Safety and Efficacy of Rituximab in Systemic Sclerosis: A Systematic Review and Meta-analysis

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Research article

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Abstract

Background: Rituximab has been widely proposed to treat systemic sclerosis (SSc) by depletion of pathogenic B cells. Nonetheless, the clinical benefit of Rituximab in SSc remains contentious.

Objective: This meta-analysis was conducted to systematically evaluate the safety and efficacy profile of Rituximab in SSc patients.

Methods: We performed a systematic online query in PubMed, Cochrane, and Web of science. Available studies about the assessment of Rituximab in SSc patients were comprehensively reviewed and investigated.

Results: In total, 14 studies comprising 597 participants were enrolled in our analysis. Pooled results showed the durable improvement of mRSS for skin involvement (ΔmRSS: 7.00 at 6-month, 9.70 at 12-month, and 10.93 at 24-month), while FVC (ΔFVC: -0.69 at 6-month, -2.62 at 12-month, -0.67 at 24-month) and DLCO (ΔDLCO -2.39 at 6-month, -3.28 at 12-month, -0.79 at 24-month) for lung involvement remain stable in SSc patients after Rituximab treatment. And safety profile of Rituximab-related adverse events rate was 12% in the pooled result.

Conclusion: The pooled results of this meta-analysis indicated that Rituximab was well-tolerated, and it was able to generate improvement of cutaneous function and stabilization of pulmonary function in SSc patients.

Introduction

Systemic sclerosis (SSc), or scleroderma, is a chronic rheumatic disease with multiorgan fibrosis, autoimmunity, and vasculopathy [1]. Even the prevalence of SSc is not as common as other rheumatic diseases, this immune-mediated disease, particularly its diffuse form, has the worst mortality even with great medical treatment and palliative care [2]. In the course of diffuse SSc, fibrosis of the skin and internal organs can elicit various clinical signs and symptoms. And those clinical manifestations and other severe complications seriously affect the quality of life in SSc patients. Currently, no potent mediator or pathogenic pathway has been clearly demonstrated and emerged to guide therapeutic strategies in SSc. The first-line treatment for SSc contains glucocorticoid and other immunosuppressive agents [3]. Therapeutic options for treating SSc keep limited and most of the drugs tested so far have shown poor or modest results. More effective and less toxic therapy for SSc is necessary [1].

The etiopathogenesis of SSc is as complicated as other autoimmune disease and it has not been completely defined yet. Current explanation of etiology is mainly addressed in environmental factors, genetic predisposition, and other epigenetic disorders [4]. Various cells are involved in the pathogenesis of SSc. The most often explored cell subsets consist of fibroblasts, endothelial cells, B lymphocytes, and T lymphocytes [5]. In particular, recent evidence suggests that hyperactivated B cells can contribute to fibrosis in SSc via releasing cytokines, autoantibodies, and cell-cell connection [6]. The important

pathogenesis role of B cells in SSc urges clinicians to transfer them as a therapeutic target for the treatment. Lately, as a chimeric monoclonal antibody targeting CD20 of B cells, Rituximab has been widely studied in SSc treatment [7]. However, consensus has not been reached about the clinical efficacy and safety profile of Rituximab in SSc. And current conclusion drawn from open-labeled trials or single institute experience is not as solid as we expected. Small sample size due to disease rarity, lack of control arm, single-center experience, discrepancies in study designs and variable duration of follow-up can dramatically affect the consolidation [8].

To apply Rituximab as first-line treatment in SSc, it is of great priority to clearly demonstrate the clinical efficacy and safety of Rituximab in SSc. In this systematic review and meta-analysis, we mainly focus on the clinical efficacy of Rituximab on the improvement of cutaneous and pulmonary functions. What's more, available data about severe adverse events rates are also summarized to comprehensively evaluate the safety profile.

Materials And Methods

Literature search strategy

This meta-analysis was conducted according to the Preferred Reporting Item for Systematic Reviews and Meta-Analyses (PRISMA) statement. A systematic literature retrieval was executed in PubMed, Cochrane, and Web of science. The time endpoint of the online search was October 31, 2019. Privately and publicly funded clinical studies posted on ClinicalTrials.gov were also screened. Following search terms were applied to comprehensively seize the articles: 1) (Systemic Sclerosis) or (Sclerosis, Systemic) or (Systemic Scleroderma) or (Scleroderma) 2) (CD20 Antibody, Rituximab) or (Rituximab CD20 Antibody) or (Mabthera) or (IDEC-C2B8 Antibody) or (IDEC C2B8 Antibody) or (IDEC-C2B8) or (IDEC C2B8) or (GP2013) or (Rituxan). All references of included studies were conditionally screened, and on-topic articles were reviewed while off-topic articles were excluded.

Inclusion criteria

Eligible studies were: (1) All patients in conventional-therapy group and/or Rituximab-treated group are diagnosed as systemic sclerosis (limited and/or diffuse SSc) fulfilling the preliminary American College of Rheumatology classification criteria of the disease; (2) Primary outcome should include: change of mRSS for skin involvement, FVC and/or DLCO for lung involvement. Studies were excluded if they were: (1) Review, letter, or conference abstract; (2) Articles published without English version; (3) Duplicated or overlapping data. If several publications involved in the same trials were identified simultaneously, the newest version and most comprehensive data were included.

Data extraction and quality assessment

Data were extracted by two independent reviews (Rui Tang and Jiangfan Yu) from eligible studies. The following parameters were extracted from each manuscript and supplementary materials: first author's name, year of publication, SSc condition, Rituximab regimen, and primary and/or secondary clinical outcome, adverse events, Newcastle-Ottawa Scale was used to assess the quality of the included studies. Each study was scored according to the selection, comparability, and outcome. Any discrepancies were solved by mutual discussion among all authors.

Statistical analysis

Stata version14 (Stata Corporation; college station, Tx, USA) and Review Manager version5 (Revman the Cochrane Collaboration; Oxford, England) was applied to perform meta-analysis. Pooled clinical outcomes of mRSS for skin involvement, FVC and/or DLCO for lung involvement were presented to evaluate the clinical outcome in SSc patients after Rituximab treatment. Heterogenicity among studies was evaluated by the Chi-squared test and I^2. A fixed-effects model was applied when there was no significant heterogenicity (I^2<50% or p-value>0.05). Otherwise, the random-effects model was in use. Funnel plot was applied to precisely estimate the publication bias of the eligible studies.

Results

Literature search and study selection

The initial search strategy identified 399 records after systematic literature retrieval (PubMed 233, Cochrane 22, Web of Science 144). After removal of 39 duplicate, the rest articles were assessed by title and abstract screening. 334 irrelevant articles were excluded after review of title and abstract. The full text of remaining 26 articles were carefully screened and assessed. 12 pieces of literature were excluded due to the following reasons: reviews (10), Letter (1), and Conference abstract (1). Thus, 14 studies were eventually selected according to predefined inclusion and exclusion criteria. Details for online database search strategies were shown in Figure 1.

characteristics of included studies

The main characteristics of included studies were summarized in Table-1. 14 studies were included to conduct a final meta-analysis. All included studies were published online before October 31, 2019. Patients in Rituximab-treated group were diagnosed as SSc. 4 studies presented data in well-matched control groups with only conventional therapy. The Rituximab regimen and other related concomitant treatment in different studies were presented. 13 studies reported the cutaneous function improvement (mRSS) and 12 studies report the pulmonary function improvement (FVC and/or DLCO). In our assessment of study quality, 3 studies have the quality scores of 7 or higher, while others were less than 7.

Skin improvement

A total of 13 studies reported improvement of mRSS for skin involvement in the Rituximab-treated group, and 4 studies reported mRSS change in conventional-therapy group. The overall mean difference of mRSS in the conventional-therapy group was 3.84 (95%CI=2.08, 5.60) without any heterogenicity (p=0.32, I^2=14%). Overall mean difference of mRSS in Rituximab-treated group at different follow-up time were: 7.00 (95%CI= 4.20, 9.80) at 6-month, 9.70 (95%CI=9.70, 4.87, 14.52) at 12-month, and 10.93 (95%CI= 8.62, 13.23) in Figure 2. As we have shown in Table 2, after treatment of Rituximab, mRSS for skin involvement in SSc were significantly improved during the follow-up period comparing with conventional-therapy group (6-month: p=0.06, 12-month: p=0.03, 24-month: p<0.00001).

Lung function improvement

FVC and DLCO were applied to assess change of pulmonary function improvement in SSc. Regarding to FVC in Figure 3, the mean difference in the conventional-therapy group was -1.23 (95%CI= -3.71, 1.26) without any heterogenicity (p=0.68, I^2=0%), while the mean difference of FVC in the Rituximab-treated group at different follow-up time were: 6-month -0.69 (95%CI=-3.19, 1.82), 12-month -2.62 (95%CI= -7.07, 1.83), 24-month -0.67 (95%CI= -4.16, 2.82). After treatment of Rituximab, FVC did not change dramatically during the follow-up period (6-month: p=0.76, 12-month: p=0.59, 24-month: p=0.80) in Table 2. As for DLCO in Figure 4, the mean difference in the conventional therapy group was 1.16 (95%CI=-1.21, 3.54) without any heterogenicity (p=0.31, I^2=16%). The change of DLCO in the Rituximab-treated group were: 6-month -2.39 (95%CI=-4.56, -0.19), 12-month -3.28 (95%CI= -8.72, 2.16), 24-month -0.79 (95%CI= -4.29, 2.71). Compared with the conventional therapy group, the mean difference of DLCO were not significantly changed in the Rituximab-treated group (6-month: p=0.06, 12-month: p=0.14, 24-month: p=0.36).

Safety profile

The safety profile of Rituximab in SSc patients was also summarized and pooled data was presented in Figure 5. Pooled results confirmed that the overall mean rate for Rituximab-related severe adverse events rate was 12.1% (p=0.733, I^2=0%) throughout treatment, which was acceptable and controllable for oncologist and rheumatologist to manage in clinic.

Publication bias

The funnel plot was applied to evaluate whether the publication bias exists in our meta-analysis. The visual estimation of funnel plot showed clear symmetry for all subgroup analyses in panel B of figure 1, figure 2, and figure 3.

Discussion

In our study, we systematically reviewed the long-term clinical efficacy and safety profile of Rituximab treatment in SSc patients. The pooled results suggested that the clinical application of Rituximab could continuously decrease the mRSS and ameliorate skin fibrosis in SSc patients. However, the mean change of parameters for pulmonary involvement in Rituximab-treated groups, either in terms of FVC and DLCO, remained as stable as in conventional therapy groups. The safety profile of Rituximab was satisfactory in our SSc patients, only a few severe adverse events were related to Rituximab throughout the treatment.

As we described previously, the crucial pathogenic role of B cells makes it an attractive therapeutic target in rheumatic autoimmune disease. Even there is no clear evidence that can explain how hyperactivated B cells regulate manifestations in SSc, depletion of them can generate clinical benefit for fibrosis and tissue damage [9]. Plenty of surface markers can be targeted to deplete dysfunctional B cells. As a non-glycosylated phosphoprotein and surface-embedded molecular, CD20 is expressed on B cells throughout development and differentiation of naïve B cells to plasma cells [10]. The first neutralizing antibody of CD20, Rituximab, is originally humanized to treat refractory CD20 + B cell non-Hodgkin lymphoma and other B-cell malignancies [11]. Soon later, this CD20 specific monoclonal antibody is widely applied for autoimmune diseases, such as rheumatoid arthritis, ANCA-associated vasculitis and SSc [12]. Lots of clinical studies have been conducted to comprehensively evaluate the efficacy and safety of this therapeutic strategy in multiple involved tissues and organs. As for Rituximab in SSc, current primary outcome often assesses the cutaneous and pulmonary function due to their importance for clinical mortality [13]. Indisputably, the articular, cardiovascular, renal, and gastrointestinal organ involvements are of great effect on patients' clinical outcome [14]. And clinical application of therapeutic drugs should also rationally generate some improvements in those systems and organs [15]. Nevertheless, assessment of other internal organs has not been sufficiently represented except skin and lung, since specific valuable scales of other internal organs are lacking. In the future, more available scales and techniques will help us learn more about the clinical efficacy in other organs. What's more, the evaluation of histological parameters and other biological markers (BAFF, IL-6, et al) evaluation will be beneficial for rheumatologists to better understand whether and how RTX affects different pathogenic pathways implicated in SSc [16].

The pathogenic role of B cells in SSc has been highlighted for years and depletion of those hyperactivated B cells should be of benefit to stop, or completely reverse the progression of the disease [17]. However, the depletion rate, clinical feasibility, efficacy, and safety profile after B cell depletion in SSc remain controversial due to several limitations and a solid consensus has not been reached yet. For example, most of studies in this area are small noncontrolled group studies or series case reports currently, large scale randomized clinical trials are lacking. The improvement of any parameters in cutaneous or pulmonary functions during treatment is just institute experience but cannot reach any solid conclusion [18]. Furthermore, the variable rituximab regimen and follow-up time in different clinical centers might induce inconsistency of results. To confirm the long-term efficacy of rituximab and bypass the heterogenicity caused by variable of disease duration and severity, we choose the change of matching

parameters for skin/lung fibrosis from baseline to end of follow-up at different time-point in our final literature analysis and restrictively select the data about the diffuse form of SSc if possible.

The safety profile of RTX is one of the main concerns in studies assessing a new drug in chronic disease [19]. As one of the most important immune cells for the immune system, depletion of B cells might affect both innate and adaptive immunity and bring up some adverse events. In our study, all rituximab-related adverse events were presented. The most often occurred adverse events in Rituximab are mild infusion-related reactions and infectious complications [9]. The infusion-related reactions are often well-controlled by prophylaxis with corticosteroid, paracetamol and diphenhydramine HCl or similar agents. The most common severe cases were infectious disease, which can be commonly controlled with antibiotic therapy and hospitalization [20]. Lately, next generation of CD20 monoclonal antibodies, such as Ofatumumab, Obinutuzumab, and Ocrelizumab, have been developed for B cell malignancies and some rheumatic autoimmune diseases [21–23]. Those novel monoclonal antibodies will be applied in SSc soon or later. More available monoclonal antibody might generate better clinical outcomes and lower the rate of severe adverse events.

Although the clinical application of rituximab can benefit the patients on cutaneous function according to current studies and our results, the modest effect on pulmonary function and complicated pathogenesis makes the treatment of SSc cannot be a monotherapy [24]. Single depletion of B cells by sequential Rituximab is insufficient to completely cure this disease. We cannot discard the clinical benefit of conventional or other innovative therapy, such as Cyclophosphamide (CYC) [25], mycophenolate mofetil (MMF) [26], et al. In the future, it still deserves more trails to demonstrate how to apply Rituximab in combination therapy and modify the combined regimen to better control the SSc-associated interstitial lung disease (ILD) [27]. For instance, the most recent data shows that patients treated concomitantly with mycophenolate mofetil had a trend for a better outcome both in skin/lung fibrosis as compared with patients receiving RTX alone [8].

We have well-demonstrated the clinical efficacy, particularly for skin fibrosis, and safety of Rituximab in SSc. Whereas our study still has some limitations that should be concerned. Firstly, even improvement of skin involvement is significant in Rituximab-treated patients, the heterogenicity exits during follow-up period. Clinical outcome for skin involvement is variable among current studies, which means more insight should be drawn to reach a more consistent consensus [28]. Secondly, exposure to prior immune-based therapy and other therapeutic agents might dramatically affect the outcome of Rituximab treatment [29]. For example, some case reports present that Rituximab can generate better efficacy for conventional steroid and immunosuppressive resistant SSc-ILD [30]. And concomitant treatment with potentially disease-modifying antirheumatic drugs (DMARDs) during Rituximab application might contribute to outcomes in those studies. Finally, current data of parameters in conventional-therapy group are insufficient. Unlike the Rituximab-treated group, it is not doable to generate pooled-data during follow-up (6-month, 12-month, and 24-month) in conventional-therapy group [7,8,18,20]. The mean changes of all parameters have been compared with data at the end of follow-up in conventional-therapy group.

Conclusion should be more convincible if parameters are compared at the same follow-up time between groups.

Conclusion

Rituximab represents to be a valid therapeutic option for treatment of SSc. Sequential Rituximab application can dramatically benefit the improvement of cutaneous function and stabilization of pulmonary function. Treatment with Rituximab appeared to be safe and well-tolerated among patients with SSc. However, demonstration of its efficacy in larger randomized control trials is still essential. Our preliminary results of the literature review suggest that more large scale, multicenter clinical trials are warranted to further confirm the clinical benefit of Rituximab in SSc patients.

List Of Abbreviations

lSSc, limited systemic sclerosis; dSSc, diffuse systemic sclerosis; FVC, forced vital capacity; DLCO, diffusing capacity for carbon monoxide; DMARDs, disease modifying anti-rheumatic drugs; NOS, Newcastle-Ottawa scale.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Competing interests

Authors declare that they have no competing interests.

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Authors' contributions

All authors participated in the study design; RT and JY participated in literature retrieval; YS, PZ, ZZ, and YW participated in data acquisition and analysis; ML and RX participated in manuscript preparation and revision.

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Tables

Table 1. Main characteristics of included studies.

Author and years	SSc condition	Rituximab regimen	Clinical outcome for skin/lung involvement	NOS Score
Lafyatis R et al. 2009	dSSc	2 doses of 1000mg Rituximab at week 0 and week 2	mRSS, FVC and DLCO	3
Bosello S et al. 2010	dSSc	2 doses of 1000mg Rituximab (with 100mg methylpresnisolone) at week 0 and week 2	mRSS	3
Daoussis D et al. 2010	SSc	4 weekly Rituximab infusions (375mg/m^2) at baseline and at 6-month	mRSS, FVC and DLCO	8
Smith V et al. 2012	dSSc	2 doses of 1000mg Rituximab (with 100mg methylpresnisolone) at week 0, week 2, week 26, and week 28	mRSS, FVC, and DLCO	4
Bosello S et al. 2015	dSSc	2 doses of 1000mg Rituximab (with 100mg methylpresnisolone) at week 0 and week 2	mRSS, FVC, and DLCO	3
Giuggioli D et al. 2015	dSSc	one or more cycles (1-5 cycles) of Rituximab (4 weekly infusions of 375 mg/m^2 for each cycle)	mRSS	3
Jordan S et al. 2014	lSSc and dSSc	2 doses of 1000mg Rituximab at week 0 and week 2 in 75% patients (49% with 100mg methylprednisolone; 65% with DMARDs)	mRSS, FVC, and DLCO	5
Lepri G et al. 2016	lSSc and dSSc	2 doses of 1000mg Rituximab (65.21% with DMARDs) at week 0 and week 2	FVC and DLCO	3
Vilela VS et al. 2016	dSSc	2 doses of 1000mg Rituximab at week 0 and week 2	mRSS and FVC	3
Daoussis D et al. 2017	lSSc and dSSc	two or more cycles (2-5 cycles) of Rituximab (4 weekly infusions of 375 mg/m^2 for each cycle)	mRSS, FVC and DLCO.	8
Sari A et al. 2017	lSSc and dSSc	one or more cycles (1-5 cycles) of Rituximab (2 infusions of 1000mg or 500 mg biweekly for each cycle)	mRSS and FVC	3
Melsens K et al. 2018	dSSc	2 doses of 1000mg Rituximab (with 100mg methylpresnisolone) at week 0, week 2, week 26, and week 28	mRSS, FVC, and DLCO	5
Thiebaut M et al. 2018	dSSc	one or two cycles of Rituximab (2 weekly infusion of 1000mg or 375mg/m^2 for each cycle) at baseline and at 6-month	mRSS, FVC and DLCO.	7
Elhai M et al. 2019	lSSc and dSSc	a dose of 1000 mg for 203 patients, 500 mg for 27 patients. 375 mg/m^2 for 4 patients at week 0 and week 2	mRSS, FVC and DLCO.	8

lSSc, limited systemic sclerosis. dSSc, diffuse systemic sclerosis. DMARDs, Disease Modifying Anti-Rheumatic Drugs. mRSS, modified Rodnan Skin Score. FVC, Forced Vital Capacity. DLCO, Diffusing Capacity for Carbon Monoxide. NOS, Newcastle-Ottawa Scale.

Table 2. Comparison of △mRSS, △FVC, and △DLCO at different follow-up times (6-month, 12-month, and 24-month) with parameters at the end of follow-up in conventional-therapy group during follow-up period.

Variable	The end of follow-up after conventional therapy	6-month after Rituximab treatment	12-month after Rituximab treatment	24-month after Rituximab treatment
△mRSS [mean, 95%CI]	3.84 [2.08, 5.60]	7.00 [4.20, 9.80] (p=0.06)	9.70 [4.87, 14.52] (p=0.03)	10.93 [8.62, 13.23] (p<0.00001)
△FVC [mean, 95%CI]	-1.23 [-3.71, 1.26]	-0.69[-3.19,1.82] (p=0.76)	-2.62[-7.07, 1.83] (p=0.59)	-0.67[-4.16,2.82] (p=0.80)
△DLCO [mean, 95%CI]	1.16 [-1.21, 3.54]	-2.39[-4.59, -0.19] (p=0.06)	-3.28[-8.72.2.16] (p=0.14)	-0.79[-4.29,2.71] (p=0.36)

Figures

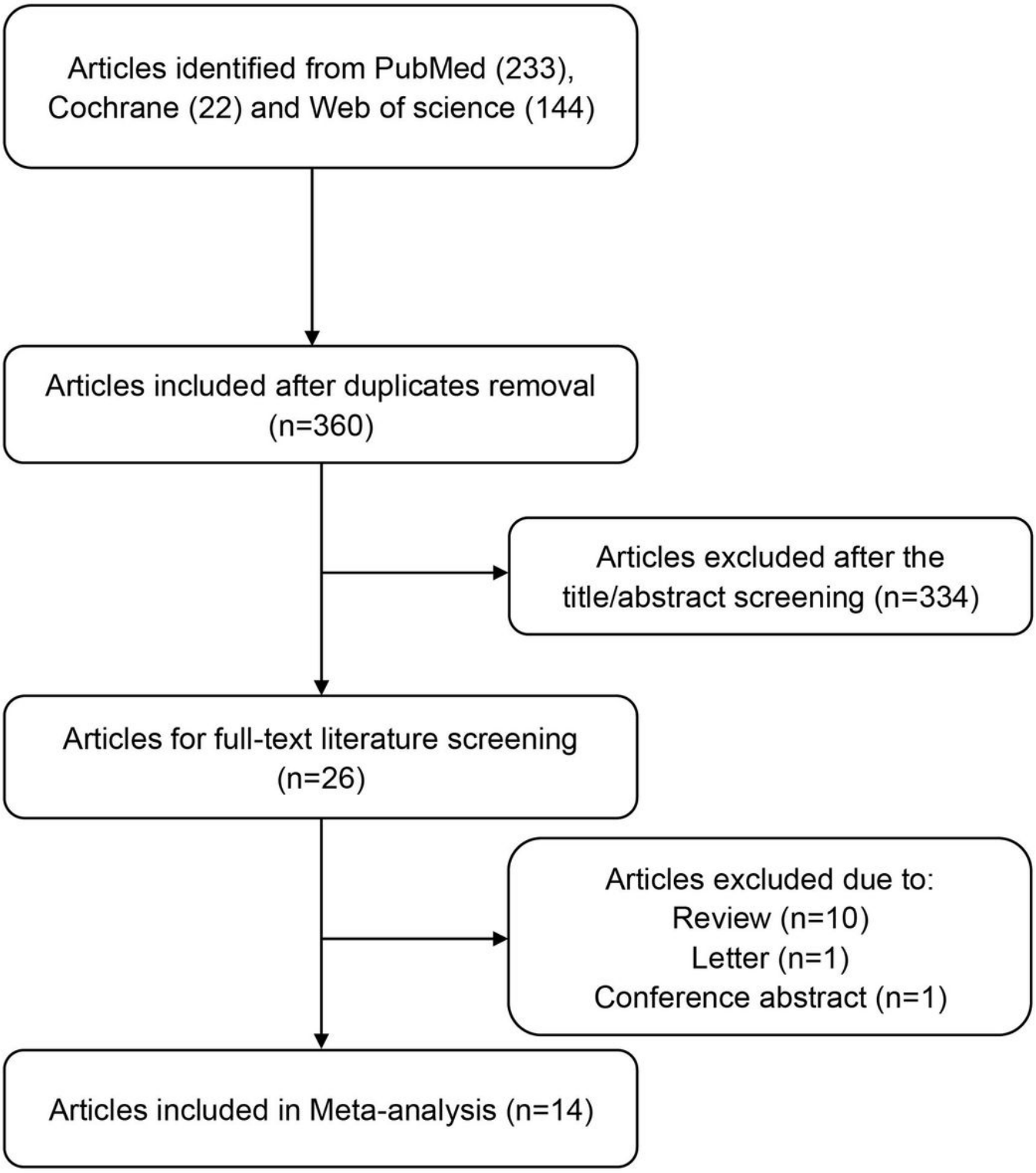

Figure 1

Details for online database search strategies

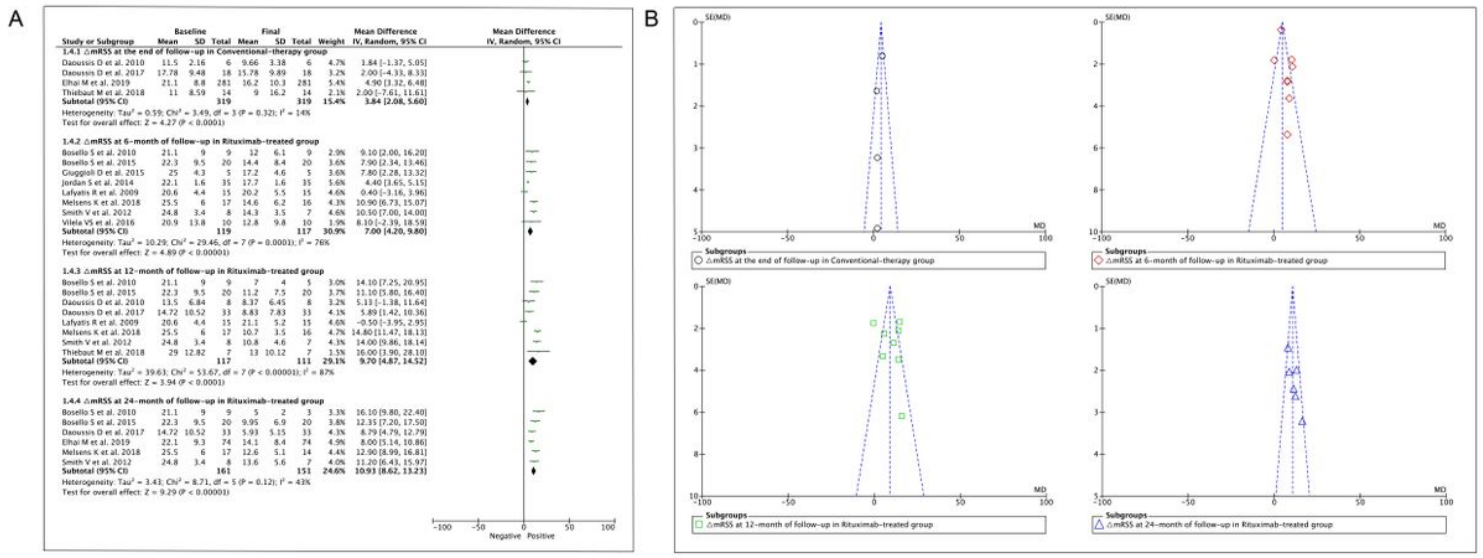

Figure 2

Rituximab-treated group at different follow-up time were: 7.00 (95%CI= 4.20, 9.80) at 6-month, 9.70 (95%CI=9.70, 4.87, 14.52) at 12-month, and 10.93 (95%CI= 8.62, 13.23)

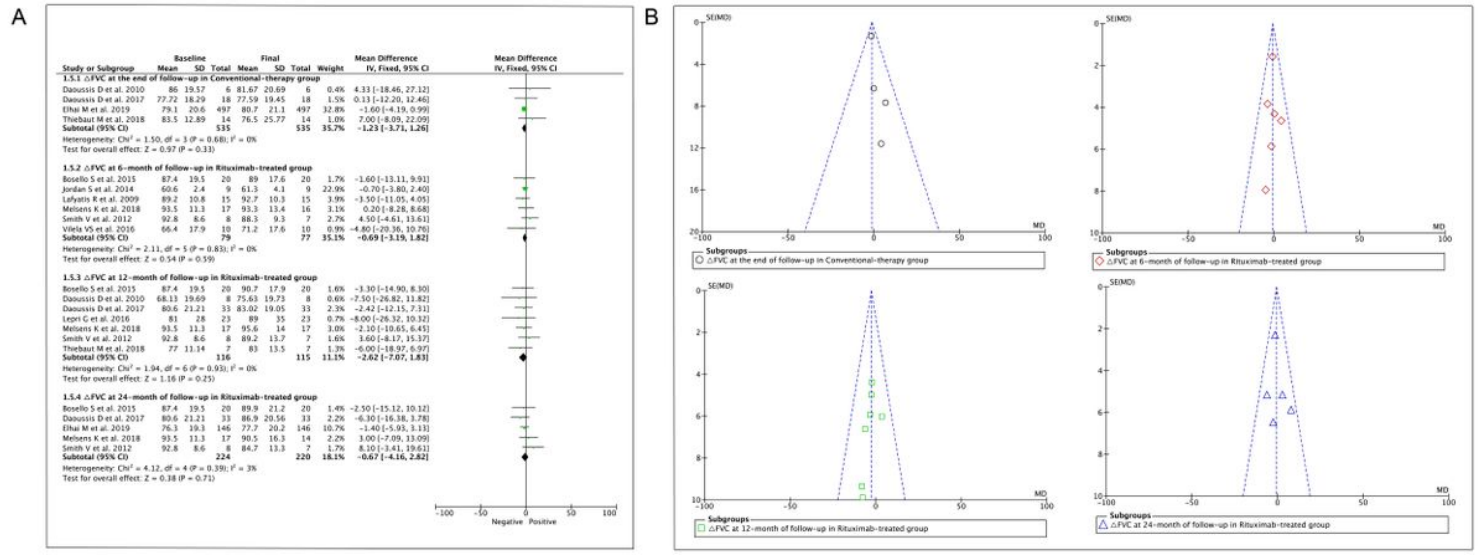

Figure 3

The mean difference in the conventional-therapy group was -1.23 (95%CI= -3.71, 1.26) without any heterogenicity (p=0.68, I2=0%), while the mean difference of FVC in the Rituximab-treated group at different follow-up time were: 6-month -0.69 (95%CI=-3.19, 1.82), 12-month -2.62 (95%CI= -7.07, 1.83), 24-month -0.67 (95%CI= -4.16, 2.82)

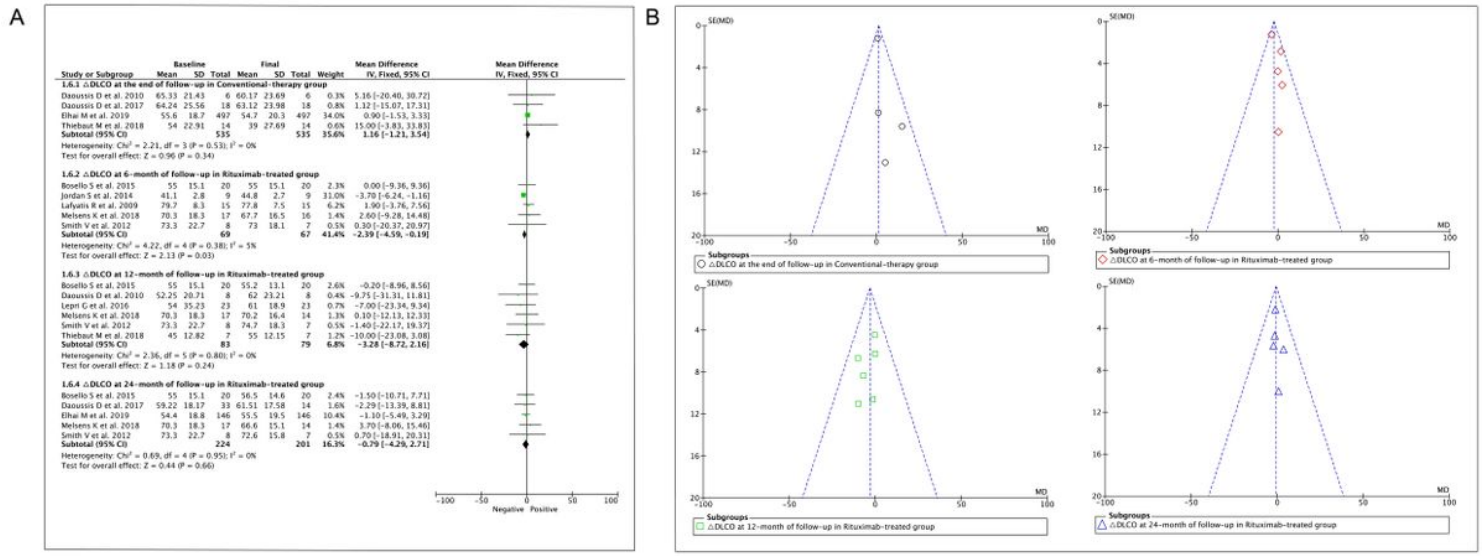

Figure 4

The mean difference in the conventional therapy group was 1.16 (95%CI=-1.21, 3.54) without any heterogenicity (p=0.31, I2=16%). The change of DLCO in the Rituximab-treated group were: 6-month -2.39 (95%CI=-4.56, -0.19), 12-month -3.28 (95%CI= -8.72, 2.16), 24-month -0.79 (95%CI= -4.29, 2.71)

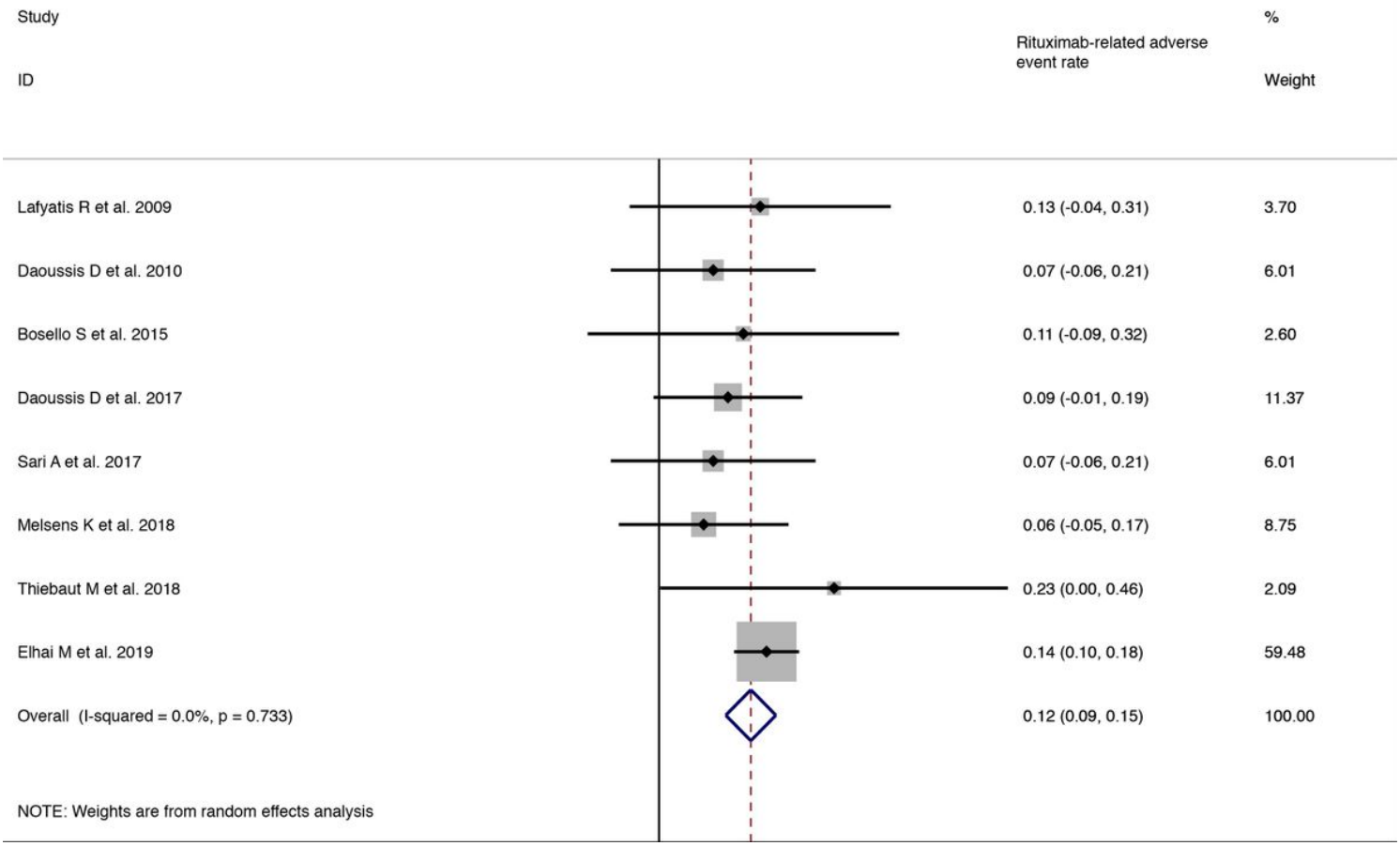

Figure 5

The safety profile of Rituximab in SSc patients was also summarized and pooled data was presented