Registries in rheumatoid arthritis and autoimmune diseases: data from the French registries

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Abstract

Objectives. Clinical registries have shown their effectiveness in capturing the long-term benefit of drugs in routine care. In France, two types of registry have been established to analyse the safety and efficacy of biological agents.

Methods. The Research Axed on Tolerance of Biotherapies (RATIO) registry was designed to prospectively collect all cases of lymphoma and opportunistic infections occurring in patients receiving anti-TNF blockers for any indication. We also examined the results from nationwide prospective cohorts in order to investigate the safety and efficacy of rituximab (RTX), abatacept (ABA) and tocilizumab in RA and other autoimmune diseases.

Results. Analysis of the RATIO registry demonstrated an increased risk of Legionella pneumophila infection in patients receiving anti-TNF therapy, a higher risk of tuberculosis [odds ratio (OR) (95% CI): 13.3 (2.6, 69.0) and 17.1 (3.6, 80.6) for infliximab and adalimumab vs etanercept, respectively], opportunistic infections and incidence of lymphoma, with mAb than with soluble-receptor anti-TNF. The characteristics of RA patients in RTX and ABA registries showed that some patients did not receive previous TNF blockers [20% in autoimmunity and RTX (AIR) and 13% in Orencia and RA (ORA)] and one-third of them were treated without concomitant DMARDs. Patients receiving RTX showed an increased proportion of severe infections (5.0/100 patient-years). Lung and cardiac comorbidities, extra-articular involvement and low immunoglobulin G before RTX were predictive factors of severe infections. In addition, the AIR registry suggested the effectiveness of RTX in patients with SLE.

Conclusion. The establishment of biological registries in rheumatic diseases, in France, with their different methods, has already provided additional data to controlled trials, mainly on the risk of severe infections and lymphoma.

Key words: Registry, Rheumatoid arthritis, Systemic lupus erythematosus, TNF blocker, Rituximab, Abatacept.

Introduction

Biologics have been a major advance for many patients with RA and other inflammatory conditions in controlling disease symptoms and progression. In the past 10 years, eight biological drugs, including five TNF-α antagonists, have been approved for RA, whereas none has been approved for autoimmune systemic diseases such as SLE.

Randomized controlled trials (RCTs) provide balanced groups for analysis of conditions; they are mandatory to demonstrate the efficacy of new drugs and to identify an unacceptable safety profile. However, RCTs usually involve a small number of patients and selected populations, and therefore represent only a limited spectrum of patients in real life. In addition, the time of exposure to the drugs and controls is usually limited. Therefore, RCTs cannot answer important questions concerning safety or therapeutic strategy, and data from RCTs...
cannot easily be extrapolated to daily practice. For example, RCTs failed to identify the risk of tuberculosis (TB) in patients receiving TNF-α inhibitors.

Observational studies such as clinical registries have shown their effectiveness in accurately capturing the long-term benefit of drugs in routine care [1–6]. Although clinical registries also have some weaknesses, including lack of controls and randomization, and bias by indication, data from these registries provide additional and complementary information on the use of biologics in clinical practice [1–7]. Therefore, in France, registries were established to collect data on safety and efficacy of biologics in real life.

As compared with other European countries such as Sweden, UK, Germany or Spain [1–4], in France no specific registry was established at the beginning of anti-TNF use in 1999–2000. This absence could be due to a different epidemiology culture, but is mainly because no specific requirements came from the health authorities. In 2003, we had the first signals indicating the risk of TB and opportunistic infections with anti-TNF therapy and the question of a possible increased risk of lymphoma was raised. At that time, a multidisciplinary group of the French societies of rheumatology, gastroenterology, internal medicine, dermatology and infectious diseases, decided to create, with the help of the French drug agency [Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS)], the Research Axed on Tolerance of Biotherapies (RATIO) registry, a pharmacovigilance network to prospectively collect for 3 years all cases in France of rare severe complications in patients treated with anti-TNF whatever the indication [8]. Due to the implications of dealing with the whole French population receiving anti-TNF therapy, capturing and validating all severe adverse events was not possible. Thus, we decided to focus on several rare severe events for which an association with anti-TNF was suspected (i.e. TB, opportunistic infections and lymphomas), and chose not to extend this survey to all severe infections, cancers or other severe adverse events. Collecting data on these rare serious events in all patients receiving treatment within a country of 60 million inhabitants is the only way to have enough power to compare the incidence of the events with that of the general population and with different drug treatments. Therefore, this original methodology was complementary to that used for other European registries.

Regarding the other biologic therapies, classical nationwide prospective cohort studies such as the autoimmunity and RTX (AIR), Orencia and RA (ORA) and Registry roac-temra (REGATE) registries were designed by the French Society of Rheumatology (FSR) to investigate the long-term safety and efficacy of rituximab (RTX), abatacept (ABA) and tocilizumab (TCZ) in patients with RA and other autoimmune diseases. This article details the establishment of these registries and provides preliminary data in terms of their value for clinical practice.

## Patients and methods

### The RATIO registry

The RATIO registry was designed to prospectively collect data on all cases of opportunistic infections, including TB, and lymphomas, occurring from 1 February 2004 to 1 January 2007, in patients who were receiving anti-TNF therapy. The data on the cases were collected by clinicians from all concerned medical specialties and the AFSSAPS and its network of 31 regional pharmacovigilance centres. To enhance the exhaustiveness of the collection of cases, different sources were used. Data were collected on all cases reported to the 31 French pharmacovigilance regional centres and cases reported directly to the companies marketing anti-TNF therapies. In addition, physicians from all French hospital centres involved in prescribing TNF blockers (i.e. rheumatology, internal medicine, gastroenterology and dermatology specialties) and/or in the management of complications (i.e. infectious disease centres, intensive care units, chest medicine units, haematology and oncology) were required to report each newly diagnosed case. Physicians received a direct mail reminder four times a year and several communications at congresses or in specialized media to encourage them to report cases. All cases included in the RATIO registry were validated by an expert committee of three experts in the field who used a detailed standardized case report form and additional documents, if necessary. For each adverse event of interest, we conducted an incidence study and a case–control analysis.

### Incidence study

We estimated the annual incidence rate of each event of interest in patients receiving anti-TNF treatment, adjusted for age and sex, with the French population used as a reference. The numerator consisted in the validated cases from the RATIO registry. For the denominator, as described in detail elsewhere [9], we estimated the number of patient-years of receipt of anti-TNF agents in France during the 3-year period of the study (2004, 2005 and 2006) from different sources: the AFSSAPS; the three pharmaceutical firms Abbott, Schering-Plough and Wyeth; and the Régime Social des Indépendants (the French health insurance fund for self-employed workers). These different estimations were concordant, for a mean 57 711 patient-years of use of anti-TNF therapy in France during the 2004–06 study period: 18% receiving adalimumab, 51% etanercept and 31% infliximab.

### Case–control study

A case–control study was performed with validated RATIO cases of severe events showing a labelling indication for anti-TNF therapy and controls without any severe adverse events, but receiving anti-TNF therapy. Control cases were from a global pool of controls from centres involved in the RATIO registry. From that pool, we randomly selected cases for a database of controls reflecting the proportion of patients in France receiving each of the three anti-TNF drugs as indicated above, to be able to detect a difference between drugs for occurrence of these side effects.
effects. We identified the risk factors for opportunistic infections by both univariate and multivariate analysis (conditional logistic regression model).

The AIR, ORA and REGATE registries

The registries for ABA, RTX and TCZ were established by the FSR with a similar methodology as soon as the drugs were announced for use in France [10]. The AIR registry study (RTX) recruited 2000 patients with RA and 600 patients with other systemic autoimmune diseases from 2005 to 2009. The ORA registry study (ABA) recruited 1000 patients with RA from June 2008 to April 2010. The REGATE registry study (TCZ) started in 2010 and plans to include 1500 patients with RA. The recruitment in REGATE is ongoing and no results are presented here. The duration of the scheduled prospective follow-up in these three registries is 5 years. The limitations of these registries include the relatively short follow-up and the absence of comparison with patients receiving treatment with classical DMARDs or TNF blockers, because unfortunately, as explained above, no prospective registry of patients receiving DMARDs or anti-TNF therapy is available in France. FSR received financial support (unrestricted educational grant) from Roche and BMS, but these drug companies were not involved in the design, protocol, data collection or statistical analysis of these registries.

All French hospital and community-based rheumatology units (and internal medicine units for autoimmune systemic diseases) were invited to take part in the registry studies. To participate, clinicians had to send a signed form indicating their willingness to prospectively follow-up patients during 5 years. All consecutive eligible patients (patients receiving biologics for RA or systemic diseases according to ACR criteria) identified in the participating centres were recruited after having given their written informed consent to be in the study. The studies were approved by the French authorities [Comité Consultatif sur le Traitement de l’Information en matière de Recherche dans le domaine de la Santé (CCTIRS) and Commission Nationale de l’Informatique et des Libertés (CNIL)]. Data were collected at the time of the patient’s first exposure to the drug, then at 3 and 6 months and every 6 months, or at disease relapse by use of an e-case report form (e-CRF). Research study nurses were specifically trained in RA, biologics and the use of the e-CRF by the coordinators of the studies. Study nurses visited each centre regularly to update the clinical and biological data for the included patients. The number of missing data was minimized by providing the physician in charge of the patient and the study nurses with summaries of missing data for each patient in each centre. Data management was also performed and inconsistencies were noted.

Each registry was conducted under the supervision of two coordinators (X.M. and J.-E.G.) and one methodologist (P.R.). A scientific committee was in charge of the scientific strategy, including the validation of research projects to be developed from the registries.

Results

The RATIO registry

Four main results were obtained:

(i) Patients receiving anti-TNF therapy show an increased risk of Legionella pneumophila infection: the risk of *L. pneumophila* infection, considered as an opportunistic infection, with anti-TNF therapy was estimated to be between 16.5 and 21 relative to that in the French community. *Legionella pneumophila* pneumonia is a potentially severe complication of anti-TNF therapy and may occur early or late in the course of therapy [11]. In patients receiving anti-TNF who present pneumonia, legionellosis should be systematically considered, and macrolides or quinolones, efficient against *L. pneumophila*, should be part of the antibiotic treatment. Recently, we reported on a higher risk of *L. pneumophila* infection in patients receiving infliximab and adalimumab than those receiving etanercept [odds ratio (OR) (95% CI): 9 (2, 45) and 9 (12, 35), respectively] [12].

(ii) The risk of TB is higher with mAb than with soluble-receptor anti-TNF therapy [9]. The registry collected 69 cases of TB. None of the cases had received correct chemoprophylaxis treatment. Two-thirds of the patients with TB had normal tuberculin skin tests, which were available in 45 cases. The sex- and age-adjusted incidence of TB was 116.7/100,000 patient-years. Compared with the general population, the standardized incidence ratio (SIR) (95% CI) for TB was 12.2 (9.7, 15.5) and was higher for therapy with infliximab and adalimumab than for that with etanercept: 18.6 (13.4, 25.8) and 29.3 (20.2, 42.4) vs 1.8 (0.7, 4.3). In the case-control analysis, the exposure to infliximab or adalimumab vs etanercept was an independent risk factor for TB: ORs (95% CI) were 13.3 (2.6, 69.0) and 17.1 (3.6, 80.6), respectively. Other risk factors were age, the first year of anti-TNF treatment and being born in an endemic area.

(iii) The risk of other opportunistic infections is higher with infliximab and adalimumab [13]: the registry collected 38 cases of opportunistic infections. The ORs (95% CI) for infliximab and adalimumab vs etanercept were 10.0 (2.3, 44.4; P = 0.0002) and 17.6 (4.3, 72.9; P < 0.0001), respectively.

(iv) The incidence of lymphoma is higher with mAb than with soluble-receptor anti-TNF therapy: the registry collected 38 cases of lymphoma, 31 non-Hodgkin’s lymphoma and 7 Hodgkin’s or Hodgkin’s-like lymphoma [14]. EBV was detected in six cases. Compared with the general population, the SIR (95% CI) of lymphoma was 2.4 (1.7, 3.2). Patients receiving adalimumab or infliximab had a higher risk of lymphoma than those treated with etanercept: SIR (95% CI) 4.1 (2.3, 7.1) and 3.6 (2.3, 5.6) vs 0.9 (0.4, 1.8). Exposure to adalimumab or infliximab vs etanercept was an independent risk factor for
lymphoma in the case–control study: ORs (95% CI) 4.7 (1.3, 17.7) and 4.1 (1.4, 12.5), respectively.

The AIR registry

Patients with RA

Patient characteristics

At the time of the first analysis, 1681 patients (1690 patient-years) were included in 88 centres [10]. Of those, 712 patients were retreated with RTX (two cycles: 466; three cycles: 176; four cycles: 45; five or more cycles: 25). Thirteen per cent of patients had a history of cancer, 20.3% had experienced previous severe or recurrent infections, including 40 previous active TB infections and 11.8% had chronic cardiac or lung disease.

The mean (s.d.) disease duration was 15.5 (8.4) years. RF was positive in 78.5% of the patients. We found RA-related extra-articular involvement, including rheumatoid nodules, SS, scleritis, RA-related lung involvement and FS in 17.3% of patients. Before RTX treatment, patients had received 3.2 (1.4) classical DMARDs; 20.5% had not had any prior anti-TNF agent, 22.9% had received one anti-TNF agent, 33.2% had two and 23.4% had been given three anti-TNF agents before RTX. Of these patients, 11.9% had received anakinra and 3.9% had received ABA before RTX.

The mean (s.d.) baseline 28-joint DAS (DAS-28) was 5.7 (2.1). Most of the patients (80.1%) were still receiving oral CSs at the onset of RTX [mean (s.d.) dose: 10.1 (10.5) mg/day]. Two-thirds of the patients (66.4%) received RTX in combination with a non-biological DMARD and one-third received RTX monotherapy. Most patients (95.7%) during the first course received two infusions of 1 g of RTX at 2-week intervals and premedication with methylprednisolone (82.8%). At baseline, 5.3% of patients had low gammaglobulin levels (<6 g/l) and 4.6% had low immunoglobulin G (IgG) (<6 g/l) before RTX.

Severe infections

We observed 82 severe infections in 78 patients (5.0 severe infections per 100 patient-years) that required hospitalization and/or i.v. antibiotics and/or resulted in death, during the 12 months after any infusion of RTX (first or subsequent cycles) [10]. The infections resulted in four deaths. (Nine additional deaths were observed in the AIR registry: three cancers and nine cardiovascular diseases.) Bronchopulmonary, skin/soft tissue, urinary, digestive, osteo-articular, eyes–nose–throat and septicaemia represented 41.5, 15.9, 13.4, 13.4, 12.2, 2.4 and 1.2% of severe infections, respectively. We observed only one opportunistic infection (a fungal septic arthritis) and no TB re-activation. Fifty-six infections occurred after the first course, 22 after the second course, 3 after the third course and 1 after the fourth course. Following RTX infusions, 79% of the severe infections occurred in the first 6 months (50.6% before 3 months).

For 1303 patients, the follow-up duration was ≥3 months and these patients were included in the analysis of predictive factors for severe infections. Univariate analysis showed age, chronic lung disease and/or cardiac insufficiency, past or current smoking, diabetes, fewer previous anti-TNF, extra-articular involvement, previous severe infection, CSs and low gammaglobulin or IgG level before initiation of RTX associated with a risk of severe infection during the 12 months after any RTX infusion. Multivariate analysis showed chronic lung disease and/or cardiac insufficiency [OR (95% CI) 3.0 (1.3, 7.3); P = 0.01], RA-related extra-articular involvement [OR (95% CI) 2.9 (1.3, 6.7); P = 0.009] and IgG level <6 g/l before the initiation of RTX [OR (95% CI) 4.9 (1.6, 15.2); P = 0.005] significantly associated with an increased risk of severe infection during the 12 months after any RTX infusion (Table 1).

Patients with other autoimmune systemic diseases

Despite RTX not being approved for other autoimmune systemic diseases, 600 patients with diseases refractory to treatment were recruited. Patients mainly had SLE [15], SS, cryoglobulinaemia [16], myositis, unclassified arthritis or MCTD [17]. Preliminary data suggest good short-term efficacy and safety for these conditions.

Recently, we reported the tolerance and efficacy of RTX in 136 patients with SLE [15]. Mean baseline SLEDAI was 11.3 (8.3). Severe infections were noted in 12 (9%) patients, corresponding to a rate of 6.6/100 patient-years. Severe infections occurred mainly within the first 3 months after the last RTX infusion. Five patients died due to severe infection (n = 3) and refractory autoimmune disease (n = 2). Overall response (decrease in SLEDAI ≥ 3) was observed in 80 (71%) of the 113 patients. Articular, cutaneous, renal and haematological improvements were noted in 72, 70, 74 and 88% of patients, respectively. A CS-sparing effect was also observed [decrease from 30.3 (23.6) mg/day at enrolment to 12.3 (10.1) mg/day at 6 (3) months].

The ORA registry

A preliminary analysis of data for the first 682 included patients was recently published [18]. The mean (s.d.) age was 57.7 (13.9) years, median disease duration 12 years and number of prior DMARDs: 3.1 (1.9). Of the patients, 5.4% had a previous cancer and 35.4% had a history of severe infection before ABA. Thirteen per cent of the patients did not receive any anti-TNF therapy before ABA, 35% received monotherapy with ABA and 65% a concomitant DMARD. Mean follow-up was 8.0 months (353 patient-years). Severe events were 4 infusion reactions resulting in ABA discontinuation, 5 deaths (1 severe infection, 1 cancer and 3 cardiovascular diseases), 16 severe infections corresponding to 4.5 severe infections per 100 patient-years and 5 cancers (1.4/100 patient-years). ABA was discontinued in 25.5% of patients because of inefficacy (76%) or adverse events (24%).
Clinical registries have shown their effectiveness in accurately capturing the long-term benefit of drugs in routine care of RA and other autoimmune diseases. Here, we analysed data on severe events with anti-TNF therapy from two types of registry established in France to collect data on the safety and efficacy of biological agents in real life. Analysis of the RATIO registry data demonstrated a higher risk of TB and also other opportunistic infections, including *L. pneumophila*, and a higher risk of lymphoma in patients receiving mAb compared with soluble-receptor anti-TNF therapy. The high risk of TB for patients receiving monoclonal anti-TNF therapy was confirmed in the British Society for Rheumatology Biologics Registry (BSRBR), but with a smaller difference between the types of drug [19]. This difference could be due to the first patients included in 1999 in the BSRBR not being screened for latent TB. The 2- to 3-fold increased risk of lymphoma that we found in patients receiving anti-TNF therapy was similar to that expected for such patients with severe inflammatory diseases. However, some lymphomas associated with immunosuppression may occur, and the risk of lymphoma was higher with mAb than with soluble-receptor therapy. Actually, in inflammatory diseases, especially RA, anti-TNF agents may have opposite effects: a beneficial effect due to the decrease in disease activity and a deleterious effect due to immunomodulatory activity, which may not only concern EBV-associated lymphoma but also more classical lymphoma [20]; this immunomodulatory effect could differ according to the type of TNF blocker. However, the possible difference in incidence of lymphoma with different types of anti-TNF therapy found in RATIO must be confirmed by analysis of data from other registries.

This study contains some limitations. First, the denominator of the incidence rate and the distribution of estimates for the three anti-TNF therapies used for the

<table>
<thead>
<tr>
<th>Variables</th>
<th>Patients with severe infection (n = 78)</th>
<th>Patients without severe infection (n = 1,229)</th>
<th>P-value, univariate analysis</th>
<th>Significant P-values, multivariate analysis</th>
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</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>64.7 (10.9)</td>
<td>57.3 (12.7)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Gender: female, %</td>
<td>71.8</td>
<td>78.1</td>
<td>0.19</td>
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<td>Disease duration, years</td>
<td>17.2 [10.9] [1.3]</td>
<td>15.4 [9.3] [1.1]</td>
<td>0.08</td>
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<td>RA-related extra-articular involvement, %</td>
<td>28.6 [1.3]</td>
<td>16.6 [2.0]</td>
<td>0.007 0.01</td>
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</tr>
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<td>Follow-up, months</td>
<td>15.8 [9.9]</td>
<td>14.9 [9.1]</td>
<td>0.43</td>
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<td>Ever smoked, %</td>
<td>31.7 [19.2]</td>
<td>23.1 [17.8]</td>
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<td>Record of cancer, %</td>
<td>16.1 [20.5]</td>
<td>12.8 [18.0]</td>
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<td>Chronic lung disease and/or cardiac insufficiency, %</td>
<td>32.8 [17.9]</td>
<td>11.4 [17.2]</td>
<td>&lt;0.0001 0.009</td>
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<tr>
<td>Diabetes, %</td>
<td>15.9 [19.2]</td>
<td>9.8 [17.8]</td>
<td>0.12</td>
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<td>Previous severe infection</td>
<td>33.3 [19.2]</td>
<td>19.5 [19.2]</td>
<td>0.008</td>
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<td>Number of previous DMARDs</td>
<td>3.4 [1.4]</td>
<td>3.2 [1.4]</td>
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<td>Previous 0–3 anti-TNF, %</td>
<td>29.5/34.6/19.2/16.7 [0]</td>
<td>20.0/22.2/34.1/23.8 [0.2]</td>
<td>0.002</td>
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<td>Previous ABA, %</td>
<td>5.3 [3.8]</td>
<td>3.8 [2.4%]</td>
<td>0.53</td>
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<td>Previous anakinra, %</td>
<td>14.5 [2.6]</td>
<td>11.7 [1.8]</td>
<td>0.47</td>
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<td>RF positive, %</td>
<td>81.5 [16.7]</td>
<td>78.3 [14.0]</td>
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<td>Anti-CCP positive, %</td>
<td>76.9 [33.3]</td>
<td>76.9 [23.4]</td>
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<td>Initial DAS-28</td>
<td>5.7 [1.1]</td>
<td>5.7 [1.2]</td>
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<td>Concomitant DMARDsb, %</td>
<td>41.0</td>
<td>51.0</td>
<td>0.21</td>
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<tr>
<td>MTX alone</td>
<td>11.5</td>
<td>7.9</td>
<td></td>
<td></td>
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<tr>
<td>LEF alone</td>
<td>10.3</td>
<td>7.1</td>
<td></td>
<td></td>
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<tr>
<td>Other/combinations</td>
<td>37.2 [0]</td>
<td>34.0 [1.2]</td>
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<td>No concomitant DMARD</td>
<td>83.3 [0]</td>
<td>75.4 [1.3]</td>
<td>0.17</td>
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<td>Dosage in patients treated with CSs, mg/day</td>
<td>10.8 [12.4] [1.3]</td>
<td>7.7 [8.0] [2.9]</td>
<td>0.002</td>
<td></td>
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<tr>
<td>Low gammaglobulin level (&lt;6 g/l) before RTX, %</td>
<td>12.0 [35.9]</td>
<td>4.9 [36.4]</td>
<td>0.04</td>
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<tr>
<td>Low IgG level (&lt;6 g/l) before RTX, %</td>
<td>16.2 [52.6]</td>
<td>3.9 [51.3]</td>
<td>0.005 0.005</td>
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<tr>
<td>Low IgM level before RTX (at least one value &lt;0.5 g/l), %</td>
<td>10.8 [52.6]</td>
<td>6.2 [51.1]</td>
<td>0.29</td>
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<tr>
<td>Neutropenia (one value &lt;1000 neutrophils/mm³, before or after RTX)</td>
<td>1.5 [14.1]</td>
<td>1.0 [33.4]</td>
<td>0.51</td>
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<tr>
<td>Number of cycles</td>
<td>1.8 (1.0) [0.0]</td>
<td>1.8 (1.0) [0.0]</td>
<td>0.82</td>
<td></td>
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</table>

Results are mean (SD) unless otherwise specified. Missing values are given in percentages within square brackets. aWithin the year following the last infusion of RTX. bDefined as the dose on the day of the last infusion of RTX.

**Discussion**

Clinical registries have shown their effectiveness in accurately capturing the long-term benefit of drugs in routine care of RA and other autoimmune diseases. Here, we analysed data on severe events with anti-TNF therapy from two types of registry established in France to collect data on the safety and efficacy of biological agents in real life. Analysis of the RATIO registry data demonstrated a higher risk of TB and also other opportunistic infections, including *L. pneumophila*, and a higher risk of lymphoma in patients receiving mAb compared with soluble-receptor anti-TNF therapy. The high risk of TB for patients receiving monoclonal anti-TNF therapy was confirmed in the British Society for Rheumatology Biologics Registry (BSRBR), but with a smaller difference between the types of drug [19]. This difference could be due to the first patients included in 1999 in the BSRBR not being screened for latent TB. The 2- to 3-fold increased risk of lymphoma that we found in patients receiving anti-TNF therapy was similar to that expected for such patients with severe inflammatory diseases. However, some lymphomas associated with immunosuppression may occur, and the risk of lymphoma was higher with mAb than with soluble-receptor therapy. Actually, in inflammatory diseases, especially RA, anti-TNF agents may have opposite effects: a beneficial effect due to the decrease in disease activity and a deleterious effect due to immunomodulatory activity, which may not only concern EBV-associated lymphoma but also more classical lymphoma [20]; this immunomodulatory effect could differ according to the type of TNF blocker. However, the possible difference in incidence of lymphoma with different types of anti-TNF therapy found in RATIO must be confirmed by analysis of data from other registries.

This study contains some limitations. First, the denominator of the incidence rate and the distribution of estimates for the three anti-TNF therapies used for the
controls in the RATIO database were estimates only. However, each pharmaceutical company providing TNF-α blockers evaluated the number of patient-years during the same period for each anti-TNF agent; thus, the difference in risk between the agents we observed cannot be explained by different methodologies used for analysis of the different agents. Furthermore, the estimates from independent sources gave consistent adjusted-incidence rates. Secondly, despite the different strategies used to identify all cases in France, we cannot exclude that we missed some cases and that our incidence rate could be underestimated, although participation in this survey was encouraged by the AFSSAPS and the French scientific societies of rheumatology, gastroenterology, dermatology and infectious diseases. Moreover, the rate of potentially missing cases is unlikely to differ by anti-TNF agent used because the adverse events are severe and require hospitalization and are thus unlikely to be under-diagnosed in patients receiving s.c. anti-TNF agents as compared with the i.v. agent, and thus with an in-hospital follow-up. Moreover, there is no reason for a potential difference in reporting the incidence of events with the two s.c. anti-TNF agents. Thirdly, etanercept might have been chosen for patients with less severe disease potentially at low risk of opportunistic infections or lymphomas. However, patients receiving infliximab could have more severe disease, because infliximab was the only anti-TNF therapy available until 2002; etanercept was introduced 2 years before adalimumab. Moreover, the general characteristics of the inflammatory diseases for patients included in RATIO did not differ among those receiving the three drugs.

Some molecular mechanisms may explain the difference in risk of TB and lymphomas found in the RATIO database for patients receiving the three anti-TNF agents. Membrane TNF with anti-TNF mAbs has been shown to have higher avidity and better stability [21], which leads in some studies to more efficient apoptosis [22–25]. However, in other studies, infliximab and etanercept did not differ in inducing apoptosis in vivo [25]. The difference in reverse signalling due to a difference in membrane TNF targeting may have different functional consequences in cells expressing membrane TNF. Thus, monocytes and macrophages controlling granuloma and T cells controlling the emergence of B-cell clones in activated RA may be less impaired with the soluble receptor than those with mAbs. These different mechanisms of action could also explain a better efficacy of mAb therapy in Crohn’s disease, in other granulomatous diseases such as sarcoidosis [26] and in uveitis [27].

Preliminary reports from the AIR and ORA registries show that patients in real life have frequent comorbidities (e.g. history of cancer in 13% of patients receiving RTX and 5% of patients receiving ABA) and that RTX or ABA are prescribed in monotherapy in about one-third of the patients. RTX may also be prescribed as a first-line biological (20%), mainly for patients with a history of cancer. In daily practice, RTX and ABA seemed to be well tolerated by patients with RA. Analysis of the AIR registry data also confirmed that the rate of severe infections in RA patients receiving RTX is ~5.0/100 patient-years, which is in the range of the data reported from the most RCTs and with all biologics. Risk factors of severe infections in RA patients receiving RTX include cardiac and lung comorbidities, RA-related extra-articular involvement and low IgG level before RTX. This last result is important because evidence of low IgG level was lacking in ~5% of real-life patients with RA before RTX treatment (probably because of previous treatments) and because patients may exhibit low IgG level after repeated courses of RTX. Thus, IgG level must be monitored before each cycle of RTX and the benefit to risk ratio carefully monitored in the case of low IgG level.

For patients with SLE, RTX was well tolerated. The main side effect attributable to RTX was severe infection noted in 9% of the patients. This proportion in real-life patients was similar to that in the Exploratory Phase II/III SLE Evaluation of RTX (EXPLORER) study (9.5%) [28]. In addition, a short-term clinical efficacy of RTX was suggested. The main differences between the negative EXPLORER study results and the data from the AIR registry are that patients in the EXPLORER study all received concomitant treatment with immunosuppressors vs only 52% in the AIR registry and received a higher prednisone dosage (45.9 vs 29.9 mg/day in AIR) and could not taper steroids before 16 days. These contrasting results with recent RCT results leave open the question of the therapeutic interest of RTX in SLE. These data suggest reassessment of the role of RTX in non-renal, non-CNS lupus by a study design including initial low dosage and subsequent tapering of prednisone.

Conclusion

The strategies used in France for evaluating the effectiveness and safety of biologics in RA and rheumatic inflammatory diseases have strengths and weaknesses. For rare but severe events with anti-TNF therapy, the collection of cases from the whole population of the country receiving these drugs increased the study power to a level not achievable with analysis of classical registry data and allowed us to compare results for these events by the drug used. However, this strategy does not allow for study of other side effects or, efficacy and maintenance of anti-TNF therapy. Moreover, since we lacked a cohort of patients treated with classical DMARDs, we could not compare results for biologics and synthetic DMARDs. Classical registries dedicated to one drug (RTX, ABA, TCZ) have the advantage of the facility of follow-up for the clinician because the specific e-CRF is completed by experienced research nurses at the site where the patient is treated. The data collection allows for easily mobilizing the whole rheumatology community both in university hospitals and general hospitals and rapid inclusion of many patients in the study. However, the data from these registries must be compared for effectiveness and safety of these new biologics and the numerous patients who receive several biologics successively must be assessed.
Rheumatology key messages

- The RATIO registry evaluated the risk of lymphoma and opportunistic infections with TNF blockers.
- The risk of opportunistic infections, TB and lymphoma was higher with mAb anti-TNF.
- The AIR registry identified risk factors of serious infections in RA patients treated with RTX.

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