Comparative effectiveness of rituximab, abatacept, and tocilizumab in adults with rheumatoid arthritis and inadequate response to TNF inhibitors: prospective cohort study

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ABSTRACT

OBJECTIVE

To compare the effectiveness and safety of three non-tumour necrosis factor (TNF) α inhibitors (rituximab, abatacept, and tocilizumab) in the treatment of rheumatoid arthritis.

DESIGN

Population based prospective study.

SETTING

53 university and 54 non-university clinical centres in France.

PARTICIPANTS

3162 adults (›18 years) with rheumatoid arthritis according to 1987 American College of Rheumatology criteria, enrolled in one of the three French Society of Rheumatology registries; who had no severe cardiovascular disease, active or severe infections, or severe immunodeficiency, with follow-up of at least 24 months.

INTERVENTION

Initiation of intravenous rituximab, abatacept, or tocilizumab for rheumatoid arthritis.

MAIN OUTCOME MEASURE

The primary outcome was drug retention without failure at 24 months. Failure was defined as all cause death; discontinuation of rituximab, abatacept, or tocilizumab; initiation of a new biologic or a combination of conventional disease modifying antirheumatic drugs; or increase in corticosteroid dose ›10 mg/d compared with baseline at two successive visits. Because of non-proportional hazards, treatment effects are presented as life expectancy difference without failure (LED_{wf}), which measures the difference between average duration of survival without failure.

RESULTS

Average durations of survival without failure were 19.8 months for rituximab, 15.6 months for abatacept, and 19.1 months for tocilizumab. Average durations were greater with rituximab (LED_{wf} 4.1, 95% confidence interval 3.1 to 5.2) and tocilizumab (3.5, 2.1 to 5.0) than with abatacept, and uncertainty about tocilizumab compared with rituximab was substantial (−0.7, −1.9 to 0.5). No evidence was found of difference between treatments for mean duration of survival without death, presence of cancer or serious infections, or major adverse cardiovascular events.

CONCLUSION

Among adults with refractory rheumatoid arthritis followed-up in routine practice, rituximab and tocilizumab were associated with greater improvements in outcomes at two years compared with abatacept.

WHAT IS ALREADY KNOWN ON THIS TOPIC

In patients with rheumatoid arthritis, non-TNF targeted biologic agents, including rituximab (a B cell depleting agent), abatacept (targeting T cell costimulation), and tocilizumab (an interleukin 6 receptor inhibitor) have shown efficacy compared with placebo

These three biologic agents have not been compared against each other in randomised controlled trials

Randomised controlled head-to-head comparisons of these three drugs will probably never be performed

WHAT THIS STUDY ADDS

Among adults with refractory rheumatoid arthritis followed-up in routine practice, treatment with rituximab or tocilizumab was associated with larger improvements in outcomes at two years compared with abatacept

Introduction

Although tumour necrosis factor (TNF) α inhibitors have greatly improved the daily quality of life of people with rheumatoid arthritis,[1] as much as one third of patients fail to respond to anti-TNF agents.[2] Alternative and more recently approved non-TNF targeted biologic agents include rituximab (a B lymphocyte depleting agent), abatacept (targets T cell co-stimulation), and tocilizumab (an interleukin 6 receptor inhibitor). These three drugs have demonstrated efficacy compared with placebo but have not been compared with each other in randomised controlled trials.[3-5] Network meta-analyses of randomised, placebo controlled trials have been conducted, but by definition they concerned highly selected patients.[6-8]

Disease activity is usually higher and comorbidities less common in randomised controlled trials than in real life. Co-treatment with methotrexate, known to improve the effectiveness of biologics, is less common in real life than in randomised controlled trials. In addition, the primary outcomes of randomised controlled trials are evaluated in the short term (usually 6-12 months) and therefore the long term drug retention rate and corticosteroid sparing effect—

two relevant markers of effectiveness—cannot be analysed. Finally, short term follow-up in randomised controlled trials limits the analysis of serious adverse events—notably, serious infections and cancers.

For these reasons registry data are useful to complement data from randomised controlled trials to investigate the external validity of drugs in routine practice. Furthermore, only a few studies have compared the effectiveness and safety of biologics, and these mainly focused on different anti-TNF agents.[9] It is highly probable that randomised controlled head-to-head comparisons of rituximab, abatacept, and tocilizumab will never be performed. As prospective academic registries and comparative effectiveness research now allow for the so far poorly addressed comparisons of non-TNF targeted biologics, we investigated the effectiveness of rituximab, abatacept, and tocilizumab in the treatment of longstanding and refractory rheumatoid arthritis.

Methods

Study data

The French Society of Rheumatology sponsors three registries: Autoimmunity and Rituximab (AIR), Orencia and Rheumatoid Arthritis (ORA), and REGistry–RoAcTEmra (REGATE). These registries contain only observational and non-interventional studies. The objectives of these registries are to determine and compare the effectiveness and safety of intravenous rituximab, abatacept, and tocilizumab in routine practice, and they aim to enrol most patients in France who initiated these drugs as soon as they were marketed.

The methodology of these registries has been reported.[10] Their methodology was similar on purpose because we wanted to compare the three drugs. Briefly, the French Society of Rheumatology sent regular mail and "push" emails to all French rheumatology departments and physicians prescribing biologics for rheumatoid arthritis on approval of these three biologics; the emails asked for the physician's agreement to participate in each registry. Such consent involved agreement to regular visits to the hospital pharmacy by a trained clinical nurse to obtain the list of patients receiving an intravenous infusion of rituximab, abatacept, or tocilizumab in the physician's department; subsequent frequent access by clinical nurses to patient charts; limiting missing data in patient charts on key prespecified items (eg, treatment, disease activity score) and the risk of lost to follow-up; and allowing the French Society of Rheumatology to contact the patients' general practitioners and rheumatologists, or the patients themselves, to obtain missing follow-up data. Twenty six trained clinical study nurses in each registry visited each centre to collect effectiveness and safety data from patient charts at the same prespecified intervals, independently of disease severity or drug mode of administration: at drug initiation and at three months and every six months thereafter or at drug discontinuation and after drug discontinuation for seven years. Even after drug discontinuation, a systematic follow-up for safety was performed. All information was drawn from the clinical charts. Data were collected in an electronic case report form (https://194.206.215.54/PR/index.ecrf, https://194.206.215.102/index.ecrf, and https://194.206.215.149/index.ecrf, for AIR, ORA, and REGATE, respectively).

Two clinical research assistants performed random on-site monitoring to control for the quality of collected data and to obtain data considered missing by study nurses. In addition, a summary of collected data for key items for each enrolled patient was sent once a year to each centre after the initiation of the registries. In case of serious adverse events (death; cancers; serious infections, defined as those requiring intravenous antibiotics, hospital admission, or resulting in death; and major cardiovascular events (ie, death of cardiovascular origin, stroke, myocardial infarction)), study nurses were asked to send a copy of the chart to each registry coordinator. All serious adverse events were adjudicated by the registry coordinators (JEG, JM, and XM).

Treatment groups and follow-up

Using observational data, we compared three groups of people with rheumatoid arthritis (those initiating intravenous rituximab, abatacept, or tocilizumab) at 24 month follow-up.[11]

Eligibility criteria

From September 2005 to August 2013, we recruited patients aged more than 18 years from 107 clinical centres in France. The inclusion criteria were diagnosis of rheumatoid arthritis according to the 1987 American College of Rheumatology criteria, age more than 18 years, and initiation of intravenous treatment with rituximab, abatacept, or tocilizumab before March 2013 (inclusion at least two years before database was locked in March 2015 to ensure a minimal theoretical follow-up of two years for all patients). The exclusion criteria were contraindications to any of the three biologics (rituximab, abatacept, or tocilizumab): severe cardiovascular disease, active or severe infections, severe immunodeficiency, or previous use of any of these three biologics. We obtained the list of patients receiving intravenous rituximab, abatacept, or tocilizumab in each centre from the pharmacist of the hospitals. Therefore all consecutive patients receiving one of the three drugs at the time of the study were included in each centre, which limited inclusion bias.

Endpoints

The primary endpoint was drug treatment retention without failure at month 24. Lack of failure was included in this context because rituximab is administered intermittently, and therefore it would be difficult to determine retention without such information. Failure was defined as all cause death, discontinuation of the drug studied in the registry, initiation of a combination of conventional disease modifying antirheumatic drugs (DMARDs), a new

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biologic, or increase in oral corticosteroids dose more than 10 mg/d at two consecutive visits compared with the baseline dose.

Secondary endpoints included European League Against Rheumatism (EULAR) response at months 6, 12, and 24. A good EULAR response was defined as a decrease in disease activity score in 28 joints—erythrocyte sedimentation rate (DAS28-ESR) more than 1.2 points and resulting score 3.2 or less. A moderate EULAR response was defined as a decrease in DAS28-ESR more than 0.6 points and resulting score 5.1 or less. Because the data were not systematically recorded at exact fixed times, we used a two month window (the closest information to the time within two months before or after this time).

Safety endpoints included time to first serious adverse events (among serious infection, major adverse cardiovascular events (MACEs), cancer, and death). Each component of this composite endpoint was considered separately. We defined a serious infection as an infection requiring hospital admission, requiring intravenous antibiotics, or resulting in death. MACEs were defined as death of cardiovascular origin, stroke, or myocardial infarction. Serious infections, MACEs, cancer, and death were considered in the analysis regardless of their time of occurrence, even after discontinuation of the study drug.

Statistical analysis

We used a propensity score approach to account for differences in observed factors that might affect both treatment assignment and outcome. The propensity score was defined as the probability of a patient receiving the drug effectively initiated among rituximab, abatacept, and tocilizumab, based on patient covariates. Covariate selection was prespecified and based on a non-parsimonious approach to account for both potential confounding factors and variables that can serve as proxies for unknown or unmeasured confounding variables.

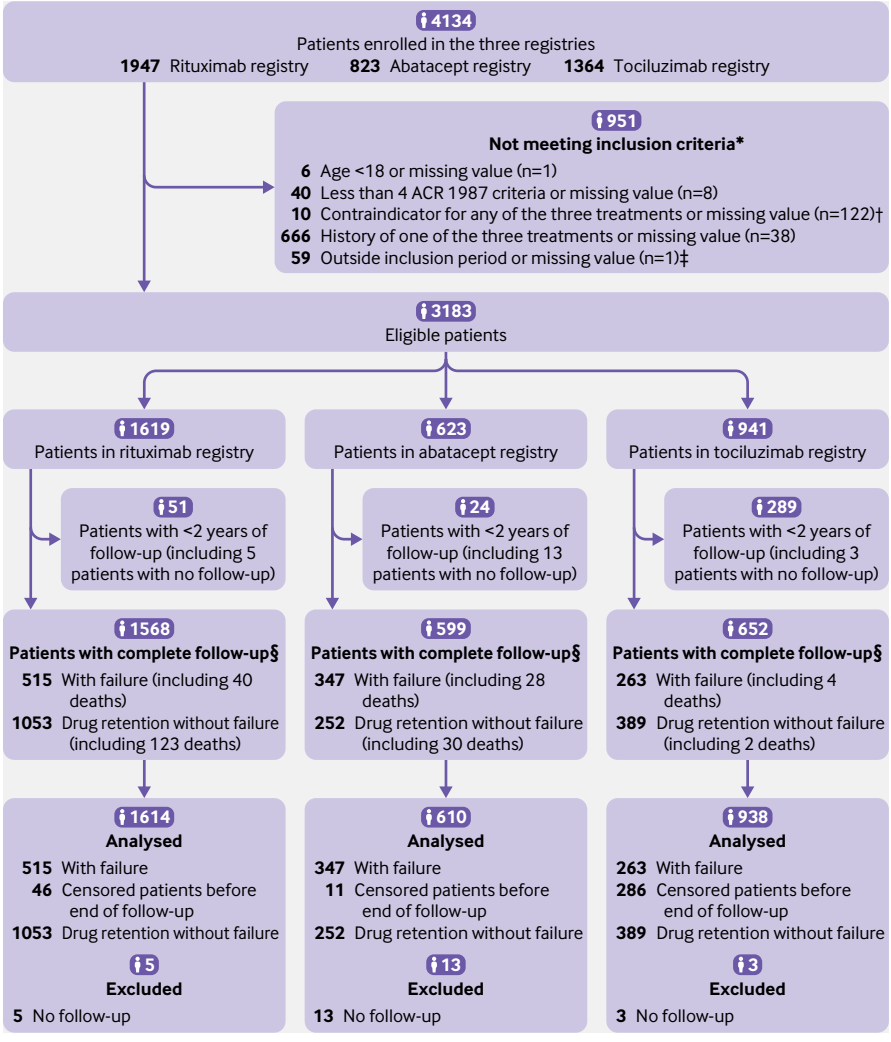

Fig 1 | Flow of participants through study. *Not meeting one of the inclusion criteria (n=781) or missing value for at least one inclusion criterion (n=170). †Severe cardiovascular disease, active or severe infections, severe immune deficiency. ‡Inclusion period: patients who initiated treatment before March 2013 (ie, two years before database was locked, in March 2015, to have at least two years of theoretical follow-up). §Patients with treatment failure before two years of follow-up or with at least two years of follow-up. ACR=American College of Rheumatology

Table 1 | Baseline characteristics of participants. Values are numbers (percentages) of participants unless stated otherwise

	Unweighted cohort			Weighted cohort		
Characteristics	Rituximab (n=1614)	Abatacept (n=610)	Tocilizumab (n=938)	Rituximab (n=1548)	Abatacept (n=620)	Tocilizumab (n=964)
Mean (SD) age (years)	58.0 (12.7)	59.7 (13.8)	56.5 (13.9)	58.1 (12.9)	57.3 (14.1)	57.9 (14.1)
Median (interquartile range) disease duration (years)	11.0 (6.0-18.0)	11.0 (5.0-19.0)	8.0 (3.0-16.0)	10.0 (5.0-18.0)	11.0 (5.0-18.0)	12.0 (5.0-21.0)
Women	1287 (79.7)	478 (78.4)	741 (79.0)	1243 (80.3)	491 (79.2)	765 (79.4)
Past serious or recurrent infection	565 (35.0)	206 (33.8)	112 (11.9)	446 (28.8)	171 (27.6)	305 (31.6)
History of cancer	232 (14.4)	32 (5.3)	39 (4.2)	158 (10.2)	55 (8.9)	69 (7.1)
Rheumatoid factor positive	1237 (80.5)	412 (75.0)	627 (79.8)	1154 (79.0)	448 (80.0)	665 (77.5)
Anti-CCP antibody positive	1074 (77.0)	382 (74.3)	631 (82.8)	1023 (76.4)	1023 (76.4)	1023 (76.4)
Median No (interquartile range) of previous anti-TNF agents	2.0 (1.0-2.0)	2.0 (1.0-2.0)	1.0 (0.0-2.0)	2.0 (1.0-2.0)	2.0 (1.0-2.0)	2.0 (1.0-2.0)
Median No (interquartile range) of conventional DMARDs	3.0 (2.0-4.0)	2.0 (1.0-4.0)	2.0 (1.0-3.0)	3.0 (2.0-4.0)	3.0 (2.0-4.0)	2.0 (1.0-4.0)
Median No (interquartile range) of tender joints	9.0 (5.0-15.0)	8.0 (3.0-15.0)	7.0 (3.0-13.0)	8.0 (4.0-15.0)	8.0 (3.0-14.0)	8.0 (4.0-12.0)
Median No (interquartile range) of swollen joints	6.0 (3.0-10.0)	5.0 (2.0-9.0)	5.0 (2.0-8.0)	6.0 (3.0-10.0)	6.0 (2.0-10.0)	5.0 (2.0-10.0)
Median (interquartile range) ESR	32.0 (17.0-51.0)	28.0 (15.0-50.0)	27.0 (13.0-48.0)	31.0 (16.0-50.0)	29.0 (16.0-45.0)	28.0 (15.0-47.0)
Median (interquartile range) CRP level	16.0 (5.6-38.0)	13.0 (4.8-28.5)	12.5 (4.0-32.0)	13.0 (5.0-36.0)	13.9 (5.0-28.0)	15.0 (5.0-37.0)
Mean (SD) patient global assessment of disease activity (range 0-100)	61.5 (22.0)	59.7 (22.8)	57.8 (24.7)	60.4 (22.3)	62.9 (21.9)	57.0 (26.4)
Mean (SD) DAS28-ESR	5.5 (1.2)	5.2 (1.3)	5.0 (1.4)	5.4 (1.3)	5.3 (1.3)	5.3 (1.3)
Concomitant treatment with conventional DMARD	1043 (64.9)	401 (66.5)	556 (59.5)	984 (63.8)	387 (62.9)	585 (60.9)
Corticosteroids	1242 (77.7)	456 (74.4)	623 (66.5)	1133 (74.3)	460 (74.9)	684 (71.2)
Mean (SD) corticosteroids dose* (mg/d)	11.8 (8.8)	11.2 (8.3)	10.3 (7.2)	11.3 (8.3)	11.6 (8.5)	11.2 (7.2)

CCP=cyclic citrullinated peptide; TNF=tumour necrosis factor; DMARD=disease modifying antirheumatic drug; ESR=erythrocyte sedimentation rate; CRP=C reactive protein; DAS28-ESR=Disease Activity Score in 28 joints-erythrocyte sedimentation rate.
Unweighted cohort, raw data; weighted cohort, pseudo-population obtained after inverse probability weighting.
*Only concerns participants receiving corticosteroids.

We used a multinomial logistic model to calculate the probability of a patient receiving the treatment effectively initiated among rituximab, abatacept, and tocilizumab to address the initial confounding between the three drugs. Propensity was estimated by using a multinomial logistic model with the drug received as the dependent variable and the following baseline factors as independent variables: age; disease duration; sex; history of serious or recurrent infection, cancer, MACE, cardiac insufficiency, renal insufficiency, hepatic disease, respiratory disease, extra-articular involvement, smoking, diabetes, arterial hypertension, dyslipidemia, γ globulin level, IgG and IgM levels, neutropenia, positive rheumatoid factor or antibodies against cyclic citrullinated peptides; number of previous conventional synthetic DMARDs; number of previous anti-TNF drugs; disease activity at initiation of study drug (number of tender joints, number of swollen joints, erythrocyte sedimentation rate, C reactive protein level, patient global assessment of disease activity, DAS28-ESR), co-treatment at initiation of study drug, including concomitant conventional synthetic DMARDs received and daily dose of corticosteroids; and number of patients receiving each treatment in the patient's centre.

Table 2 | Causes of drug failure at 24 month follow-up. Values are numbers (percentages) of participants

	Unweighted cohort			Weighted cohort		
Causes of drug failure	Rituximab (n=515)	Abatacept (n=347)	Tocilizumab (n=263)	Rituximab (n=480)	Abatacept (n=373)	Tocilizumab (n=315)
Death	26 (5.0)	19 (5.5)	4 (1.5)	25 (5.3)	20 (5.3)	14 (4.3)
Introduction of a new biologic DMARD or combination of DMARDs	206 (40.0)	128 (36.9)	171 (65.0)	185 (38.6)	164 (44.1)	215 (68.3)
Discontinuation of biologic	454 (88.2)	322 (92.8)	241 (91.6)	424 (88.5)	347 (93.1)	288 (91.3)
Cause of discontinuation:						
Death	4 (0.9)	0 (0.0)	2 (0.9)	3 (0.7)	0 (0.0)	4 (1.4)
Adverse event	64 (14.1)	58 (18.0)	97 (41.6)	66 (15.7)	58 (16.6)	115 (42.5)
Inefficacy	332 (73.1)	205 (63.7)	107 (45.9)	306 (72.1)	224 (64.7)	121 (44.5)
Other reason	54 (11.9)	59 (18.3)	27 (11.6)	49 (11.5)	65 (18.7)	31 (11.6)
Increase of corticosteroids dose (>10 mg/d of baseline)	2 (0.4)	6 (1.7)	4 (1.5)	2 (0.5)	5 (1.5)	3 (1.0)

DMARD=disease-modifying antirheumatic drug.
Unweighted cohort, raw data; weighted cohort, pseudo-population obtained after inverse probability weighting.

Table 3 | Survival without failure at 24 months

	Rituximab		Abatacept		Tocilizumab	
Weighting	No of failures	% surviving without failure (95% CI)	No of failures	% surviving without failure (95% CI)	No of failures	% surviving without failure (95% CI)
Unweighted	515	67.6 (65.2 to 69.8)	347	42.5 (38.5 to 46.4)	263	68.0 (64.6 to 71.1)
Weighted	480	68.6 (65.3 to 71.5)	373	39.3 (34.1 to 44.5)	315	63.4 (56.1 to 69.8)

Unweighted cohort, raw data; weighted cohort, pseudo-population obtained after inverse probability weighting.

The analysis was based on inverse probability weighting[12]; patients were each weighted by the inverse probability that they would receive the treatment effectively initiated among rituximab, abatacept, or tocilizumab, allowing average treatment effects to be estimated. Stabilised weights were used to reduce the variability of weights and standard errors of estimated treatment effects.[13] We used multiple imputation by chained equation, using all baseline variables of the propensity score model as well as the drug received to impute missing values for variables included in the propensity score approach. Ten independent imputed datasets were generated. For each dataset, we estimated a propensity score and pooled the resulting scores according to Rubin's rules. Covariate balance was checked after weighting by computing standardised differences. A standardised difference of 10% or more is generally considered meaningful.[14]

We estimated survival without failure using weighted Kaplan-Meier product limit estimator. According to the Grambsch and Therneau test[15] (P<0.001), proportional hazards assumption of the planned marginal Cox model was violated (see supplementary eTable 1). Restricted mean survival times (ie, area under the curve between the time of inclusion and end of follow-up) were computed by numerical integration of the Kaplan-Meier curve for each drug (rituximab, abatacept, or tocilizumab) in the weighted cohort.[16] Restricted mean survival time measures the average duration of survival without failure for each drug over the follow-up period. To quantify the between group differences, we calculated the life expectancy difference without failure (LED_{wf}, difference between restricted mean survival times) and the life expectancy ratio without failure (LER_{wf}, ratio of restricted mean survival times) and their 95% confidence intervals with normal approximation (estimated by bootstrap with 1000 replications).[17] Statistical significance for these analyses was indicated by a 95% confidence interval for the LER_{wf} that excludes 1 or for the LED_{wf} that excludes 0. Patients were analysed in the groups to which they were initially treated. Three sensitivity analyses were performed for the primary outcome (results were expressed as $LED_{wf,}$ 95% confidence interval). In the first analysis, we computed estimates in the unweighted cohort. Secondly, we used truncated weights (with truncation at the fifth and 95th centiles) to analyse the influence of extreme weights in the weighted cohort. Thirdly, to evaluate the consistency of our analyses regarding the definition of failure, we duplicated our main analysis (in the weighted cohort) with three alternative definitions of failure: death or discontinuation of the study drug, death or initiation of a combination of conventional DMARDs or a biologic DMARD, and death or discontinuation of the study drug or initiation of a combination of conventional DMARDs or a biologic DMARD.

To compare EULAR response, we used logistic regression with weighted generalised estimating equations, with drug as the only covariate. We considered participants to be EULAR non-responders if they discontinued the study drug or initiated a combination of conventional DMARDs, or a new biologic, or increased dosage of oral corticosteroids greater than 10 mg/d at two consecutive visits. Results for this outcome are expressed as odds ratio and 95% confidence intervals.

Survival without serious adverse events was estimated globally and for each type of event (serious infection, MACE, cancer, death) by weighted Kaplan-Meier product limit estimator. We estimated the average durations of survival without serious adverse events in each drug group over the follow-up period by restricted mean survival times and compared these by using LED_{wf} and LER_{wf} (and 95% confidence intervals) in the weighted cohort.

Statistical analyses were carried out in SAS 9.4 (SAS Institute, Cary, NC) and R 3.2.2 (R Core Team, 2015, R Foundation for Statistical Computing, Vienna, Austria, www.R-project.org/).

Patient and public involvement

Patients were not involved in the design of the study. Since data were being retrospectively analysed, patients

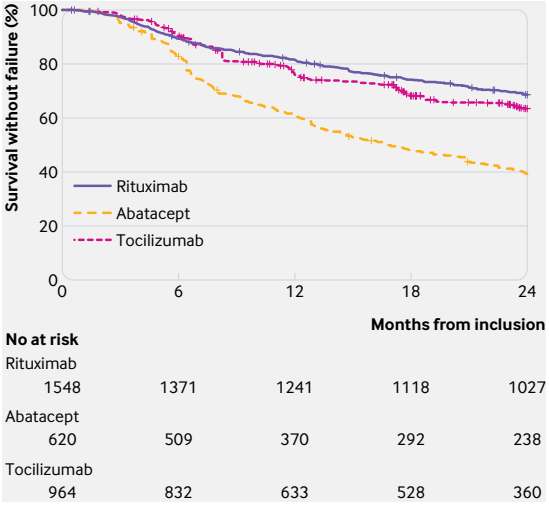

Fig 2 | Kaplan-Meier curves of drug retention without failure at 24 months (after inverse probability weighting). Vertical bars represent censored patients

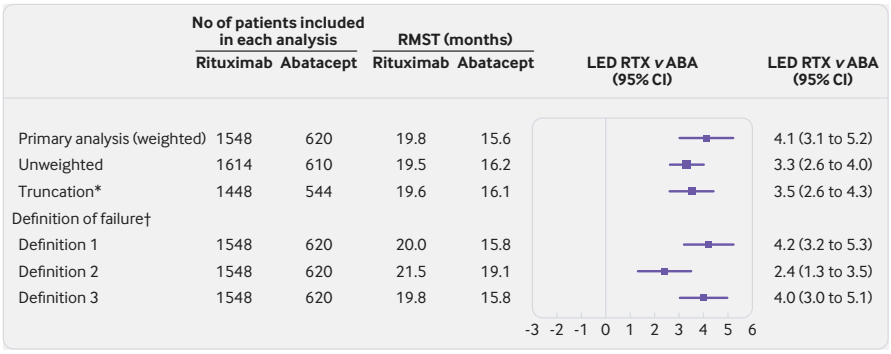

Fig 3 | Sensitivity analyses of drug retention without failure at month 24 for abatacept and rituximab. RMST=restricted mean survival time; LED=life expectancy difference (difference between RMST); RTX=rituximab; ABA=abatacept. *Truncated weights used in weighted cohort. †1=death or discontinuation of study drug; 2=death or initiation of a combination of conventional disease modifying antirheumatic drugs (DMARDs) or a biologic DMARD; 3=death or discontinuation of study drug or initiation of a combination of conventional DMARDs or biologic DMARD

could not effectively contribute to improvements on the study design.

Results

Baseline characteristics of patients and follow-up

From September 2005 to June 2013, the AIR, ORA, and REGATE registries included 4134 patients (rituximab, 1947 patients from September 2005 to January 2010; abatacept, 823 from January 2007 to October 2010; and tocilizumab, 1364 from April 2010 to June 2013) from 107 centres: 53 university and 54 non-university centres (86 centres participated in AIR, 82 in ORA, 77 in REGATE, and 53 in all three registries) (fig 1). Among the 4134 enrolled patients, 3183 fulfilled the eligibility criteria for analysis, and data for 3162 could be analysed at 24 months. The database was frozen in March 2015 for the present analysis. Baseline characteristics for the three drug groups differed in the unweighted cohort (table 1 and supplementary eTable 2), notably in median duration of disease (rituximab: 11 years (interquartile range 6-18); abatacept: 11years (5-19); tocilizumab: 8 years (3-16)); history of cancer (14.4%, 5.3%, and 4.2% of patients, respectively); rheumatoid factor positivity (80.5%, 75.0%, and 79.8% of patients, respectively); disease activity (mean DAS28-ESR 5.5 (SD 1.2), 5.2 (1.3), and 5.0 (1.4), respectively); and co-treatment with a conventional DMARD (64.9%, 66.5%, and 59.5% of patients, respectively) or corticosteroids (prednisone: 77.7%, 74.4%, and 66.5% of patients, respectively).

Propensity weighted analysis

Propensity scores were calculated for 3162 patients. Weights ranged from 0.2 to 31.2. The weighted groups were well balanced for recorded baseline variables, with standardised differences ranging from 0% to 25% and exceeding 10% for only 16 of the 99 comparisons (table 1, and supplementary eTable 2, eTable 3, and eFigure 1).

Effectiveness results

Table 2 describes the causes of drug failure (all cause death; discontinuation of the study drug; initiation of a combination of conventional DMARDs, or a new biologic; increase of oral corticosteroids dose >10 mg/d at two consecutive visits compared with baseline). At month 24 (weighted cohort), 68.6% of patients (95% confidence interval 65.3% to 71.5%)

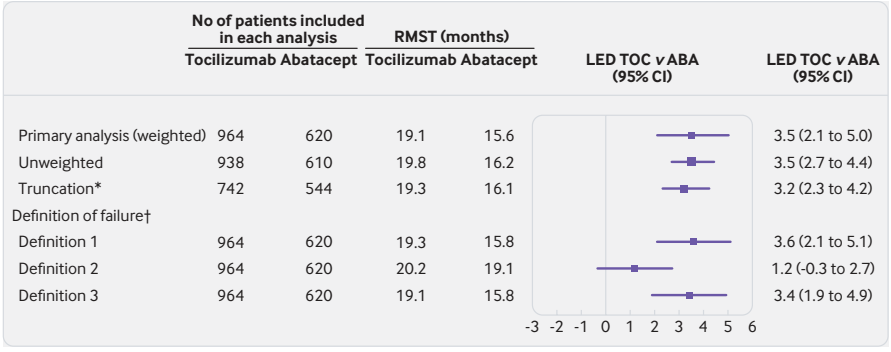

Fig 4 | Sensitivity analyses of drug retention without failure at month 24 for abatacept and tocilizumab. RMST=restricted mean survival time; LED=life expectancy difference (difference between RMST); TOC=tocilizumab; ABA=abatacept. *Truncated weights used in weighted cohort. †1=death or discontinuation of study drug; 2=death or initiation of a combination of conventional disease modifying antirheumatic drugs (DMARDs) or a biologic DMARD; 3=death or discontinuation of study drug or initiation of a combination of conventional DMARDs or biologic DMARD

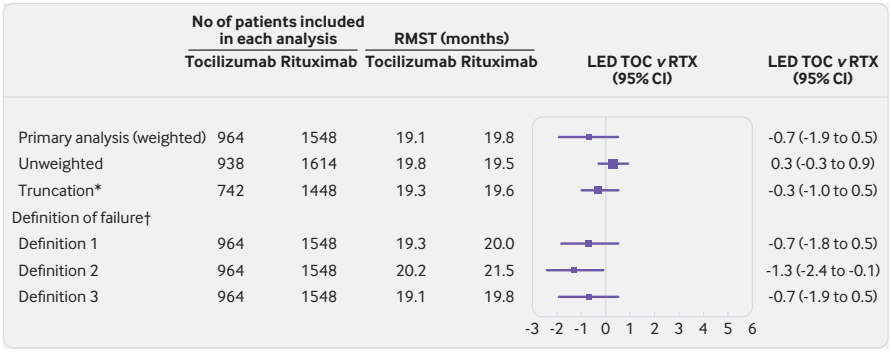

Fig 5 | Sensitivity analyses of drug retention without failure at month 24 for rituximab and tocilizumab. RMST=restricted mean survival time; LED=life expectancy difference (difference between RMST); TOC=tocilizumab; RTX=rituximab. *Truncated weights used in weighted cohort. †1=death or discontinuation of study drug; 2=death or initiation of a combination of conventional disease modifying antirheumatic drugs (DMARDs) or a biologic DMARD; 3=death or discontinuation of study drug or initiation of a combination of conventional DMARDs or biologic DMARD

were still using rituximab without failure, 39.3% (34.1% to 44.5%) were using abatacept, and 63.4% (56.1% to 69.8%) were using tocilizumab (table 3, fig 2). Average durations of survival without drug failure estimated by restricted mean survival times were 19.8 months for rituximab, 15.6 months for abatacept, and 19.1 months for tocilizumab. Restricted mean survival times for LED_{wf} were greater with rituximab (4.1, 95% confidence interval 3.1 to 5.2) and tocilizumab (3.5, 2.1 to 5.0) than with abatacept, as well as LER_{wf} (1.26, 1.18 to 1.35, and 1.22, 1.12 to 1.33, respectively). Uncertainty about tocilizumab compared with rituximab was substantial (LED_{wf} −0.7, −1.9 to 0.5; LER_{wf} 0.97, 0.91 to 1.03; figs 3-5). At month 24, more participants treated with rituximab or tocilizumab than with abatacept showed a good or moderate EULAR response (table 4, eTable 4).

Safety

At month 24 (weighted cohort), 436 patients had experienced at least one adverse event of serious infection, MACE, cancer, or death: 224 (14.5%) in the rituximab group, 101 (16.2%) in the abatacept group, and 111 (11.6%) in the tocilizumab group (table 5). Table 6 and figure 6 describe survival without serious adverse events among the three drug groups. Average durations of survival without serious adverse events were 22.1 months for rituximab, 21.8 months for abatacept, and 22.3 months for tocilizumab. No evidence of a difference in average duration of survival without serious adverse events was found with rituximab or tocilizumab versus abatacept in terms of LED without serious adverse events (0.3, 95% confidence interval −0.4 to 1.0 and 0.5, −0.4 to 1.4, respectively) nor with tocilizumab versus rituximab (0.2, −0.4 to 0.9). Results in terms of LERs without serious adverse events were similar, with no evidence of a difference with rituximab or tocilizumab versus abatacept (1.01, 0.98 to 1.05 and 1.02, 0.98 to 1.06, respectively) nor with tocilizumab versus rituximab (1.01, 0.98 to 1.04).

Additional analyses

Figures 3-5 present the findings of sensitivity analysis (unweighted cohort, truncated weights, three definitions of failure).

Discussion

The present study found that drug retention without failure at month 24 was better in patients treated with rituximab or tocilizumab than in those treated with abatacept. Drug retention seems a good surrogate marker of the balance between effectiveness and adverse events and appears particularly adequate in registry studies and relevant in routine practice. We chose month 24 for the primary endpoint so that we could study drug retention in the long term and because that duration corresponded to the median follow-up time in the most recent registry (the tocilizumab registry, which therefore had a higher rate of losses to follow-up given its more recent onset).

Table 4 | Comparison of moderate and good EULAR response (weighted cohort) at 6, 12, and 24 months

	No (%)			Odds ratio (95% CI)		
Follow-up time	Rituximab	Abatacept	Tocilizumab	ABA v RTX	TOC v RTX	ABA v TOC
6 months	511 (54.5)	235 (48.0)	508 (72.9)	0.77 (0.55 to 1.07)	2.26 (1.51 to 3.37)	0.34 (0.21 to 0.54)
12 months	377 (43.3)	171 (34.0)	417 (59.9)	0.66 (0.52 to 0.84)	1.98 (1.30 to 3.03)	0.33 (0.22 to 0.51)
24 months	322 (34.6)	125 (22.7)	272 (44.2)	0.55 (0.39 to 0.78)	1.51 (0.95 to 2.41)	0.37 (0.21 to 0.63)

EULAR=European League Against Rheumatism; ABA=abatacept; RTX=rituximab; TOC=tocilizumab.
Weighted cohort, pseudo-population obtained after inverse probability weighting.
EULAR non-response was considered death, discontinuation of the drug studied in the registry and/or initiation of a combination of conventional disease-modifying antirheumatic drugs and/or a new biologic and/or increase in oral corticosteroids dose >10 mg/day at 2 consecutive visits.

Table 5 | Description of serious adverse events (SAEs) in unweighted and weighted cohorts. Values are numbers (percentages) of participants unless stated otherwise

	Unweighted cohort			Weighted cohort		
Variables	Rituximab (n=1614)	Abatacept (n=610)	Tocilizumab (n=938)	Rituximab (n=1548)	Abatacept (n=620)	Tocilizumab (n=964)
Patients with at least one SAE	237 (14.7)	104 (17.0)	104 (11.1)	224 (14.5)	101 (16.2)	111 (11.6)
First SAE:						
Serious infection	172 (72.6)	69 (66.3)	83 (79.8)	157 (70.2)	69 (68.5)	88 (78.9)
Death	18 (7.6)	15 (14.4)	3 (2.9)	19 (8.4)	15 (14.3)	10 (9.1)
Cancer	34 (14.3)	16 (15.4)	12 (11.5)	37 (16.6)	13 (13.1)	10 (8.9)
MACE	13 (5.5)	4 (3.8)	6 (5.8)	11 (4.8)	4 (4.1)	3 (3.0)
No (rate) of events:						
Serious infections	220 (13.6)	87 (14.3)	92 (9.8)	205 (13.2)	88 (14.2)	100 (10.4)
Death	39 (2.4)	26 (4.3)	4 (0.4)	34 (2.2)	26 (4.2)	14 (1.4)
Cancers	42 (2.6)	19 (3.1)	17 (1.8)	43 (2.8)	14 (2.3)	17 (1.8)
MACEs	16 (1.0)	5 (0.8)	6 (0.6)	13 (0.8)	5 (0.8)	3 (0.3)

MACE=major adverse cardiovascular event (death of cardiovascular origin, stroke, or myocardial infarction).
Unweighted cohort, raw data; weighted cohort, pseudo-population obtained after inverse probability weighting; SAE: serious adverse event (serious infection, major adverse cardiovascular event, cancer, or death).

Comparison with other studies

Only a few comparative effectiveness studies have examined rituximab, abatacept, and tocilizumab. However, these studies had limited population samples, compared disease activity in the short term, and had discrepant results.[18-22] Registry data on the retention rate of non-TNF targeted biologics, notably rituximab and tocilizumab, is limited. In a recent collaboration between nine European registries, including the French registry, the median crude retention rate for abatacept varied from 1.4 to 2.1 years depending on autoantibody status,[23] which is similar to the median abatacept retention rate in the present study.

Randomised clinical trials are the standard strategy for drug comparisons. However, although a few trials compared non-TNF biologics with anti-TNF agents,[24 25] no randomised clinical trial has compared rituximab, abatacept, and tocilizumab with each other, and probably no direct head-to-head randomised clinical trial will compare these drugs in the future.

Strengths and limitations of this study

As with observational studies, the main limitations of our study are lack of randomisation and the channelling bias (tendency of clinicians to prescribe treatment based on patient's characteristics) inherent in this type of study. Using observational data, we compared estimated drug effectiveness in three groups of people with rheumatoid arthritis (those initiating intravenous rituximab, abatacept, or tocilizumab) at 24 month follow-up. Drug retention is the most robust outcome for comparing registry based patients treated with different drugs. We used a propensity score approach to account for differences in observed factors that might affect both treatment assignment and outcome. Despite the use of such an approach, confounding remains a problem. Regardless of these limitations, observational studies are relevant to study effects of treatments.[26]

To minimise the likelihood of incorrect associations being observed, we included many baseline characteristics of participants in the propensity score, including comorbidities, previous treatments, disease activity, and co-treatments. To test the robustness of our results, we used truncated weights and multiple outcome criteria on the cohort. Results were consistent among these different approaches. Analysis of EULAR response yielded similar results to those of the primary endpoint. However, missing data and the differential effect of tocilizumab on acute phase reactants included in the definition of EULAR response compared with abatacept and rituximab should be noted (the Clinical Disease Activity Index, which excludes acute phase reactants, is not collected in AIR and ORA). Some confidence intervals were wide, resulting in uncertainty; particularly in the comparison between rituximab and tocilizumab.

Because our study included rituximab, a drug that is administered intermittently, we used drug retention

Table 6 | Survival without serious adverse events (SAEs) for weighted cohort

	Rituximab		Abatacept		Tocilizumab	
Adverse events	No of events	% surviving without event (95% CI)	No of events	% surviving without event (95% CI)	No of events	% surviving without event (95% CI)
SAE	224	85.0 (82.5 to 87.2)	101	83.4 (78.5 to 87.2)	111	86.7 (80.6 to 91.1)
Serious infection	163	89.1 (86.8 to 91.0)	71	88.2 (83.8 to 91.4)	88	89.5 (83.8 to 93.3)
Death	34	97.7 (96.4 to 98.5)	26	95.7 (92.6 to 97.5)	14	98.3 (94.7 to 99.5)
Cancer	42	97.1 (95.8 to 98.1)	14	97.6 (94.9 to 98.9)	12	98.5 (94.9 to 99.6)
MACE	12	99.2 (98.3 to 99.6)	5	99.1 (96.9 to 99.7)	3	99.6 (95.8 to 99.9)

MACE=major adverse cardiovascular event (death of cardiovascular origin, stroke, or myocardial infarction).
Weighted cohort, pseudo-population obtained after inverse probability weighting; SAE: serious adverse event (serious infection, major adverse cardiovascular event, cancer, or death).

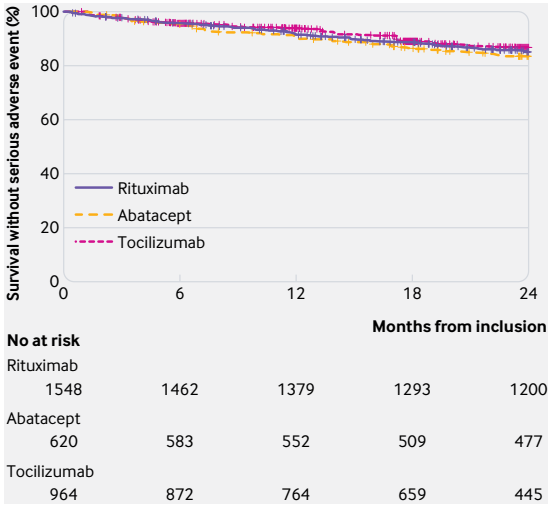

Fig 6 | Kaplan-Meier curves of survival without serious adverse events (among serious infection, major adverse cardiovascular events, cancer, and death) at 24 months (after inverse probability weighting). Vertical bars represent censored patients

without failure to avoid problems associated with intermittent administration. Failure was defined as death or initiation of a new biologic or combination of conventional DMARDs, or noticeable increase in oral corticosteroid dose (>10 mg/d from baseline). Monthly evaluation of drug retention before drug infusion might result in an earlier decision to discontinue abatacept or tocilizumab compared with rituximab. To limit the risk of rituximab being favoured over abatacept or tocilizumab, we chose a primary endpoint evaluation at month 24. The possible bias from using a different infusion schedule only concerns the comparison of abatacept with rituximab retention and not abatacept and tocilizumab retention (both drugs are given monthly).

Most of the patients enrolled in the study were refractory to previous treatment with anti-TNF agents. The results of our study therefore should not be extrapolated to biologic (anti-TNF) naïve patients (for whom abatacept and tocilizumab have marketing authorisations). In addition, all participants received intravenous abatacept and tocilizumab. Therefore, the characteristics and comorbidities of outpatients who receive subcutaneous abatacept or tocilizumab might differ from those of the study participants.

The strengths of our registry data include its real life setting (as reflected by the burden of comorbidities; in the ORA registry, only about 20% of patients would have fulfilled all the inclusion criteria for at least one of the pivotal controlled trials[27]); the large number of unselected patients enrolled corresponding to most people who initiated a non-TNF biologic (eg, >85% of prescriptions of rituximab in non-haematology and non-oncology departments between 2005 and 2009[28]); enrolment in university and non-university centres; the systematic collection at prespecified intervals of effectiveness and safety data from patient charts independent of any physician's intervention; patient lists obtained from pharmacists and therefore the inclusion of consecutive patients in each centre without bias; the intravenous administration of drugs in hospital, which ensures adherence to treatment and accurate information on baseline characteristics, drug retention, and co-treatments; the long term prospective follow-up; and centralised validation of serious adverse events.

Conclusions and policy implications

The originality of this study is its evaluation of the effectiveness of non-TNF biologics in real life (most of the literature describes only the effect of methotrexate and anti-TNF agents in this setting) and in providing some new insights into the benefit-risk ratio of non-TNF biologics. Serious adverse events did not differ between the three non-TNF biologics. Such events were more common in association with tocilizumab than with rituximab and abatacept. Therefore, the observed higher drug retention rate of rituximab and tocilizumab compared with abatacept is related to greater effectiveness rather than a better safety profile. At month 24, the study drug was discontinued in about 30% of those using rituximab and tocilizumab and 60% of those using abatacept, which emphasises the continued need for enlargement of the armamentarium of new biologic and targeted DMARDs in the treatment of rheumatoid arthritis.

In this national registry based cohort of people with rheumatoid arthritis, those receiving rituximab or tocilizumab showed a larger improvement in outcomes at two years than those receiving abatacept. These results apply to patients with longstanding and refractory rheumatoid arthritis who had previously received one or more biologics, and not biologic agent naïve patients with shorter disease duration.

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Contributors: JEG, JM, PR, and XM designed the study. EP, GB, and PR carried out the statistical analyses. JEG, JM, TB, BC, MD, RMF, AS, TS, JS, MS, OV, AC, PR, and XM interpreted the data. JEG drafted the manuscript. All coauthors edited the manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. JEG, PR, and XM are guarantors for the study.

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Data sharing: Additional data are available on reasonable request to the scientific committee of the registries.

Transparency: The lead authors (JEG, PR, and XM) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Supplementary information: eTables1-4 and eFigure 1