



**HAL**  
open science

## Can efficacy and safety data from clinical trials of rituximab in RA be extrapolated? Insights from 1984 patients from the AIR-PR Registry

Yann Nguyen, Xavier Mariette, Jacques Gottenberg, Michele Iudici, Jacques Morel, Olivier Vittecoq, Arnaud Constantin, Rene-Marc Flipo, Thierry Schaefferbeke, Jean Sibilia, et al.

### ► To cite this version:

Yann Nguyen, Xavier Mariette, Jacques Gottenberg, Michele Iudici, Jacques Morel, et al.. Can efficacy and safety data from clinical trials of rituximab in RA be extrapolated? Insights from 1984 patients from the AIR-PR Registry. *Rheumatology*, 2023, 10.1093/rheumatology/kead495 . hal-04211960

**HAL Id: hal-04211960**

**<https://hal.science/hal-04211960>**

Submitted on 7 Jan 2024

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

# **Can efficacy and safety data from clinical trials of rituximab in RA be extrapolated? Insights from 1984 patients from the AIR-PR Registry**

Yann Nguyen 1,2 , Xavier Mariette 1,2 , Jacques E. Gottenberg 3 , Michele Iudici 4,5 , Jacques Morel 6 , Olivier Vittecoq 7 , Arnaud Constantin 8 , René-Marc Flipo 9 , Thierry Schaevebeke 10 , Jean Sibilia 11 , Philippe Ravaud 4,12 , Raphaël Porcher<sup>4,12, \*, ‡</sup> , Raphaël le Seror 1,2, ‡

1 Department of Rheumatology, Hôpital Bicêtre Assistance Publique-Hôpitaux de Paris, Le Kremlin-Bicêtre, France

2 Center for Immunology of Viral Infections and Auto-immune Diseases (IMVA), Université Paris-Saclay, Institut pour la Santé et la Recherche Médicale (INSERM) UMR 1184, Le Kremlin Bicêtre, France

3 Rheumatology Department, Hôpitaux Universitaires de Strasbourg, Université de Strasbourg, Strasbourg, France

4 INSERM, UMR1153 Epidemiology and Statistics Sorbonne Paris Cité Research Centre (CRESS), Team METHODS, Paris, France

5 Division of Rheumatology, Department of Internal Medicine Specialties, Geneva University Hospitals, Geneva, Switzerland

6 Rheumatology Department, CHU and University of Montpellier, PhyMedExp, Université de Montpellier, INSERM, CNRS, Montpellier, France

7 Department of Rheumatology, Rouen University Hospital & Inserm U905, Rouen, France

8 Rheumatology Department, Purpan University Hospital, Paul Sabatier Toulouse III University, INSERM U1291 Infinity, Toulouse, France

9 Rheumatology Department, CHRU de Lille, Université de Lille, Lille, France

10 Rheumatology Department, CHU Bordeaux, Bordeaux, France

11 Rheumatology Department, Hôpitaux Universitaires de Strasbourg, Université de Strasbourg, Strasbourg, France

12 Assistance Publique des Hôpitaux de Paris (AP-HP), Hôpital Hôtel-Dieu, Center for Clinical Epidemiology, Paris, France

## **\*Correspondence to:**

Raphaël Porcher, Centre d'Épidémiologie Clinique, Hôtel-Dieu de Paris, 1 Place du Parvis Notre-Dame, 75181 Paris Cedex 04, France.

**E-mail:** raphael.porcher@aphp.fr

‡ **R.P. and R.S. contributed equally.**

**Keywords:**

rheumatoid arthritis, rituximab, clinical trials, adverse events

# Abstract

## Objectives:

To investigate whether the efficacy and safety data from drug-registration trials can be extrapolated to real-life RA patients receiving RTX.

## Methods:

The 'AutoImmunity and Rituximab' (AIR-PR) registry is a French multicentre, prospective cohort of RA patients treated with RTX in a real-life setting. We compared treatment responses at 12 months and serious adverse events (AEs) between eligible and non-eligible patients, by retrieving the eligibility criteria of the three rituximab-registration trials. We determined critical eligibility criteria and modelled the benefit–risk ratio according to the number of fulfilled critical eligibility criteria.

## Results:

Among 1984 RA patients, only 9–12% fulfilled all eligibility criteria. Non-eligible patients had fewer EULAR responses at 12 months (40.3% vs 46.9%,  $P = 0.044$ ). Critical inclusion criteria included swollen joints count  $\geq 4$ , tender joints count  $\geq 4$ , CRP  $\geq 15$  mg/l and RF positivity. Critical exclusion criteria were age  $>80$  years, RA-associated systemic diseases, ACR functional class IV, DMARD other than MTX and prednisone  $>10$  mg/day. Only 20.8% fulfilled those critical eligibility criteria. During the first year, serious AEs occurred for 182 (9.2%) patients (70.3% serious infections) and patients with 1 critical exclusion criterion were at higher risk (hazard ratio 3.03; 95% CI 2.25–4.06; for 3 criteria vs 0). The incremental risk–benefit ratio decreased with the number of unmet critical inclusion criteria and of fulfilled exclusion criteria.

## Conclusion:

Few real-life RA patients were eligible for the drug-registration trials. Non-eligible patients had lower chance of response, and higher risk of serious AEs. Efficacy and safety data obtained from those trials may not be generalizable to RA patients receiving RTX in real-world clinical practice.

---

# Introduction

Most randomized controlled trials (RCT) examine whether a therapy can work under ideal circumstances. Therefore, highly selective and rigorous eligibility criteria are generally used to select the population under study [1]. This represents a limitation of RCT designs because excluding patients who can potentially benefit from the drug in routine care can severely limit the generalizability of study results [2]. Furthermore, it has been observed that some exclusion criteria in RCT are overly restrictive, and add little to patient safety or study internal validity[1].

The poor representativeness of patients enrolled in RCT is a common finding in medical field and has been already pointed out in RA patients [3, 4]. In 2016, a large study showed that only a minority of RA patients taken from two large American cohorts would have been eligible for the main trials on biologic agents (TNF and non-TNF inhibitors) performed over the last decades [5]. A systematic literature review comparing patients enrolled in RCT and in observational studies showed that there were substantial systematic differences in patient characteristics and in treatment efficacy [6].

Three RCT [7–9], including about 1000 patients, have been carried out before approval and registration of rituximab (RTX), a monoclonal anti-CD20 antibody for RA treatment [10]. RTX has been since then widely used and is included in RA treatment guidelines [11]. However, as observed for other biologics in RA, <10% of real-life patients was found to be eligible for two of the three main RTX-registration trials in a study conducted in the USA because of restrictive inclusion criteria or exclusion criteria such as comorbidities or undesired co-medication [5]. However, to our knowledge, no study has primarily aimed to identify the main barrier to RCT enrolment for RTX. Moreover, whether the efficacy, tolerance or safety data obtained in highly selected RCT patients can be extrapolated to a more heterogeneous patients population receiving RTX in real-life practice remains to be elucidated.

Thus, we used data from the French Multicentre Prospective Registry of RA patients treated with RTX ‘AutoImmunity and Rituximab’ (AIR-PR), to identify the main reasons limiting the eligibility of routine care patients in RTX-registration RCT, and to investigate the relationships between the number of eligibility criteria (both inclusion and exclusion) fulfilled by such patients, and the drug-related efficacy and safety observed in a real-life scenario.

# Methods

## Source of data

The AIR-PR registry was a French nationwide, multicentre, prospective cohort study, conducted by the French Society of Rheumatology, aimed at investigating efficacy and safety of RTX for treating RA in a real-life setting [12]. The registry received administrative and ethical approval from the French authorities (Comité Consultatif sur le Traitement de l'information en matière de Recherche dans le domaine de la Santé and Commission Nationale de l'Informatique et des Libertés), and patients gave informed consent for participation [12, 13]. The ethical approval includes broad consent to perform clinical research on behalf of the registry related to the aims of the registry. As this project falls within these research aims, no additional ethical approval was required.

## Drug-registration trials

We considered as drug-registration trials the three RCT carried out before approval of RTX for RA and used to support its approval: Edwards et al., REFLEX and DANCER [7–9]. We searched for these trials in the label and medical review available from the Food and Drug Administration (FDA), European Medicine Agency assessment reports and French Haute Autorité de Santé documents. We then retrieved eligibility criteria of the drug-registration trials from regulatory agency documents as well as published articles reporting the trials, and then rearranged by inclusion/exclusion criteria according to Van Spall et al. classification [14]. Inclusion criteria were defined as criteria driving the recruitment of patients into the trial and describing the medical condition of interest, and all other criteria limiting the eligibility of individuals were considered as exclusion criteria.

## Baseline data

Baseline patient characteristics were extracted from the AIR-PR registry to evaluate whether patients would have been eligible for trials: age, disease duration, presence of RF, previous or current use of MTX, treatment by other conventional DMARDs (cDMARDs) or biologic DMARDs (bDMARDs) including RTX, tender and swollen 28-joint counts, current prednisone dose, ESR, CRP, presence of erosive changes on X-ray, any associated autoimmune disease, presence of rheumatoid vasculitis or other systemic complication, presence

of a severe functional disability (ACR stage IV), history of severe or recurrent infections, history of neoplasia (except basal cell carcinoma) and history of allergy to mAbs.

**Table 1.** Percentage of patients in the AIR-RA registry who met trial eligibility criteria

| Eligibility criteria                           | Edwards | DANCER | REFLEX | N evaluated | N fulfilled | % (of evaluated) | % imputed |
|--|---------|--------|--------|-------------|-------------|------------------|-----------|
| <b>Inclusion criteria</b>                      |         |        |        |             |             |                  |           |
| ACR criteria for RA                            | +       | +      | +      | 1984        | 1949        | 98.2             | 98.2      |
| Disease duration >6 months                     |         |        |        | 1876        | 1428        | 76.1             | 76.0      |
| Previous use of MTX ≥10 mg                     | +       | +      | +      | 1972        | 1887        | 95.7             | 95.7      |
| SJC ≥8   | +       | +      | +      | 1636        | 690         | 42.2             | 41.8      |
| SJC ≥5   | +       | +      | +      | 1636        | 1072        | 65.5             | 65.0      |
| SJC ≥4   | +       | +      | +      | 1636        | 1213        | 74.1             | 73.6      |
| TJC ≥8   | +       | +      | +      | 1629        | 960         | 58.9             | 58.2      |
| TJC ≥5   | +       | +      | +      | 1629        | 1234        | 75.8             | 74.2      |
| TJC ≥4   | +       | +      | +      | 1629        | 1343        | 82.4             | 81.0      |
| CRP ≥15 mg/L or ESR ≥28 mm/h                   | +       | +      | +      | 1704        | 1201        | 70.5             | 67.5      |
| or morning stiffness >45 min                   | +       |        |        | 1974        | 1764        | 89.4             | 89.3      |
| Presence of RF                                 | +       |        |        | 1885        | 1518        | 80.5             | 80.4      |
| Erosive change                                 |         |        | +      | 1979        | 1344        | 68.2             | 68.1      |
| Use of 1–5 DMARDs or biologics                 |         | +      |        | 1979        | 1889        | 98.5             | 95.5      |
| Previous use of ≥1 anti-TNF-α                  |         |        | +      | 1981        | 1543        | 77.9             | 77.9      |
| IA injection ≤1 month                          |         | +      |        | NA          |             |                  |           |
| All inclusion criteria (imputed), %            | 48.1    | 29.7   | 19.0   |             |             |                  |           |
| <b>Exclusion criteria</b>                      |         |        |        |             |             |                  |           |
| Age <18 years                                  | +       | +      | +      | 1983        | 1           | 0.1              | 0.1       |
| Age >80 years                                  |         | +      |        | 1983        | 68          | 3.4              | 3.4       |
| Other auto-immune disease <sup>a</sup>         | +       | +      | +      | 1892        | 236         | 12.5             | 12.6      |
| Rheumatoid vasculitis                          | +       |        |        | 1941        | 70          | 3.6              | 4.0       |
| Systemic disease associated with RA            | +       | +      | +      | 1937        | 73          | 3.8              | 4.2       |
| ACR functional class IV                        | +       |        | +      | 1555        | 222         | 14.3             | 14.9      |
| Concurrent use of any other DMARD (except MTX) | +       | +      | +      | 1971        | 317         | 16.1             | 16.1      |
| Current infection                              | +       |        |        | NA          |             |                  |           |
| Previous severe or recurrent infection         | +       | +      |        | 1917        | 664         | 34.6             | 34.8      |
| Immunodeficiency (primary or secondary)        | +       |        |        | 1892        | 28          | 1.5              | 1.6       |
| Other severe uncontrolled disease              | +       |        |        | 1947        | 308         | 15.8             | 15.9      |
| Chronic fatigue syndrome                       | +       |        |        | NA          |             |                  |           |
| Previous neoplasia <sup>b</sup>                | +       |        |        | 1924        | 270         | 14.0             | 14.2      |
| Allergic or anaphylactic reactions to mAbs     |         | +      |        | 1874        | 66          | 3.5              | 3.6       |
| Previous use of RTX                            |         | +      |        | 1942        | 52          | 2.7              | 2.7       |
| Prednisone dose >12.5 mg/day                   | +       |        |        | 1940        | 429         | 22.1             | 22.1      |
| Prednisone dose >10 mg/day                     |         | +      | +      | 1940        | 494         | 25.5             | 25.5      |
| No exclusion criteria (imputed), %             | 73.9    | 65.9   | 53.4   |             |             |                  |           |
| Eligible for the trial (imputed), %            | 12.3    | 9.7    | 9.2    |             |             |                  |           |

<sup>a</sup> Except SS.

<sup>b</sup> Except basal cell carcinoma. SJC: swollen joints count; TJC: tender joints count; AIR: autoimmunity and rituximab; RTX: rituximab; NA: not available.

Since RCT eligibility criteria required involvement of 8 joints out of 66 or 68 counts and only 28 joint counts were recorded in the AIR-PR registry, we used a cut-off of 4 tender or swollen joints instead. Sensitivity analyses were carried out with thresholds at 5 and 8, instead of 4.

We considered a patient to be eligible for enrolment in a drug-registration trial if s/he would meet the inclusion criteria and had no exclusion criteria of one of the drug-registration trials.

## Outcomes definitions

To assess drug efficacy, the primary outcome was treatment response at 12 months, as defined by moderate-to-good EULAR response [15], without treatment discontinuation, introduction of a new drug because of lack of efficacy or increase of the CS dose. A moderate EULAR response was defined as a decrease in DAS in 28 joints (DAS28)-ESR  $>0.6$  points and resulting score 5.1. A good EULAR response was defined as a decrease in DAS28  $>1.2$  points and resulting score 3.2. Patients who died before 12 months were also considered as non-responders. As secondary outcome, we also analysed changes in DAS28 between baseline and 12 months.

For safety, we used as primary outcome the occurrence of any of the following adverse events (AEs): occurrence of any of severe infection (defined as an infection requiring hospital admission, requiring intravenous antibiotics or resulting in death), malignant cancer, major adverse cardiovascular events (defined as death from cardiovascular cause, myocardial infarction or stroke) and death at 12 months.

## **Data analysis**

Mean DAS28 changes from baseline and the proportion of responders were described and compared between patients eligible and non-eligible to drug-registration trials. The probability of occurrence of severe AEs over follow-up was estimated by the Kaplan–Meier estimator.

The association between the fulfilment of each eligibility criterion with treatment response at 12 months was assessed by logistic regression. The risk of severe AEs occurring during the first 12 months according to each criterion was assessed by Cox proportional hazards regression.

We then defined as critical eligibility criteria the inclusion and/or exclusion criteria associated with treatment response, and with severe AEs, respectively, after backward stepwise variable elimination. We then categorized patients according to the number of critical eligibility criteria, and performed risk–benefit assessment according to these categories, starting from patients fulfilling all critical eligibility criteria with no critical exclusion criteria.

We also expressed the risk–benefit trade-off as the number needed to harm over number needed to treat ratio (NNH/NNT), also termed incremental risk–benefit ratio (IRBR), owing



to its simplicity [16, 17]. If we denote by BE and BC the probability of benefit (response), and RE and RC the risk with experimental and control treatments, respectively, the NNH/NNT is  $[1 : (RE - RC)] / [1 : (BE - BC)] \times (BE - BC) / (RE - RC)$ , or equivalently DB/DR, where D stands for the difference between treatments E and C. We calculated the NNH/NNT in the whole AIR-PR registry for increasing departures from eligibility to drug-registration trials, to illustrate the potential for inverse-benefit law to be verified, accounting for the prevalence of each category of patients.

To compute the NNH and NNT, values under RTX treatment RE and BE were estimated using the AIR-PR registry data. Since the registry only includes patients treated with RTX, we derived estimates of BC from the NNT obtained by the pooled effect of RTX of EULAR response in the drug-registration trials. More precisely, the absolute difference in EULAR response between RTX in association with MTX and control arms (MTX þ placebo) in the drug-registration trials was estimated with a random-effects meta-analysis model. It was then considered that the same NNT would be obtained in the AIR patients who would have been eligible to the drug-registration trials, which yielded an estimated value for BC.

Since long-term cumulative incidence of severe infection and other severe AEs were rarely reported in drug-registration trials, we derived the NNH for eligible patients from a published network meta-analysis of the risk of serious infection in biological treatments of RA [18]. We thus estimated RC as the proportion yielding the same odds ratio (OR) in AIR-PR patients eligible to drug-registration trials as the one reported for standard-dose biological drug with or without traditional DMARD compared with traditional DMARD monotherapy (and placebo) in the population of MTX experienced patients. In this study [18], the pooled OR (95% CI) for the risk of serious infection was 1.48 (1.17–1.90) in patients treated with standard-dose bDMARDs compared with traditional DMARD.

In the main analysis, we considered that the response and risk under the control treatment would be constant irrespective of the number of eligibility criteria fulfilled. We then ran sensitivity analyses where BC and RC were considered to vary in the same sense as BE and RE, so that DR and DB would be less affected by departures from the eligible population. The standard errors of NNH/NNT were obtained by bootstrapping [19].

Missing values for eligibility criteria or outcomes in the AIR registry were handled by multiple imputation by chained equations, using all variables analysed and the baseline cumulative hazard of severe adverse event in the imputation model [20, 21]. Variables with the highest rate of missing data were numbers of tender (33%) and swollen joints (32%), DAS28 changes at 12 months (54%) and response at 12 months (43%). Owing to the frequency of missing data, we generated and analysed separately 75 independent imputed data

sets [22]. Convergence of the multiple imputation algorithm was assessed by visual inspection of the mean and variance of the imputation streams. Estimates were then pooled over the 75 imputations according to Rubin's rules to provide point estimates and CIs for each parameter.

All analyses were carried with R 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria).

## Results

### Study population

The AIR-PR registry included 1984 RA patients treated with RTX, followed for a mean ( $\pm$ SD) of 5.3 years ( $\pm$ 2.3). Among them, 1561 (78.7%) were women, mean ( $\pm$ S.D) age was 58.0 ( $\pm$ 12.7) years at inclusion, mean ( $\pm$ S.D) disease duration was 13.2  $\pm$  9.6 years and mean DAS28 was 5.5 ( $\pm$ 1.7). Baseline characteristics of the patients are described in Supplementary Table S1, available at Rheumatology online. Patients' characteristics were similar to those from other real-world RTX registries (Supplementary Table S2, available at Rheumatology online).

### Eligibility criteria

Detailed inclusion and exclusion criteria of the three drug-registration trials are described in Table 1. Only 48.1% fulfilled the inclusion criteria of Edwards et al., 29.7% of DANCER and 19% of REFLEX (Table 1). The main limiting inclusion criteria were an elevated CRP or ESR level (67.5%), erosive changes on bone X-ray (68.1%) and a swollen joint count  $\geq$ 4/28 (73.6%).

At least one exclusion criteria of each of the three RCT was present for 73.9%, 65.9% and 53.4%, respectively (Table 1). Some 73.9% had no exclusion criteria of Edwards et al., 68.9% of DANCER and 53.4% of REFLEX. The main limiting exclusion criteria were a history of severe or recurrent infection (34.8%), another severe uncontrolled disease (15.9%), neoplasia (14.2%), prednisone dose  $>$ 10 mg/day (25.5%), the use of a DMARD other than MTX (16.1%) and the presence of severe functional disability (ACR functional class IV; 14.9%).

After combining both inclusion and exclusion criteria, only 12.3%, 9.7% and 9.2% fulfilled the eligibility criteria for each RCT, respectively (Table 1). Based on imputed data, 20.0% met the eligibility criteria for at least one trial and were defined as eligible for drug-registration trials. DAS28 at inclusion was more elevated in the eligible patients than in the non-eligible patients (6.1 vs 5.4,  $P < 0.0001$ ) (Table 2).

### **Treatment response**

Data on DAS28 was available for 1021 (51.5%) patients at 12 months (172 eligible and 849 non-eligible patients). On this non-imputed population, treatment response was obtained for 87/172 (50.6%) eligible patients vs 343/849 (40.4%) non-eligible patients (D ¼  $-10.2\%$ ; 95% CI  $-18.3$  to  $-2.1$ ; P ¼  $0.014$ ) (Table 2).

On the imputed data, the observed difference in treatment response remained statistically significant (46.9% in eligible patients vs 40.3% in non-eligible patients; D ¼  $-6.5\%$ ; 95% CI  $-12.9$  to  $-0.2$ , P ¼  $0.044$ ), and the mean change in DAS28 at 12 months was higher in eligible patients ( $-1.4$  vs  $-1.2$ ; D ¼  $0.3$ ; 95% CI  $0.1$ – $0.5$ ; P ¼  $0.005$ ) (Table 2).

The association between all eligibility criteria and treatment response at 12 months is presented in Table 3.

### **Safety**

During the first year, severe AEs occurred for 182 (9.2%) patients: severe infection (N ¼ 128; 6.5%), malignant cancer (N ¼ 19; 1.0%) including 1 lymphoma, major adverse cardiac event (N ¼ 25; 1.2%) and death (N ¼ 14; 0.7%). Table 3 describes the association between all eligibility criteria and the risk of severe AEs within the first year following inclusion.

**Table 1.** Percentage of patients in the AIR-RA registry who met trial eligibility criteria

| Eligibility criteria                           | Edwards | DANCER | REFLEX | N evaluated | N fulfilled | % (of evaluated) | % imputed |
|--|---------|--------|--------|-------------|-------------|------------------|-----------|
| <b>Inclusion criteria</b>                      |         |        |        |             |             |                  |           |
| ACR criteria for RA                            | +       | +      | +      | 1984        | 1949        | 98.2             | 98.2      |
| Disease duration >6 months                     |         | +      | +      | 1876        | 1428        | 76.1             | 76.0      |
| Previous use of MTX ≥10 mg                     | +       | +      | +      | 1972        | 1887        | 95.7             | 95.7      |
| SJC ≥8   | +       | +      | +      | 1636        | 690         | 42.2             | 41.8      |
| SJC ≥5   | +       | +      | +      | 1636        | 1072        | 65.5             | 65.0      |
| SJC ≥4   | +       | +      | +      | 1636        | 1213        | 74.1             | 73.6      |
| TJC ≥8   | +       | +      | +      | 1629        | 960         | 58.9             | 58.2      |
| TJC ≥5   | +       | +      | +      | 1629        | 1234        | 75.8             | 74.2      |
| TJC ≥4   | +       | +      | +      | 1629        | 1343        | 82.4             | 81.0      |
| CRP ≥15 mg/L or ESR ≥28 mm/h                   | +       | +      | +      | 1704        | 1201        | 70.5             | 67.5      |
| or morning stiffness >45 min                   | +       |        |        | 1974        | 1764        | 89.4             | 89.3      |
| Presence of RF                                 | +       |        |        | 1885        | 1518        | 80.5             | 80.4      |
| Erosive change                                 |         |        | +      | 1979        | 1344        | 68.2             | 68.1      |
| Use of 1–5 DMARDs or biologics                 |         | +      |        | 1979        | 1889        | 98.5             | 95.5      |
| Previous use of ≥1 anti-TNF-α                  |         |        | +      | 1981        | 1543        | 77.9             | 77.9      |
| IA injection ≤1 month                          |         | +      |        | NA          |             |                  |           |
| All inclusion criteria (imputed), %            | 48.1    | 29.7   | 19.0   |             |             |                  |           |
| <b>Exclusion criteria</b>                      |         |        |        |             |             |                  |           |
| Age <18 years                                  | +       | +      | +      | 1983        | 1           | 0.1              | 0.1       |
| Age >80 years                                  |         | +      |        | 1983        | 68          | 3.4              | 3.4       |
| Other auto-immune disease <sup>a</sup>         | +       | +      | +      | 1892        | 236         | 12.5             | 12.6      |
| Rheumatoid vasculitis                          | +       |        |        | 1941        | 70          | 3.6              | 4.0       |
| Systemic disease associated with RA            | +       | +      | +      | 1937        | 73          | 3.8              | 4.2       |
| ACR functional class IV                        | +       |        | +      | 1555        | 222         | 14.3             | 14.9      |
| Concurrent use of any other DMARD (except MTX) | +       | +      | +      | 1971        | 317         | 16.1             | 16.1      |
| Current infection                              | +       |        |        | NA          |             |                  |           |
| Previous severe or recurrent infection         | +       | +      |        | 1917        | 664         | 34.6             | 34.8      |
| Immunodeficiency (primary or secondary)        | +       |        |        | 1892        | 28          | 1.5              | 1.6       |
| Other severe uncontrolled disease              | +       |        |        | 1947        | 308         | 15.8             | 15.9      |
| Chronic fatigue syndrome                       | +       |        |        | NA          |             |                  |           |
| Previous neoplasia <sup>b</sup>                | +       |        |        | 1924        | 270         | 14.0             | 14.2      |
| Allergic or anaphylactic reactions to mAbs     |         | +      |        | 1874        | 66          | 3.5              | 3.6       |
| Previous use of RTX                            |         | +      |        | 1942        | 52          | 2.7              | 2.7       |
| Prednisone dose >12.5 mg/day                   | +       |        |        | 1940        | 429         | 22.1             | 22.1      |
| Prednisone dose >10 mg/day                     |         | +      | +      | 1940        | 494         | 25.5             | 25.5      |
| No exclusion criteria (imputed), %             | 73.9    | 65.9   | 53.4   |             |             |                  |           |
| Eligible for the trial (imputed), %            | 12.3    | 9.7    | 9.2    |             |             |                  |           |

<sup>a</sup> Except SS.<sup>b</sup> Except basal cell carcinoma. SJC: swollen joints count; TJC: tender joints count; AIR: autoimmunity and rituximab; RTX: rituximab; NA: not available.

## Critical eligibility criteria

Critical inclusion criteria (associated with the EULAR response in multivariate analysis) included a swollen joints count 4/28, a tender joints count 4/28, a CRP level  $\geq 15$  mg/l or ESR 28 mm/h, and RF positivity.

Critical exclusion criteria (associated with severe AEs within the first year in multivariate analyses) included age >80 years, a history of systemic diseases associated with RA, ACR functional class IV disease, a concurrent use of any other DMARD (other than MTX) and a daily oral dose of glucocorticoids >10 mg/day.

In the whole cohort, 44.0% met those four critical inclusion criteria, 50.0% had none of the five critical exclusion criteria and only 20.8% met all critical inclusion criteria with no critical exclusion criteria.

**Table 2.** Changes in DAS28 according to eligibility to drug-registrations trials

| Outcome                            | Eligible   | Non-eligible | Difference (95% CI)   | P       |
|------------------------------------|------------|--------------|-----------------------|---------|
| Evaluated cases                    |            |              |                       |         |
| DAS28 at inclusion                 | 6.1 (1.0)  | 5.4 (1.3)    | -0.7 (-0.9 to -0.6)   | <0.0001 |
| N evaluated                        | 276        | 1402         |                       |         |
| Changes in DAS28 at 12 months      | -1.6 (1.6) | -1.3 (1.6)   | 0.3 (0.1-0.6)         | 0.019   |
| EULAR response at 12 months, N (%) | 87 (50.6%) | 343 (40.4%)  | -10.2 (-18.3 to -2.1) | 0.014   |
| N evaluated                        | 172        | 869          |                       |         |
| Imputed data                       |            |              |                       |         |
| Average N                          | 396.4      | 1587.6       |                       |         |
| DAS 28 at inclusion                | 6.1 (1.0)  | 5.3 (1.3)    | -0.8 (-0.9 to -0.6)   | <0.0001 |
| Changes in DAS28 at 12 months      | -1.4 (1.6) | -1.2 (1.6)   | 0.3 (0.1-0.5)         | 0.005   |
| EULAR response at 12 months, %     | 46.9%      | 40.3%        | -6.5 (-12.9 to -0.2)  | 0.044   |

Results are expressed as mean (s.d.) unless stated otherwise. DAS28: DAS in 28 joints; N: number.

**Table 3.** Association between drug-registration trials eligibility criteria and treatment response and severe AEs

| Eligibility criteria  | OR for EULAR response (95% CI) | HR for severe AE (95% CI) |
|---|--------------------------------|---------------------------|
| Inclusion criteria  |                                |                           |
| Disease duration >6 months                                  | 1.00 (0.78-1.29)               | 1.05 (0.73-1.51)          |
| Previous use of MTX $\geq$ 10 mg/day                        | 0.51 (0.31-0.85)               | 0.95 (0.47-1.94)          |
| Swollen joints count $\geq$ 4 <sup>a</sup>                  | 1.49 (1.15-1.92)               | 1.06 (0.74-1.52)          |
| Tender joints count $\geq$ 4 <sup>a</sup>                   | 1.41 (1.03-1.94)               | 0.91 (0.62-1.34)          |
| CRP $\geq$ 15 mg/l or ESR $\geq$ 28 mm <sup>a</sup>         | 1.53 (1.19-1.98)               | 1.09 (0.89-1.51)          |
| Presence of RF <sup>a</sup>                                 | 1.94 (1.42-2.65)               | 1.23 (0.92-1.83)          |
| Erosive change  | 0.92 (0.73-1.16)               | 1.20 (0.87-1.66)          |
| Previous use of 1-5 DMARDs or biologics                     | 0.90 (0.54-1.49)               | 0.72 (0.39-1.32)          |
| Previous use of $\geq$ 1 anti-TNF- $\alpha$                 | 0.78 (0.61-1.00)               | 0.61 (0.45-0.84)          |
| All inclusion criteria of Edwards                           | 1.58 (1.25-2.00)               | 1.07 (0.79-1.45)          |
| All inclusion criteria of DANCER                            | 1.57 (1.24-1.97)               | 0.98 (0.70-1.37)          |
| All inclusion criteria of REFLEX                            | 1.29 (0.98-1.69)               | 1.10 (0.76-1.59)          |
| Exclusion criteria  |                                |                           |
| Age >80 years <sup>a</sup>                                  | 0.95 (0.53-1.70)               | 3.00 (1.80-5.01)          |
| Other auto-immune disease <sup>b</sup>                      | 1.07 (0.77-1.47)               | 1.23 (0.80-1.88)          |
| Rheumatoid vasculitis                                       | 1.01 (0.54-1.88)               | 2.78 (1.66-4.68)          |
| Systemic disease associated with RA <sup>a</sup>            | 1.05 (0.57-1.93)               | 2.64 (1.57-4.44)          |
| ACR functional class IV <sup>a</sup>                        | 1.03 (0.75-1.42)               | 1.42 (0.94-2.13)          |
| Concurrent use of any other DMARD (except MTX) <sup>a</sup> | 1.06 (0.80-1.42)               | 1.39 (0.97-1.99)          |
| Previous severe or recurrent infection                      | 1.26 (1.02-1.56)               | 1.37 (1.01-1.85)          |
| Immunodeficiency (primary or secondary)                     | 0.98 (0.38-2.52)               | 2.04 (0.84-4.96)          |
| Other severe uncontrolled disease                           | 1.31 (0.98-1.77)               | 1.96 (1.40-2.74)          |
| Previous neoplasia <sup>c</sup>                             | 1.32 (0.98-1.77)               | 1.27 (0.86-1.89)          |
| Allergic or anaphylactic reactions to mAbs                  | 0.87 (0.48-1.55)               | 0.82 (0.34-1.99)          |
| Previous use of rituximab                                   | 0.97 (0.49-1.93)               | 0.44 (0.11-1.77)          |
| Prednisone dose >10 mg/day <sup>a</sup>                     | 0.97 (0.76-1.25)               | 1.35 (0.98-1.85)          |
| Any exclusion criterion of Edwards                          | 1.20 (0.94-1.54)               | 2.05 (1.35-3.09)          |
| Any exclusion criterion of DANCER                           | 1.07 (0.86-1.35)               | 1.55 (1.10-2.18)          |
| Any exclusion criterion of REFLEX                           | 0.98 (0.78-1.21)               | 1.47 (1.07-2.01)          |

At 12 months and incidence of severe adverse events within 12 months.

<sup>a</sup> Critical eligibility criteria independently associated with treatment response or with severe AEs within the first year after stepwise regression.

<sup>b</sup> Except SS.

<sup>c</sup> Except basal cell carcinoma. OR: odds ratio; HR: hazard ratio; AE: adverse event.

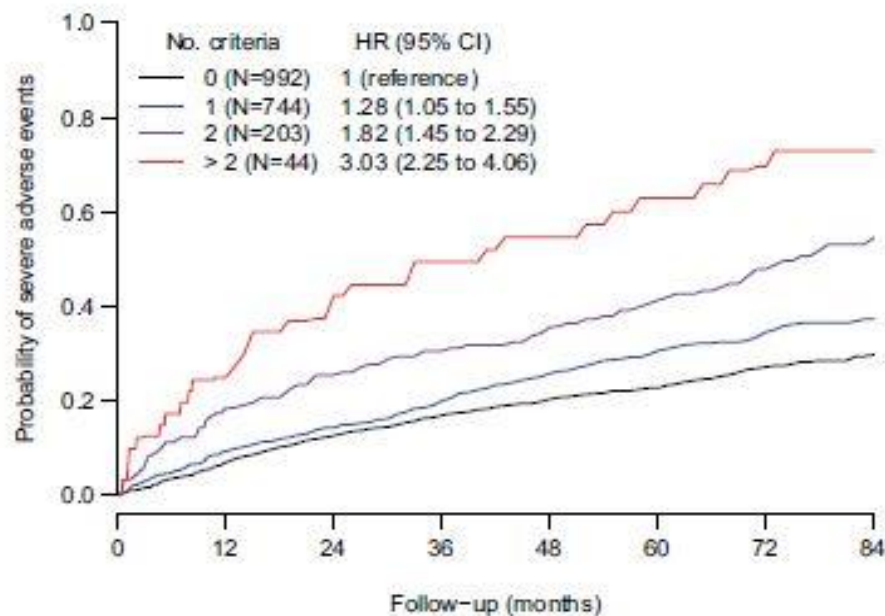
The probabilities of treatment response and of severe AEs within the first year according to the number of critical eligibility criteria fulfilled are illustrated in Fig. 1. While the probability of treatment response decreases with the number of unmet inclusion criteria, the probability of severe AEs increased with the number of fulfilled exclusion criteria.



Cumulative incidence of severe AEs according to the number of fulfilled critical exclusion criteria is described in Fig. 2. Compared with patients with no exclusion criterion, patients with at least one critical exclusion criterion had a higher risk of severe AEs (HR 3.03; 95% CI 2.25–4.06; for  $\geq 3$  criteria).

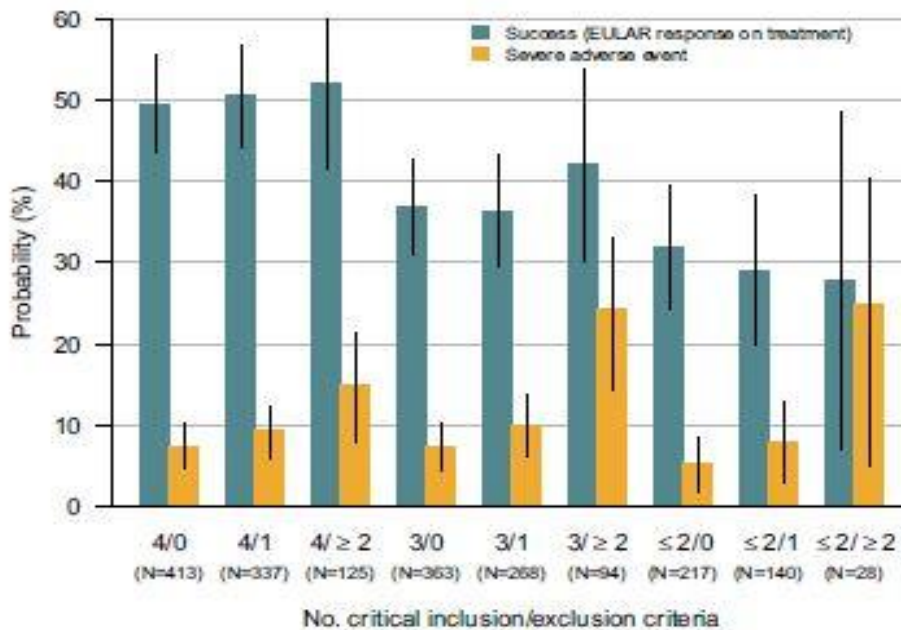
### Modelling the risk–benefit ratio

The NNT varied with the number of fulfilled critical inclusion criteria: 2.4–2.6 for 4 inclusion criteria; 3.2–3.9 for 3 criteria; and 3.8–5.9 for  $\leq 2$  criteria. Similarly, the estimated NNH considerably decreased with the number of critical exclusion criteria: 66.7–83.3 for no exclusion criterion; 24.6–47.8 for 1; and 5.3–11.2 for  $\geq 2$  (Fig. 3).



**Figure 1.** Probability of treatment response and of severe adverse events according to the number of fulfilled critical inclusion and exclusion criteria. Critical inclusion criteria included a swollen joints count  $\geq 4$  (of 28 joints assessed), a tender joints count  $\geq 4$  (of 28 joints assessed), CRP level  $\geq 15$  mg/l or ESR  $\geq 28$  mm, and presence of RF. Critical exclusion criteria included age  $> 80$  years, systemic disease associated with RA, ACR functional class IV, concurrent use of any other DMARD (except MTX) and a prednisone dose  $> 10$  mg/day. EULAR response on treatment: moderate or good response according to the EULAR criteria without treatment discontinuation, introduction of a new drug because of lack of efficacy or increase of the CS dose

We then modelled the evolution of the risk–benefit tradeoff (or IRBR; NNH/NNT) according to the number of fulfilled eligibility criteria (Supplementary Fig. S1, available at Rheumatology online). In the main analysis, considering that RC and BC would be constant irrespective of the number of fulfilled eligibility criteria, the ratio decreased by adding exclusion criteria and removing inclusion criteria. In sensitivity analyses where BC and RC were considered to vary in the same sense as BE and RE, similar results were found (Supplementary Fig. S1, available at Rheumatology online).



**Figure 2.** Cumulative incidence of serious adverse events according to the number of critical exclusion criteria. Critical exclusion criteria included age >80 years, systemic disease associated with RA, ACR functional class IV, concurrent use of any other DMARD (except MTX) and a prednisone dose >10 mg/day. Severe adverse events included severe infections, major adverse cardiac events, cancer including lymphoma or death. HR: hazard ratios

## Discussion

The present study found that only a minority of patients met the eligibility criteria for participations in the three pivotal RCT that led to the authorization of RTX use for RA. Moreover, patients who did not meet eligibility criteria were less likely to respond to RTX and were more prone to experiencing severe AEs. Our findings support the inversebenefit law, where the benefit-risk ratio appears to be decrease when the treated population diverges from the trial initial population. Patients' selection in RCT is stringent, often not accurate with the real-life setting, and may select a subgroup with a higher potential of drug efficacy [23].

Our study highlights the discrepancy between patients selected for RCT and real-life data, and confirms the poor representativeness of RA patients enrolled in RCT [3, 4, 24, 25]. In a previous study, Vashisht et al. reported that <10% of two large American cohorts would be eligible for inclusion in the RCT evaluating RTX for RA [5]. Our study goes further by evaluating patients who have been treated with RTX without fulfilling all eligibility criteria, and by assessing their efficacy and safety profiles. As a reminder, while the FDA approved the use of RTX in combination with MTX for the treatment of adult patients with moderately to severely active RA who have had an inadequate response to one or more TNF antagonist therapies, it does not give precise specific contraindications for its use. Our study highlights the need for more pragmatic and inclusive randomized trials, where eligibility criteria would

better allow including patients who could benefit from treatment in real-life situations and enhance generalizability of the results. Nevertheless, given the possible reduced difference in terms of efficacy, such trials would require more patients, be more costly and last longer.

We found four critical inclusion criteria associated with the treatment response, including a highly active disease, with four or more swollen or tender joints, a high CRP level or high ESR, and the presence of RF. Some of these have already been reported as associated with a good response, including in real-world data [26]. While 44% fulfilled these four critical criteria, this was not the case for most patients. Critical exclusion criteria included an advanced age, systemic manifestations of RA, ACR functional class IV, concurrent use of any other DMARD (except MTX) and a daily prednisone dose >10 mg/day. Those criteria represent patients with more comorbidities, or with a more severe disease, requiring additional therapy. While those criteria did not seem to influence the response rate, they clearly increased the risk of AEs. Some of these characteristics have previously been showed to be associated with a higher risk of AEs [12, 27]. The use of other DMARD except MTX, such as LEF, has also been shown to increase the risk of infections in previous reports [28].

Patients in clinical trials are usually highly selected in order to maximize the chances of a treatment response, and to decrease the risk of severe AEs. This is illustrated in our cohort, as only 21% of patients met all critical inclusion criteria without having any critical exclusion criteria. Thus, when less severely affected patients are treated by the evaluated therapy, more patients must be treated for one patient to benefit (increasing the NNT). This has important implications in public health, depending on the drug's cost. In addition, when more patients are exposed to the drug, including those more prone to have AEs, the number of adverse reactions increases, the NNH decreases and the benefit-to-harm ratio worsens [23].

This is of interest, as some targeted measures could be taken to improve this ratio, such as giving very low doses of RTX [29, 30]. Indeed, in a previous study of the AIR-PR registry, compared with standard treatment dose, reduced RTX doses following a first course of RTX standard dose were associated with a comparable efficacy, and a lower rate of serious infections [30]. Thus, some patients could potentially benefit from reduced dose and decrease their risk of AEs. This could improve both benefit–risk ratio and cost-effectiveness of the RTX treatment.

We acknowledge some limitations of our study. First, we used data from only one registry without any replication in another registry. Even if efforts were made to maintain exhaustivity of the data, some data including the treatment response were missing due to the real-life setting of our largescale multicentre registry, compared with the more intensive and regular follow-up of RCT patients. Although the missing data mechanism might be not at random, we performed analyses on both complete (i.e. not imputed) and multiply imputed data, which showed similar results. We used as many variables as possible in the imputation model in order to make the missing at random assumption more plausible and to reduce bias if data were missing not at random. Another limitation is the difference of the evaluated joints count in the RCT, which used denominators of 66 for swollen joint counts and 68 for tender joint counts, while we only had a 28-joint count in our registries. While there is no study comparing the 28-joint counts with the 68/66 joint counts, we performed sensitivity analyses with different cut-offs for the inclusion criteria, and even if three-quarters of our population had 4/28 or more swollen joints, the proportion of eligible patients remained low. In addition, because of this difference in joint counts number and the absence of available HAQ, we were unable to evaluate the ACR response used in the three RCT leading to the approval of RTX,



and we used the EULAR response instead. Thus, we could not directly compare our findings with the three RCT. Finally, the AIR-PR registry only included patients treated with RTX, preventing comparisons of treatment efficacy and safety between treated and untreated patients according to the critical criteria. We thus modeled the risk–benefit ratio of RTX instead, based on the pooled benefits of RTX in the registration RCT, and another network meta-analysis on the risk of serious infections of biologic DMARDs (thus, not including early cancers, cardiovascular events and deaths within 12 months). However, serious infections accounted for >70% of serious AEs, limiting this bias. In addition, NNT and NNH were derived from comparison with placebo, and not with other biologic DMARDs, limiting the comparisons of risk–benefit ratios with other active medication.

The strengths of the AIR-PR registry include its real-life setting, with enrolment in both university and non-university centres, and the large number of unselected enrolled patients, with a large number of comorbidities. In addition, as patients were comparable to other real-world RTX registries from other countries, we believe that our results can be more widely generalizable.

To conclude, we demonstrated that patients included in the three RCT leading to the approval of RTX for RA are highly selected, and that the obtained efficacy and safety data cannot be extrapolated to a more heterogeneous sample of patients in daily practice. Physicians should be aware of the decreased efficacy and the higher risk of AEs when prescribing RTX for some RA patients in real practice.

### **Data availability**

Data are available upon reasonable request to the corresponding author.

### **Contribution statement**

R.P., R.S., P.R. and X.M. designed the study. R.P. and Y.N. were responsible for statistical analyses. Y.N., R.P. and R.S. analysed and interpreted the data. Y.N., R.S. and R.P. wrote the first version of the manuscript. All other authors approved the final version of the manuscript.

### **Funding**

The ‘AutoImmunity and Rituximab’ (AIR-PR) registry was supported by Roche through an unrestricted educational grant. However, Roche was not involved in the design, protocol, data collection or statistical analysis of this study; review or approval of the manuscript; or decision to submit the manuscript for publication.

### **Disclosure statement:**

X.M. received consulting fees from AstraZeneca, Bristol Myer Squib, Galapagos, GSK, Novartis and Pfizer. J.E.G. received grants from Pfizer, Abbvie and Lilly, and consulting fees from Abbvie, AstraZeneca, Sanofi, Lilly, Galapagos, Gilead, Roche Chugai, Pfizer, Bristol Myer Squib and MSD. M.I. received consulting fees from Boehringer Ingelheim and participated in advisory boards for Galapagos. J.M. received grants from Bristol Myers Squib, Fresenius Kabi, Lilly, Novartis, Pfizer and Roche-Chugai; honoraria from Abbvie, Boehringer Ingelheim, Biogen, Lilly, Mylan, Pfizer, Sanofi, Bristol Myers Squib, Fresenius

Kabi, Galapagos, Medac, Novartis and Roche Chugai; travel fees from Bristol Myers Squibb, Lilly and Fresenius Kabi; and participated in advisory boards for Abbvie, Pfizer and Galapagos. A.C. received consulting fees and honoraria from Abbvie, Amgen, BMS, Boehringer, Celltrion, Fresenius-Kabi, Galapagos, Jansse, Lilly, Medac, MSD, Novartis, Pfizer and UCB; and travel fees from Celltrion, Janssen, Lilly and Novartis. R.-M.F. received grants from Janssen, Abbvie and Pfizer; consulting fees from Abbvie, Janssen, MSD, Bristol Myer Squib, Medac and Lilly; honoraria from Abbvie, Bristol Myer Squib, MSD, Janssen, Lilly, Medac, Novartis, Roche Chugai and Pfizer; travel fees from Abbvie, MSD, Janssen; and participated in advisory boards for Abbvie, BMS, Janssen, Roche Chugai, Sanofi Genzyme and Pfizer. R.S. received consulting fees from GSK, Bristol Myer Squib, Boehringer and Janssen; honoraria from GSK, Bristol Myer Squib, Boehringer, Amgen, Pfizer and Roche; and travel fees from Amgen and GSK. All other authors (Y.N., O.V., T.S., J.S., P.R., R.P.) declared no competing interest associated with the present study.

### **Acknowledgements**

The authors would like to thank all participants in the AIR-PR registry, and all clinicians who included patients in the registry.

## **References**

1. Kennedy-Martin T, Curtis S, Faries D, Robinson S, Johnston J. A literature review on the representativeness of randomized controlled trial samples and implications for the external validity of trial results. *Trials* 2015;16:495.
2. Guyatt GH, Sackett DL, Cook DJ. Users' guides to the medical literature. II. How to use an article about therapy or prevention. A. Are the results of the study valid? Evidence-Based Medicine Working Group. *JAMA* 1993;270:2598–601.
3. Sokka T, Pincus T. Eligibility of patients in routine care for major clinical trials of anti-tumor necrosis factor agents in rheumatoid arthritis. *Arthritis Rheum* 2003;48:313–8.
4. Kievit W, Fransen J, Oerlemans AJM et al. The efficacy of anti-TNF in rheumatoid arthritis, a comparison between randomised controlled trials and clinical practice. *Ann RheumDis* 2007;66:1473–8.
5. Vashisht P, Sayles H, Cannella AC, Mikuls TR, Michaud K. Generalizability of patients with rheumatoid arthritis in biologic agent clinical trials. *Arthritis Care Res* 2016;68:1478–88.
6. Kilcher G, Hummel N, Didden EM, Egger M, Reichenbach S; GetReal Work Package 4. Rheumatoid arthritis patients treated in trial and real world settings: comparison of randomized trials with registries. *Rheumatology (Oxf Engl)* 2018;57:354–69.
7. Edwards JCW, Szczepanski L, Szechinski J et al. Efficacy of B-celltargeted therapy with rituximab in patients with rheumatoid arthritis. *N Engl J Med* 2004;350:2572–81.

8. Cohen SB, Emery P, Greenwald MW et al.; REFLEX Trial Group. Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. *Arthritis Rheum* 2006;54:2793–806.
9. Emery P, Fleischmann R, Filipowicz-Sosnowska A et al.; DANCER Study Group. The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment: results of a phase IIB randomized, double-blind, placebo-controlled, doseranging trial. *Arthritis Rheum* 2006;54:1390–400.
10. EMA. MabThera. Eur. Med. Agency. 2018. <https://www.ema.europa.eu/en/medicines/human/EPAR/mabthera> (14 February 2023, date last accessed).
11. Smolen JS, Landewe´ RBM, Bergstra SA et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update. *Ann Rheum Dis* 2023;82:3–18.
12. Gottenberg JE, Ravaud P, Bardin T et al.; AutoImmunity and Rituximab registry and French Society of Rheumatology. 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.
13. Mariette X, Gottenberg JE, Ravaud P, Combe B. Registries in rheumatoid arthritis and autoimmune diseases: data from the French registries. *Rheumatology* 2011;50:222–9.
14. Van Spall HGC, Toren A, Kiss A, Fowler RA. Eligibility criteria of randomized controlled trials published in high-impact general medical journals: a systematic sampling review. *JAMA* 2007; 297:1233–40.
15. van Gestel AM, Anderson JJ, van Riel PL et al. ACR and EULAR improvement criteria have comparable validity in rheumatoid arthritis trials. *American College of Rheumatology European League of Associations for Rheumatology. J Rheumatol* 1999;26:705–11.
16. Lynd LD, O’Brien BJ. Advances in risk-benefit evaluation using probabilistic simulation methods: an application to the prophylaxis of deep vein thrombosis. *J Clin Epidemiol* 2004;57:795–803.
17. March JS, Klee BJ, Kremer CME. Treatment benefit and the risk of suicidality in multicenter, randomized, controlled trials of sertraline in children and adolescents. *J Child Adolesc Psychopharmacol* 2006;16:91–102.
18. Singh JA, Cameron C, Noorbaloochi S et al. Risk of serious infection in biological treatment of patients with rheumatoid arthritis: a systematic review and meta-analysis. *Lancet* 2015;386:258–65.
19. Shaffer ML, Watterberg KL. Joint distribution approaches to simultaneously quantifying benefit and risk. *BMC Med Res Methodol* 2006;6:48.

20. Rubin DB, Schenker N. Multiple imputation in health-care databases: an overview and some applications. *Stat Med* 1991;10:585–98.
21. White IR, Royston P. Imputing missing covariate values for the Cox model. *Stat Med* 2009;28:1982–98.
22. White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. *Stat. Med* 2011;30:377–99.
23. Brody H, Light DW. The inverse benefit law: how drug marketing undermines patient safety and public health. *Am J Public Health* 2011;101:399–404.
24. Sokka T, Pincus T. Most patients receiving routine care for rheumatoid arthritis in 2001 did not meet inclusion criteria for most recent clinical trials or American college of rheumatology criteria for remission. *J Rheumatol* 2002;29:2521–4.
25. Kingsley GH, Khoshaba B, Smith CM, Choy EH, Scott DL. Are clinical trials in rheumatoid arthritis generalizable to routine practice? A re-evaluation of trial entry criteria. *Rheumatology* 2005;44:629–32.
26. Cañameres I, Merino L, López J et al. Experience with the use of rituximab for the treatment of rheumatoid arthritis in a tertiary hospital in Spain: RITAR study. *J Clin Rheumatol Pract Rep Rheum Musculoskelet Dis* 2019;25:258–63.
27. Md Yusof MY, Vital EM, McElvenny DM et al. Predicting severe infection and effects of hypogammaglobulinemia during therapy with rituximab in rheumatic and musculoskeletal diseases. *Arthritis Rheumatol* 2019;71:1812–23.
28. Lacaille D, Guh DP, Abrahamowicz M, Anis AH, Esdaile JM. Use of nonbiologic disease-modifying antirheumatic drugs and risk of infection in patients with rheumatoid arthritis. *Arthritis Rheum* 2008;59:1074–81.
29. Verhoef LM, Broeder N, den Thurlings RM et al. Ultra-low doses of rituximab for continued treatment of rheumatoid arthritis (REDO study): a randomised controlled non-inferiority trial. *Lancet Rheumatol* 2019;1:e145–53.
30. Henry J, Gottenberg JE, Rouanet S et al.; Auto-Immunity and Rituximab investigators. Doses of rituximab for retreatment in rheumatoid arthritis: influence on maintenance and risk of serious infection. *Rheumatology (Oxf Engl)* 2018;57:538–47.