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RESEARCH PAPER

Treatment of active rheumatoid arthritis: comparison of patients younger vs older than 75 years (CORPUS cohort)

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ABSTRACT

Objectives: Little information is available on the characteristics of elderly patients starting TNFα antagonist treatment for rheumatoid arthritis (RA). The objective of this work was to compare prescription patterns in RA patients younger vs. older than 75 years.

Methods: Biologic-naive patients with active RA (DAS28 > 3.2) despite first-line therapy were included between 2007 and 2009 in the prospective, multicentre, longitudinal, observational, population-based CORPUS-RA cohort. TNFα antagonist users were defined as having received at least one TNFα antagonist during the first study year. The groups < 75 years and ≥ 75 years were compared regarding comorbidities, inflammation (CRP and ESR), disease activity (DAS28), disability (HAQ-DI), number of physician visits, and treatment. To verify the impact of the cut off, we also compared patients aged 70 years or more to patients younger than 70 years.

Results: Of 543 RA patients, 382 had complete one-year follow-up data, including 114 TNFα antagonist users, 3 (6%) among the 49 patients aged 75 years or over and 111 (32%) of the 333 patients younger than 75 years ($p < 0.01$). Disease activity in the two age groups was similar at inclusion and after one year. Comorbidities and a history of auto-immunity were more common in the older group. Compared to their younger counterparts, the older patients received glucocorticoids more often ($p = 0.003$) and synthetic disease-modifying anti-rheumatic drugs less often ($p = 0.01$).

Conclusion: TNFα antagonists are used less often and glucocorticoids more often in elderly patients with active RA compared to their younger counterparts. The fact that this study was performed in 2007–9 is a limitation in terms of relevance to today's patients and further studies should be conducted in new cohorts of active RA.

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Introduction

Rheumatoid arthritis (RA) is among the most common chronic inflammatory joint diseases. It manifests as polyarthritis with joint destruction that causes functional disability, thereby adversely affecting quality of life. The current ageing of the general population is mirrored by ageing of the population with RA. Thus, cases of RA diagnosed after 60 years of age are on the rise. Most older patients with RA have an active lifestyle that requires good disease control.

To obtain a remission or low disease activity without further joint destruction, synthetic disease-modifying anti-rheumatic drugs (sDMARDs) should be prescribed as soon as possible after the diagnosis of RA. If these drugs fail, biologics such as TNFα antagonists may provide disease control. TNFα antagonists are licensed for use in older patients. However, the small number of older patients included in randomised controlled trials of TNFα antagonists[1-4] has left gaps in our knowledge of the benefits and risks in this age group. In the few meta-analyses of randomised controlled trials comparing biologics (TNFα antagonists, abatacept, tocilizumab, or anakinra) with or without methotrexate to a placebo in patients with RA, mean age was less than 55 years.[5-7] Compared to their younger counterparts, patients older than 75 years had a heavier burden of comorbidities (e.g., kidney dysfunction and heart failure) and more often took multiple chronic medications. These differences suggest a greater risk of adverse drug effects that may lead physicians to limit the aggressiveness of the treatments they prescribe to older patients.[8,9] Although driven by concern over patient safety, this attitude may deprive older patients of optimal disease control and quality of life. Several trials comparing patients younger than 65 years and 65 years or over showed similar drug safety profiles and treatment discontinuation rates.[10-14]

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Efficacy also seems unrelated to age,[14,15] although questions have been raised about the efficacy of second-line drugs.[16,17]

In France, although fully reimbursed by the statutory health insurance system, TNFα antagonists may be under-prescribed. In the subgroup of CORPUS cohort patients who had active RA,[18] TNFα antagonist initiation was more strongly associated with younger age, longer disease duration, glucocorticoid use, and poorer quality of life than with higher disease activity.

This study is a post hoc analysis of the data of the French Corpus cohort conducted at the request of the French health authorities to assess TNFα antagonist prescription patterns in patients with active RA. We have chosen this cohort because it is an opportunity to have a longitudinal prospective population-based cohort study of active RA. The primary objective of this work was to compare two age groups, < 75 years and ≥ 75 years, regarding second-line drugs used to treat RA insufficiently controlled by first-line therapy. Secondary objectives were to compare the two age groups among patients started on TNFα antagonist therapy, regarding glucocorticoid dosage and changes in C-reactive protein (CRP) levels, disease activity, and disability over the first study year.

Results

Study population

Patients with RA were recruited by 80 rheumatologists working throughout continental France. Of 550 patients with RA, 382 (69.5%) had complete follow-up data and were naive to biologics, including 333 (87.2%) younger than 75 years and 49 (13%) 75 years or older (Figure 1).

Data at study inclusion (Table 1)

Few characteristics differed significantly between the two age groups. In particular, all patients in both age groups were taking sDMARD therapy, usually methotrexate (74.6%) or leflunomide (18.5%). However, comorbidities and a history of auto-immunity were more common in the older group, which had a higher proportion of patients on glucocorticoid therapy, although the dosage was not different between groups.

Data at follow-up (Table 2)

At follow-up, the older group had fewer patients receiving TNFα antagonist therapy and sDMARD therapy but more patients receiving glucocorticoids. However, the proportion of older patients on glucocorticoid therapy was lower at follow-up than at inclusion, and the glucocorticoid dosage at follow-up was similar in the two age groups. Despite these treatment differences, the two age groups were not significantly different regarding inflammation severity, disease activity, or disability. The main sDMARDs used were methotrexate (81%) and leflunomide (14%).

Older patients receiving TNFα antagonist therapy (Table 3)

Of the 49 patients 75 years or older, only 3 were prescribed TNFα antagonist therapy during the study (Table 3). None

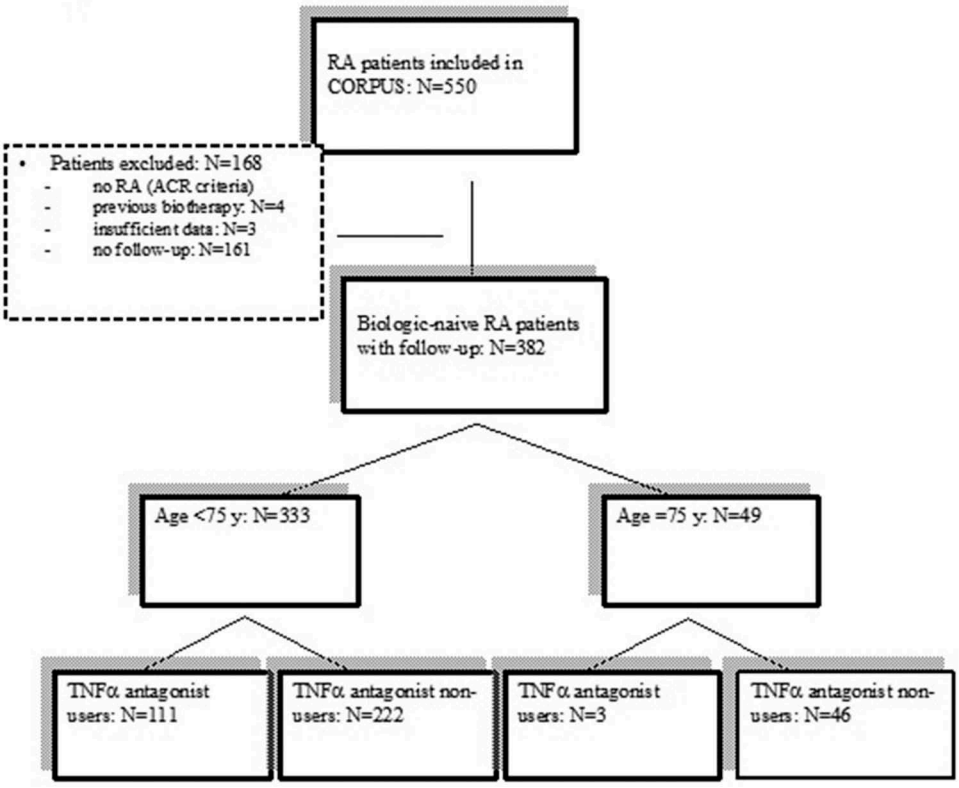

Figure 1. Patient flow chart.

Table 1. Patient characteristics at inclusion into the CORPUS cohort.

	< 75 years of age (mean age, 56.7 years) n = 333	≥ 75 years of age (mean age, 80.8 years) n = 49	*p* value
Women, n (%)	265/333 (79)	41/49 (84)	0.57
CRP, mg/L, mean (SD)	9.67 (12.9)	17.7 (34.1)	0.13
CRP > 10 mg/L, n (%)	126/290 (43.4)	17/39 (43.6)	0.99
ACPA-positive, n (%)	212/333 (63.7)	28/49 (57.1)	0.43
RF-positive, n (%)	230/330 (69.7)	32/49 (65.3)	0.62
ESR> 20 mm, n (%)	161/325 (49.5)	25/47 (53.2)	0.75
DAS28, mean (SD)	3.71 (1.40)	3.89 (1.51)	0.38
HAQ-DI, mean (SD)	0.75 (0.68)	0.94 (0.75)	0.19
Physician visits, n (%)	158/185 (85.4)	24/30 (80.0)	0.42
Admissions, n (%)	33/186 (17.7)	5/30 (16.6)	1.00
Heart failure, n (%)	3/330 (0.9)	3/49 (6.1)	0.03
Kidney failure, n (%)	1/330 (0.3)	2/49 (4.1)	0.04
Respiratory failure, n (%)	10/330 (3.0)	5/49 (10.2)	0.03
History of cancer, n (%)	4/329 (1.2)	2/49 (4.1)	0.18
History of infections, n (%)	24/329 (7.3)	4/49 (8.2)	0.77
High risk of infection[¥], n (%)	1/330 (0.3)	1/49 (2.0)	0.24
History of stroke, n (%)	4/330 (1.2)	0/49 (0.0)	1.00
History of autoimmunity, n (%)	5/330 (1.5)	5/49 (10.2)	< 0.01
Hypertension[·], n (%)	36/330 (10.9)	9/49 (18.4)	0.15
History of thrombosis, n (%)	5/330 (1.5)	3/49 (6.1)	0.07
Glucocorticoid treatment, n (%)	238/330 (72.1)	40/46 (86.7)	0.03
Daily prednisone-equivalents at inclusion, mg, mean (SD)	18.1 (48.6)	15.6 (20.4)	0.86
sDMARD therapy, n (%)	330/330 (100.0)	49/49 (100.0)	1.00

[¥]*defined by chronic ulcer skin, suspected prosthetic joint infection, long-term indwelling urinary catheter or other implanted material*

[·] *defined as systolic blood pressure > 140 mmHg and diastolic blood pressure > 90 mmHg*

Table 2. Characteristics of patient at follow-up.

	< 75 years of age	≥ 75 years of age	*p* value
CRP> 10 mg/L, n (%)	65/270 (24.1)	13/36 (36.1)	0.15
ESR> 20 mm, n (%)	111/305 (36.4)	14/46 (30.4)	0.51
DAS28, mean (SD)	3.69 (1.42)	4.04 (1.36)	0.08
HAQ-DI, mean (SD)	0.40 (0.42)	0.60 (0.50)	0.08
sDMARDs, n (%)	235/287 (81.8)	27/42 (64.3)	0.01
Glucocorticoid treatment, n (%)	155/286 (54.2)	33/42 (78.6)	< 0.01
Daily prednisone-equivalents at inclusion, mg, mean (SD)	7.8 (9.67)	6.04 (5.10)	0.26
TNFα antagonist treatment, n (%)	111/333 (33.3)	3/49 (6.1)	< 0.01
First TNFα antagonist	*Etanercept: 55 Adalimumab:41 Infliximab: 14 Unknown: 1*	*Adalimumab:2 Infliximab: 1*	

had comorbidities. At the follow up visit, two were taking adalimumab and one infliximab. TNFα antagonist therapy was associated with improvements in the DAS28, HAQ-DI, and morning stiffness duration, whereas the asthenia persisted. No adverse effects were noted during the first year of follow-up.

Comparison of patients < 70 years and 70 years or more of age

At follow-up, 290 patients were younger than 70 years and 43 were 70 to 75 years of age. TNFα antagonist use was significantly more common in the younger patients (102/290 (35.2%) vs. 11/92 (11.9%); $p < 0.01$).

Continuation of the first-line drug was more common in the younger patients (207/250 (82.8%) vs. 55/79 (69.6%); $p = 0.02$), whereas glucocorticoid therapy was less common (128/249 vs. 60/79; $p < 0.01$).

Table 3. Characteristics of the three patients 75 years or older who received TNFα antagonist therapy.

	Patient 1	Patient 2	Patient 3
At inclusion			
Age, years	75.0	76.8	82.8
Sex	man	woman	woman
CRP, mg/L	10.9	8.5	4.0
ACPA-positive	yes	yes	no
RF-positive	yes	yes	no
DAS-28	5.5	6.2	8.9
HAQ-DI	0.87	2.12	1.12
Physician visit in the past 6 months	6	7	3
Admission in the past 6 months	0	1	0
Daily prednisone-equivalents, mg	5	0	8
sDMARD therapy	methotrexate	methotrexate	methotrexate
Asthenia	7/10	3/10	2/10
Morning stiffness, minutes	120	15	30
At follow up			
CRP, mg/L	6.0	11.0	-
DAS-28	3.3	2.2	6.0
HAQ-DI	0.87	1.6	0.87
Physician visit in the past 6 months	3	0	6
Admission in the past 6 months	0	1	0
Glucocorticoid therapy	yes	no	-
sDMARD therapy	none	methotrexate	none
Asthenia	7/10	4/10	2/10
Morning stiffness, minutes	15	30	15

CRP, plasma C-reactive protein level; ACPA, anti-citrullinated peptide antibodies; RF, rheumatoid factors; DAS28, Disease Activity Index on 28 joints; HAQ-DI, Health Assessment Questionnaire Disability Index; sDMARD, synthetic disease-modifying anti-rheumatic drug

Discussion

This study identified significant differences in the treatment of RA between patients < 75 and ≥ 75 years, during the first year of follow-up. TNFα antagonist therapy was used more often in the younger patients, despite similar disease activity in the two age groups. Glucocorticoid therapy was used more often and sDMARD therapy less often in the older age group.

Short-term glucocorticoid therapy is often prescribed to patients with RA, to control flares and while waiting for DMARD therapy to take effect. Long-term glucocorticoid therapy, in contrast, is not recommended, as its risk/benefit ratio remains unclear. In everyday practice, however, 50% to 60% of patients with RA take glucocorticoid therapy.[19,20] A systematic literature review showed that long-term low-dose glucocorticoid therapy combined with DMARD therapy was generally effective but that glucocorticoid-related adverse events, although dose-related, occurred even with low doses[21] and were of greatest concern in older patients with multiple comorbidities. Of six studies that assessed major cardiovascular events, four found an increase associated with low-dose glucocorticoid therapy.[21] In a study of mortality in RA, taking more than 5 mg/d of glucocorticoids was associated with a significantly higher risk of death.[22] Glucocorticoid therapy is also associated with a higher frequency of serious infections.[21-23]

The differences in first-line therapy between our two age groups are consistent with earlier reports. In a registry study reported in 2006, onset of RA after 60 years of age was

associated with significantly less use of biologics (25% vs. 33.1% for onset < 60 years) and DMARDs (30.9% vs. 40.5%) despite similar disease duration, activity, and severity.[8] A cross-sectional study done in 2008 found that treatment was less aggressive in older patients with RA compared to their younger counterparts; in particular, initial methotrexate therapy was significantly less commonly prescribed (47% vs. 57% of patients) and methotrexate dosages were lower (5.46 ± 1.66 mg/week vs. 5.96 ± 1.77 mg/week).[9]

In general, the risk of adverse drug events increases with advancing age, due to the gradual accumulation of comorbidities such as heart failure and kidney dysfunction, as well as to the age-associated decline in immune function. Also, drugs are often less effective in older patients. In a review of four randomised and five open-label studies of etanercept, treatment efficacy was independent from age.[15] Similarly, an analysis of data from two randomised trials showed no age-related differences in the efficacy of methotrexate alone or of TNFα antagonist therapy with or without methotrexate.[14] In four randomised trials and two long-term extensions, etanercept used to treat RA was slightly less effective in patients older than 65 years than in younger patients, but the difference was small and the frequency of adverse events was similar in the two groups.[16]

These data suggest that older patients with RA should be treated aggressively if needed to achieve good disease control and quality of life. A prospective study evaluated a treat-to-target strategy in 151 patients with elderly-onset RA (mean age, 74.9 years).[24] Adherence to the strategy was 83.4% after 6 months and 75.5% after 1 year. Importantly, after 1 year, nearly 50% of patients were in structural remission and 63% were in functional remission. Similarly, Cho et al shown the retention rate of TNF alpha was comparable in the elderly and younger patients although the major cause of discontinuation was AEs in the elderly patients, while it was drug ineffectiveness in younger patients.[25]

A 2005 review article indicated that sDMARDs and TNFα antagonists were similarly tolerated by patients younger than 65 years and those aged 65 years or over.[11] Nevertheless, older patients were at higher risk for non-serious infections and tuberculosis reactivation. The risk of cardiac events is higher in patients with NYHA class II, II, or IV heart failure treated with TNFα antagonists, and the risk of lymphoma increased with age although there is no proven association with biologics. In patients with RA aged 65 years or over, the higher risk of infections associated with etanercept therapy seemed related to age-related comorbidities rather than to the drug itself.[14]

The first strength of this study is its nationwide, longitudinal, prospective design. The second strength is that it included patients based on disease activity and not on prescription criteria. This point allowed us to assess the rates and reasons of prescribing or not TNFα antagonist therapy.

This study had two main limitations. One is the small number of patients with RA older than 75 years and treated by TNFα antagonists. The other is the moderate relevance of this study performed in 2007–9, to today's patients as new biologics agents are now available. Nevertheless, adalimumab and etanercept remain the most frequently used anti TNF in France.

In conclusion, older patients (≥ 75 years or ≥ 70 years) with active RA receive sDMARDs and TNFα antagonists less often, and glucocorticoids more often, than do their younger counterparts. A personalised evaluation of the risk/benefit ratio of various drugs is mandatory, with a special regard to comorbidities in older patients with RA. Further studies should be conducted in new cohorts of active RA.

Materials and methods

Study design and population

CORPUS is a French, prospective, observational, multicentre, longitudinal, population-based cohort of biologics-naive patients with inflammatory joint disease (RA, spondyloarthritis, or juvenile idiopathic arthritis) recruited in private practices and hospitals between 2007 and 2009 by 102 rheumatologists, internists, and paediatricians.[18] This cohort was established at the request of French health authorities to assess TNFα antagonist use in patients with these disorders. The patients were monitored prospectively for at least one year.

Before inclusion, all patients gave their written consent to participate in the CORPUS study. The study was approved by the Ethics Committee of Nancy, France.

This study was conducted in the subset of CORPUS patients[18] older than 18 years who met American College of Rheumatology (ACR) criteria for RA,[26] had active disease (DAS28 > 3.2) at inclusion despite first-line therapy, had never taken biologics, and underwent at least one follow-up evaluation 3 to 24 months after inclusion. All treatments were at the discretion of the managing rheumatologists. TNFα antagonist users were defined as patients who received at least one TNFα antagonist injection between inclusion and 3 months before the follow-up visit. Between 2007 and 2009, the TNFα antagonists available in France were etanercept, adalimumab, and infliximab.

Data collection

The study data were collected on standardized forms by the rheumatologists who recruited the patients to the cohort. Each patient was evaluated twice, at inclusion and 12 months later. Each evaluation consisted of a standardised interview, general physical examination, laboratory tests, and self-administered questionnaires.

The following data were recorded at inclusion: age; sex; disease duration; anti-citrullinated peptide antibody (ACPA) and rheumatoid factor (RF) status; ACR criteria for RA; history of treatment with sDMARDs, biologics, and glucocorticoids; extra-articular signs of RA; and medical history and comorbidities. Data recorded at both visits were the tender and swollen joint counts, plasma CRP level, erythrocyte sedimentation rate (ESR), patient visual analogue scale (VAS) score for global disease activity, DAS28 (calculated with ESR if available and CRP otherwise),[27] Health Assessment Questionnaire Disability Index (HAQ-DI),[28] radiographic erosions, and treatments (sDMARDs, biologics, and glucocorticoids) with their start and stop dates and dosages.

Statistical analyses

The data collected at inclusion and at follow-up were described as mean± SD or median (range) for quantitative data and n (%) for qualitative data (missing data were excluded when computing percentages).

The groups < 75 years and ≥ 75 years were compared regarding comorbidities, inflammation (CRP and ESR), disease activity (DAS28), disability (HAQ-DI), number of physician visits and admissions, and first-line treatment. TNFα antagonist use was compared in the two age groups. Univariate analyses were performed to identify variables associated with TNFα antagonist use in each age group, using the chi-square test or Fisher's exact test, as appropriate, for qualitative variables and the Mann-Whitney test for quantitative variables.

To verify the impact of the cut off to separate old and young patients, we also compared patients aged 70 years or more to patients younger than 70 years.

All tests were two-sided and p values ≤ 0.05 were considered significant. Statistical analyses were performed using SPSS 23.0 (SPSS Inc., Chicago, IL, USA).

Abbreviations

CRP	plasma C-reactive protein level
ACPA	anti-citrullinated peptide antibodies
RF	rheumatoid factors
ESR	erythrocyte sedimentation rate
DAS28	Disease Activity Index on 28 joints
HAQ-DI	Health Assessment Questionnaire Disability Index
sDMARD	synthetic disease-modifying anti-rheumatic drug

Disclosure of potential conflicts of interest

No potential conflict of interest was reported by the authors.

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