European Journal of Internal Medicine 67 (2019) 59–64

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Original Article

Rituximab-induced serum sickness is more frequent in autoimmune diseases as compared to hematological malignancies: A French nationwide study

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ARTICLE INFO

Keywords:
Rituximab
Serum sickness
Delayed reaction
Immune complexes
Adverse effect

ABSTRACT

Introduction: Rituximab induced serum sickness (RISS) is a rare delayed hypersensitivity reaction. The aim of this study was to describe the epidemiological and clinical characteristics of the RISS cases reported in France.
Method: Serum sickness cases involving rituximab were identified from the French PharmacoVigilance Database from 1998 to 2016.
Results: We analyzed 37 cases of RISS. Rituximab was prescribed for an autoimmune disease in 78% of cases. Serum sickness occurred mainly after the first injection (54%) with a median time to onset of 12 days. The most frequent manifestations were rheumatologic symptoms (92%), fever (87%), and skin lesions (78%). The incidence was significantly higher when rituximab was used for autoimmune diseases than for a hematological malignancies. Taking into account the existence of a Systemic Lupus Erythematosus (SLE) as the indication of rituximab or as a comorbidity, the incidence of RISS in patients with SLE was even higher.
Discussion: We report on the largest series of RISS studied to date and confirm that this reaction preferentially occurs in patients with autoimmune disease, especially SLE. This may be due to B-cell lysis, leading to the release of intracellular antigens into the serum and subsequent antigen-antibody complex formation, especially in patients with elevated autoantibody production. This could also explain why RISS often occurred after a single injection.
Conclusion: Patients generally recovered from RISS rapidly without obvious benefit from corticosteroid therapy. The risk of recurrence should prompt clinicians to question the use of rituximab after an episode of RISS.

1. Introduction

Rituximab is a murine-human chimeric monoclonal IgG1-kappa antibody that targets the CD20 cell surface molecule. Registered in France since 1998, rituximab is approved to treat non-Hodgkin's lymphoma, chronic lymphocytic leukemia, rheumatoid arthritis (RA), granulomatosis with polyangiitis, and microscopic polyangiitis. Rituximab is also used “off label” to treat other diseases, such as immune thrombocytopenic purpura (ITP) [1], Sjögren's syndrome (SS) [2], cryoglobulinemia [3], pemphigus [4], membranous nephropathy [5], and other refractory autoimmune diseases [6].

The most common side effects described with rituximab therapy are infusion-related reactions, such as fever, chills, and shivering, which occur frequently after the first infusion and are often related to cytokines release [7]. Apart from these immediate reactions, other serious adverse drug reactions (ADR) have been reported with rituximab, including neutropenia, thrombocytopenia, hypogammaglobulinemia, bacterial and viral infections, skin reactions, as well as pulmonary, neurological, and cardiac problems [8,9]. Serum sickness, a delayed immunological reaction, have also been reported [10].

Serum sickness is a type III hypersensitivity reaction which was first described in 1905 as a complication of horse serum given as antitoxin to treat diphtheria. Later, similar cases were reported after the injection of other equine-based antitoxins or antivenins, hormones from other

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https://doi.org/10.1016/j.ejim.2019.06.009
Received 13 November 2018; Received in revised form 13 May 2019; Accepted 14 June 2019
Available online 03 July 2019

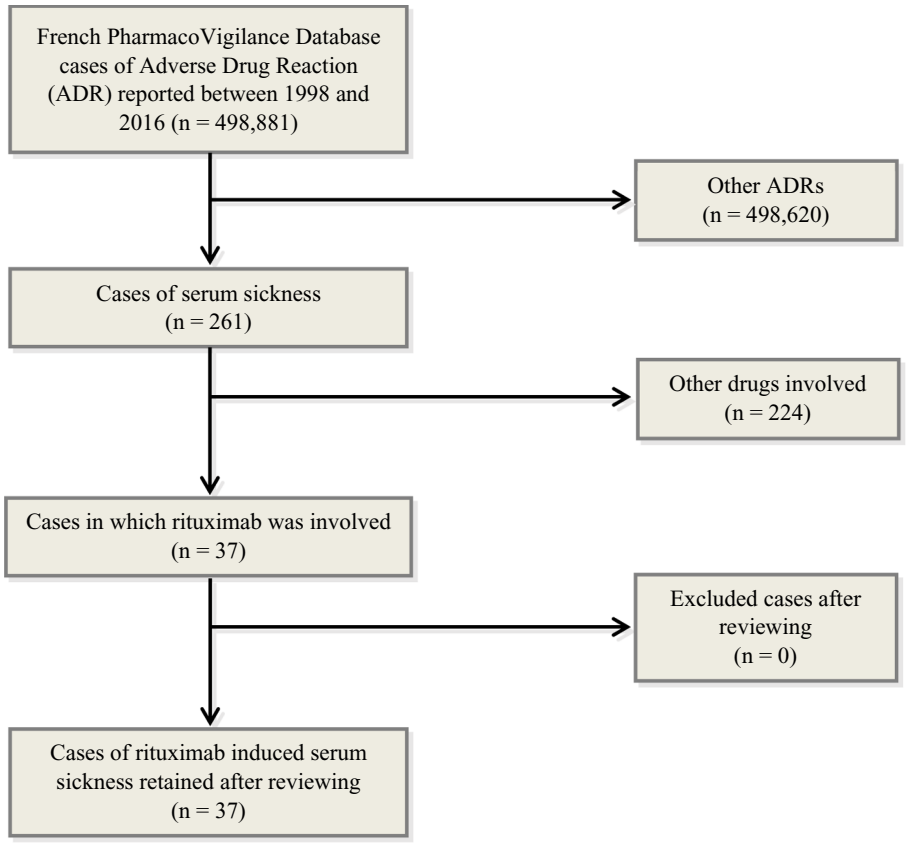

Fig. 1. Study flow chart.

species, streptokinase, vaccines, antibiotics, or monoclonal antibodies prepared from animal serum [11,12]. The frequency of serum sickness depends on the type of antigen exposure, and ranges from 0.007% for amoxicillin to 86% for horse antithymocyte globulin [12,13].

The first case of rituximab-induced serum sickness (RISS) was reported in 2001 in a patient treated for refractory autoimmune polyneuropathy [14]. More recently, a systematic review described 33 published cases [15] but in this study, there was no detailed assessment of the adverse reactions observed with rituximab. Thus, we conducted the present study to describe the epidemiological and clinical characteristics of RISS cases reported in France since the marketing of rituximab. More precisely, the first aim of the study was to determine the delay from rituximab infusion to RISS onset, clinical and biological features of RISS, and finally RISS outcome. The second aim of the present study was to compare both RISS characteristics and incidence according to the indication of rituximab for hematological malignancies *vs* autoimmune diseases. We analyzed all cases reported to the French Pharmacovigilance authorities since 1998.

2. Materials and method

Cases of serum sickness were identified from the French Pharmacovigilance Database (FPVD) which includes every spontaneous adverse drug reaction (ADR) reported to the 31 Regional French Pharmacovigilance Centers since 1985 [16]. Briefly, every health practitioner must report ADRs to their Regional Pharmacovigilance Centre according to French law regulations [17]. All suspected ADRs reported are analyzed with a data extraction form, validated, and then registered in the FPVD, which allows an evaluation of drug-related ADRs. For each case, the causal relationship between the ADR and the drugs is evaluated. Drugs involved in the ADR are classified as “suspect” or “concomitant” according to the World Health Organization (WHO) criteria [18]. Thus, ADRs are encoded according to the Medical Dictionary for Regulatory Activities (MedDRA) classification in the FPVD.

For the present study, we collected all cases of serum sickness, recorded from 1998 (year of rituximab's marketing) to November 2, 2016 in which rituximab was involved. Serum sickness was defined as PT (preferred term, MedDRA 11.0, Medical Dictionary for Regulatory Activities) “serum sickness”, or as PT “reaction serum sickness-like”. For each case, drugs associated with the serum sickness were classified as suspect (drug with the highest chronological and semiological score) or other (drug with the lowest chronological and semiological score) to retain only cases of serum sickness for which rituximab was solely involved. To confirm the diagnosis of RISS, all selected cases were reviewed by the investigators using the clinical and biological data included in the case description.

The following information was abstracted from the medical records: patient characteristics, including age, sex, and comorbidities, disease for which rituximab was prescribed, administered dose, associated treatment, time from rituximab infusion to RISS onset, and clinical and biological presentation and outcome.

The number of cases of RISS recorded between 2011 and 2015 was divided by the total number of doses of rituximab delivered to all French healthcare institutions during the same period to approximate the incidence of RISS according to the therapeutic indication of rituximab, for each indication (“hematological malignancy” and “autoimmune disease”). This period was chosen because it was the only period for which data was available about the number of doses of rituximab delivered. The number of doses administrated was obtained through the data of reimbursement of all biopharmaceuticals to hospitals from the French hospital discharge database, called “Programme de Médicalisation des Systèmes d'Information” (PMSI). Indeed, a standard discharge summary report is generated for each hospitalization, containing information about the primary diagnosis and treatments

Table 1
Indication for rituximab.

	Patients (%)
Hematological malignancy	8 (21.6%)
Follicular lymphoma	2 (25%)
Chronic lymphocytic leukemia	2 (25%)
Waldenström's macroglobulinemia	1 (12.5%)
Marginal zone cell lymphoma	1 (12.5%)
Mantle cell lymphoma	1 (12.5%)
EBV induced lymphoma	1 (12.5%)
Autoimmune disease	29 (78.4%)
Systemic lupus erythematosus	8 (27.6%)
Immunological thrombocytopenic purpura	6 (20.7%)
Cryoglobulinemia in Sjögren's syndrome	3 (10.3%)
Thrombotic thrombocytopenic purpura	2 (6.9%)
Rheumatoid arthritis	2 (6.9%)
Membranous nephropathy	2 (6.9%)
ANCA associated vasculitis	1 (3.4%)
Autoimmune hemolytic anemia	1 (3.4%)
Systemic juvenile idiopathic arthritis	1 (3.4%)
Paraneoplasic syndrome	1 (3.4%)
Pemphigus	1 (3.4%)
Interstitial lung disease	1 (3.4%)

delivered during hospitalization.

For statistical analysis, a chi-squared test was used to compare qualitative data. For each incidence, a 95% confidence interval was calculated.

3. Results

Of the 498,881 reported ADRs recorded in the FPVD between 1998 and November 2, 2016, 261 were coded as serum sickness according to our MeDdra research term. Among them, 37 involved rituximab and were included in this study (Fig. 1). In two cases, another concomitant medication was also suspected to have induced serum sickness with the same imputability score (cytarabine in one case and pneumococcal 23-polyvalent vaccine in the other).

Rituximab was prescribed for an autoimmune disease in 29 cases (78.4%) and a hematological malignancy in eight (21.6%). All indications are described in Table 1. Twenty-six patients (70%) were women and the median age was 38 years (IQR 29–53), but the sex ratio and median age were different between indications (Table 2). Fourteen patients (37.8%) had concomitant treatment with corticosteroids. Five of the eight patients (62.5%) treated for hematological malignancy had concomitant antineoplastic chemotherapy and four of 29 (13.8%) treated for autoimmune disease received at least one other immunosuppressive therapy along with rituximab and corticosteroids.

Serum sickness occurred after a median dose of 700 mg rituximab, following a single injection in most cases (54.1%), with a median time from infusion to RISS onset of 12 days.

The characteristics of the serum sickness and clinical and biological features are compared according to therapeutic indication in Table 3. The three most common clinical findings were rheumatologic symptoms, such as arthritis or arthro-myalgia in 34 patients (91.9%), fever in 32 (86.5%), and skin lesions, such as purpura, urticaria, or indeterminate erythema, in 29 (78.4%). Cutaneous manifestations were significantly more frequent in patients treated for autoimmune disease ($p = 0.0276$). When data were available, systemic inflammation was found in 92.3% of cases, complement consumption in 75%, proteinuria in 69.2%, and acute kidney injury in 46.7%.

Therapy for RISS included corticosteroids for 25 patients (68%). The median time to complete resolution, available for 21 patients, was 3.5 days (IQR 2–5.3). *Re*-challenge with rituximab was performed in 7 patients (18.9%), leading to the recurrence of the symptoms in one (14.3%). Six patients (16.2%) also had cytokine release syndrome during the rituximab infusion. Non-optimal efficacy of rituximab was reported in 8 cases (21.6%).

Table 2
Comparison of patient characteristics according to the indication of rituximab.

	Total	Hematological malignancy	Autoimmune disease
	N = 37	N = 8	N = 29
Characteristics of patients			
Female gender	26 (70%)	3 (37%)	23 (82%)
Age (median [IQR]) (years)	38 [29–53]	64 [52–69]	35 [29–46]
Comorbidity			
Other autoimmune disease (1)	11 (29.7%)	1 (12.5%)	10 (34.5%)
Polyclonal hypergammaglobulinemia	2 (5.4%)	1 (12.5%)	1 (3.4%)
Rheumatoid factor	1 (2.7%)	0	1 (3.4%)
Hepatitis C virus infection	1 (2.7%)	0	1 (3.4%)
Concomitant treatment			
Hydroxychloroquine	6 (16.2%)	0	6 (20.7%)
Corticosteroids	14 (37.8%)	1 (12.5%)	13 (44.8%)
Antineoplasic (2)	6 (16.2%)	5 (62.5%)	1 (3.4%)
Immunosuppressive (3)	4 (10.8%)	0	4 (13.8%)

(1) Associated dysimmune comorbidity which was not the indication of rituximab: Immunological thrombocytopenic purpura, myasthenia, antiphospholipid syndrome, pericarditis and 3 cases of systemic lupus erythematosus
(2) Chlorambucil, etoposide, lenalidomide, aracytine, bendamustine or carboplatin.
(3) Azathioprine, mycophenolate mofetil, tacrolimus or leflunomide.
IQR: interquartile range

The reporting of RISS was significantly higher ($p < 0.5$) for patients treated for autoimmune disease or systemic lupus erythematosus (SLE) than those treated for hematological malignancy (Table 4). Moreover, taking into account the existence of a SLE as the indication of rituximab or as a comorbidity (n = 5 patients), the incidence of RISS in patients with SLE was even higher (121.4 [39.4; 283.1]/10^5 doses).

4. Discussion

The present study reports 37 cases of well-documented RISS reported in France between 1998 and 2016, which is to our knowledge the largest series of RISS published so far. The most striking result for this series is that RISS occurred much more frequently (12-fold) when rituximab was prescribed to treat an autoimmune disease than a hematological malignancy. Although rituximab is not an approved treatment for patients with SLE, this pathology was the more representative autoimmune disorder in our study and furthermore seemed to be at higher risk for developing RISS (20-fold) than other autoimmune diseases.

In 2015, a systematic review identified 33 cases of RISS from 25 articles [15]. The patients were mostly women (77%) and the mean age of presentation was 39 years, probably because most of the cases were associated with an auto immune condition (85%), which is similar to our series. The actual prevalence of RISS is unknown but may be approximately 10% in autoimmune disorders. Indeed, in the five trials of rituximab to treat Sjogren's syndrome, six of the 61 patients (9.8%) developed RISS [6,19–22]. In trials of rituximab for pediatric immune cytopenia, the prevalence ranged from 6% to 12.5% [1,23], and a prospective study reported 9.1% frequency of RISS in patients with hepatitis C virus-induced cryoglobulinemic vasculitis [24]. Patients with some autoimmune diseases may be at higher risk of RISS than others. Although systemic lupus erythematosus (SLE) is not a first-line indication for rituximab [25], 11 of the 28 patients (39%) treated for autoimmune disease had SLE, which is the most highly represented disease in our series. The predisposition of patients with SLE to develop serum sickness following rituximab therapy requires further investigation.

Reporting RISS more commonly in auto immune diseases than in

Table 3
Comparison of the characteristics of serum sickness (occurrence, clinical and biological features) according to the indication of rituximab.

	Total	Hematological malignancy	Autoimmune disease
	N = 37	N = 8	N = 29
Characteristics of serum sickness occurrence			
Time after beginning of rituximab (median [IQR]) (days)	12 [8–15]	22 [17–29]	9 [8–12]
Rituximab dose before SS (median [IQR]) (mg)	700 [643–1000]	692 [680–758]	706 [634–1000]
"1 g on days 1 and 15" dosing regimen	10 (27%)	0	10 (34.5%)
Number of infusions before SS (median [IQR])	1 [1–2]	2 [2–3]	1 [1–2]
SS after a single infusion	20 (54.1%)	1 (12.5%)	19 (65.5%)
SS after 2 infusions	10 (27%)	4 (50%)	6 (20.7%)
SS after 3 infusions or more	7 (18.9%)	3 (37.5%)	4 (13.8%)
Time after last infusion (median [IQR]) (days)	6 [4–8]	5 [2.5–6.3]	7 [4–8]
Onset if after the first infusion	8 [7.8–12]	12	8 [7.5–10.5]
Onset if after the 2nd infusion	2.5 [1–4.5]	3.5 [1–6.3]	2.5 [1.3–3]
Onset if after the 3rd infusion or more	4 [3.5–5.5]	4 [3.5–5]	4.5 [3.5–5.5]
Rechallenge with rituximab	7 (18.9%)	2 (25%)	5 (17.2%)
Recurrence after re-challenge	1 (14.3%)	0	1 (20%)
Clinical characteristics			
Fever	32 (86.5%)	8 (100%)	24 (82.8%)
Polyarthralgia or arthritis	34 (91.9%)	7 (87.5%)	27 (93.1%)
Cutaneous manifestations	29 (78.4%)	4 (50%)	25 (86.2%)
Odynophagia, cheilitis, or conjunctivis	7 (18.9%)	1 (12.5%)	6 (20.7%)
Digestive disorders	7 (18.9%)	0	7 (24.1%)
Hypotension	6 (16.2%)	3 (37.5%)	3 (10.3%)
Adenopathy	3 (8.1%)	1 (12.5%)	2 (6.9%)
Biological characteristics			
Inflammatory syndrome	24/26 (92.3%)	6/6 (100%)	18/20 (90%)
Complement consumption	12/16 (75%)	4/4 (100%)	8/12 (66.7%)
Proteinuria	9/13 (69.2%)	3/4 (75%)	6/9 (66.7%)
Thrombocytopenia	8/31 (25.8%)	4/8 (50%)	4/23 (17.4%)
Treatment of serum sickness			
Corticosteroids	25 (68%)	4 (50%)	21 (72%)
Time to healing (median [IQR]) (days)	3.5 [2–5.3]	5 [3.8–6.3]	3 [2–4.3]
With corticosteroids	4 [3.5–5.3]	5 [4.5–5.5]	4 [2.5–4.8]
Without corticosteroids	3 [2–3.8]	5 [4–6]	2.5 [2–3]

Table 4
Estimation of the French incidence of reported cases of RISS according to the indication of rituximab.

	Number of RISS reported (2011–2015)	Number of doses of rituximab reimbursed (2011–2015)	Incidence of RISS /10^5 doses [95% CI] (2011–2015)
Hematological malignancy	5	945,335	0,5 [0,2; 1,2]
Autoimmune diseases[a]	16	248,719	6.4 [3.7; 10.4]
Systemic lupus erythematosus	2	4118	48.6 [5.9; 175.3]

CI: confidence interval.
[a] other than SLE.

hematological malignancies suggests that the B-cell lysis induced by rituximab may lead to serum delivery of intracellular antigens and subsequent antigen-antibody complex formation and precipitation, especially in patients with autoimmune disorders. Indeed, these patients are characterized by elevated autoantibody production and reduced clearance of immune complexes. Rheumatoid factor and hypergammaglobulinemia have even been proposed as risk factors [24,26,27]. Our results support a mechanism of cytokine release syndrome as another possible risk factor [15], but only a small amount of hypergammaglobulinemia or rheumatoid factor was reported in our study.

The pathophysiological hypothesis mentioned above could also explain cases of RISS in the absence of previous rituximab administration, which is not generally the case for serum sickness. This is the second important result of our study. In our series, RISS following a single infusion accounted for 65.5% of patients with autoimmune disease. In the systematic review of 2015 [15], 37% of RISS cases occurred after the first dose of rituximab as well. Thus, the absence of previous administration of rituximab should not exclude the diagnosis of serum sickness when suggestive symptoms occur.

In some cases of RISS, human anti-chimeric antibodies (HACA) directed against the murine component of rituximab has been detected [14,28]. Other studies reported the presence of HACA in pretreated patients [29], which could provide another explanation for the cases of RISS that occurred after the first infusion of rituximab [15]. Altered immune responses to foreign antigens may predispose patients with autoimmunity to develop HACA, but the true origin of these antibodies remains uncertain. Indeed, only 1% of the patients in first phase II trials developed antibodies to rituximab, and none developed serum sickness [30]. Moreover, HACA may have been undetectable in patients diagnosed with RISS because of the limits of the detection methods [14] or because the excessive amounts of rituximab completely consumed the HACA [15,27]. For example, in the systematic review of Karmacharya [15], HACA was present in only 6 of 11 cases. Finally, some studies have shown that patients who develop HACA do not always present RISS in SLE [31] or in rheumatoid arthritis (RA) [32]. Thus, the presence or absence of HACA has not been found to be consistent with the development of RISS and there are no commercially available assays to measure it in clinical practice, making it difficult to adequately address this issue.

The third possibility to explain why rituximab causes serum sickness more frequently in patients treated for autoimmune conditions is that

concurrent polychemotherapy used for hematological malignancies may be protective [33–35]. In our study, nearly 38% of patients with RISS in the context of hematological malignancy did not receive concomitant antineoplastic chemotherapy. Conversely, only 14% of patients with autoimmune disease had another immunosuppressive treatment (except corticosteroids). It is thus possible that the association of another immunosuppressive treatment (except corticosteroids), whether antineoplastic or not, reduces the risk of RISS. The effect could also vary from one molecule to another. For example, none of our 37 patients received cyclophosphamide, a treatment that is widely used to treat both lymphomas and autoimmune diseases. If corticosteroid therapy provides a protective effect, such an effect is minimal as most patients with RISS were taking corticosteroids at the time of rituximab administration, both in our series and in the systematic review of Karmacharya [15].

There may be a dose-dependent effect in RISS. Indeed, in one study, 10% of patients who received 10 mL tetanus antitoxin developed serum sickness, whereas the administration of 80 mL produced the disease in almost all patients [36]. A dose-dependent effect concerning rituximab remains uncertain. In onco-hematology, rituximab is administrated at a dose of 375 mg/m^2 per injection, and in rheumatology, it is historically prescribed at a dose of one gram per injection, hence slightly more than in onco-hematology. However, most autoimmune diseases are treated with a dose of 375 mg/m^2, except for RA. Among our patients, 34.5% treated for an autoimmune disease received 1 g rituximab, whereas only 5% were treated for RA. It is possible that this dose was over-represented among our patients, which would support the hypothesis of a dose-dependent effect.

Serum sickness usually resolves within days and can be managed with anti-histamine or corticosteroid treatment [33], but occasional reports showed substantial mortality resulting from progressive glomerulonephritis or severe neurological complications [11]. No RISS led to death in our study, but 14% of our patients experienced hemodynamic failure. Corticosteroid therapy did not seem to accelerate recovery, perhaps because some cases quickly resolved spontaneously. Some authors have suggested the use of plasmapheresis in cases with severe manifestations [37], but the benefits of any treatment are difficult to assess without a placebo arm, especially because the natural history of serum sickness is to resolve spontaneously. A desensitization protocol has also been proposed [38] and authors even reported cases without recurrence after the second infusion of rituximab [15,34]. In our study, there was a single recurrence in seven re-challenges (14.3%). However, recurrence is certainly more frequent, because retrospective analysis of clinical data finds a probable history of RISS in > 14% of the patients. This testifies to the difficulty of diagnosing RISS from the first episode. This was already noticed in a blinded review of potential cases of serum sickness in children after antibiotic exposure, which reported that 75% of cases were not correctly identified by the patient's physician [13].

Finally, the fact that the efficacy of rituximab was not optimal in almost a quarter of our patients may be explained by the incomplete administration of treatment and the information bias related to the mode of data collection, but also by the neutralization of rituximab within immune complexes. Indeed, studies have described a correlation between HACA and an incomplete clinical response to rituximab [39–42].

Certain limitations must be considered in interpreting our findings. First, our study was a retrospective study, which explains why some clinical or biological data were not always available from the medical records. Second, it is not possible to exclude that the number of rituximab induced serum sickness was overvalued. Indeed, rituximab was reported to be non-optimally effective in some patients and the complex syndrome occurring a few days after the infusion could have be an exacerbation of the autoimmune disease instead of serum sickness. However, clinicians are accustomed to these exacerbations and since all cases were obtained from spontaneous notification (not from a systematic registry), it is probable that this differential diagnose was excluded before they declared the case, especially when the evolution was quickly favorable. Third, the number of RISS could be underestimated. Indeed, this complication without pathognomonic sign and with fast healing is poorly known, and therefore probably underdiagnosed. In addition, under-notification is a general limitation of spontaneous reporting systems for all ADR, even though notification of severe ADR is mandatory in France. The absence of underreporting would have led to greater accuracy of the estimated incidence of RISS according to indication (with lower confidence interval widths). Nevertheless, even if the true incidence is higher, we estimate that this bias was probably similar for both major groups of indications (autoimmune diseases *vs* hematological malignancies), which makes the comparison between groups possible. Finally, the main objective of this study was to compare the characteristics of RISS according to therapeutic indication, which does not require that all cases be collected.

5. Conclusion

RISS is a delayed hypersensitivity reaction due to tissue deposition of immune complexes following the administration of rituximab. The present study included 37 cases of RISS, which is the largest series published so far. The clinical signs most frequently found were rheumatologic manifestations, fever, and, especially in case of autoimmune disease, skin lesions. RISS generally arised after the first or second rituximab infusion and resolved rapidly without any obvious benefit from corticosteroid therapy. In this study, RISS was at least 12 times more frequent when rituximab was used to treat an autoimmune disease than a hematological malignancy, confirming that this reaction preferentially occurs in cases of autoimmune conditions, especially during SLE (20-fold). Although rarely severe, the recurrence of RISS and its frequent association with other side effects should prompt clinicians to question the use of rituximab after an episode of serum sickness.

Funding

None.

Conflicts of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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