38, $P < 0.001$) (Table 4). The main infection sites were bronchopulmonary, genitourinary and articular. We observed a statistically significant increase in the onset of cancer (per 100 patient-years: 0.19, 1.46, 1.7 and 3.81, $P < 0.001$) and death (per 100 patient-years: 0.19, 1.06, 2.09 and 8.65, $P < 0.001$) with age (Table 4). Few factors appeared to influence tolerance in multivariate analysis. RF positivity seemed to decrease the risk of treatment discontinuation for lack of effectiveness, but only among young patients (HR = 0.56, 95% CI: 0.38, 0.84, P = 0.005). Treatment discontinuation for adverse events was more frequent among young patients with a history of SI (HR = 2.19, 95% CI: 1.02, 4.72, P = 0.04). These relations were not significant among old patients.

Discussion

Our study is one of the first to investigate the impact of age on the effectiveness and safety of abatacept in RA, especially in very elderly subjects. Our cohort confirms the demographic weight of subjects aged over 65 (31.2%) and even over 75 (10.1%) in daily practice, and provides valuable information on a population usually excluded from clinical trials. In our study, the effectiveness of abatacept did not differ significantly according to age, and the remission rate, EULAR response and reduction in DAS28-ESR were all similar in the four age groups. Furthermore,

Fig. 2 Change in DAS28-ESR score over time in the four age groups



Each point represents a mean DAS score. Vertical bars represent standard deviations.

Table 3 Reasons for discontinuation of abatacept treatment

Characteristics	<50 years, n = 293	50–64 years, n = 406	65–74 years, n = 215	⩾75 years, n = 103	P-values (trend[a])
At least one treatment discontinuation during follow-up, n (%)	206 (73.1)	275 (69.8)	161 (75.6)	74 (73.3)	0.61
Retention period, median (IQR), month	11.5 (6.4–21)	12.9 (6.7–23.6)	14.9 (7.1–26.6)	9.7 (6.2–17.9)	0.31
Reasons for first treatment discontinuation					
Discontinuation because of lack of effectiveness, n (%)	150 (72.8)	189 (68.7)	92 (57.1)	41 (55.4)	<0.001
Primary lack of effectiveness, n (%)	67 (44.7)	70 (37)	27 (29.4)	21 (51.2)	0.45
Loss of effectiveness, n (%)	83 (55.3)	119 (63)	65 (70.6)	20 (48.8)	
Discontinuation because of adverse event, n (%)	16 (7.8)	40 (14.6)	35 (21.7)	15 (20.3)	<0.001
Related to an infusion reaction, n (%)	8 (50)	3 (7.5)	5 (14.3)	2 (13.3)	0.04
Related to other adverse event, n (%)	8 (50)	37 (92.5)	30 (85.7)	13 (87.7)	
Discontinuation for another reason, n (%)	40 (19.4)	44 (16)	33 (20.5)	17 (23)	0.44
Unspecified reason, n (%)	0 (0)	2 (0.7)	1 (0.6)	1 (1.4)	0.20

[a]Taking into account the ordered nature of age groups. n: number.

Table 4 Causes of adverse events

Characteristics	<50 years, n = 293	50–64 years, n = 406	65–74 years, n = 215	⩾75 years, n = 103	P-values (trend[a])
Follow-up duration (patient-years)	1040	1506	763	289	
Severe infections					
Total number (per 100 patient-years)	18 (1.73)	70 (4.65)	45 (5.90)	30 (10.38)	<0.001
Types of infection, number (%)					
Joint, non-prosthetic	0 (0)	9 (12.9)	2 (4.7)	3 (10)	
Joint, prosthetic	1 (5.6)	2 (2.9)	4 (9.3)	1 (3.3)	
Respiratory	4 (22.2)	23 (32.9)	18 (41.9)	12 (40)	
Cutaneous	2 (11.1)	2 (2.9)	5 (11.6)	1 (3.3)	
Genitourinary	1 (5.6)	7 (10)	4 (9.3)	4 (13.3)	
Septicaemia	0 (0)	5 (7.1)	5 (11.6)	1 (3.3)	
Post-operative	0 (0)	2 (2.9)	0 (0)	0 (0)	
Other	10 (55.6)	20 (28.6)	5 (11.6)	8 (26.7)	
Cancer, total number (per 100 patient-years)	2 (0.19)	22 (1.46)	13 (1.7)	11 (3.81)	<0.001
Death, number (per 100 patient-years)	2 (0.19)	16 (1.06)	16 (2.09)	25 (8.65)	<0.001

[a]Taking into account the ordered nature of age groups.

disease activity, significantly higher at baseline in the >75 age group, became equivalent among the groups during follow-up, showing that the very elderly benefit as much, if not more, from treatment. Our remission rate after 6 months of abatacept therapy was lower than that observed in a large US registry of RA patients with previous anti-TNF exposure (12 *vs* 20.2%) [14].

The few data that exist for efficacy of boDMARDs in elderly RA patients are often contradictory and mainly concern anti-TNF. A review showed that the benefit of adding etanercept to MTX for the treatment of RA, in terms of ACR response and radiographic progression, was maintained after the age of 65, albeit less markedly, without statistically significant differences compared with subjects under age 65 [16]. Age had no effect on the response to anti-TNF therapy in the British register [17]. In the Swiss and Dutch registries, anti-TNF agents appeared to be less effective in the elderly [18, 19].

Regarding rituximab, the AIR (autoimmunity and rituximab) register has shown no statistically significant difference in EULAR response (moderate or good) or remission between the young (<65 years) and the elderly (⩾65 years) after 2 years of follow-up. However, patients aged 65–75 were more likely than patients aged ⩾75 to be good responders than non-responders at 1 year of follow-up [20].

Previous studies have given conflicting results with regard to clinical or biological factors influencing efficacy and tolerance of boDMARDs in RA. Our overall results at 24 months corroborate a previous report at the first 6-month follow-up in the ORA registry showing a better response to abatacept among ACCP-positive patients [15]. However in our study, ACCP positivity was not a predictor of response in very elderly patients. Similarly, RF positivity was not a predictor of response in our study, and this finding is consistent with a recent

meta-analysis [21]. RF positivity was not a predictor of response to anti-TNF [22]. Inversely, positivity for RF or ACCP antibodies is instead a predictive factor for RTX efficacy [22–24].

In our study, age is strongly associated with discontinuation for adverse events, and especially for SIs (Fig. 2). An age-related increase in infection risk was previously documented in cohorts of anti-TNF users. Among the 3796 patients treated with anti-TNF therapy (mean age 59.4), the rate of hospitalization for SI was consistent with the rate of SI in our cohort (3.59 *vs* 4.53/100 patient-years) [25]. Curtis *et al*. showed an increased rate of hospitalization for SI in elderly comorbid patients (mean age 72.8) compared with younger (mean age 47.9) and less comorbid patients (14.2 *vs* 4.8/100 patient-years). This rate is consistent with the rate of SI in our 103 patients aged over 75 (10.38/100 patient-years). They also noted that the rate of SI for anti-TNF agents compared with other DMARDs was incrementally increased by a fixed absolute difference regardless of age and comorbidities [26]. In a prospective observational study of 11 798 RA patients treated with anti-TNF (mean age 56), the rate of SI increased with age, ranging from 1.8 for those under 55 to 4.6 for those above 75 [27]. The effect of age was stronger in our cohort, showing a 6-fold difference between the same age groups. These results conflict with those from three large registries (American, Swiss and Dutch) that showed no increased risk of infection with age in RA patients treated with anti-TNF [18, 19, 28]. However, no increase in overall infection risk according to age was reported in two randomized, placebo-controlled studies of etanercept in RA [29, 30]. A recent review of forty-nine observational studies showed a higher risk of SI (adjusted HR 1.1–1.8) and a higher risk of tuberculosis in patients on anti-TNF compared with patients on conventional synthetic DMARDs [31]. These contradictory results reflect methodological differences concerning the prevalence of associated comorbidities in the populations, differences in duration of biologic treatment and the completeness of the infection report. In a cohort of elderly RA patients on second-line therapy with rituximab, we recently reported an increase in SI with ageing [20].

The few studies including a safety assessment of abatacept in RA often concerned a younger population, and the specific effects of ageing were not analysed. Thus, randomized placebo-controlled trials and subsequent open-label long-term extensions revealed no marked elevation in SI or malignancy [12, 32]. Among aged (mean age 64–69) RA patients treated with boDMARDs who had previously developed an infection during treatment with anti-TNF, abatacept and etanercept users had the lowest risk of hospitalization for SI [33].

Concomitant use of other immunosuppressant treatment is a potential bias that may influence the risk of adverse events including infections; oral corticosteroids are associated with an increased risk of SI in a dose-dependent manner, starting from 5 mg/day [28, 34]. Glucocorticoid use was equivalent in the four age groups and concerned three-quarters of our population at baseline. Moreover, the high rate of abatacept use seemed to have an interesting steroid-sparing effect, with a one-third reduction in the proportion of corticosteroids users.

In our study, despite the short follow-up, the incidence of cancer and death was higher in elderly subjects. These data are consistent with the increased incidence of cancer and death observed in the general population with age [35, 36]. The lack of a control group does not allow us to identify a potential excess of risk related to abatacept use. The existing literature has not shown a specific increased risk of cancer associated with use of boDMARDs. The pooled data of 12 132 patient-years' exposure to abatacept revealed comparable tissue-specific malignancy rates compared with control RA cohorts [32]. In a meta-analysis of randomized controlled trials, the use of biotherapies in RA was not statistically significantly associated with an increased risk of malignancy in the short term, compared with other DMARDs or placebo [37]. In the DANBIO registry, age and use of anti-TNF therapy had no effect on the incidence of cancer in patients on anti-TNF therapy for RA, PsA or AS [38].

Our study has some methodological limitations. Lack of data concerning change in the HAQ score or radiographic progression prevents us from assessing these important aspects of efficacy in the elderly. Lastly, as the incidence of infection, cancer and mortality increase with age, even in the general population, a control group would be essential for clarifying the specific risk associated with abatacept.

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