

Risque infectieux chez les patients atteints de polyarthrite rhumatoïde, traités par Tocilizumab ou un autre traitement de fond biologique en relais du Rituximab : étude rétrospective observationnelle multicentrique sur 157 patients

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Risque infectieux chez les patients atteints de polyarthrite rhumatoïde, traités par tocilizumab ou un autre traitement de fond biologique en relais du rituximab : étude rétrospective observationnelle multicentrique sur 157 patients.

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Jeunes chercheurs

J'ai eu l'occasion de réaliser mon travail de thèse, ayant fait l'objet de ce manuscrit, sur « le risque infectieux chez les patients atteints de polyarthrite rhumatoïde, traités par tocilizumab ou un autre traitement de fond biologique en relais du rituximab », dans le cadre du groupe de travail des Jeunes chercheurs du Grand-Ouest en collaboration avec Gaëlle Vial et Anaïs de Pouilly (internes en rhumatologie respectivement à Clermont-Ferrand et Limoges).

Ce groupe de travail, créé en 2012, rassemble, tous les 2 ans, 6 nouveaux internes en rhumatologie, appartenant chacun à un Centre Hospitalier Universitaire différent (Clermont-Ferrand, Limoges, Toulouse, Nimes, Montpellier et Bordeaux). L'encadrement est assuré par des rhumatologues de ces différents CHU (les Docteurs Anne Tournadre, Claire Daïen, Adeline Ruyssen-Witrand ainsi que les Professeurs Christophe Richez, Cécile Gaujoux-Viala, et Cédric Lukas).

Chaque interne participant aux jeunes chercheurs mène un travail de mémoire ou de thèse, et participe au recueil de données de chaque étude. Les jeunes chercheurs ont en effet pour but premier de permettre la mise en commun des données de ces différents services de rhumatologie afin de démultiplier les effectifs de chaque étude. Il m'a ainsi été donné la possibilité de participer à une étude sur « l'évaluation des connaissances sur les anti-TNF alpha chez les patients atteints de rhumatisme inflammatoire, 3 mois après leur initiation » (Anaïs Nutz), ainsi que sur « l'impact de la consommation en sel sur la polyarthrite rhumatoide » (Sarah Marouen) et la « concordance de l'évaluation de l'activité de la polyarthrite rhumatoïde par le patient et le médecin » (Gisèle Khoury).

Ce groupe de travail permet également, à raison d'une réunion tous les 6 mois, de définir un sujet, puis une méthode de travail basée à la fois sur le recueil de données, les bases statistiques et la rédaction d'un article médical, en vue d'une soumission à la publication. Chaque réunion était également l'occasion de présenter l'avancement des différents travaux et d'apporter le cas échéant les corrections nécessaires.

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Liste des abréviations

ABA : abatacept

ACPA : Anti-Citrullinated Protein Antibodies

ACR : American College of Rheumatology

ADA : adalimumab

bDMARD : biological Disease-Modifying Anti-Rheumatic Drug

BMI : Body Mass Index

CD : Cluster of Differentiation

CDAI: Clinical Disease Activity Index

CTC: corticosteroids

CTZ : certolizumab

CMV : cytomegalovirus

CRP : C-Reactive Protein

DAS-28 : Disease Activity Score based on 28 joints

DMARD : Disease-Modifying Anti-Rheumatic Drug

EBV : Epstein-Barr Virus

ESR : Erythrocyte Sedimentation Rate

ETA : etanercept

EULAR : European League Against Rheumatism

GH : global health

GP : general practitioner

HSV : Herpes Simplex Virus

IgG : immunoglobulin G

IgM : immunoglobulin M

IL : interleukin

INF : infliximab

M : month

n: number of patients

N : times upper limit of normal

PY: patient-year

RA : rheumatoid arthritis

RF : rheumatoid factor

RR : relative risk

SD : standard deviation

SDAI: Simplified Disease Activity Index

sDMARD : synthetic Disease-Modifying Anti-Rheumatic Drug

SJC : swollen joint count

TJC : tender joint count

TNF : tumor necrosis factor

TCZ : tocilizumab

VAS : visual analogue scale

I. Introduction

Management of rheumatoid arthritis significantly improved over the years, as a result of early introduction of conventional sDMARDs such as methotrexate (1,2) and bDMARDs (3), and the close monitoring with frequent adjustments of treatments to the target in order to supress disease activity (4). In spite of it, the widening gap in mortality between RA patients and the general population still exists, mostly due to RA-related comorbidities (5–7) (8). Infections remain a major concern among patients with RA, who are up to 2 fold at increased risk of developing infections requiring hospitalization compared with non-RA subjects (9,10). Although the three leading causes of death are cardiovascular diseases, cancers and respiratory diseases (11), infections remain the acute cause of death with highest increased frequency in a 3.5-fold rate between RA patients (14.3%) and the general population (4.4%) (12) and infection-related standardised mortality rate in RA patients ranges from 4.2 to 14.9 (13). The increased susceptibility of patients with RA to infections can be related to the disease itself, which alters immunological functions, the impact of chronic comorbidities, as well to immunosuppressive treatments (14). Moreover, infections are suboptimally screened for and prevented in RA patients (15). Monitoring and management of comorbidities in RA patients remain challenging in daily practice and recommandations have been made in order to improve prevention of infections (15–17), particularly for vaccinations.

Corticosteroids are major risk factors of infections in RA patients, with a 1.67-fold increased rate, in a positive dose-dependent way (18), whereas synthetic DMARDs, including methotrexate, sulfasalazine and leflunomide, do not significantly impact the risk of infection in RA (19). bDMARDs such as TNF-inhibitors increase in a 2-fold rate the infectious risk in comparaison to sDMARDs (20)(21). No real-world safety data are available to compare the infectious risk between sDMARDS and the other bDMARDs (abatacept, tocilizumab and rituximab) or to compare the infectious risk among bDMARDs (22). A meta-analysis of 6 clinical trials found a 1.30-fold increased rate of infections on tocilizumab compared to methotrexate (CI 1.07, 1.58) (23), while another one based on the analysis of 12 placebo-controlled trials did not found any increased risk of infections in RA patients treated with abatacept, and rituximab (24). Registries provided observational safety data for each bDMARD. The incidence of severe infections in RA patients was 5.0 per 100 patient-years for rituximab in the AIR registry (25), 4.1/100 patient-years for abatacept in the ORA registry (26), and 5.2/100 PY for tocilizumab in the REGATE registry (27).

Rituximab is a monoclonal chimeric mouse/human anti-CD20 glycosylated IgG1 kappa immunoglobulin which binds specifically to the human cell surface antigen CD20 (28), expressed on pre-B and mature B lymphocytes (29). Rituximab, originally used as a treatment for B-cell lymphoma (30), is now widely used as second line bDMARD to treat RA patients resistant to one or more TNF-inhibitor, as recommended in the last EULAR guidelines (22). In case of discontinuation of rituximab, a subsequent bDMARD may be used: TNF-inhibitor, abatacept or tocilizumab. Since rituximab may have long lasting effect, particularly on B-cell depletion (circulating B cell counts recover to the lower limit of normal in 10% of patients by week 24 and in 36% of patients by week 48 (16)), subsequent bDMARD is often initiated before total B-cell repopulation.

Few data are available on the optimal sequencing of bDMARDs (31), and on the safety and efficacy of switching among different bDMARDs, particularly on subsequent bDMARD after rituximab. Five studies (32–36) have already investigated switch from rituximab to subsequent bDMARD, but they included a small number of patients (32,36). These studies showed other limitations, by not assessing tocilizumab as subsequent bDMARD (32), real-world patients (33) or safety (35). One real-world cohort based on 215 patients assessed the infectious risk depending of the wash-out duration between rituximab and subsequent bDMARD but not of bDMARD types. Moreover, this study did not provide any efficacy data (34).

In the university hospital of Bordeaux, we observed several cases of severe infectious diseases among patients diagnosed with rheumatoid arthritis and treated by tocilizumab at the time of its launch on the market in 2009. All these patients had received multiple bDMARDs prior to tocilizumab therapy and all of them had been treated recently by rituximab. A retrospective study conducted in our department showed no increased infectious risk on tocilizumab in comparison with other biological therapies after rituximab treatment (37). However, limitations of this monocentric study was the small number of patients (34 patients).

The aim of our multicentric study was to determine the incidence of severe infectious events during a 18-month period following the initiation of either tocilizumab or non-tocilizumab bDMARDs in RA patients who had been receiving rituximab. Secondary outcomes were also assessed: incidence of non-severe infections, types and risk factors of severe infectious diseases, efficacy on rheumatoid arthritis activity at 3 months and discontinuation rate of the bDMARD following rituximab treatment, and efficacy at 3 months of bDMARD stopped before rituximab for secondary escape or primary inefficacy and resumed after rituximab.

II. Methods

II.1. Study design and population

We conducted a retrospective multicentric observational study in rheumatology departments of 5 French university hospitals (Limoges, Montpellier, Toulouse, Bordeaux and Clermont-Ferrand) from 6 July 2006 (when rituximab obtained marketing authorization) to 15 July 2016.

We included patients over 18 years diagnosed with rheumatoid arthritis according to the 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis (38), treated by at least one infusion of rituximab, and switched to a bDMARD of another mechanism after rituximab discontinuation (such as TNF-inhibitors, abatacept, anakinra or tocilizumab) within 18 months after the last infusion of rituximab.

Non-inclusion criteria included overlap syndromes, other rheumatism than rheumatoid arthritis, prior treatment by rituximab for another indication than rheumatoid arthritis, concomitant use of rituximab and a bDMARD of another mechanism, retreatment by rituximab, and insufficient data to calculate the duration of time between the last infusion of rituximab and the first injection of the subsequent bDMARD.

We retrieved potential included patients through computerized database cross-linked with pharmacy databases in each center.

II.2. Data collection

Three investigators (GV in Clermont-Ferrand, AP in Limoges, LS in Bordeaux, LS and AP in Toulouse, and GV, AP and LS in Montpellier) collected following clinical and biological data according to a Excel® standardized file after examination of patient's paper files and computerized records: demographic data (age, gender) and medical history (severe infectious disease before or on rituximab or during the wash out period between the last rituximab's infusion and the first injection of the subsequent bDMARD, cardiac and pulmonary involvement, renal failure, cerebrovascular accident, diabetes, cancer, hepatic cirrhosis, alcoholism, smoking, and body mass index). We reported prior vaccinations (tetanus, pneumococcus, influenza). We gathered details about rheumatoid arthritis (disease duration, positivity and rate of RF and ACPA, radiographic erosions, extra-articular involvement). Prior treatments before rituximab (corticosteroids, synthetic DMARDs (leflunomide, methotrexate and sulfasalazine) and biologic disease modifying anti-rheumatic drug (abatacept, tocilizumab, anakinra, TNF-inhibitors) were reported. We collected data about rituximab treatment (date of the last infusion, total number of cycles, total dose (mg), reason for stopping) and about the first follow-on bDMARD after rituximab (type, wash-out duration between the last infusion of rituximab and the first infusion of the subsequent bDMARD, maintenance duration, reason for stopping). Other data were systematically collected at baseline (M0), 3 months (M3), 6 months (M6) and 12 months (M12) after the first

administration of subsequent biologic DMARD after rituximab: associated treatments (corticosteroids and its dose, synthetic DMARDs), rheumatoid arthritis activity (swollen and painful joints, patient and provider VAS- global health (mm, 0-10), CRP (mg/L) and ESR (mm at first hour)), and biological data (neutrophils, lymphocytes, B and T cells counts (per mm^3), IgG, IgM and total immunoglobulins (g/L)). In case of the occurrence of an infectious disease within 18 months after the first infusion of bDMARD following rituximab, we collected following data: time between the first subsequent bDMARD after rituximab and the first day of infection, severity, type, microbial agent, duration of hospitalization, need for parenteral antibiotics, and occurrence of death.

In case of lost-to-follow-up before 18 months after the first administration of biological DMARD after rituximab after paper and computerized files assessment, we contacted patients' liberal referring rheumatologist or GP.

II.3. Definitions

Severe infectious diseases were defined as infections requiring intravenous antibiotics, hospitalization, and/or leading to death or prolonged disability within the considered duration of follow-up (24,33,34). Opportunistic infections are defined as any of the following: tuberculosis, atypical mycobacterial infection, systemic fungal infection (aspergillosis, cryptococcosis, esophageal or systemic candidiasis, histoplasmosis, or other endemic fungal infection), listeriosis, legionellosis, salmonellosis, pneumocystosis, toxoplasmosis, opportunistic parasitic infection of the gastrointestinal tract, opportunistic viral infection (extensive recurrent herpes virus infection, herpes zoster, CMV, respiratory viral infection, adenovirus infection, PML, or EBV infection), or any severe documented opportunistic infection (39).

Pulmonary involvement was defined as bronchiectasis, interstitial pneumonitis, chronic obstructive pulmonary disease, respiratory insufficiency or chronic pleural effusion. Cardiac involvement was defined as myocardial infarction or cardiac failure.

Duration of follow-up was defined as time between the first infusion of the subsequent bDMARD after rituximab discontinuation and the earliest event among the following: 18-month elapse, last visit in case of lost-to-follow-up, death, during the 3 months (corresponding to 5 half-lifes of tocilizumab(40)) following withdrawal of subsequent bDMARD without any initiation of a new biologic, first infusion of the second bDMARD in case of discontinuation of the subsequent bDMARD and switch to a second bDMARD occurring within 3 months after discontinuation.

Time to first severe infection was defined as time between the first infusion of the subsequent bDMARD after rituximab and the first day of the first severe infectious event.

Baseline (M0) was defined as the day of the first infusion of the subsequent bDMARD after rituximab discontinuation.

A rituximab's cure was defined as an infusion of 1000mg of rituximab even if stopped before the end, and possibly repeated after 2 weeks.

Each bDMARD was prescribed according to the licensed dose in France.

II.4. Analytic design and outcomes

Patients were classified into 2 groups depending on the type of subsequent bDMARD initiated after rituximab discontinuation: tocilizumab and non-tocilizumab bDMARDs (TNF-inhibitor, abatacept, anakinra).

The primary outcome was the incidence of severe infectious events during a 18-month period following the initiation of either tocilizumab or non-tocilizumab bDMARDs in RA patients who had been receiving rituximab.

Secondary outcomes were also assessed: incidence of non-severe infections, types and risk factors of severe infectious diseases, efficacy at 3 months of subsequent bDMARD on rheumatoid arthritis activity, and survival at 2 years of the subsequent bDMARD. We also assessed efficacy at 3 months of bDMARD stopped before rituximab for secondary escape or primary inefficacy and resumed after rituximab.

We used EULAR response criteria (41), DAS-28 based on ESR, CDAI and SDAI to assess bDMARDs efficacy.

II.5. Statistical analysis

Quantitative values were expressed as median (with minimum and maximum range) or mean (± SD). Qualitative values were reported as effective of patients, with correspondant frequencies. Missing values are reported for all parameters.

We compared in both groups (tocilizumab and non-tocilizumab bDMARDs) patients clinical, demographic and biological characteristics at baseline, using a Z-test.

We compared the incidence of severe and non-severe infections during the period of follow-up in tocilizumab and non-tocilizumab bDMARDs groups, using a Z-test. Follow-up was expressed as patient-year and incidence of severe and non severe infections as event/100 patient-years. For the incidence rate calculation of non severe and severe infections, time to first non severe and severe infections was respectively used as right censoring rule. A survival curve estimated by Kaplan-meier analysis based on the cumulative probability of not experiencing any severe and/or non-severe infection between baseline and 18 months was used for each group: comparison between tocilizumab and non-tocilizumab bDMARDs group was performed with a log-rank test. We described in both groups types of severe and non-severe infections. We assessed association between potential risk factors and severe infections on bDMARDs after rituximab treatment using a Chi-2 test, or a Fisher exact test if needed.

We compared efficacy at 3 months and drug survival at 6 months, 1 year and 2 years of tocilizumab and non-tocilizumab bDMARDs using a Z-test. Patients who discontinuated subsequent bDMARD after rituximab before 3 months of follow-up were considered as non-

responders according to an intention-to-treat analysis for EULAR response criteria. A survival curve estimated by Kaplan-meier analysis based on the cumulative probability of not stopping the bDMARD between baseline and 2 years was used for each group: comparison between tocilizumab and non-tocilizumab bDMARDs group was performed with a log-rank test. We described the efficacy at 3 months of each bDMARD received before rituximab and resumed after its last infusion.

Statistical analysis were performed with STATA 13.1 software. P-values less than 0.05 were considered as significant.

III. Results

III.1. Patients characteristics at baseline

We included 157 patients meeting our inclusion criteria (24 in Limoges, 32 in Bordeaux, 45 in Toulouse, 39 in Montpellier and 17 in Clermont-Ferrand) with a mean follow-up of 14 (+/- 5) months (180.5 patient-years): 42 switched to tocilizumab and 115 to a non-tocilizumab bDMARD (65 to a TNF-inhibitor, 48 to abatacept and 2 to anakinra). Five patients were lost to follow-up before 18 months after the first injection of the subsequent bDMARD after rituximab (2 on tocilizumab and 3 on non-tocilizumab bDMARD).

Baseline characteristics of included patients were similar in tocilizumab and non-tocilizumab bDMARDs groups (table 1 and 2, supplementary data 1). They were mostly female in both group. Mean age was 55 years (minimum-maximum range: 24-85) in tocilizumab group and 59 (31-84) years in non-tocilizumab bDMARDs group. Rheumatoid arthritis was ACPA-positive in 79% of patients in tocilizumab and 68% in non-tocilizumab bDMARDs group, erosive in 85% of patients in both groups, and active with a median DAS 28-ESR of 4.5 (1.9-6.2) and 4.3 (1.4-7.4) points respectively. Median disease duration was 13 years (1-52) and one third of patients had RA-related extra-articular involvement in both groups. Prevalence of serious infections before the first dose of the subsequent bDMARD after rituximab was 26% in tocilizumab group and 31% in non-tocilizumab group. 18 patients (44%) in tocilizumab group and 50 patients (43%) in non-tocilizumab group had at least one organ involvement, mostly pulmonary (for one third of patients). Patients had received in both groups in average 2 (0-3) synthetic and 2 (0-5) biological DMARDs before rituximab, mostly TNF-inhibitors, and then a cumulated dose of rituximab of 4000mg (range: 1000-19000 in non-tocilizumab group and 1000-10000 in tocilizumab group). Reason for rituximab's discontinuation was mostly primary inefficacy in non tocilizumab group (47%) and secondary escape in tocilizumab group (52%). Median wash out duration between rituximab and subsequent bDMARD was 6 months (0-18) in both groups. No patient in tocilizumab group had history of tocilizumab treatment, compared to 7% in non-tocilizumab bDMARD group. Corticosteroids dose at baseline was slightly higher in non-tocilizumab bDMARDs group (7mg/d (0-30) than in tocilizumab group (5mg/d (0-20)), without reaching statistical significance. Baseline biologic data were available for few patients but remained similar between both groups, with a total B-cell depletion (14/mm3 (0-268) in tocilizumab group and 0 (0-531) in non-tocilizumab group), without hypogammaglobulinemia (10.0 (2.8) g/L and 9.5 (3.5) g/L respectively).

III.2. Infections

III.2.1. Incidence of severe and non severe infections on tocilizumab and non-tocilizumab bDMARDs after rituximab treatment

Mean follow-up after the introduction of the treatment was 14 (+/- 5) months in both tocilizumab and non-tocilizumab bDMARD groups (49.9 and 130.6 patients-years respectively).

The incidences of severe infections (table 3) were similar in the tocilizumab and non-tocilizumab bDMARDs groups (15 and 9 per 100 PYs respectively, p = 0.14). However, the incidence of non-severe infections was higher in tocilizumab group than in non-tocilizumab bDMARDs group (94 and 43 per 100 PYs respectively, $p= 10^{-4}$).

129 infections (111 non severe and 18 severe) occured in 81 patients: 55 infections (48 non severe and 7 severe) among 29 patients in the tocilizumab group and 74 (63 non severe and 11 severe) among 52 patients in the non tocilizumab bDMARDs group. Nine infections among the 129 occured after discontinuation of the subsequent bDMARD (within 3 months and before any initiation of a new bDMARD).

Cumulative probability of severe infection over time was similar for tocilizumab and non-tocilizumab bDMARDs (p= 0.535, figure 1) contrary to cumulative probability of non-severe infections which was higher for tocilizumab group (p=0.004).

III.2.2. Type of infections

Non severe and severe infections types (table 4) were mostly respiratory (respectively 58 and 4 infections), cutaneous-mucosal (respectively 19 and 3) and urinary (respectively 15 and 3). Two patients had multiorgan infections on TNF-inhibitors: 1 hypoxemic pneumonia with bacteremia and 1 hypoxemic pneumonia with 2 septic arthritis.

Median time to severe infection after first dose of bDMARD following rituximab was 7 months (3-14). All 18 patients with severe infections were hospitalized, during 15 (1-116) days. Only one severe infection resulted in death in a patient on etanercept and corticosteroids (17.5 mg per day) without sDMARD, after a angiocholitis leading to diagnosis of a metastatic hepatic cancer with peritoneal carcinomatosis.

Nine severe infections could be documented, of which 7 were bacterial. Most common microbial agents were Staphylococcus (n=3), Escherichia coli (n=2) and Streptococcus (n=2). No opportunistic infection and no tuberculosis were reported. Cumulated dose of corticosteroids between baseline and severe infection was reported for 15 patients with severe infections with a median of 1470 mg (0-2400). 3 patients had no corticosteroids.

No significant difference in term of infectious types in tocilizumab and non-tocilizumab bDMARDs groups was observed. Details about each severe infection and non-severe infections are provided in supplementary data 2 and 3.

III.2.3. Risk factors of severe infections

Having at least one comorbidity (renal, cardiac, neurologic, hepatic or pulmonary) was statistically associated with an increased risk of severe infection (p=0.01) and this risk tended to increase with the number of comorbidities (p=0.003 for patients with at least 2 comorbidities). Renal failure, cardiac and pulmonary involvement were statistically associated with risk of severe infections (table 5), p=0.02 and 0.01 respectively.

Level of IgG at initiation of subsequent bDMARD after rituximab were significantly lower in RA patients with severe infections (6.4 g/L, range: 5.8-14.0) than with non-severe infections (10.3 g/L, range: 3.2-19.7), p=0.03.

Prevalence of ACPA was statistically higher in non severe infection group than in severe infection group: n=8 (44%) and n=97 (75%), p=0,04.

Prevalence of severe infections before switching from rituximab to a subsequent biologic tended to be slightly higher in severe infections group (n=9, 50%) than in non severe infections group (n=37, 27%) but did not reach statistical significance (p=0.06), as well as median age (respectively 63 years (24-84) and 58 years (29-85), p=0,06).

No other parameter was statistically associated to severe infections on bDMARDs after rituximab.

III.3. Efficacy at 3 months of tocilizumab and non tocilizumab bDMARDS after rituximab treatment

Data on DAS-28 ESR at baseline and at 3 months were available respectively for 90 patients (33 on tocilizumab and 57 on bDMARDs of other mechanism) and the EULAR response for 103 patients (respectively 37 and 66 patients) (table 6).

Tocilizumab was more effective on DAS-28 ESR at 3 months than non tocilizumab bDMARDs, with a mean reduction of DAS-28 ESR of respectively 2.2 points (±1.2 ; 33 patients) and 1.0 point (±1.3 ; 57 patients), p=0.0002.

21 patients (57%) reached remission on tocilizumab versus 17 (26%) on non-tocilizumab bDMARDs (p <0.0001). EULAR response was significantly better on tocilizumab than on non-tocilizumab bDMARD group (p= 0.01) : 6 patients (16%) did not respond to Tocilizumab and 33 patients (50%) to non-tocilizumab bDMARDs and 10 patients (27%) had good or moderate response according to EULAR criteria on tocilizumab compared to 16 (24%) on non tocilizumab bDMARD.

Variation at 3 months of the total joint count, the swollen joint count and visual analogue scale of global health was similar in tocilizumab and non-tocilizumab groups. On the contrary, decrease of ESR and CRP was more significant at 3 months in tocilizumab group than in non-tocilizumab group (p=0.001 and 0.003 respectively).

Variation of SDAI and CDAI was similar in tocilizumab and in non-tocilizumab group (respectively p=0.19 and 0.10).

III.4. Drug survival of tocilizumab and non tocilizumab bDMARDS after rituximab treatment

Cumulative drug survival between baseline and 2 years was similar (p= 0.944) in tocilizumab and non-tocilizumab bDMARDs groups (table 7 and figure 2). Drug survival at 6 months and 1 year was similar in both groups (p=0.55 and p= 0.84 respectively), but slightly higher in tocilizumab group at 2 years (p=0.04).

Main reason for discontinuation was toxicity for Tocilizumab (10 patients, 43%) and secondary escape for non-tocilizumab bDMARDs (35 patients, 45%).

III.5. Efficacy at 3 months of biological DMARDs stopped for primary non-response or secondary escape and resumed after rituximab treatment

Data on DAS-28 ESR at baseline and 3 months were available for 14 patients, treated by one bDMARD resumed after rituximab (table 8): 1 on abatacept stopped for secondary escape, 13 on TNF-inhibitors (4 stopped for primary non-response and 9 for secondary escape). No patients previously treated by tocilizumab received tocilizumab again after rituximab treatment. 7 patients (50%) obtained good (2 patients, 14%) or moderate (5 patients, 36%) response at 3 months according to EULAR criteria. Remission was obtained in 3 patients (21%).

IV. Discussion

The incidence of severe infectious events was similar on tocilizumab and non-tocilizumab bDMARDs, contrary to the incidence of non severe infectious events which was slightly higher on tocilizumab. Non severe and severe infections types were mostly respiratory, cutaneous-mucosal and urinary, consistent with those observed on RA patients treated with bDMARDs. No opportunistic infections occured. Only one death occured on etanercept but was due to an underlying cancer. Two potential risks factor of severe infections were statistically associated with the risk of severe infections on bDMARDs after rituximab treatment, having at least one comorbidity (particularly renal, cardiac, or pulmonary) and lower level of IgG at initiation of the subsequent bDMARD. Decline of DAS-28 ESR at 3 months was statistically more important for tocilizumab than other bDMARDs contrary to decline CDAI and SDAI, which were similar in both groups. Drug survival was similar for tocilizumab and non-tocilizumab bDMARDs. Interestingly, 50% of patients who resumed bDMARD after rituximab (previously stopped for secondary escape or primary inefficacy) obtained good or moderate response at 3 months according to EULAR criteria.

To our knowledge, this is the largest real-world multicentric study based on non-selected RA patients of routine-care and assessing both safety and efficacy of subsequent bDMARDs after rituximab. Main limitations of this study were its observational nature without randomization to assess efficacy of bDMARDs. Other limitatons were the few number of reported severe infections which constituted our primary outcome, linked to the small number of included patients, the high number of missing data and potential recall bias due to the retrospective design.

Few data are available on the optimal sequencing of bDMARDs, and on the safety and efficacy of switching among different bDMARDs, particularly on subsequent bDMARDs after rituximab. Only 5 studies have already investigated switch from rituximab to subsequent bDMARDs.

Three studies assess safety of bDMARDs after rituximab. Harrold et al. (34) published an observational retrospective real-world study based on 215 RA patients from the Corrona national registry in the United States with a total follow-up slighlty more limited than in our study of 130 patient-years. Patients characteristics at baseline were mostly comparable to our cohort, except for the rate of prior severe infections and pulmonary involvement which were lower than in our study. Incidence of severe infections was slightly lower than our findings (5,4 event per 100 patient-years), which can be explained by a shorter period of follow-up (12 months instead of 18 months in our study). Types of infections were consistent in both studies. No association between wash out duration and infection, which was the primary outcome, was reported, as in our study. However, no data was provided on the infectious risk according to the type of subsequent bDMARD after rituximab discontinuation, and to the level of B-cell depletion. Genovese et al. (33) reported among 185 RA patients no increased risk of serious infections on bDMARDs after rituximab treatment. However, 2 main limitations have to be noticed: only patients who have participated to a previous international rituximab clinical trial were included, and patients with severe comorbidities, which constitute according to our study a risk factor of severe infections, were excluded. Furthermore,

tocilizumab, launched on the market on 2009, could not be assessed. Mishra et al. (32) showed also no increased risk of serious infections on TNF-inhibitors and abatacept after rituximab treatment in a retrospective monocentric observational study, limited by its small number of patients (22 patients). No data on tocilizumab were provided.

Recently, efficacy at 6 months of bDMARDs in RA patients who had been receiving rituximab was the point of a retrospective study conducted by Walker et al. (35), based on 265 patients from a multinationale prospective industry supported european registry (The European Collaborative Registries for the Evaluation of Rituximab in RA (CERERRA)). Patients at baseline were more active (DAS-28 ESR of 5,7 (4.8-6.6) and received less corticosteroids than in our study. Tocilizumab, in particular, was more effective than the alternative bDMARDs with a good EULAR response rate of 65%, 14% and 31% on tocilizumab, TNF-inhibitors and abatacept respectively. No data on safety was reported.

One study provided data on both efficacy and safety. Das et al. (36) reported a superior efficacy of tocilizumab compared to abatacept after rituximab discontinuation. This observational prospective monocentric study was based on only 51 RA patients. Only 2 infectious episod were reported: one culture-negative endocarditis on tocilizumab and recurrent lower respiratory tract infections on abatacept. However, TNF-inhibitors were not assessed and duration of follow-up was not reported.

According to our study, decrease of DAS-28 ESR at 3 months was more significant in tocilizumab than in non-tocilizumab group. However, ESR was the only component of DAS-28 ESR to be significantly decrease at 3 months in tocilizumab group in comparison to non-tocilizumab bDMARDs group. CDAI, a composite score based only on clinical parameters and excluding ESR, was similar between both groups, as well as SDAI. Smolen et al. (42) pooled tocilizumab clinical trial data and showed that remission rates according to the CDAI or SDAI were similar for both tocilizumab and TNF inhibitors. However, DAS28 remission was attained by almost twice as many patients receiving tocilizumab than TNF-inhibitor. Tocilizumab-treated patients with DAS28 remission but without CDAI remission had significantly higher SJC but lower ESRs compared with patients with SDAI or CDAI remission. This could be explained by the high weight of the ESR in the DAS28, in comparison to the CDAI and SDAI in which acute-phase reactants have respectively no and less weight, and the effect of tocilizumab on the ESR. Indeed, IL-6 plays an important role in the production by the liver of the acute-phase reactant (43,44). Tocilizumab is an inhibitor of IL-6 receptor and leads to a rapid reduction in the levels of acute-phase reactants (45). The direct biologic effects of tocilizumab on the reduction of acute-phase reactant levels might lead to an overestimation of the response to treatment with tocilizumab and affect changes in disease activity indices that include acute-phase reactants, such as the DAS28. CDAI and SDAI could be considered as more stringent and reliable than DAS-28 to assess tocilizumab efficacy and compare tocilizumab and non-tocilizumab bDMARDs. Among both studies which had been investigated tocilizumab efficacy after rituximab discontinuation, Das et al. (36) took only into account the DAS-28 ESR contrary to Walker et al. (35). Walker et al. showed a more significant decrease in both DAS-28 ESR and CDAI for tocilizumab than for non-tocilizumab bDMARDs : this could be explained by their higher number of patients (n=265), the lenghter assessement endpoint (6 months) and and the higher DAS-28 ESR at baseline compared to our study.

Some RA remain active in a few patients treated with repeated rituximab cycles, despite complete B-cell depletion, suggesting B-cell-independent disease (36). Das et al. (36) showed a dissociation between B-cell depletion and IL-6 expression in patients non-responder to rituximab (despite complete B-cell depletion) in comparison to responders. Better clinical response to IL6-blockade than to costimulation blockade after rituximab was linked to higher IL-6 expression, probably from many non-B cells sources (46). B and T cells functions may be co-dependant mechanism, limiting the interest of abatacept after rituximab treatment. This could support the superior efficacy of tocilizumab compared to other bDMARD after rituximab discontinuation.

Concerning risk factors of severe infections on bDMARDs after rituximab in RA patients, our findings are consistent with prior studies: Gottenberg et al. (25) reported after analysis of 1303 RA patients from the Autoimmunity and Rituximab (AIR) registry a significant association between severe infections on rituximab and cardiopulmonary involvement, and low level of IgG (< 6g/L) before initiation of rituximab. Another risk factor, not significant in our study was RA-related extra-articular involvement. Doran et al. (10) found that increasing age and comorbidities (chronic lung disease, alcoholism, organic brain disease, and diabetesmellitus), as well as use of corticosteroids, presence of extraarticular manifestations of RA and leukopenia (not significant in our study) were strong predictors of infection ($P < 0.004$) in both univariate and multivariate analyses. Widdifield et al. (47) showed on a total of 86,039 seniors with RA experiencing 20,575 infections that factors associated with infection included higher comorbidity, and history of previous infection, as well as rural residence (not assessed in our study), markers of disease severity, anti–tumor necrosis factor agents and disease-modifying antirheumatic drugs (not significant in our study) with an adjusted odds ratio ranging from 1.2–3.5. The drug category with the greatest effect estimate was glucocorticoids, which exhibited a clear dose response with an OR ranging from 4.0 at low doses to 7.6 at high doses. Cumulated doses of glucocorticoides could not be assessed in our study given the high number of missing data. Curtis et al. (48) estimated that most of the variability in patients infectious risk infection was driven by factors other than biological agent exposure, which is consistent with our results. In our study, prevalence of ACPA was significantly higher in RA patients without severe infections. We did not found any pathophysiological explanation to support this result. Iguchi-Hashimoto et al. (49) showed no association between ACPA and infections in RA patients. This statistical result could be explained by the lack of power of our study, as well as the small number of patients in the severe infections group.

Our study provides insights that may contribute to choose the most appropriate subsequent bDMARD after rituximab treatment: tocilizumab could be considered as a great option as subsequent bDMARD after rituximab in RA patients, due to his higher efficacy on DAS-28 ESR with a similar safety profile to bDMARDs of other mechanism. However, effect on DAS-28 ESR could be overestimated by the high weight of ESR in this composite score and the direct effect of tocilizumab on the production of acute-phase reactants. CDAI and SDAI could be considered as more relevant to compare tocilizumab and non-tocilizumab bDMARDs. Our results should be carefully considered and confirmed in a randomized prospective long-term study or in national registries before any definitive conclusion could be drawn regarding the

safety and efficacy of subsequent bDMARDs after rituximab. No clinical trial is currently ongoing to assess these outcomes, according to clinicaltrial.gov.

V. Conclusion

Our retrospective multicentric non-randomized study based on 157 RA patients showed a similar safety profile concerning severe infections for tocilizumab and non-tocilizumab bDMARDs. Non severe and severe infections types were mostly respiratory, cutaneous-mucosal and urinary. Risk factors for severe infections were having at least one comorbidity and lower level of IgG at initiation of the subsequent bDMARD. Superior efficacy of tocilizumab at 3 months based on DAS-28 ESR was not confirmed by both CDAI and SDAI, which could be explained by the direct biologic effect of tocilizumab on ESR. Drug survival was similar for tocilizumab and non-tocilizumab bDMARDs. bDMARDs stopped for primary inefficacy or secondary escape had 50% chance of working again after rituximab treatment. Further investigations are needed to confirm our results.

Tables and figures

Table 1: Baseline characteristics of patients (demography and comorbidities and their rheumatoid arthritis) at the initiation of tocilizumab or non-tocilizumab bDMARDs (TNF-inhibitors, and abatacept) after rituximab

bDMARDs / Baseline characteristics	Tocilizumab (n= 42)	Non-tocilizumab bDMARDs			*p*
		Total (n=115)	TNF-inhibitors (n=65)	Abatacept and Anakinra (n=50)	
Patients demography and comordities					
Age (years), median (range)	55 (24-85)	59 (31-84)	58 (32-81)	61 (31-84)	0.16
Gender, female, n (%)	34 (81)	89 (77)	51 (78)	38 (76)	0.63
Severe infections before baseline, n (%)	11 (26)	35 (31)[c]	23 (36)[a]	12 (25)[b]	0.60
≥ 1 organ involvement, n (%)	18 (44)	50 (43)	25 (38)	25 (50)	0.94
Current smoker, n (%)	15 (38)[c]	33 (31; 105 patients)	18 (29)[c]	15 (35; 43 patients)	0.61
Vaccination status at baseline					
Vaccination Tetanus, n (%)	14 (82; 17 patients)	31 (57; 54 patients)	17 (24 patients)	23 (30 patients)	0.22
Vaccination Influenza, n (%)	11 (46; 24 patients)	33 (57; 58 patients)	15 (31 patients)	18 (27 patients)	0.46
Vaccination Pneumococcus, n (%)	26 (79; 33 patients)	52 (68; 76 patients)	25 (40 patients)	28 (36 patients)	0.35
Rheumatoid arthritis characteristics					
Disease duration (years), median (range)	13 (3-34)[a]	13 (1-52)[e]	13 (1-41)[d]	14 (2-52)[a]	0.79
RF seropositive, n (%)	29 (72)[b]	80 (70)	45 (69)	35 (70)	0.95
ACPA seropositive, n (%)	31 (79)[c]	74 (68; 108 patients)	39 (65)[e]	35 (73)[b]	0.52
Erosion, n (%)	35 (85)[a]	98 (85)	58 (89)	40 (80)	0.77
Extra-articular involvement[f], n (%)	13 (32)[a]	36 (31)	18 (28)	18 (36)	0.96
CDAI at M0, mean (SD)	28.5 (11,.2)[b]	26.9 (12.0; 91 patients)	28.0 (11.4; 51 patients)	25.3 (12.7, 40 patients)	0.46
DAS-28 ESR at M0, median (range)	4.5 (1.9-6.2)[c]	4,3 (1.4-7.4; 87 patients)	4.5 (1.4-7.4; 49 patients)	4.0 (2.4-6.1; 38 patients)	0.88
ESR at M0 (mm at 1 hour), median (range)	19 (2-89)[a]	23 (0-103; 103 patients)	26 (2-99) (59 patients)	18 (0-103) (44 patients)	0.19
CRP at M0 (mg/L), median (range)	10.5 (0.0-62.0)[b]	9.9 (0.2-177.0) (101 patients)	12.2 (0.2-117.0) (52 patients)	5.8 (0.2-177.0)[a]	0.78

bDMARD : biological Disease-Modifying AntiRheumatic Drug (excluding rituximab). TNF-inhibitor : Tumour Necrosis Factor inhibitor. RF : Rheumatoid Factor (positive > 3.5UI/mL). ACPA : Anti-Cyclic Citrullinated Peptide Antibody (positive > 7 U/mL). CDAI: Clinical Disease Activity Index. DAS 28 : Disease Activity Score based on 28 joints. ESR : Erythrocyte Sedimentation Rate. CRP : C-Reactive Protein. SD : standard deviation. n: number of patients.mm: millimeter. mg/L: milligrams per liter. Quantitative data are presented as mean (SD) or median (minimum-maximum range). Qualitative data are presented as effective of corresponding patients with frequency. p-values refer to Z-tests comparing baseline characteristics between tocilizumab group and non-tocilizumab bDMARDs group. Missing values are displayed with an exponent when data were not available for 1 to 5 patients (a.1 missing value, b. 2 missing values, c. 3 missing values, d. 4 missing values, e. 5 missing values). Beyond 5 missing values, number of patients with available data are written in brackets. f.Extra-articular involvement of RA included rheumatoid nodules, sicca syndrom without meeting Sjögren's syndromes criteria, episcleritis, RA-related interstitial pneumonitis or pleural effusion, Raynaud's phenomenon and vasculitis.

Table 2 : Baseline characteristics (rheumatoid arthritis treatments and biological parameters) at the initiation of tocilizumab or non-tocilizumab bDMARDs (TNF-inhibitors and abatacept) after rituximab

bDMARDs / Baseline characteristics	Tocilizumab (n= 42)	Non-tocilizumab bDMARDs Total (n=115)	TNF-inhibitors (n=65)	Abatacept (n=50)	*p*
Prior treatment before rituximab					
Corticosteroids, n (%)	40 (95)	108 (95)[a]	63 (97)	45 (92)[a]	1
Number of prior sDMARD received per patient, median (range)	2 (0-3)	2 (0-3)	2 (0-3)	2 (0-3)	1
Number of prior bDMARD received per patient, median (range)	2 (0-4)	2 (0-5)	2 (0-5)	2 (0-4)	0.59
0, n (%)	3 (7)	19 (16)	14 (22)	5 (10)	0.19
1, n (%)	6 (14)	21 (18)	10 (15)	11 (22)	-
2, n (%)	22 (52)	38 (33)	17 (26)	21 (42)	-
3, n (%)	9 (21)	24 (21)	15 (23)	9 (18)	-
More than 3, n (%)	2 (5)	13 (11)	9 (14)	4 (8)	0.21
TNF-inhibitor, n (%)	39 (93)	93 (81)	49 (75)	44 (88)	0.07
Abatacept, n (%)	8 (19)	16 (14)[a]	14 (22)[a]	2 (4)	0.43
Tocilizumab, n (%)	0 (0)	9 (8)[a]	7 (11)[a]	2 (4)	0.11
Rituximab treatment					
Cumulated dose (mg), median (range)	4000 (1000-10000)	4000 (1000-19000)[a]	3000 (1000-14000)[a]	4000 (1000-19000)	0.08
Number of cycles, median (range)	2 (1-10)	2 (1-10)	2 (1-8)	2 (1-10)	0.13
Wash out (months), median (range)	6 (0-18)	6 (0-18)	6 (0-18)	6 (0-18)	0.31
Severe infections during rituximab therapy, n (%)	3 (7)	6 (5)	4 (6)	2 (4)	0.70
Concomittant treatments at baseline					
Corticosteroids, n (%)	29 (69)	82 (74)[d]	49 (78)[b]	33 (69)[b]	0.55
CTC dose (mg), median (range)	5 (0-20)[b]	7 (0-30)[d]	7 (0-30)[b]	5 (0-25)[b]	0.49
Methotrexate, n (%)	21 (50)	55 (49)[c]	35 (55)[a]	20 (42)[b]	0.81
Leflunomide, n (%)	4 (9)	10 (9)[c]	5 (8)[a]	5 (10)[b]	1
Sulfasalazine, n (%)	1 (2)	5 (4)[c]	4 (6)[a]	1 (2)[b]	1
Biological parameters at baseline					
Neutrophil polynuclear(mm3), mean (SD)	5731 (3094)[c]	6021 (2521) (100 patients)	6103 (2324) (54 patients)	5926 (2755)[e]	0.28
Lymphocytes (mm3), mean (SD)	2017 (1408)[c]	1739 (918) (96 patients)	1559 (668) (53 patients)	1961 (1123) (43 patients)	0.27
Total immunoglobulines (g/L), mean (SD)	10.0 (2.8) (25 patients)	9.5 (3.5) (66 patients)	9.4 (3.2) (33 patients)	9.6 (3.7) (33 patients)	0.42
B-lymphocytes (mm3), median (range)	14 (0-268) (10 patients)	0 (0-531) (41 patients)	0 (0-531) (19 patients)	5.10^{-4} (0-385) (22 patients)	0.08
T-lymphocytes (mm3), median (range)	1028 (39-3984) (10 patients)	974 (425-2383) (32 patients)	1179 (608-2383) (14 patients)	829 (425-1668) (18 patients)	0.98

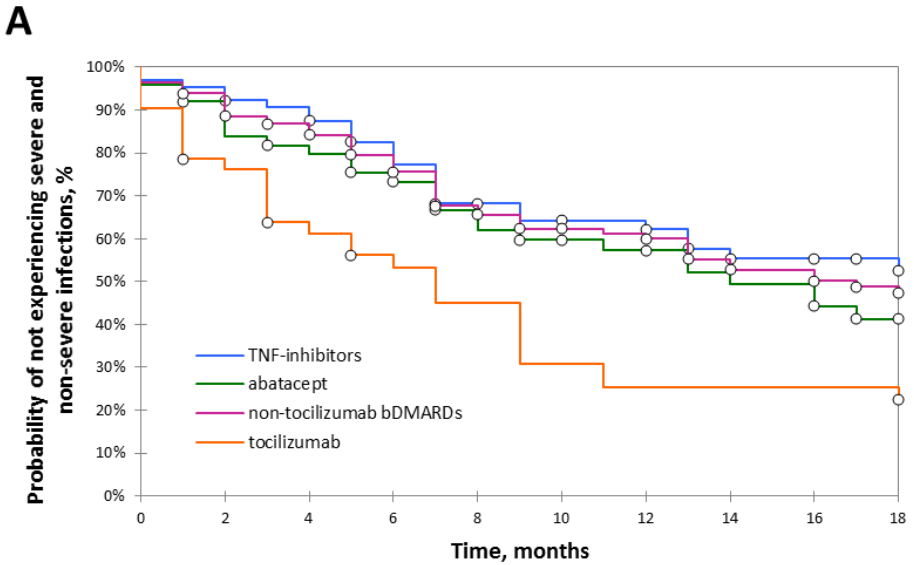
bDMARD : biological Disease-Modifying AntiRheumatic Drug (excluding rituximab). TNF-inhibitor : Tumour Necrosis Factor inhibitor. sDMARD: synthetic Disease-Modifying AntiRheumatic Drug. CTC: corticosteroids. SD : standard deviation. n: number of patients.mm: millimeter. g/L: grams per liter. Quantitative data are presented as mean (SD) or median (minimum-maximum range). Qualitative data are presented as effective of corresponding patients with frequency. *p*-values refer to Z-tests comparing baseline characteristics between tocilizumab group and non-tocilizumab bDMARDs group. Missing values are displayed with an exponent when data were not available for 1 to 5 patients (a.1 missing value, b. 2 missing values, c. 3 missing values, d. 4 missing values, e. 5 missing values). Beyond 5 missing values, number of patients with available data are written in brackets.

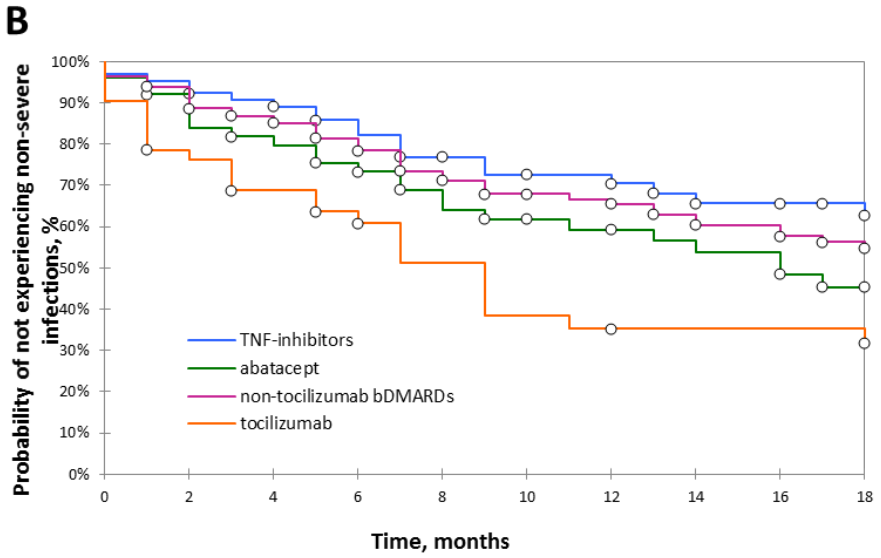
Table 3 : Incidence of non-severe and severe infections within 18 months after the first dose of tocilizumab or non-tocilizumab bDMARDS (TNF-inhibitors and abatacept) after rituximab

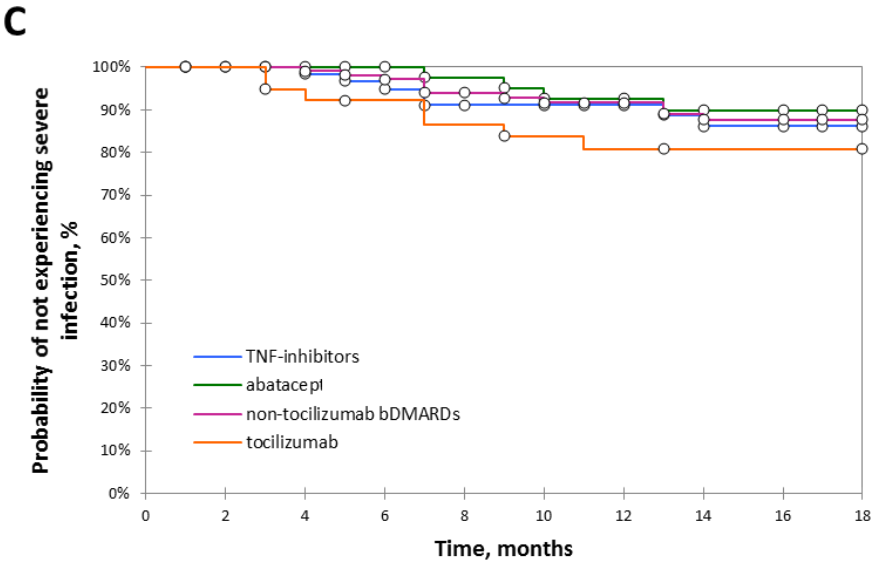
bDMARDs	Tocilizumab (n=42)	Non-tocilizumab bDMARDS			Total	*p*
		Total (n=115)	TNF-inhibitors (n=65)	Abatacept (n=50)		
Total duration of follow-up, PY	49.9[a]	130.6[a]	71.2[a]	59.4	180.5	-
Non-severe infections						
Total number of non severe infections, n	48	63	26	37	111	-
Number of patients experiencing non severe infection, n	24	43	19	24	67	-
Time to first non-severe infection, PY	25.4	101.0	57.7	43.3	126.4	-
Incidence rate of non-severe infections, events/100 PY	94	43	33	55	53	10^{-4}
Severe infections						
Total number of severe infections, n	7	11	7	4	18	-
Time to first severe infection, PY	47.3	126.6	68.2	58.3	173.9	-
Incidence rate of first severe infections, events/100 PY	15	9	10	7	10	0.14

bDMARD : biological Disease-Modifying AntiRheumatic Drug. TNF: Tumor Necrosis Factor. n:number of patients. PY: patent-year. *p*-values refer to Z-tests comparing incidence rate of severe and non severe infections between tocilizumab group and non-tocilizumab bDMARDs group. a.one missing value.

Figure 1 : Survival analysis: probability of not experiencing a severe and/or non-severe infection over time by type of subsequent bDMARDs after rituximab







(A) Eighteen-month survival without severe and non-severe infections. Kaplan–Meier plots over 18-months, according to year of treatment start. Log-rank test for 18-months survival without severe infections; p=0.001.

(B) Eighteen-month survival without non-severe infections. Kaplan–Meier plots over 18-months, according to year of treatment start. Log-rank test for 18-months survival without non-severe infections; p=0.004.

(C) Eighteen-month survival without severe infections. Kaplan–Meier plots over 18-months, according to year of treatment start. Log-rank test for 18-months survival without severe and non-severe infections; p=0,535.

TNF: tumor necrosis factor. bDMARDs: biological Disease-Modifying AntiRheumatic Drugs.

Table 4 : Type of infections occuring within 18 months after the first dose of tocilizumab or non-tocilizumab bDMARDs (TNF-inhibitors and abatacept) following rituximab treatment

Infections		Tocilizumab (n=42)	Non-tocilizumab bDMARDS		
			Total (n=115)	TNF-inhibitors (n=65)	Abatacept (n=50)
Non severe infections (n=111)					
Respiratory tract (n)		27	31	12	19
Cystitis (n)		5	10	1	9
Meningoencephalitis (n)		0	0	0	0
Gastrointestinal tract (n)		3	3	2	1
Cutaneous-mucosal (n)		11	8	6	2
Septic bursitis (n)		0	1	0	1
Tooth infection (n)		1	8	3	5
Other (n)		1 (grippal syndrome)	2	2 (fever without documentation, grippal syndrome)	0
Severe infections (n=18)					
Type	Respiratory tract (n)	1	3	1	2
	Urinary tract (n)	2	1	1	0
	Meningoencephalitis (n)	1	0	0	0
	Gastrointestinal (n)	1	1	1	0
	Cutaneous-mucosal (n)	1	2	2	0
	Septic arthritis (n)	0	2	0	2
	Multi-organ	0	2	2	0
	Other (n)	1 (febrile agranulocytosis)	0	0	0
Hospitalization, n (%)		7	11	7	4
Duration of hospitalization (days), median (range)		10.0 (1-95)	17.5 (7-116)[a]	17.5 (7-116)[a]	18.0 (13-60)
Death, n (%)		0	1	1	0
Microbial agent (type, n)		Methicillin-Sensitive Staphylococcus aureus (1) Listeria (1) wild-type Escherichia coli CMV (1) EBV (1) Unknown (3)	Streptococcus (1) Staphylococcus Capitis (1) Pneumococcus and Staphylococcus Epidermidis (1) Escherichia coli (1) HSV 2 (1) Unknown (6)	Pneumococcus and Staphylococcus Epidermidis (1) Escherichia coli (1) HSV 2 (1) Unknown (4)	Streptococcus (1) Staphylococcus Capitis (1) Unknown (2)
Time between severe infection and first dose of bDMARD after rituximab (months), mean (SD)		6.2 (3.1)	8.6 (3.4)	8.0 (3.9)	9.7 (2.5)

CMV: Cytomegalovirus. HSV : Herpes Simplex Virus. EBV : Epstein-Barr Virus. bDMARD : biological Disease-Modifying AntiRheumatic Drug. TNF: Tumor Necrosis Factor. n:number of patients. Quantitative data are presented as mean (SD) or median (minimum-maximum range). Qualitative data are presented as effective of corresponding patients with frequency. a.one missing value.

Table 5 : Risk factors of severe infections on bDMARDs after rituximab treatment

Potential risk factor	Severe infectious group (n=18)	Non severe infection and no infections group (n=139)	*p*
Patients and comorbidities			
Age (years), median (range)	63 (24-84)	58 (29-85)[b]	0.06
Gender, female, n (%)	14 (78)	109 (78)	1
Severe infections before switching,n (%)	9 (50)	37 (27)[d]	0.06
≥ 1 organ involvement, n (%)	13 (72)	55 (39)	0.01
≥ 2 organ involvements, n (%)	7 (39)	14 (10)	0,003
Renal Failure, n (%)	5 (28)	11 (8)	0.02
Cardiac involvement, n (%)	7 (39)	21 (15)[a]	0.02
Pulmonary involvement, n (%)	9 (50)	30 (22)	0.01
Cancer, n (%)	2 (11)	22 (16)	1
Diabetes, n (%)	3 (17)	26 (19)	1
BMI > 25, n (%)	10 (56)[a]	67 (53 ; 128 patients)	0.55
Current smoker, n (%)	6 (33)[a]	42 (33 ; 126 patients)	0.87
Rheumatoid arthritis			
Disease duration (years), median (range)	12 (2-52)	14 (1-43 ; 131 patients)	0.61
FR positivity, n (%)	10 (56)	99 (73)[c]	0.13
ACPA positivity, n (%)	8 (44)[b]	97 (75 ; 129 patients)	0.04
Erosion, n (%)	13 (72)	120 (88)[b]	0.14
Extra-articular involvement, n (%)	7 (39)	42 (30)[a]	0.59
DAS-28 ESR, median (range)	4.2 (1.9-7.4)[b]	4.3 (1.4-6.6 ; 109 patients)	0.59
Treatments			
Number of prior bDMARD received per patient before rituximab, median (range)	2 (0-3)	2 (0-5)	0.09
Cumulated dose of rituximab (mg), median (range)	4000 (1000-10000)	4000 (1000-19000)[a]	0.95
Wash out (months), median (range)	6 (3-13)	6 (0-18)	0.23
Current treatment at baseline			
Corticosteroids, n (%)	16 (88)	95 (70)[c]	0.10
Corticosteroids dose (mg/d), mean (SD)	7.3 (4.2)[a]	6.4 (5.8 ; 129 patients)	0.52
Methotrexate, n (%)	7 (39)	69 (51)[c]	0.35
Leflunomide, n (%)	2 (11)	12 (9)[c]	0.67
Sulfasalazine, n (%)	1 (6)	5 (4)[c]	0.53
Biological parameters at baseline			
Total immunoglobulins < 6g/L, n (%)	3 (27 ; 10 patients)	9 (11; 79 patients)	0.13
IgG (g/L), median (range)	6.4 (5.8-14.0; 11 patients)	10.3 (3.2-19.7 ; 75 patients)	0.03
IgM (g/L), median (range)	0.49 (0.23-1.37; 11 patients)	0.68 (0.17-3.37 ; 75 patients)	0.23
B-lymphocytes (mm3), mean (SD)	3.8 (6.7 ; 6 patients)	55 (120 ; 37 patients)	0.59

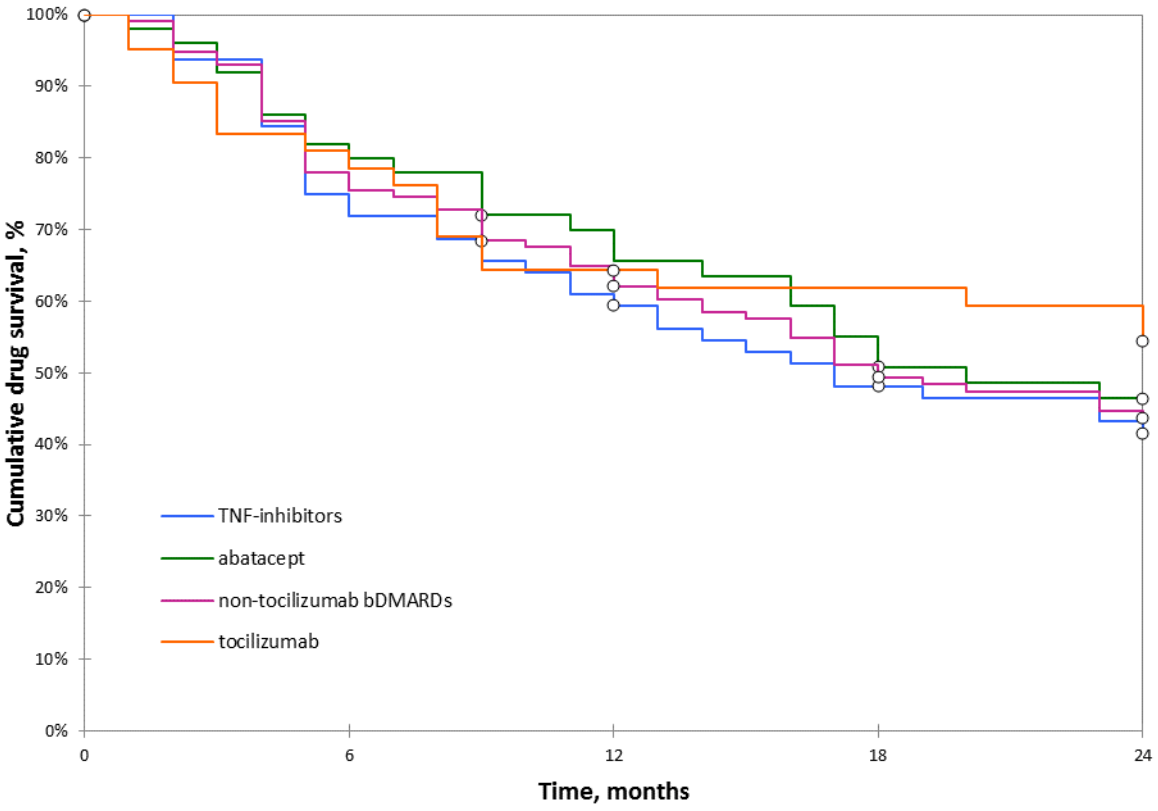
bDMARD : biological Disease-Modifying AntiRheumatic Drug. BMI : Body Mass Index. RF : Rheumatoid Factor. ACPA : Anti-Cyclic Citrullinated Peptide Antibody.CDAI: Clinical Disease Activity Index. DAS 28 : Disease Activity Score based on 28 joints. ESR : Erythrocyte Sedimentation Rate. Ig : immunoglobulin. SD : standard deviation. n: number of patients. mg: milligram. g/L: gram per liter. d :day. Quantitative data are presented as mean (SD) or median (minimum-maximum range). Qualitative data are presented as effective of corresponding patients with frequency. *p*-values refer to Chi-2 test, or Fisher exact test if needed to assess potential risk factors of severe infections on bDMARDs after rituxmab. Missing values are displayed with an exponent when data were not available for 1 to 4 patients (a.1 missing value, b. 2 missing values, c. 3 missing values, d. 4 missing values). Beyond 5 missing values, number of patients with available data are written in brackets.

Table 6 : Efficacy at 3 months of tocilizumab and non-tocilizumab bDMARDs (TNF-inhibitors and abatacept) after rituximab

bDMARD	Tocilizumab		Non-tocilizumab bDMARDs						*p*
			Total		TNF-inhibitors		Abatacept		
Efficacy	Baseline (n=42)	M3 (n=39)	Baseline (n=115)	M3 (n=109)	Baseline (n=65)	M3 (n=61)	Baseline (n=50)	M3 (n=48)	
TJC, median (range)	8 (0-25) 38 patients	3 (0-20) 38 patients	7 (0-28) 97 patients	2 (0-28) 87 patients	8 (0-28) 53 patients	2 (0-28) 45 patients	6 (0-28) 44 patients	3 (0-21) 42 patients	-
SJC, median (range)	5 (0-22)	1 (0-15)	5 (0-19) 99 patients	2 (0-12) 85 patients	6 (0-19) 55 patients	2 (0-12) 44 patients	3 (0-15) 44 patients	2 (0-10) 41 patients	-
ESR (mm at 1 hour), median (range)	19 (2-89) 41 patients	3 (2-20) 35 patients	23 (0-103) 103 patients	17 (1-82) 85 patients	26 (2-99) 59 patients	23 (1-82) 46 patients	18 (0-103) 44 patients	16 (2-77) 39 patients	0,001[a]
CRP (mg/L), median (range)	10.5 (0-62) 40 patients	1.0 (0-9) 35 patients	9.9 (0-177) 101 patients	5.0 (0-180) 89 patients	12.2 (0-117) 52 patients	5.0 (0-180) 47 patients	5.8 (0-177) 49 patients	4.8 (0-65) 42 patients	0,003[a]
VAS patient GH, mean (SD)	6.5 (2.0) 40 patients	4.0 (2.5) 38 patients	6.0 (2.0) 91 patients	4.0 (2.5) 71 patients	6.0 (2.0) 51 patients	4.0 (2.5) 35 patients	6.0 (2.0) 40 patients	4.0 (2.5) 36 patients	-
CDAI, mean (SD)	28.5 (11.2) 40 patients	14.5 (10.7) 40 patients	26.9 (12.0) 91 patients	16.6 (11.7) 71 patients	28.0 (11.4) 51 patients	17.1 (12.0) 35 patients	25.3 (12.7) 40 patients	16.2 (11.5) 36 patients	-
Decline in CDAI, mean (SD)	-	-14.3 (14.6) 39 patients	-	-9.8 (12.3) 63 patients	-	-9.5 (12.1) 30 patients	-	-10.1 (12.7) 33 patients	0.10
SDAI, mean (SD)	30,0 (11.3) 38 patients	15.2 (10.8) 34 patients	2.,8 (12.9) 84 patients	17.4 (12.3) 68 patients	30.6 (12.0) 45 patients	18.0 (13.2) 35 patients	26.9 (13.8) 39 patients	16.6 (11.5) 33 patients	-
Decline in SDAI, mean (SD)	-	-15.3 (15.5) 31 patients	-	-11.2 (13.4) 61 patients	-	-12.1 (12.6) 30 patients	-	-10.3 (14.3) 31 patients	0.19
DAS-28 ESR, mean (SD)	4.3 (1.1) 39 patients	2.2 (1.0) 35 patients	4.4 (1.2) 86 patients	3.4 (1.3) 65 patients	4.5 (1.2) 49 patients	3.5 (1.5) 33 patients	4.1 (1.1) 37 patients	3.2 (1.2) 32 patients	-
Decline in DAS-28 ESR, mean (SD)	-	-2.2 (1.2) 33 patients	-	-1.0 (1.3) 57 patients	-	-1.1 (1.2) 30 patients	-	-0.9 (1.4) 27 patients	0.0002
EULAR response	-	37 patients	-	66 patients	-	35 patients	-	31 patients	0.01
Good, n (%)	-	7 (19)	-	5 (8)	-	3 (9)	-	2 (6)	-
Moderate, n (%)	-	3 (8)	-	11 (17)	-	5 (14)	-	6 (19)	-
None, n (%)	-	6 (16)	-	33 (50)	-	18 (51)	-	15 (48)	-
Remission, n (%)	-	21 (57)	-	17 (26)	-	9 (26)	-	8 (26)	$<10^{-4}$

bDMARD: biological Disease-Modifying AntiRheumatic Drug (excluding rituximab). TNF: Tumor Necrosis Factor. TJC : Tender Joint Count (0-28). SJC : Swollen Joint Count (0-28). ESR : Erythrocyte Sedimentation Rate. CRP : C-Reactive Protein. VAS : Visual Analogue Scale (0-10). GH : Global Health. CDAI: Clinical Disease Activity Index.DAS 28 : Disease Activity Score based on 28 joints. EULAR: European League Against Rheumatism. SD : standard deviation. n: number of patients. M3 : 3 months after the first dose of biological DMARDS. Quantitative data are presented as mean (SD) or median (minimum-maximum range). Qualitative data are presented as number of corresponding patients with frequency. In case of missing values, number of patients with available data are displayed. *p* values refer to Z-tests comparing 3 months-values between the tocilizumab group and the other bDMARDs group. a. p-values refer to Z-test comparing 3-months variation of ESR and CRP between tocilizumab and non-tocilizumab groups. Reason for discontinuation before 3 months : TOC (n=3) : toxicity (n=2), patient's wish (n=1) ; TNF (n=4) : toxicity (n=2), primary non response (n=2) ; ABA (n=2) : toxicity (n=1), allergy (n=1).

Figure 2 : Drug survival analysis over time on tocilizumab and non-tocilizumab bDMARDs (TNF-inhibitors and abatacept)



Drug survival	6 months	1 year	2 years
Tocilizumab, n (%)	34 (81)	27 (64)	25 (60)
Non-tocilizumab bDMARDs, n (%)	88 (77)	72 (63)	47 (41)
TNF-inhibitors, n (%)	48 (74)	39 (60)	26 (40)
Abatacept, n (%)	40 (80)	33 (66)	21 (42)
p	0,55	0,84	0,04

Two-year drug survival of bDMARDs after rituximab discontinuation. Kaplan–Meier plots over 2-year retention to bDMARDs, according to year of treatment start. Log-rank test for 2-year cumulative drug survival; p=0.944. TNF: tumor necrosis factor. bDMARDs: biological Disease-Modifying AntiRheumatic Drugs.

Table 7 : Reason for discontinuation of tocilizumab and non-tocilizumab bDMARDs

bDMARD / Reason for discontinuation	Tocilizumab (n=42)	Non-tocilizumab bDMARDs		
		Total (n=115)	TNF-inhibitors (n=65)	Abatacept (n=50)
Primary non-response, n (%)	6 (26)	21 (27)	14 (27)	7 (26)
Secondary escape, n (%)	6 (26)	35 (45)	24 (47)	11 (41)
Toxicity, n (%)	10 (43)	19 (24)	13 (25)	6 (22)
Allergy, n (%)	0 (0)	1 (1)	0 (0)	1 (4)
Other, n (%)	1 (4)[a]	2 (3)	0 (0)	2 (7)[b]

bDMARD: biological Disease-Modifying AntiRheumatic Drug (excluding rituximab). TNF: Tumor Necrosis Factor. n: number of patients. Qualitative data are presented as number of corresponding patients with frequency. a: myeloma. b: surgery, predominant non-inflammatory pain.

Table 8 : Efficacy at 3 months of bDMARDs stopped for primary non-response or secondary escape and resumed after rituximab treatment

Reason for discontinuation		Primary non-response (n=4)	Secondary escape (n=13)[a]	Total (n=17)[b]
bDMARD	Abatacept, n (%)	0 (0)	1 (100)	1 (100)
	TNF-inhibitors, n (%)	4 (23)	12 (71)	16 (100)
DAS-28 ESR at baseline, mean (SD)		4.5 (0.9)	4.5 (0.6)	4.5 (0.7)
DAS-28 ESR at 3 months, mean (SD)		3.4 (0.7)	3.9 (1.2)	3.7 (1.1)
Reduction in DAS-28 ESR, mean (SD)		-1.2 (1.1)	-0.6 (1.1)	-0.7 (1.1)
Good or moderate EULAR respondeur at 3 months, n (%)		2 (50)	5 (38)	7 (50)
Remission, n (%)		1 (25)	2 (20)	3 (18)

bDMARD : biological Disease-Modifying AntiRheumatic Drug (excluding rituximab). TNF: Tumor Necrosis Factor. DAS 28 : Disease Activity Score based on 28 joints. ESR : Erythrocyte Sedimentation Rate. EULAR : European League Against Rheumatism. SD : standard deviation. n: number of patients. Quantitative data are presented as mean (SD). Qualitative data are presented as number of corresponding patients with frequency. No patient previously treated by tocilizumab resumed this bDMARD after rituximab. a.10 patients with available data on DAS 28 ESR at baseline and 3 months. b.14 patients with available data on DAS 28 ESR at baseline and 3 months

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Supplementary data

Supplementary data 1 : Complementary baseline characteristics at the initiation of tocilizumab or non-tocilizumab bDMARDs (abatacept and TNF-inhibitors) within 18 months after the last infusion of rituximab

bDMARDs / Baseline characteristics	Tocilizumab (n= 42)	Non-tocilizumab bDMARDs Total (n=115)	TNF-inhibitors (n=65)	Abatacept (n=50)
Renal Failure, n (%)	4 (9)	12 (10)	5 (8)	7 (14)
Cardiac involvement, n (%)	8 (19)	20 (17)	9 (14)	11 (22)
Cerebrovascular accident, n (%)	2 (5)	8 (7)	5 (8)	3 (6)
Pulmonary involvement, n (%)	12 (29)	38 (33)	16 (25)	22 (44)
Hepatic cirrhosis, n (%)	0 (0)	1 (1)	0 (0)	1 (2)
Cancer, n (%)	6 (14)	17 (15)	10 (15)	7 (14)
Diabetes, n (%)	7 (17)	22 (19)	11 (17)	11 (22)
≥ 2 organ involvements, n (%)	4 (10)	17 (15)	6 (9)	11 (22)
BMI < 17,5, n (%)	1 (2)[b]	2 (2; 105 patients)	1 (2)[e]	1 (2)[e]
BMI > 25, n (%)	20 (50)[b]	57 (54; 105 patients)	33 (55)[e]	24 (53)[e]
Alcoholism, n (%)	0 (0)	2 (2)	0 (0)	2 (4)
RF > 3N, n (%)	22 (56)[c]	62 (55)[b]	35 (54)	27 (56)[b]
ACPA > 3N, n (%)	28 (74)[d]	63 (61; 104 patients)	32 (55; 58 patients)	31 (67)[d]
TJC at M0, median (range)	8 (0-25)	7 (0-28) (97 patients)	8 (0-28) (53 patients)	6 (0-28) (44 patients)
SJC at M0, median (range)	5 (0-22)	5 (0-19) (99 patients)	6 (0-19) (55 patients)	3 (0-15) (44 patients)
VAS patient GH at M0, median (range)	7.0 (1.0-10.0)[b]	6.0 (0.5-10.0) (91 patients)	6.0 (2.0-10.0) (51 patients)	6.0 (0.5-10) (40 patients)
SDMARDs before rituximab				
Methotrexate, n (%)	40 (95)	109 (95)	61 (94)	48 (96)
Leflunomide, n (%)	26 (63)[a]	78 (68)	42 (65)	36 (72)
Sulfasalazine, n (%)	21 (50)	57 (50)	31 (48)	26 (52)
Other, n (%)	17 (41)[a]	73 (63)	41 (63)	32 (64)

DMARD : Disease-Modifying AntiRheumatic Drug. bDMARD : biological Disease-Modifying AntiRheumatic Drug (excluding rituximab). TNF-inhibitor : anti-tumour necrosis factor inhibitor. BMI : body mass index. RF : rheumatoid factor. ACPA : anti-cyclic citrullinated peptide antibody. TJC: tender joint count. SJC: swollen joint count. VAS : Visual Analogue Scale (0-10). SD : standard deviation. n: number of patients. N : times upper limit of normal. GH : global health. Quantitative data are presented as mean (SD) or median (minimum-maximum range). Qualitative data are presented as number of corresponding patients with frequency. Missing values are displayed with an exponent for 1 to 5 patients. Beyond 5 missing values, number of patients with available data are written in brackets. a.1 missing value, b. 2 missing values, c. 3 missing values, d. 4 missing values, e. 5 missing values.

Supplementary data 2 : Details on each 18 reported severe infections on bDMARDs after rituximab discontinuation

bDMARD		Infection type	Time between severe infection and first dose of bDMARD (months)	Microbial agent	Duration of hospitalization (days)	Death (n)
Tocilizumab		Meningoencephalitis	11	CMV, listeria	95	0
		Prostatitis	9	wild-type Escherichia coli	10	0
		Fecal peritonitis (ulcerative ileitis due to a EBV-induced lymphoma with CMV coinfection)	4	EBV	32	0
		Erysipelas	7	Methicillin-Sensitive Staphylococcus aureus	9	0
		Pyelonephritis	3	Unknown	1	0
		Hypoxemic pneumonia	7	Unknown	32	0
		Febrile agranulocytosis	3	Unknown	8	0
TNF-inhibitors	ETA	Urinary tract infection without precision	7	Unknown	23	0
	CTZ	Hypoxemic pneumonia with bacteremia	4	Escherichia coli	20	0
	ETA	Pneumonia	7	Unknown	7	0
	INF	Ischial abscess (with diagnosis 16 months later of a psoas abscess with infection of a hip prosthesis)	14	Unknown	Unknown	0
	ADA	Hypoxemic pneumonia with septic arthritis of the left ankle and the right knee prosthesis	13	Pneumococcus, staphylococcus epidermidis	116	0
	ETA	Angiocholitis (with peritoneal carcinomatosis)	5	Unknown	15	1
	ETA	Cutaneous herpetic infection	6	HSV 2	7	0
Abatacept		Pneumonia	10	Unknown	21	0
		Bronchitis complicated with acute pulmonary edema	9	Streptococcus	13	0
		Septic arthritis of a hip prosthesis	13	Staphylococcus capitis	60	0
		Septic arthritis of the wrist	7	Unknown	15	0

ETA : etanercept. CTZ : certolizumab. INF : infliximab. ADA : adalimumab. TNF : tumor necrosis factor. bDMARD : biological Disease-Modifying AntiRheumatic Drug. n : number of patients. CMV : cytomegalovirus. EBV : epstein barr virus. HSV : herpes simplex virus.

Supplementary data 3 : Details on non severe infections types on bDMARDs after rituximab discontinuation

bDMARDs	Tocilizumab	TNF-inhibitors	Abatacept
Respiratory infections	1 sinusitis, 8 rhinopharyngitis, 15 bronchitis, 1 angina, 2 tracheitis	1 rhinitis, 2 sinusitis, 1 rhinopharyngitis, 4 bronchitis, 1 tracheitis, 2 angina, 1 flu	12 bronchitis, 1 angina, 1 bronchiectasis superinfection, 1 sinusitis, 2 tracheitis, 1 otitis, 1 without precision
Gastro-intestinal infections	3 gastroenteritis	1 sigmoiditis and 1 gastroenteritis	1 colitis (clostridium difficile)
Cutaneous-mucosal infections	1 palpebral cellulitis, 3 herpetic infections (1 keratitis, 2 cutaneous infection), 1 erysipelas, 1 zona, 1 vaginal candidiasis, 1 inguinal hydradenitis, 1 superinfection of a cervical cyst, 1 superinfection of a corn and 1 superinfection of an ingrown nail	1 cutaneous herpetic infection, 1 axillary furunculus, 1 zona, 1 intertrigo, 1 without precision	1 zona, 1 ecthyma.

Serment d'Hippocrate

Au moment d'être admise à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité.

Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux.

Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions. J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité. Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences. Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences. Je donnerai mes soins à l'indigent et à quiconque me les demandera. Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admise dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçue à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les moeurs.

Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission. Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.

J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité. Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses ; que je sois déshonorée et méprisée si j'y manque.

Abstract

Introduction: Infections remain a major concern in rheumatoid arthritis (RA). Few data are available on the optimal bDMARDS sequencing after rituximab. The aim of our study was to determine the incidence of severe infections during a 18-month period following the initiation of either tocilizumab or non-tocilizumab bDMARDs in RA patients who had been receiving rituximab.

Methods: We conducted a retrospective observational study in 5 French university rheumatology departments from July 2006 to July 2016, including patients over 18 diagnosed with RA according to 2010 ACR/EULAR criteria, treated by at least one infusion of rituximab, followed by another bDMARD within 18 months. Primary outcome was incidence of severe infections.

Results: We included 157 patients: 42 on tocilizumab and 115 on other bDMARDs. Baseline characteristics were similar in both groups, as the incidence of severe infections (15 and 9 per 100 PYs respectively, p=0,14). The incidence of non severe infections was higher on tocilizumab (94 and 43 per 100 PYs respectively, $p=10^{-4}$). Infections types were mostly respiratory (n=62), cutaneous-mucosal (n=22) and urinary (n=18). Two risks factor were strongly associated with severe infections, having at least one comorbidity (p=0,01), and lower level of IgG at the time of initiation of the subsequent bDMARD (p=0,03). Mean reduction of DAS-28 ESR at 3 months was higher in tocilizumab than in-tocilizumab groups respectively 2,2 (±1,2) and 1,0 point (±1,3), p=0,0002, but decline of CDAI (p=0.10) and SDAI (p=0.19) was similar in both groups. Cumulative drug survival at 2 years was similar in both groups (p=0.94).

Conclusion: We showed similar incidence of severe infections on tocilizumab and other bDMARDs after rituximab. Higher decline of DAS-28 ESR compared to CDAI and SDAI could be explained by the direct biologic effect of tocilizumab on ESR. Further investigations are needed to confirm our results.

Résumé

Introduction: Les infections sont un enjeu majeur de la prise en charge des patients atteints de polyarthrite rhumatoïde. Notre étude avait pour but de comparer l'incidence des infections sévères chez les patients atteints de polyarthrite rhumatoide (PR) sous tocilizumab par rapport aux autres biotherapies.

Méthodes: Notre étude retrospective observationnelle menée dans 5 services universitaires de rhumatologie entre juillet 2006 et juillet 2016, incluait des patients majeurs, diagnostiqués PR selon les critères ACR/EULAR 2010, traités par au moins une cure de rituximab puis par une autre biothérapie dans les 18 mois. Le critère de jugement principal était l'incidence des infections sévères sous tocilizumab par rapport aux autres biotherapies.

Résultats: Nous avons inclus 157 patients: 42 sous tocilizumab et 115 sous une autre biothérapie. Les caractéristiques à l'inclusion étaitent similaires entre les 2 groupes, tout comme l'incidence des infections sévères (15 et 9 pour 100 patients-années (PA) respectivement, p=0,14). L'incidence des infections non sévères était plus élevée sous tocilizumab (respectivement 94 et 43 pour 100 PA, $p=10^{-4}$). Les principaux types d'infection étaient respiratoires (n=62), cutanéo-muqueuses (n=22), et urinaires (n=18). Deux facteurs de risques étaient associés aux infections sévères: avoir au moins une comorbidité, en particulier rénale, cardiaque ou pulmonaire (p=0,01), et un taux d'IgG bas lors de l'initiation de la biothérapie (p=0,03). La reduction du DAS-28 VS à 3 mois était plus importante sous tocilizumab qu'avec les autres biotherapies: respectivement 2,2 (±1,2) et 1,0 (±1,3) points (p=0,0002), contrairement au CDAI (p=0,10) et le SDAI (p=0,19). Le taux de maintien cumulé à 2 ans était similaire entre les 2 groupes (p=0,94).

Conclusion: L'incidence des infections sévères était similaire sous tocilizumab par rapport aux autres biotherapies en relais du rituximab. La baisse significativement plus importante du DAS-28VS sous tocilizumab par rapport aux autres biothérapies pourrait être expliquée par l'effet propre du tocilizumab sur les protéines inflammatoires. Des investigations complémentaires sont nécessaires pour confirmer nos résultats.