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## Treatment of active rheumatoid arthritis: comparison between young and elderly patients (corpus cohort)

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**Faculté de Médecine & des Sciences de la Santé**

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Mme : Sachiyo OISHI

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**TREATMENT OF ACTIVE RHEUMATOID ARTHRITIS : COMPARISON BETWEEN  
YOUNG AND ELDERLY PATIENTS (CORPUS COHORT)**

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## **TABLE DES MATIERES**

<b>ABSTRACT</b>	<b>3</b>
<b>INTRODUCTION</b>	<b>4</b>
<b>PATIENTS AND METHODS</b>	<b>5</b>
<b>Study design and population</b>	<b>5</b>
<b>Data collection</b>	<b>6</b>
<b>Statistical analyses</b>	<b>7</b>
<b>RESULTS</b>	<b>7</b>
<b>Study group</b>	<b>7</b>
<b>Baseline patients and treatment characteristics</b>	<b>8</b>
<b>Follow-up patients and treatment characteristics at one year</b>	<b>8</b>
<b>Characteristics of elderly patients treated by anti TNF</b>	<b>9</b>
<b>Characteristics of subgroup of patient between 70 and 75 year old</b>	<b>9</b>
<b>DISCUSSION</b>	<b>10</b>
<b>ANNEXES</b>	<b>13</b>
<b>REFERENCES</b>	<b>17</b>

# **Treatment of active rheumatoid arthritis: Comparison between young and elderly patients (CORPUS Cohort)**

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**Key Indexing Terms:** Rheumatoid arthritis. Glucocorticoids. Prednisone. Biologics. Elderly.

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**Running footline:** Comparison of rheumatoid arthritis treatment between young and elderly patients

## **ABSTRACT:**

**Objectives:** Anti-TNF $\alpha$  have proven its effects on optimisation of rheumatoid arthritis (RA) treatment but there is only few and limited information about the characteristics of elderly patients with an active RA starting a second line's treatment. The objective of this work was to compare the prescription patterns between RA patients older and younger than 75 years.

**Methods:** Patients with active RA (DAS28 > 3.2 despite a first line therapy) naive to biologics, were included between 2007 and 2009 in a multicenter, longitudinal, prospective, observational population-based cohort: the CORPUS-RA cohort. Patients who received other biologics than anti-TNF $\alpha$  during the follow-up period and patients without follow-up were excluded. Patients were considered as anti-TNF $\alpha$  receivers if they had at least one injection between the inclusion visit and the follow-up visit.

**Results:** Among the 543 RA patients, 382 had complete one-year follow-up data. Among these patients, 114 received at least one TNF $\alpha$  antagonist dose during the one-year follow-up. Three of 49 elderly patients (6%) versus 111 of 333 young patients (32%) (p<0.01) received an antiTNF $\alpha$  despite a similar disease activity at inclusion. Disease activity was not statistically different between the two groups after a one year follow up, but the older group received more glucocorticoids (p=0.003) and less synthetic disease-modifying anti-rheumatic drugs (DMARDs) (p=0.01) than the youngers.

**Conclusion:** In France, elderly active RA patients are less treated by biologics and more by glucocorticoids than younger patients.

## INTRODUCTION

Rheumatoid arthritis (RA) is one of the most frequent chronic inflammatory rheumatic diseases, characterized by polyarthritis which is responsible of joint destruction leading to functional disability and therefore degradation of quality of life. With the aging of the population, RA patients are more and more aged and diagnostics of RA after 60 year-old become common. Most of the time, they are active people and they need a good control of their disease.

To obtain remission or a low disease activity without evolution of joint destruction, synthetic disease-modifying anti-rheumatic drugs (DMARDs) should be prescribed as soon as possible after the diagnostic. In case of failure, biologics including anti-TNF $\alpha$ , allowed the optimisation of the treatment of RA. Unfortunately, there is few data about elderly patients treated by anti-TNF $\alpha$  in randomized controlled trials (RCTs) (1-4) and even if there is a marketing authorization for them, very little is known about positive or negative effects of anti-TNF $\alpha$  on these patients.

In few meta-analysis of RCTs referring to RA patients treated by biologics (anti-TNF $\alpha$ , abatacept, tocilizumab, anakinra), associated or not to methotrexate versus placebo, the mean age does not go over 55 years (5-7). Elderly patients older than 75 had different profiles compared to younger patients, with more comorbidities (kidney failure, cardiac failure...) and polymedication. So, practitioners are more reluctant to prescribe treatment because of the potential risk for important adverse effects (8,9).

But being aged and having a good quality of life must be possible. The background treatment has not to be optimised to tend to clinical remission because the priority is still to achieve a good tolerance to the treatment. Quite few trials found same tolerance between patients less and more than 65 year-old, with a same rate of therapeutic discontinuation (10-14). Moreover, the

background treatment's efficiency seems to be comparable regardless of age of patients (14-15) but the question about efficiency of second line treatment can be asked (16-17).

In France, despite anti-TNF $\alpha$  reimbursement in RA without restrictions by the National Health insurance system, there is still reluctance to the prescription of these drugs. According to CORPUS trial (18), in RA, younger age, duration of the illness, use of glucocorticoids (GCs) and poorer quality of life were stronger determinants of TNF $\alpha$  antagonist initiation than higher disease activity.

The primary objective of this work was to compare the prescription patterns in second-line of RA therapeutic between elderly patients older than 75 years and younger patients under 75 years, with an active RA despite a background treatment already initiated. Secondary objectives were to compare differences between the younger population receiving a treatment by anti-TNF $\alpha$  and the elderly population; in particular, comparison of GCs doses, biological (CRP) and clinical (HAQ, DAS28) evolution during the first year of monitoring. Similar analysis was then conducted in elderly patients older than 70 years versus younger patients.

## **PATIENTS AND METHODS**

### **Study design and population**

The CORPUS cohort is a French, non-interventional, multicenter, longitudinal, prospective, population-based cohort of patients with RA, spondyloarthritis (SA), or juvenile idiopathic arthritis (JIA), naive to biologics, recruited prospectively in private practices and hospitals, between 2007 and 2009 by 102 rheumatologists, internists and pediatricians (18). This cohort was established to assess anti-TNF $\alpha$  prescription patterns in patients with active RA, SA or JIA,



at the request of French health authorities. The patients were monitored prospectively for at least one year.

For this study we limited our population to RA patients. Patients included in this study were older than 18 years, had RA according to the American College of Rheumatology (ACR) criteria (19), active RA (DAS28 > 3.2) despite receiving a first line therapy at baseline and with at least one follow-up evaluation visit between 3 and 24 months. Rheumatologists prescribed freely any medication. The patients were excluded if they were not naive to biologics. Patients were considered as anti-TNF $\alpha$  receivers if they had at least one injection between the inclusion visit and the last trimester before the follow-up visit. Between 2007 and 2009, the anti-TNF $\alpha$  available in France were etanercept, adalimumab and infliximab.

### **Data collection**

Baseline and follow-up assessment included a standardized interview, general physical examination, laboratory tests, and self-reported questionnaires. Participating physicians were asked to fill out an interview form for each patient at inclusion and at follow-up. Patients who did not filled the follow up data at one year were excluded.

The data collected at baseline included age, sex, disease duration, anti-citrullinated peptide antibodies (ACPA) and rheumatoid factors (RF) status, RA ACR criteria, previous synthetic or biologic DMARDs and GCs, medical history and comorbidities, extra-articular signs. We also collected at baseline and at follow-up information about tender and swollen joint count, plasma C-reactive protein level (CRP), erythrocyte sedimentation rate (VS), patient visual analogue scale (VAS) for global assessment of disease activity, DAS28 (calculated with ESR or CRP when ESR was not available) (20), Health Assessment Questionnaire Disability Index (HAQ-DI) (21), presence of erosive change on X-rays.

Regarding GCs, DMARDs and anti-TNF $\alpha$  treatments, the data collected were dosage, type, date of initiation and date of discontinuation.

The collected data were analyzed at baseline and follow-up visits. In order to identify the variables associated with anti-TNF $\alpha$  initiation, treatment and patients characteristics were compared between patients receiving anti-TNF $\alpha$  and those who did not receive it. The number of patients having initiated the anti-TNF $\alpha$  within the elderly group and those within the younger group was compared. Then, the characteristics between the young group and the older group were compared; in particular, comorbidities, inflammatory factor (CRP, VS), DAS28, HAQ, medical consultation and hospitalisation, background treatment.

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

### **Statistical analyses**

All tests were two-sided with  $\alpha$  risk at 5%. The statistical analyses were performed using SPSS 21.0 (SPSS Inc., Chicago, IL, USA). Quantitative data were expressed as mean (standard deviation) or median (range) and qualitative data as number and percentages (percentages were calculated excluding missing data). For univariate analysis, we used chi square test or Fisher's exact test when appropriate for qualitative variables, and Mann-Whitney test for quantitative variables. For all statistical analyses, p values lower than 0.05 were considered statistically significant.

## **RESULTS**

### **Study group**

Eighty physicians recruited RA patients and all geographic regions of continental France were represented. Among the 550 RA patients, 382 (69.5%) had complete follow-up data available and were naive to biotherapy. Among these patients, 333/382 (87.2%) were under 75 year-old, 49/382 (13%) were 75 year-old and more (figure 1).

### **Baseline patients and treatment characteristics**

The baseline characteristics are represented in table 1. There were no differences between the elderly group and the younger group regarding the gender, inflammatory activity, ACPA and RF positivity; no differences were detected either on clinical activities evaluated through DAS 28, HAQ or on medical consultation or hospitalisation.

Nevertheless, elderly patients had statistically more comorbidities: cardiac failure (6.1% vs 0.9%,  $p=0.03$ ), kidney failure (4.1% vs 0.3,  $p=0.04$ ), respiratory failure (10.2% vs 3.0%,  $p=0.03$ ) and history of autoimmunity ( $p=0.005$ ). There was no statistically significant differences in neoplasia history, high infectious risk (defined by chronic ulcer skin, suspected prosthetic joint infection, long-term indwelling urinary catheter or other implanted material),infection history (such as tuberculosis, opportunistic infections) or high blood pressure.

At baseline, there were all treated by a DMARDs, almost by methotrexate (74.6%), leflunomide (18.5%) and GCs (73.9%). There were significant differences in treatment by GCs, as the group of elderly patients received more GCs than the younger group (86.7% vs 72.1%,  $p=0.03$ ) but the daily doses were not statistically different (15.6mg +/- 20.4 vs 18.1mg +/- 48.6,  $p=0.86$ ).

### **Follow-up patients and treatment characteristics at one year**

The follow-up patients characteristics are detailed in table 2. At follow-up, elderly patients received less anti-TNF $\alpha$  than younger patients, respectively 3/49 (6%) and 111/333 (32%) ( $p < 0.01$ ). They were lesser patients treated by DMARDs (64% vs 82%,  $p = 0.01$ ) but received more GCs (79% vs 54%,  $p < 0.01$ ) even if GCs' daily dose were similar and seems to be less than at baseline (6.04mg +/- 5.1 vs 7.8mg +/- 9.67,  $p = 0.26$ ). Regarding DMARDs, they were almost treated by methotrexate (81%), leflunomide (14%). In spite of those differences, there was no differences in terms of inflammatory status (CRP, VS), clinical activity (DAS28) or disability (HAQ).

### **Characteristics of elderly patients treated by anti TNF**

In the current study, three 75, 77, 83 year-old patients have been treated by anti-TNF $\alpha$  (table 3). They did not have other comorbidities. At baseline, they were all treated by methotrexate and two received GCs dosed at 5 and 8 mg/per day. At the follow up, two of them received adalimumab and the last one infliximab. There was an improvement in clinical evolution in DAS28, HAQ, duration of morning stiffness despite the same asthenia sensation. The youngest one maintained his GCs treatment, and the one aged of 77 years maintained his methotrexate. No adverse effects were noted during the first year of follow-up.

### **Characteristics of subgroup of patient between 70 and 75 year old**

A subgroup of patients aged 70 or more was also compared to the younger. At follow-up, 43 patients were aged 70 to 75 years. So, 11/92 patients (11.9%) older than 70 have had a second line therapy against 102/290 patients (35.2%) younger ( $p < 0.01$ ). Moreover, 55/79 patients older than 70 (69.6%) maintained their first line therapy against 207/250 younger patients (82.8%) ( $p = 0.02$ ). Patients older than 70 are more treated by GCs (60/79 VS 128/249) than the remainders ( $P < 0.01$ ).

## DISCUSSION

This study showed significant differences in therapeutics of RA between patients older and younger than 75 years during the first year of follow-up in a French multicenter cohort of 382 RA patients. Younger patients are more treated by anti-TNF $\alpha$  than older patients, despite their similarity in biological and clinical activities of RA. Elderly patients received less DMARDs and more GCs.

GCs are frequently prescribed in RA, for short-term treatment during the flares and during the initiation of DMARDs waiting for their efficacy, but they are not also recommended as long-term therapy because of the unclear risk-benefit ratio. Actually, in daily practice, 50 to 60% of RA patients are taking GCs (22,23). A RCTs review of efficacy (structural and clinical) and safety of long-term low-dose GCs in combination with DMARDs showed an efficacy in most studies but the safety data indicated that GCs-associated adverse events are dose-related and still occurred with low-dose GCs (24) even more for aged patients with many comorbidities. They trend to increase in risk of major cardio-vascular events in 4 of 6 studies (25) and in mortality rate with a daily equivalent prednisone dose threshold of 5 mg independent of disease activity (26).

The differences in background therapy prescription is not really unusual, Tutuncu and al (8) had already noted limited use of biotherapy (25% vs 33.1%) or DMARDs (30.9% vs 40.5%) in RA patients older than 60 years ( $p < 0.01$ ) despite the same evolution in duration, activity and harshness. Similarly, Ogasawara and al (9) demonstrated that elderly patients had less aggressive treatment than younger patients. The hesitation is also perceptible since the initial

prescription of methotrexate (47% vs 57%  $p=0.03$ ) with a lower dosage in elderly (5.46 [SD, 1.66] mg/wk vs. 5.96 [SD, 1.77] mg/wk;  $P < 0.01$ ).

It is understood that elderly patients can be frail because of their comorbidities, decline of immunity, cardiac or kidney function. These patients are more susceptible to adverse effects and respond less to treatment. Nevertheless, the efficiency seems to be the same for anti-TNF $\alpha$  associated or not to methotrexate or methotrexate alone regardless of age, even for patients older than 70 year-old (15). On the other hand, few trials showed a trend to lower efficiency of anti-TNF $\alpha$  over the long-term (14, 16, 17). After this discussion, the question about the possibility of being elderly and having a good quality can be raised. Sugihara and al (27) supported the fact that achieving a lower degree of activity for RA elderly patients was a realistic goal. In their population of 151 patients, the strategy « treat to target » was followed in 83% of patients at 6 months and in 75% at one year. The absence of structural evolution was obtained in 50% of the cases and a functional remission in 63%.

Regarding DMARD's tolerance, Ranganath and al showed in their review article published in 2005 (11) that the examined population of RA older than 65 years treated by DMARDs present the same tolerance as younger patients to this treatment. Nevertheless, older patients seem to have twice more simple infection and the risk of tuberculosis reactivation is more important, needing prophylactic antibiotics when in doubt. The authors noticed a higher risk of cardiac failure for patients with an NYHA III and IV and a risk of lymphoma. Baton and al (14) take the reflection a little further by noting that the higher risk of infection was inherent to patient's comorbidity and aging more than related to the usage of etanercept.

In the present study, only 5 explanations of stopping methotrexate were available for the elder group. Such explanations were the patient's wish, a chirurgical intervention, asthma, clinical and biological remission and the last one was the entrance of the patient in an institution. In the younger group, 41 explanations were given and they were almost due to adverse events (51%),

22% according to patients' wish, 15% for remission, 7% for inefficacy and 5% for surgical intervention. There was no explanation on starting anti-TNF $\alpha$  in both groups.

This study had two main limitations, the first one was the low number of RA patients older than 75 years and treated by anti-TNF $\alpha$ . The second limitation was the fact that the follow-up period was short after anti-TNF $\alpha$  initiation and such follow-up data was based on a single evaluation visit.

In conclusion, elderly patients (older than 75 years, but also older than 70) with an active RA receive less DMARDs but more GCs than younger patients. A personalized evaluation of benefit/risk of each elderly RA patient is mandatory.

**Table 1: Characteristics of patients at baseline**

	under 75 year-old (mean age 56.7 years) n=333	more 75 year-old (mean age 80.8 years) n=49	p
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 > 10mg/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
FR positive, n (%)	230/330 (69.7)	32/49 (65.3)	0.62
VS > 20mm, n (%)	161/325 (49.5)	25/47 (53.2)	0.75
DAS-28, mean (SD)	3.71 (1.40)	3.89 (1.51)	0.38
HAQ, mean (SD)	0.75 (0.68)	0.94 (0.75)	0.19
Medical consultation	158/185 (85.4)	24/30 (80.0)	0.42
Hospitalization	33/186 (17.7)	5/30 (16.6)	1.00
Cardiac 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
Neoplasia history, 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 infectious**, n (%)	1/330 (0.3)	1/49 (2.0)	0.24
History of strokes, 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
High blood pressure***, 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
GCs treatment, n (%)	238/330 (72.1)	40/46 (86.7)	0.03
Daily equivalent prednisone at baseline, mg, mean (SD)	18.1 (48.6)	15.6 (20.4)	0.86
Associated DMARDs, n (%)	330/330 (100.0)	49/49 (100.0)	1.00

\*history of tuberculosis, opportunistic infections or others \*\*High risk infectious defined by chronic ulcer skin, suspected prosthetic joint infection, long-term indwelling urinary catheter, other material implanted suspect at risk of infection \*\*\*Systolic > 140mmHg and diastolic > 90mmHg



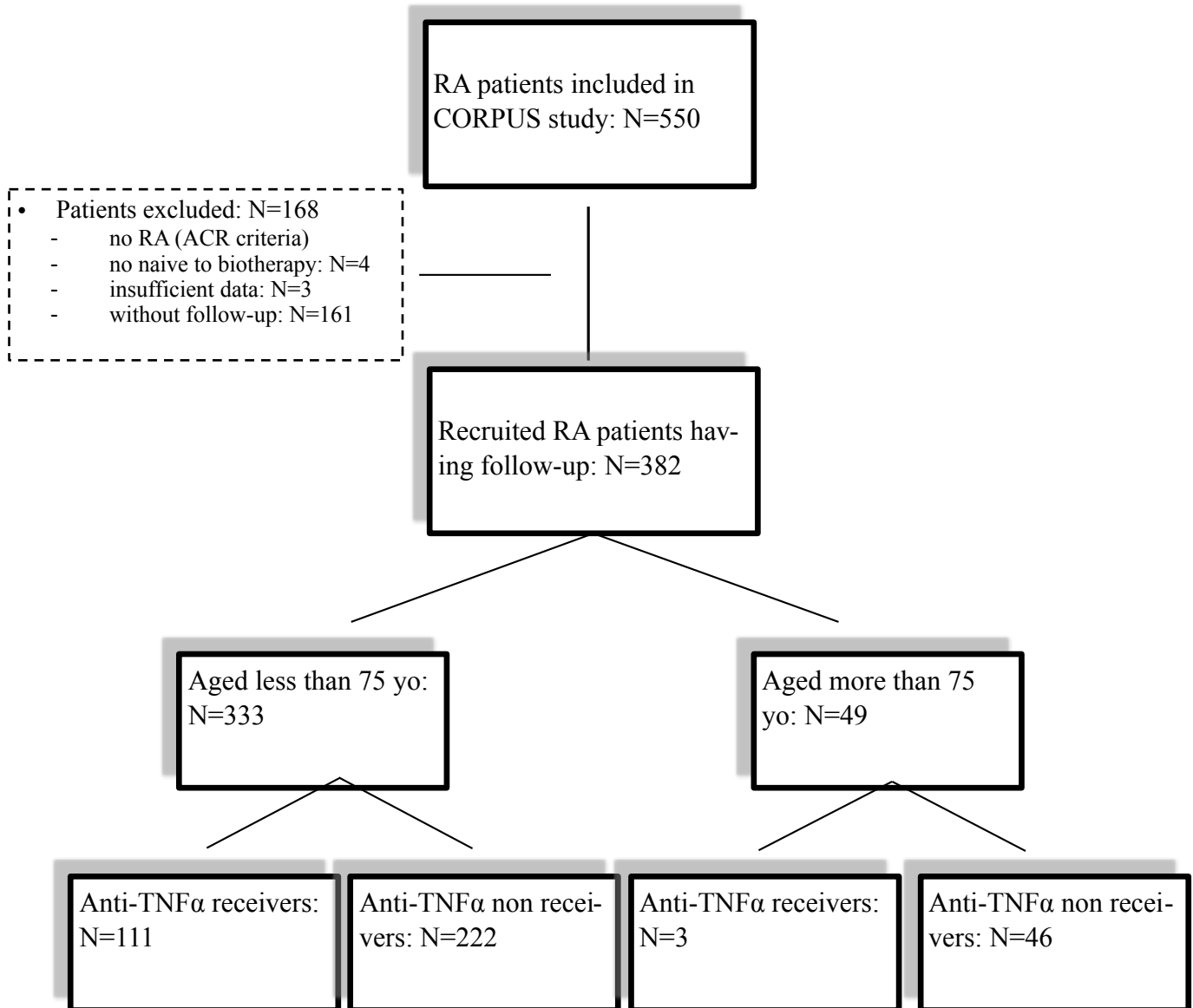
**Table 2: Characteristics of patient at follow-up**

	under 75 year-old	more 75 year-old	p
CRP > 10mg/L, n (%)	65/270 (24.1)	13/36 (36.1)	0.15
VS>20mm, n (%)	111/305 (36.4)	14/46 (30.4)	0.51
DAS-28, mean (SD)	3.69 (1.42)	4.04 (1.36)	0.08
HAQ, mean (SD)	0.40 (0.42)	0.60 (0.50)	0.08
Associated DMARDs, n (%)	235/287 (81.8)	27/42 (64.3)	0.01
GCs treatment, n (%)	155/286 (54.2)	33/42 (78.6)	<0.01
Daily equivalent prednisone at follow-up, mg, mean (SD)	7.8 (9.67)	6.04 (5.10)	0.26
Anti-TNF $\alpha$ treatment, n (%)	111/333 (33.3)	3/49 (6.1)	<0.01

**Table 3: Characteristics of anti TNF receivers in the elderly group (3 patients)**

	Patient 1	Patient 2	Patient 3
<b>At baseline</b>			
Age at baseline, years	75.0	76.8	82.8
Sexe	man	woman	woman
CRP, mg/L	10.9	8.5	4.0
ACPA positive	yes	yes	no
FR positive	yes	yes	no
DAS-28	5.5	6.2	8.9
HAQ	0.87	2.12	1.12
Medical consultation during the last 6 months	6	7	3
Hospitalisation during the last 6 months	0	1	0
Daily equivalent prednisone, mg/per day	5	0	8
Associated DMARDs	methotrexate	methotrexate	methotrexate
Asthenia	7/10	3/10	2/10
Morning stiffness, minutes	120	15	30
<b>At follow up</b>			
CRP, mg/L	6.0	11.0	-
DAS-28	3.3	2.2	6.0
HAQ	0.87	1.6	0.87
Medical consultation during the last 6 months	3	0	6
Hospitalisation during the last 6 months	0	1	0
Gcs treatment	yes	no	-
Associated DMARDs	none	methotrexate	none
Asthenia	7/10	4/10	2/10
Morning stiffness, minutes	15	30	15

**Figure 1: flow chart of the selection to include RA patients who receive anti-TNF $\alpha$**



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**UNIVERSITE DE BREST - BRETAGNE OCCIDENTALE**  
**Faculté de Médecine & des Sciences de la Santé**

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**AUTORISATION D'IMPRIMER**

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Présentée par Monsieur le Professeur GENTRIC-----

Titre de la thèse (en MAJUSCULES) :

TREATMENT OF ACTIVE RHEUMATOID ARTHRITIS : COMPARISON BETWEEN  
YOUNG AND ELDERLY PATIENTS (CORPUS COHORT)

TRAITEMENT DE LA POLYARTHRITE RHUMATOÏDE ACTIVE: COMPARAISON ENTRE  
LES PATIENTS JEUNES ET AGÉES (COHORTE CORPUS)-----

**ACCORD DU PRESIDENT DU JURY DE THESE SUR L'IMPRESSION DE LA THESE**

OUI :

En foi de quoi la présente autorisation d'imprimer sa thèse est délivrée à

Madame: Sachiyo OISHI-----

Interne en DES de : médecine générale -----

Fait à BREST, le 07/06/2016

VISA du Doyen de la faculté  
A BREST, le 15-06-16.

Professeur C. BERTHOU



La Présidente du Jury de Thèse,

(Pr. Annelise Gauthier)



# FICHE RESUME

\*\*\*\*

**NOM & PRENOM** : OISHI Sachiyo

**MOTS CLES** : Rheumatoid arthritis. Glucocorticoids. Biologics. Elderly.

**Titre de la Thèse** : TREATMENT OF ACTIVE RHEUMATOID ARTHRITIS : COMPARISON BETWEEN YOUNG AND ELDERLY PATIENTS (CORPUS COHORT)

## Résumé de Thèse :

Objectifs: Les anti-TNF $\alpha$  ont prouvé leur efficacité dans l'optimisation du traitement de 2ème ligne de la polyarthrite rhumatoïde (PR) active. Peu de données existent sur les caractéristiques des patients âgés ayant une PR nécessitant un traitement de deuxième ligne. L'objectif de ce travail était de comparer la stratégie thérapeutique de deuxième ligne entre les patients de 75ans et plus, et les patients de moins de 75 ans.

Méthodes: Les patients ayant une PR active, naïfs de biothérapie, consultants entre 2007 et 2009 ont été inclus dans la cohorte CORPUS et ont été suivi prospectivement. Cette étude porte sur les patients ayant reçu ou non un anti TNF, à l'exclusion de toutes autre traitement biologique, et qui ont été suivi au moins une année.

Résultats: Parmi les 543 patients ayant une PR, 382 ont été suivi jusqu'à un an. Parmi ces patients, 114 ont reçu au moins une dose d'anti-TNF $\alpha$  dont 111/333 des moins de 75 ans et 4/49 des 75 ans et plus ( $p<0.01$ ). A un an, il n'y avait pas de différence significative entre les 2 groupes pour le DAS-28, HAQ, CRP $>10$ mg/L ( $p=0.08$ ,  $p=0.08$ ,  $p=0.15$ ). Le groupe des plus de 75 ans recevait plus de gluco-corticoïdes ( $p<0.01$ ) mais moins de traitement de fond ( $p=0.01$ ) que le groupe des moins de 75 ans.

Conclusion: En France, les patients âgés ayant un PR active sont moins traités par anti TNF et reçoivent plus de gluco-corticoïdes que les patients plus jeunes.

NOM & signature du DIRECTEUR de THESE

Date : 14 juin 2016

