EXTENDED REPORT

Predictive risk factors of serious infections in patients with rheumatoid arthritis treated with abatacept in common practice: results from the Orencia and Rheumatoid Arthritis (ORA) registry

J H Salmon,[1] J E Gottenberg,[2] P Ravaud,[3] A Cantagrel,[4] B Combe,[5] R M Flipo,[6] T Schaeverbeke,[7] E Houvenagel,[8] P Gaudin,[9] D Loeuille,[10] S Rist,[11] M Dougados,[12] J Sibilia,[13] X Le Loët,[14] O Meyer,[15] E Solau-Gervais,[16] C Marcelli,[17] T Bardin,[18] I Pane,[3] G Baron,[3] E Perrodeau,[3] X Mariette,[19] on behalf of all the investigators of the ORA registry and the French Society of Rheumatology

Handling editor Tore K Kvien

▶ Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2015-207362).

For numbered affiliations see end of article.

Correspondence to
Dr X Mariette, Service de Rhumatologie, Hôpital de Bicêtre, 78 rue du Général Leclerc, Le Kremlin Bicêtre 94275, France; xavier.mariette@bct.aphp.fr and JE Gottenberg, CHU Strasbourg, 1 avenue Molière, 67000 Strasbourg, France; jacques-eric gottenberg@chru-strasbourg.fr

JHS and JEG contributed equally to this work.

Received 27 January 2015
Revised 29 April 2015
Accepted 14 May 2015
Published Online First 5 June 2015

ABSTRACT

Objectives Little data are available regarding the rate and predicting factors of serious infections in patients with rheumatoid arthritis (RA) treated with abatacept (ABA) in daily practice. We therefore addressed this issue using real-life data from the Orencia and Rheumatoid Arthritis (ORA) registry.

Methods ORA is an independent 5-year prospective registry promoted by the French Society of Rheumatology that includes patients with RA treated with ABA. At baseline, 3 months, 6 months and every 6 months or at disease relapse, during 5 years, standardised information is prospectively collected by trained clinical nurses. A serious infection was defined as an infection occurring during treatment with ABA or during the 3 months following withdrawal of ABA without any initiation of a new biologic and requiring hospitalisation and/or intravenous antibiotics and/or resulting in death.

Results Baseline characteristics and comorbidities: among the 976 patients included with a follow-up of at least 3 months (total follow-up of 1903 patient-years), 78 serious infections occurred in 69 patients (4.1/100 patient-years). Predicting factors of serious infections: on univariate analysis, an older age, history of previous serious or recurrent infections, diabetes and a lower number of previous anti-tumour necrosis factor were associated with a higher risk of serious infections. On multivariate analysis, only age (HR per 10-year increase 1.44, 95% CI 1.17 to 1.76, p=0.001) and history of previous serious or recurrent infections (HR 1.94, 95% CI 1.18 to 3.20, p=0.009) were significantly associated with a higher risk of serious infections.

Conclusions In common practice, patients treated with ABA had more comorbidities than in clinical trials and serious infections were slightly more frequently observed. In the ORA registry, predictive risk factors of serious infections include age and history of serious infections.

INTRODUCTION

Pivotal controlled clinical trials are usually performed on selected populations of patients. Patients with cancer, recurrent infections or serious concomitant illness are excluded from these trials. There is, therefore, some uncertainty as to whether safety data obtained in randomised controlled trials (RCTs) can be extrapolated to patients in daily practice. The potential increased risk of infections is an important safety concern in patients with rheumatoid arthritis (RA) receiving biological therapies.[1] Abatacept (ABA) inhibits T cell co-stimulation and does not directly antagonise cytokines, such as antitumour necrosis factor (TNF), anti-interleukin (IL)-6R or IL-1RA, nor results in lymphocyte depletion, as anti-CD20 antibodies. Whether this mechanism of action results in a different safety profile as the other biologics is poorly addressed in common practice. The French Society of Rheumatology has set up the Orencia and Rheumatoid Arthritis (ORA) registry, a national multicentre prospective registry of patients treated with ABA for RA to determine the tolerance to and efficacy of ABA in daily practice. The present study analysed the rates and predicting factors of serious infections in patients with RA included in ORA.

PATIENTS AND METHODS

The ORA registry

The ORA registry is an ongoing nationwide prospective cohort study for investigating the long-term safety and efficacy of intravenous ABA for treating RA using the same design and protocol as the AutoImmunity and Rituximab registry.[2–4] It is promoted by the French Society of Rheumatology and receives financial support (unrestricted educational grant) from Bristol-Myers-Squibb. However, Bristol-Myers-Squibb was not involved in the design, protocol, data collection or statistical analysis of the study. At baseline, 3 months, 6 months and every 6 months or at disease relapse, during 5 years, standardised information are prospectively collected by trained clinical nurses or technicians in each centre. Central reviewing of charts of patients with serious adverse events is performed by the two coordinators of the study. A serious infection was defined as an infection occurring during treatment with ABA or during the 3 months following withdrawal of ABA without any initiation of a new biologic and requiring hospitalisation and/or intravenous antibiotics and/or resulting in death. Opportunistic infections were defined as previously reported.[5]

To cite: Salmon JH, Gottenberg JE, Ravaud P, *et al*. *Ann Rheum Dis* 2016;**75**:1108–1113.

Ann Rheum Dis: first published as 10.1136/annrheumdis-2015-207362 on 5 June 2015. Downloaded from http://ard.bmj.com/ on July 1, 2022 by guest. Protected by copyright.

Statistical analysis

Patients contributed person-years of follow-up between first infusion of the first cycle and death, or last follow-up visit. For the incidence rate calculation of serious infections, time of serious infections was used as right censoring rule. Rates of serious infections are presented as event/100 patient-years. We investigated the relationships between serious infections occurring during treatment with ABA and potential predictors. Both univariate and multivariate analyses were performed using time to first serious infection during the follow-up as outcome of interest. In univariate analysis, variables were compared with log-rank tests. For the multivariate analysis, we performed a Cox model with a bootstrap model selection variable method[6] to assess all relevant variables. We used 1000 bootstrap samples. Variables with $p<0.20$ in univariate analysis were selected for possible inclusion in the multivariate model. Variables identified as independent factors associated with serious infection in at least 60% of the bootstrap samples were kept in the multivariate model. The interactions between the remaining variables in the final model were tested. Results are expressed as the HR with 95% CIs. To analyse the role of cumulated disease activity level and cumulated oral corticosteroid doses, we estimated for each patient the mean disease activity score in 28 joints (DAS28) level and the mean corticosteroid dosage during follow-up and compared those means between patients without serious infections and patients with serious infections using a Student's t test. To estimate the mean DAS28 and corticosteroid dosage during follow-up, we calculated the area under the corticosteroid curve (AUC) between baseline and last available value of DAS28 and corticosteroid dosage, respectively. We then divided these AUC by the length of follow-up to take into account the potential difference in terms of follow-up due to the healthy survivor effect between patients with and without serious infections. Statistical analysis was performed with R V.3.0.1.[7]

RESULTS

Characteristics of the patients at enrolment in the ORA registry

In total, 1012 patients with RA from 88 centres, all enrolled at the time of their first exposure to the drug, were included in the ORA registry. At the time of analysis of the results, 36 patients were missing any follow-up or had a follow-up duration inferior to 3 months and could not be analysed for the risk of serious infections (see online supplementary table S1 and figure S1). The analysis was therefore carried out on 976 patients. In total, 335 patients (34.8%) had previous serious or recurrent infections, 106 (11.5%) had diabetes, 53 patients (5.5%) a history of cancer and 19 (2%) had a chronic lung and/or cardiac insufficiency (table 1). Thirty-five patients (3.6%) had a previous tuberculosis primoinfection and 20 (2%) a previous tuberculosis disease.

Mean disease duration was 17.5±9.5 years. Rheumatoid factor (RF) was positive in 622 patients (72.9%). Ninety-eight patients (10.3%) had RA-related extra-articular involvement, including rheumatoid nodules, Sjögren's syndrome, scleritis, RA-related lung involvement and Felty's syndrome. Patients had been given 2.8±1.5 previous synthetic disease-modifying antirheumatic drugs (DMARDs). Before ABA, 126 patients (12.9%) had no anti-TNF. Rituximab (RTX) had been previously prescribed in 290 (29.7%) patients, including 185 patients as the last biologic prior to ABA.

Table 1 Baseline characteristics of 976 patients with RA treated with abatacept in the ORA registry

	Value mean (SD) or n (%)	Number of available data per outcome (%)
Age, mean±SD years	58 (13.6)	970 (99.4)
Sex	Male: 204 (20.9%) Female: 771 (79.1%)	975 (99.9)
Disease duration, mean±SD months	17.5 (9.5)	961 (98.5)
Smoking	Ever: 98 (10.2%) Never: 866 (89.8%)	964 (98.8)
History of cancer	53 (5.5%)	968 (99.2)
Chronic lung disease and/or cardiac insufficiency	19 (2)	946 (96.9)
Diabetes	106 (11.5%)	918 (94.1)
Previous severe infection	335 (34.8%)	962 (98.6)
Previous DMARDs, mean±SD	2.83 (1.5)	898 (92)
Previous anti-TNF treatment	0: 126 (12.9%) 1: 232 (23.8%) 2: 356 (36.5%) 3: 261 (26.8%)	975 (99.9)
Previous rituximab treatment	290 (29.7%)	975 (99.9)
RF-positive	622 (72.9%)	853 (87.4)
Anti-CCP-positive	554 (70.9%)	781 (80)
RA-related extra-articular involvement	98 (10.3%)	955 (97.8)
Swollen joint count, mean±SD	6.14 (5.3)	671 (68.8)
ESR, mean±SD mm/h	35.6 (27.9)	655 (67.1)
DAS28-ESR, mean±SD	5.34. (1.3)	648 (66.4)
DMARDs* Methotrexate alone Leflunomide alone Other/combinations	630 477 (75.7%) 91 (14.4%) 62 (9.8%)	963 (98.7)
Corticosteroids*, mean±SD mg/day	732 (76.2%) 8.7 (9)	960 (98.4)

Except where indicated otherwise, values are the number (%) of patients.
*Defined as the day of ABA first infusion.
ABA, abatacept; CCP, cyclic citrullinated peptide; DAS28, disease activity score in 28 joints; DMARDs, disease-modifying antirheumatic drugs; ESR, erythrocyte sedimentation rate; ORA, Orencia and Rheumatoid Arthritis; RF, rheumatoid factor.

The mean DAS28-erythrocyte sedimentation rate (ESR) before ABA was 5.34±1.3. Most of the patients (732; 76.2%) were still receiving oral corticosteroids at the onset of ABA (median dose: 8 mg/day (3; 10). Approximately one-third of patients (34.6%) were treated with ABA as monotherapy (eg, without cs DMARD) and two-thirds with ABA and a concomitant synthetic DMARD. Baseline data on serum gammaglobulin and IgG levels were available for 494 (50.6%) and 333 patients (34.1%), respectively. Before the initiation of ABA, hypogammaglobulinemia (<6 g/L) and hypoIG (<6 g/L) were observed in 31 (6.3%) and 21 (6.3%) patients, respectively. Only 4 of the 39 patients with hypoIgG had previously been treated with RTX.

Rate of serious infections

The mean follow-up of the 976 analysed patients was 23.4 ±10.5 months (1903 patient-years). Seventy-eight serious infections occurred in 69 patients during treatment with ABA or during the 3 months following withdrawal of ABA without any initiation of a new biologic (4.1 serious infections/100 patient-years). The mean follow-up of the patients with serious

Ann Rheum Dis: first published as 10.1136/annrheumdis-2015-207362 on 5 June 2015. Downloaded from http://ard.bmj.com/ on July 1, 2022 by guest. Protected by copyright.

infections (n=69) or without serious infections (n=907) was 24.2±11.7 and 23.4±10.4 years, respectively (p=0.405). Fifty-eight infections occurred in 51 patients during treatment with ABA (3.0/100 patient-years), and 20 infections occurred in 18 patients during the 3 months following withdrawal of ABA (1.1/100 patient-years).

Serious infections were bronchopulmonary (32 infections, 41%), osteoarticular (11, 14%, including 5 arthrodesis or prosthetic joint infections), urinary (10, 12.5%), involved skin or soft tissues (6, 7.5%), the gastrointestinal tract (10, 12.5%), eye–nose–throat (2, 2.5%) or were septicaemias (2, 2.5%), catheter infection (1, 1.5%), endocarditis (1, 1.5%), pericarditis (1, 1.5%), keratitis (1, 1.5%) or viral hepatitis (1, 1.5%).

A pathogen could be identified in 39 infections (50%) (*Escherichia coli*: 9; *Staphylococcus aureus*: 5; *Enterobacterium*: 4; *Streptococcus pneumonia*: 3; varicella zoster virus (VZV): 3; *Pseudomonas aeruginosa*: 2; *Haemophilus influenza*: 1; *Streptococcus pyogenes*: 1; influenza virus: 2; *Salmonella enterica*: 2; *Capnocytophaga*: 1; coagulase-negative *Staphylococcus*: 1; *Enterococcus faecalis*: 1; *Corynebacterium*: 2; herpes simplex virus: 1; hepatitis E virus infection (HEV): 1. The patient with HEV had previously been treated with leflunomide and 3 anti-TNF (etanercept, adalimumab, infliximab, which was stopped 1 month before the initiation of ABA) and was concomitantly treated with methotrexate (MTX) (15 mg/w) at diagnosis of hepatitis E, 20 months after the initiation of ABA. The patient had elevated liver enzymes, a normal level of bilirubin and no feature of liver insufficiency. Diagnosis was established by serology and PCR. No antiviral treatment was introduced, ABA and MTX were discontinued, and the viral load disappeared. ABA and MTX were reintroduced 4 months after the infection, and no viral reactivation was observed.

One opportunistic infection (0.05/100 patient-years) was reported during treatment with ABA: one severe VZV infections involving ≥3 more contiguous dermatomes. At the time of infection, that patient had a concomitant treatment with prednisone 10 mg/day and ketoprofen 200 mg/day and had to be treated with intravenous acyclovir. No tuberculosis was reported.

Serious infections resulted in two deaths by pneumonia, with no identification of the involved pathogen: one patient had AA amyloidosis, end-stage renal disease and was concomitantly treated with MTX and one patient had coronary artery disease and was concomitantly treated with leflunomide and prednisone (7.5 mg/day).

Baseline risk factors of serious infections during treatment with ABA or within 3 months of its discontinuation

Univariate analysis showed that an older age, diabetes, history of previous serious or recurrent infections and fewer previous anti-TNF were associated with a higher risk of serious infections during treatment with ABA or within 3 months of its discontinuation. Disease duration, disease activity and concomitant treatment with a synthetic DMARD were not significantly associated with an increased risk of serious infections (table 2). No difference was observed in the proportion of serious infections between patients treated with ABA in monotherapy, with concomitant MTX or with concomitant leflunomide. No difference was observed in patients with prior treatment with RTX: 14 patients (20.3%) with serious infection had previously been treated with RTX compared with 276 (30.5%) patients without serious infection. The proportion of patients with IgG<6 g/L was not significantly different among patients with or without serious infections (7.1% and 6.2%, respectively). Multivariate analysis showed that age (HR per 10-year increase 1.44, 95% CI 1.17 to 1.76, p=0.001) and history of previous serious or recurrent infections (HR 1.94, 95% CI 1.18 to 3.20, p=0.009) were significantly associated with a higher risk of serious infections during ABA (table 2). In a sensitivity analysis, we only considered the infections that occurred while patients were treated with ABA. Multivariate analysis yielded similar results showing an association between serious infections during ABA treatment with age and history of previous or recurrent infections (HR per 10-year increase 1.51, 95% CI 1.20 to 1.89, p<0.001 and HR 2.11, 95% CI 1.21 to 3.69, p=0.008, respectively).

Role of persistent disease activity and change in oral corticosteroid dose

In total, 774 patients had at least both a baseline DAS28 value and a DAS28 value during follow-up. The mean (SD) AUC DAS28/length of follow-up was 4.34 (1.2) in the 721 patients without infection and 4.4 (1.1) in the 53 patients with serious infections (p=0.705). Also, 917 patients had at least both a baseline corticosteroid value and a value during follow-up. The mean (SD) AUC corticosteroid/length of follow-up was 6.07 (5.28) in the 853 patients without infection and 6.63 (5.44) in the 64 patients with serious infections (p=0.410).

DISCUSSION

To our knowledge, this is the largest prospective study, based on a national registry of serious infections in patients with RA treated with ABA in common practice. Limitations of the study include the observational design, missing data and the absence of comparison with patients treated with synthetic DMARDs or other biologic. Many of the patients had comorbidities including more than one-third with previous serious or recurrent infections, conversely to patients included in clinical trials. This high proportion of comorbidities probably led to the prescription of ABA with no concomitant synthetic DMARD in one-third of the patients. A similar proportion of patients treated in monotherapy can be observed in patients treated with other biologics all over the world[4 8–11] and with ABA in other countries.[12]

Depending on the way the at-risk period are defined, different analyses can be performed. Similarly as performed to analyse serious infections in anti-TNF-treated patients, our first choice was to analyse the rate of serious infections that occurred during ABA treatment or within 3 months of its discontinuation, provided that no other biologic had been initiated.[13] A second hypothesis was to only consider the serious infections that occurred while patients were treated with ABA since there is no demonstration of a persistent immunological effect of ABA after its discontinuation. Whatever the way of defining the at-risk period, the rate of serious infections was slightly higher than that observed in controlled trials of intravenous ABA during the double-blind period (3.7/100 patient-years) or in their open-phase follow-up (2.9/100 patient-years)[14] and than that in five controlled trials of subcutaneous ABA (1.9/100 patient-years).[15] In patients with RA treated with RTX in the AutoImmunity and Rituximab registry, a registry with the same methodology as ORA, the occurrence of serious infections was similar (5.0/100 patient-years) as in the present study,[4] being aware that the patient characteristics might differ. Of note, the mean follow-up was not very long (23.4±10.5 months) and could be considered as a limitation of the study. However, this relatively short follow-up allows to decrease the 'healthy drug survivor' effect consisting of the selection with time of the good patients who

Ann Rheum Dis: first published as 10.1136/annrheumdis-2015-207362 on 5 June 2015. Downloaded from http://ard.bmj.com/ on July 1, 2022 by guest. Protected by copyright.

Table 2 Univariate and multivariate analysis of risk factors of serious infections that occurred during treatment with ABA or within 3 months of its discontinuation

	Patients with severe infection (n=69)	Patients without severe infection (n=907)	HR univariate analysis (95% CI)	p Value, univariate analysis	HR multivariate analysis (95% CI)	p Values, multivariate analysis
Age, mean±SD years*	64.6±12.1	57.5±13.6	1.48 (1.22 to 1.79)	<0.001	1.44 (1.17 to 1.76)	0.001
Female	53 (76.8)	718 (79.2)	1.15 (0.66 to 2.02)	0.616		
Disease duration, mean±SD months	18.7±10.3	17.4±9.5	1.01 (0.99 to 1.04)	0.358		
RA-related extra-articular involvement	8 (11.8)	90 (10.1)	1.19 (0.57 to 2.48)	0.648		
Ever smoking	4 (5.9)	94 (10.5)	0.54 (0.20 to 1.48)	0.231		
Record of cancer	5 (7.4)	48 (5.3)	1.53 (0.62 to 3.81)	0.359		
Cardiac insufficiency	2 (2.9)	11 (1.2)	2.69 (0.66 to 10.98)	0.169		
Diabetes	13 (20.6)	93 (10.9)	2.08 (1.13 to 3.83)	0.019	1.67 (0.90 to 3.09)	0.105
Previous serious or recurrent infection	37 (53.6)	298 (33.4)	2.30 (1.43 to 3.70)	0.001	1.94 (1.18 to 3.20)	0.009
Previous DMARDs, mean±SD	3±1.6	2.8±1.5	1.07 (0.91 to 1.26)	0.404		
Previous anti-TNF			0.55 (0.30 to 0.98)	0.044		
0 anti-TNF	14 (20.3)	112 (12.4)				
1 anti-TNF	20 (29)	212 (23.4)				
2 anti-TNF	16 (23.2)	340 (37.5)				
3 anti-TNF	19 (27.5)	242 (26.7)				
Previous rituximab	14 (20.3)	276 (30.5)	0.62 (0.34 to 1.11)	0.110		
RF positive	52 (82.5)	570 (72.2)	1.78 (0.93 to 3.42)	0.081		
Anti-CCP positive	46 (80.7)	508 (70.2)	1.79 (0.92 to 3.45)	0.084		
Initial DAS28-ESR, mean±SD	5.5±1.4	5.3±1.3	1.11 (0.91 to 1.37)	0.304		
IgG <6 g/L	2 (7.1)	19 (6.2)	1.28 (0.30 to 5.4)	0.737		
Hypogammaglobulinemia <6/L	3 (7.1)	28 (6.2)	1.29 (0.40 to 4.18)	0.671		
Concomitant DMARDs†	41 (59)	589 (65)	0.88 (0.53 to 1.45)	0.608		
Methotrexate alone	30 (73.2)	447 (75.9)				
Leflunomide alone	10 (24.4)	81 (13.8)				
Other/combinations	1 (2.4)	61 (10,3)				
Concomitant corticosteroids†	54 (83.1)	678 (75.8)	1.57 (0.82 to 3.00)	0.175		
Dosage in patients treated with corticosteroids, mean±SD (mg/day)	9.5±7.9	8.6±9.0	1.01 (0.99 to 1.03)	0.406		

Except where indicated otherwise, values are number of patients (%).
*HR is given for an increase of 10 years.
†Defined as the dose on the day of ABA first infusion.
ABA, abatacept; CCP, cyclic citrullinated peptide; DAS28, disease activity score in 28 joints; DMARDs, disease-modifying antirheumatic drugs; ESR, erythrocyte sedimentation rate; RA, rheumatoid arthritis; RF, rheumatoid factor.

tolerate the drug. Thus, concerning the infectious risk in registries, it is probably useful to analyse the data with a relatively short follow-up.

After a mean follow-up of nearly 2 years, no reactivation of tuberculosis was observed despite previous tuberculosis disease in 20 patients and previous primoinfection in 35 patients. This suggests, as previously reported in mice infected with *Mycobacterium tuberculosis*, that CTLA-4 does not favour tuberculosis reactivation,[16] also a longer follow-up is needed to confirm these results. In the ORA registry, the only opportunistic infections were viral: three VZV infections and one herpetic keratitis, which required either hospitalisation and/or intravenous antiviral drugs. In ABA trials, the frequency of herpes simplex virus was slightly higher in ABA than placebo-treated patients (0.5 vs 0.2/100 patient-years), the occurrence of herpes zoster was similar (1.8 vs 2.0/100 patient-years). A significant increased rate of herpes zoster infections was also reported in patients with RA treated with synthetic DMARDs, anti-TNF[17] or tociluzimab.[18] The rate of herpes zoster infections in eight RCTs and two open-label extension trials of RTX was consistent with those observed in MTX-treated patients with RA.[19]

In addition, we report the first HEV infection under ABA and MTX. A recent study reported acute and chronic HEV infections among transplant recipients and other immunocompromised individuals including patients with HIV/AIDS. Like hepatitis A virus, acute HEV infection usually runs a self-limited course in immunocompetent individuals and evolution to chronicity only occurs in the setting of immunodepression.[20] Interestingly discontinuation of ABA and MTX was sufficient to allow the resolution of HEV infection and ABA could be reintroduced thereafter. Of note, the prevalence of acute hepatitis E and the risk of chronicity in patients treated with biologics are not currently known. In view of the increasing prevalence of hepatitis E, it therefore seems important to assess the epidemiology of this infection in RA.

Serious infections were associated with age and history of serious or recurrent infections. Although a history of serious or recurrent infections was intensively searched in the charts of patients before the initiation of ABA, the risk of recall bias cannot be ruled out regarding history of serious or recurrent infections. The occurrence of serious infections was not associated with baseline characteristics of RA such as disease duration, disease activity or concomitant treatments, including oral

Ann Rheum Dis: first published as 10.1136/annrheumdis-2015-207362 on 5 June 2015. Downloaded from http://ard.bmj.com/ on July 1, 2022 by guest. Protected by copyright.

corticosteroids. Of note, concomitant treatment with leflunomide, an association with ABA for which few safety data are available, resulted in a similar rate of serious infections as concomitant MTX or as monotherapy with ABA. Since time-dependent changes in the clinical status and treatment of individual patients were associated with the risk of serious infections in the RABBIT registry, we evaluated the impact of cumulated disease activity level and cumulated oral corticosteroid doses during the whole follow-up. No significant differences were observed between patients with and without serious infections. This might be related to differences in characteristics of patient populations between the present registry of patients treated with ABA and the RABBIT registry, or to differences in the effect of these cofactors on the infectious risk between ABA and anti-TNF since the data from the RABBIT registry concern mainly anti-TNF.[21]

The study also provides an important message for clinical practice on the similar risk of serious infections irrespective of previous biologics prior to ABA. Until the present study, very limited data were available regarding the safety of ABA, which predominantly targets T cells, after B cell depletion with RTX.[22] Data of the ORA registry show a similar rate of serious infections in patients previously treated with RTX as in those previously treated with another biologic. A last message of clinical interest is the absence of increased risk of serious infections in patients with low IgG before ABA, conversely to what is observed in patients with low IgG treated with RTX.[4]

To conclude, in the ORA registry, serious infections in patients treated with ABA were slightly more frequent than in clinical trials. This might be related to the fact that a high proportion of patients with comorbidities, who would have been excluded from controlled trials, are treated with ABA in real life. Predictive risk factors of serious infections in patients treated for RA with ABA in common practice include age and history of previous serious infections.

Author affiliations
[1]Rheumatology Department, CHU Reims, Reims, France
[2]Rheumatology Department, National Center for Rare Systemic Autoimmune Diseases, Hôpitaux Universitaires de Strasbourg, CNRS, Institut de Biologie Moléculaire et Cellulaire, Immunopathologie et Chimie Thérapeutique/Laboratory of Excellence Medalis, Université de Strasbourg, Strasbourg, France
[3]Centre de Recherche en Epidémiologie et Statistiques, INSERM U1153, Centre d'Épidémiologie Clinique, Hôpital Hôtel-Dieu, Assistance Publique-Hôpitaux de Paris (AP-HP), Descartes University, Paris, France
[4]Rheumatology Center, Purpan Hospital, Paul Sabatier University, Toulouse, France
[5]Rheumatology Department, Lapeyronie University Hospital, Montpellier I University, Montpellier, France
[6]Rheumatology Department, CHRU de Lille, Université de Lille-2, Lille, France
[7]Rheumatology Department, CHU Bordeaux, Bordeaux, France
[8]Rheumatology Department, CHU Lomme, Lomme, France
[9]Rheumatology Department, CHU Grenoble, Grenoble, France
[10]Rheumatology Department, CHU Nancy, Nancy, France
[11]Rheumatology Department, CHR Orléans, Orléans, France
[12]Medicine Faculty, Paris-Descartes University, Paris, UPRES-EA 4058, Cochin Hospital, Rheumatology B, Paris, France
[13]Rheumatology department, National Center for Rare Systemic Autoimmune Diseases, Hôpitaux Universitaires de Strasbourg, INSERM UMRS_1109, Université de Strasbourg, Strasbourg, France
[14]Rheumatology Department, Rouen University Hospital & Inserm U905, Rouen, France
[15]Rheumatology Department, Groupe Hospitalier Bichat-Claude Bernard (AP-HP), Paris, France
[16]Rheumatology Department, CHU Poitiers, Poitiers, France
[17]Rheumatology Department, CHU Caen, Caen, France
[18]Rheumatology Department, Hôpital Lariboisière, Paris, France
[19]Rheumatology Department, Hôpitaux Universitaires Paris-Sud, AP-HP, INSERM U1184, IMVA: Center of Immunology of Viral Infections and Autoimmune Diseases, Paris, France

Acknowledgements We thank all the investigators of the ORA registry, the French Society of Rheumatology, Euraxipharma and Claire Lacoste (BMS).

Contributors JHS and JEG contributed equally. All the authors contributed to data collection, interpretation of results and edited the manuscript. JEG, XM and JHS initiated the study and wrote the manuscript. PR and GB, IP and EP performed statistical analyses.

Funding BMS provided an unrestricted educational grant to the French Society of Rheumatology but was not involved in the design, protocol, data collection or statistical analysis of the study.

Competing interests None declared.

Patient consent Obtained.

Ethics approval The studies were approved by the French authorities (Comité Consultatif sur le Traitement de l'information en matière de Recherche dans le domaine de la Santé (CCTIRS) and Commission Nationale de l'Informatique et des Libertés (CNIL)).

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Khraishi M. Comparative overview of safety of the biologics in rheumatoid arthritis. *J Rheumatol Suppl* 2009;82:25–32.
2 Mariette X, Gottenberg JE, Ravaud P, *et al*. Registries in rheumatoid arthritis and autoimmune diseases: data from the French registries. *Rheumatology (Oxford)* 2011;50:222–9.
3 Terrier B, Amoura Z, Ravaud P, *et al*. Safety and efficacy of rituximab in systemic lupus erythematosus: results from 136 patients from the French AutoImmunity and Rituximab registry. *Arthritis Rheum* 2010;62:2458–66.
4 Gottenberg JE, Ravaud P, Bardin T, *et al*. Risk factors for severe infections in patients with rheumatoid arthritis treated with rituximab in the autoimmunity and rituximab registry. *Arthritis Rheum* 2010;62:2625–32.
5 Salmon-Ceron D, Tubach F, Lortholary O, *et al*. Drug-specific risk of non-tuberculosis opportunistic infections in patients receiving anti-TNF therapy reported to the 3-year prospective French RATIO registry. *Ann Rheum Dis* 2011;70:616–23.
6 Austin PC, Tu JV. Bootstrap methods for developing predictive models. *Am Stat* 2004;58:131–7.
7 R Core Team. *A language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing, 2013. http://www.R-project.org/
8 Chatzidionysiou K, Lie E, Nasonov E, *et al*. Effectiveness of disease-modifying antirheumatic drug co-therapy with methotrexate and leflunomide in rituximab-treated rheumatoid arthritis patients: results of a 1-year follow-up study from the CERERRA collaboration. *Ann Rheum Dis* 2012;71:374–7.
9 Hetland ML, Christensen IJ, Tarp U, *et al*. Direct comparison of treatment responses, remission rates, and drug adherence in patients with rheumatoid arthritis treated with adalimumab, etanercept, or infliximab: results from eight years of surveillance of clinical practice in the nationwide Danish DANBIO registry. *Arthritis Rheum* 2010;62:22–32.
10 Gawert L, Hierse F, Zink A, *et al*. How well do patient reports reflect adverse drug reactions reported by rheumatologists? Agreement of physician- and patient-reported adverse events in patients with rheumatoid arthritis observed in the German biologics register. *Rheumatology (Oxford)* 2011;50:152–60.
11 Brennan A, Bansback N, Nixon R, *et al*. Modelling the cost effectiveness of TNF-alpha antagonists in the management of rheumatoid arthritis: results from the British Society for Rheumatology Biologics Registry. *Rheumatology (Oxford)* 2007;46:1345–54.
12 Finckh A, Iannone F, Florenzo GR, *et al*. The impact of inadequate response to prior biologic agents on abatacept drug retention in rheumatoid arthritis patients. A Pan-European analysis of RA registries [abstract]. *Arthritis Rheum* 2013;65(Suppl 10):495.
13 Dixon WG, Symmons DP, Lunt M, *et al*. Serious infection following anti-tumor necrosis factor alpha therapy in patients with rheumatoid arthritis: lessons from interpreting data from observational studies. *Arthritis Rheum* 2007;56:2896–904.
14 Schiff M. Abatacept treatment for rheumatoid arthritis. *Rheumatology (Oxford)* 2011;50:437–49.
15 Schiff M. Subcutaneous abatacept for the treatment of rheumatoid arthritis. *Rheumatology (Oxford)* 2013;52:986–97.
16 Bigbee CL, Gonchoroff DG, Vratsanos G, *et al*. Abatacept treatment does not exacerbate chronic Mycobacterium tuberculosis infection in mice. *Arthritis Rheum* 2007;56:2557–65.
17 Strangfeld A, Listing J, Herzer P, *et al*. Risk of herpes zoster in patients with rheumatoid arthritis treated with anti-TNF-alpha agents. *JAMA* 2009;301:737–44.

Ann Rheum Dis: first published as 10.1136/annrheumdis-2015-207362 on 5 June 2015. Downloaded from http://ard.bmj.com/ on July 1, 2022 by guest. Protected by copyright.

18 Kubandova Z, Mathieu S, Pourtier C, *et al*. Serious herpes zoster in rheumatoid arthritis under anti-interleukin-6 receptor antibody. *Joint Bone Spine* 2010;77:623–4.
19 Van Vollenhoven RF, Emery P, Bingham CO III, *et al*. Long-term safety of rituximab in rheumatoid arthritis: 9.5-year follow-up of the global clinical trial programme with a focus on adverse events of interest in RA patients. *Ann Rheum Dis* 2013;72:1496–502.
20 Halleux D, Kanaan N, Kabamba B, *et al*. Hepatitis E virus: an underdiagnosed cause of chronic hepatitis in renal transplant recipients. *Transpl Infect Dis* 2012;14:99–102.
21 Zink A, Manger B, Kaufmann J, *et al*. Evaluation of the RABBIT Risk Score for serious infections. *Ann Rheum Dis* 2014;73:1673–6.
22 Genovese MC, Breedveld FC, Emery P, *et al*. Safety of biological therapies following rituximab treatment in rheumatoid arthritis patients. *Ann Rheum Dis* 2009;68:1894–7.

Ann Rheum Dis: first published as 10.1136/annrheumdis-2015-207362 on 5 June 2015. Downloaded from http://ard.bmj.com/ on July 1, 2022 by guest. Protected by copyright.