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REVIEW ARTICLE

Efficacy and safety of rituximab therapy in patients with systemic sclerosis disease (SSc): systematic review and meta-analysis

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Abstract

The clinical benefits of rituximab in systemic sclerosis (SSc) are still contentious. The present meta-analysis aimed to systematically assess rituximab's safety and efficacy profile in SSc patients. A systematic online query was performed in PubMed, Scopus, Web of Science, and Embase. The studies on the application of rituximab for patients with SSc were reviewed comprehensively for over two years. In terms of efficacy profile, mRSS, MS, LVEF, sPAP, FVC, DLCO, TLC, FEV, DAS, severity activity, HAQ-DI and SF36 were assessed for organ involvement and quality of life. The level of biological and immunological markers was also evaluated in SSc patients treated with RTX. In total, 24 studies met the criteria. Although they did not have a high quality, they were free from heterogeneity and publication bias. The pooled results revealed a long-term improvement in mRSS and MS. HAQ-DI was improved to 0.78 after 12 months, and DAS was significantly reduced to 0.33, 0.23, and 0.24 following 6, 12, and 24 months of treatment, respectively (p = 0.00 for both parameters). The rest of the parameters remained stable over time in patients with SSc. The pooled analysis of these patients demonstrated that the induction of death, cancer, infection, and infusion were 9, 5, 18 and 10%, respectively. Based on the pooled results of this meta-analysis, rituximab improves skin score and disease indices and stabilizes organ involvement in SSc patients. Rituximab seems to possess reasonable safety, similar to previous data from other autoimmune diseases.

Keywords Efficacy · Organ involvement · Rituximab · Safety · Skin function · Systemic sclerosis

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Introduction

Systemic sclerosis (SSc) is an autoimmune connective tissue disease characterized by excessive collagen deposition and vascular dysfunction, resulting in skin fibrosis and internal organ involvement [1]. Based on the degree of skin involvement, SSc is classified into limited and diffuse forms that can lead to different clinical signs and symptoms. The quality of life of SSc patients is seriously affected by these clinical manifestations as well as other severe complications. Even though SSc prevalence is not as high as that of other rheumatic diseases, this immune-mediated disease, especially in its diffuse form, has the highest mortality rate, even when appropriate medical treatment and palliative care are provided [2].

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The pathogenesis of this complex disorder is not well understood yet, but B cell abnormalities (hypergammaglobulinemia, autoantibody production, and polyclonal B cell hyperactivity) are involved in SSc [3, 4]. The first-line treatment for SSc comprises glucocorticoids and other immunosuppressive agents [5]. There are limited therapeutic options available for SSc treatment, and the majority of the drugs tested so far have yielded poor or modest results. Accordingly, a more effective and less toxic therapy is important for SSc [1]. On the other hand, in the last years, other immune-based therapies have emerged, including B-cell depletion therapy and hematopoietic stem cell transplantation, with encouraging results [6, 7]. Rituximab (RTX) is a monoclonal chimeric antibody against CD20 which depletes peripheral B cells, and is applied in systemic rheumatic diseases. Its use in SSc has also been suggested owing to the growing evidence supporting the role of B cells in SSc [8].

To the best of the authors' knowledge, one systematic review and meta-analysis was published on this topic in 2020 [9]. The sources are limited, and three papers were missed up to the mentioned date (October 31, 2019) [10–12]. Also, there are some relevant abstracts related to the efficacy of RTX in SSc patients with details on skin and lung function tests [13–18]. The data of the articles that were pooled were not all of the same type. The mean parameter was extracted from one series of articles, while the median parameter was extracted from others [19, 20]. Moreover, one series of included papers were lost in some parameters that seemed to affect the meta-analysis results, e.g., the pooled analysis of the mRSS parameter in 6 and 12 months [19, 20].

Therefore, the present systematic review mainly focused on the safety and efficacy of rituximab for the skin score and organ involvement. The available data were also analyzed to comprehensively assess the effect of RTX on the quality of life of SSc patients.

Material and methods

Protocol registration

The protocol of the present meta-analysis is in agreement with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [21]. It was registered in the international prospective register of systematic reviews and received the registration number 42018103751. The protocol is available at the PROSPERO website:

http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018103751 [22].

Search strategy and study identification

PubMed, Web of Science, Scopus, and Embase electronic databases were searched using a combination of MeSH terms and Emtree words related to "Systemic Sclerosis" and "rituximab". We also screened privately and publicly funded clinical studies which were posted on ClinicalTrials.gov. The references of the included studies were screened manually. On-topic articles (the papers related to systemic sclerosis and rituximab) were reviewed, while the titles of the articles on non-RTX and non-SSc were excluded. The electronic searches were performed until 31 December 2019.

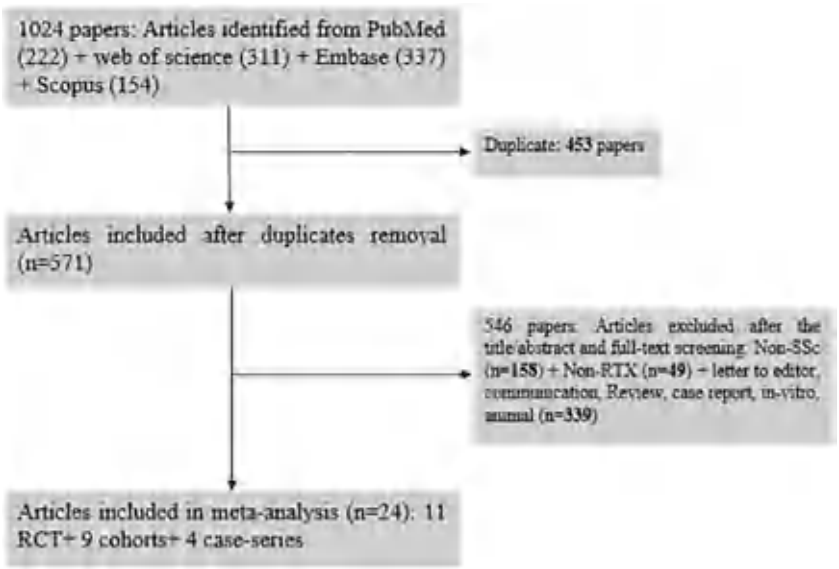


Fig. 1 Flow diagram of literature retrieval strategy

Table 1 Main characteristics of included studies

No.	Author and year	Study design	N patients on RTX	RTX scheme	Length of study	Primary objectives	Secondary objectives
1	Lafyatis R et al. 2009 [29]	Open label trial	15	1 g RTX weeks 0–2 (prednisone <10 mg/d and MTX)	6 months	mRSS, FVC and DLCO	IgM, IgG, IgA, B cell, Myofibroblast score and HAQ-DI
2	Bosello S et al. 2010 [3]	Open label trial	9	1 g RTX weeks 0–2 (+MTX)	36 months	mRSS	IgM, IgG, IgA, B cell, HAQ-DI, Severity index and DAS
3	Daoussis D et al. 2010 [30]	Randomized open label trial	8	375 mg/m^2/week RTX at months 0–6 (MMF and prednisone)	12 months	mRSS, FVC and DLCO	-
4	Smith V et al. 2013 [31]	Open pilot study	7	2 × 1 g RTX at weeks 0-2-26-28 (+100 mg methylprednisolone)	24 months	mRSS, FVC, and DLCO	TLC, FEV, SF-36, HAQ-DI, DAS, sPAP and LVEF
5	Bosello S et al. 2015 [7]	Open label trial	20	2 × 1 g RTX at weeks 0–2 (+ 100 mg methylpresnisolone)	48 months	mRSS, FVC, and DLCO	TLC, DAS, severity index and IgM
6	Daoussis D et al. 2017 [32]	Open label multicentre trial	33	4 × 375 mg/m^2/week RTX	84 months	mRSS, FVC and DLCO	-
7	Melsens K et al. 2017 [33]	Open label multicentre trial	17	2 × 1 g RTX at weeks 0-2-26-28 (+ 100 mg methylpresnisolone)	24 months	mRSS, FVC, and DLCO	TLC, FEV, SF-36, HAQ-DI, DAS, sPAP and LVEF
8	Daoussis et al.2012 [10]	Open label trial	8	4 × 375 mg/m^2/week RTX (+prednisone and MMF every 6 months)	24 months	mRSS, FVC and DLCO	HAQ-DI and MS
9	Daoussis et al. 2013 [15]	Open label study	25	375 mg/m^2/week RTX at months 0–6	12 months	mRSS, FVC and DLCO	-
10	Melissaropoulos et al.2015 [17]	Randomized clinical trial	22	RTX every 6 months	24 months	FVC and DLCO	-
11	Sircar et al. 2018 [11]	Randomized clinical trial	30	1 g RTX weeks 0–2	6 months	mRSS and FVC	-
12	Giuggioli D et al. 2015 [34]	Retrospective cohort	10	4 × 375 mg/m^2/week RTX	37 months	mRSS	-
13	Lepri G et al. 2016 [20]	Retrospective cohort	23	2 × 1 g RTX at weeks 0–2 (+DMARDs)	24 months	FVC and DLCO	TLC
14	Sari A et al. 2017 [35]	Retrospective cohort	14	2 × 1 g or 500 mg biweekly RTX	30 months	mRSS and FVC	-
15	Elhai M et al. 2019 [36]	Multicentric prospective cohort	146	1 g or 500 mg or 375 mg/m^2/week at weeks 0–2	24 months	mRSS, FVC and DLCO	HAQ-DI
16	Sancho et al.2014 [13]	Multicentric retrospective cohort	30	2 cycles of RTX with a dosing interval 12.8 months of MMF	12 months	mRSS	-
17	Ebata et al.2019 [37]	Retrospective cohort	9	RTX every 6 months	24 months	FVC	-
18	Kiryttopoulos et al. 2017 [18]	cohort	12	RTX	12 months	FVC	-
19	Jordan S et al. 2014 [38]	Multicentre nested case control	63	1 g RTX weeks 0–2 (+methylprednisolone	84 months	mRSS, FVC, and DLCO	-

Table 1 (continued)

No.	Author and year	Study design	N patients on RTX	RTX scheme	Length of study	Primary objectives	Secondary objectives
		observational study		and DMARDs)			
20	Thiebaut M et al. 2018 [19]	Retrospective case control study	13	2 × 1 g or 375 mg/m^2/week RTX at months 0–6	24 months	mRSS, FVC and DLCO	-
21	Vilela VS et al. 2016 [39]	Case series	10	2 × 1 g RTX at weeks 0–2	6 months	mRSS and FVC	-
22	Ananyeva et al. 2013 [14]	Case series	6	RTX	12 months	FVC and DLCO	-
23	Guzelant et al. 2017 [16]	Case series	14	RTX	24 months	FVC and DLCO	-
24	Fraticelli et al. 2018 [12]	Case series	15	1 g × 2 or 375 mg/m^2/week RTX at months 0–6 (+2 g/day MMF)	12 months	mRSS, FVC and DLCO	-

Abbreviations: *DMARDs*, Disease Modifying Anti-Rheumatic Drugs; *mRSS*, modified Rodnan Skin Score; *FVC*, Forced Vital Capacity; *DLCO*, Diffusing Capacity for Carbon Monoxide; *TLC*, Total Lung Capacity; *FEV*, Forced Expiratory Volume; *LVEF*, Left Ventricular Ejection Fraction; *sPAP*, systolic Pulmonary Artery Pressure; *HAQ-DI*, Health Assessment Questionnaire - Disability Index; *SF-36*, medical outcome study short form 36; *DAS*, Disease Activity Score; *MTX*, Methotrexate; *MMF*, Mycophenolate Mofetil

Inclusion and exclusion criteria

All randomized clinical trials (RCTs) and observational studies (cohort, case–control, and case series) examining the effect of RTX on the survival of patients with SSc in baseline and follow-up were included. Data about the following parameters were extracted as mean ± standard deviation (SD) before and after RTX-therapy. In cases that the median is reported for parameters, the mean ± SD was calculated based on the research by Wang et al. [23]. The significance level has been provided by G*Power (version 3.1.9.4) software for the studies that did not report a *p* value [24].

The inclusion criteria were: (1) All the patients in the RTX-treated group were diagnosed with limited and/or diffuse SSc and met the preliminary American College of Rheumatology classification criteria of SSc; (2) the primary study outcome reported variations in the modified Rodnan skin score (mRSS) for skin function and forced vital capacity (FVC) and/or diffusing capacity of the lungs for carbon monoxide (DLCO) for lung function; 3) additional outcomes could include the assessment of pulmonary involvement by total lung capacity (TLC) and forced expiratory volume (FEV), skin function by myofibroblast score (MS), cardiac involvement by left ventricular ejection fraction (LVEF) and systolic pulmonary artery pressure (sPAP), daily functioning and quality of life by health the Assessment Questionnaire Disability Index (HAQ-DI), and the medical outcome study short form 36 (SF-36), disease indices by the disease activity score (DAS) and severity activity, and the disease in the microscopic level by biological and immunological markers (the percentage of infiltrated B-cell in the skin and IgG, IgM and IgA); and 4) safety outcomes had to be evaluated based on the induction of death, infusion, infection, and cancer. Safety outcomes were extracted from all the included studies.

The exclusion criteria were: (1) reviews, case report, letters, animal models and cell culture studies; (2) articles without an English version; (3) overlapping or duplicated data, and (4) studies without data on the efficacy of RTX on SSc patients. When several publications of the same trial were found, the most recent version and most comprehensive data were included.

Selection, assessment, and data extraction

Two reviewers screened the title, abstract, and keywords of every record independently, and then the full-text of the articles which met our criteria was retrieved and assessed for data extraction. A checklist was designed in Excel to extract the relevant data from the articles. Two investigators crosschecked the checklists, and any

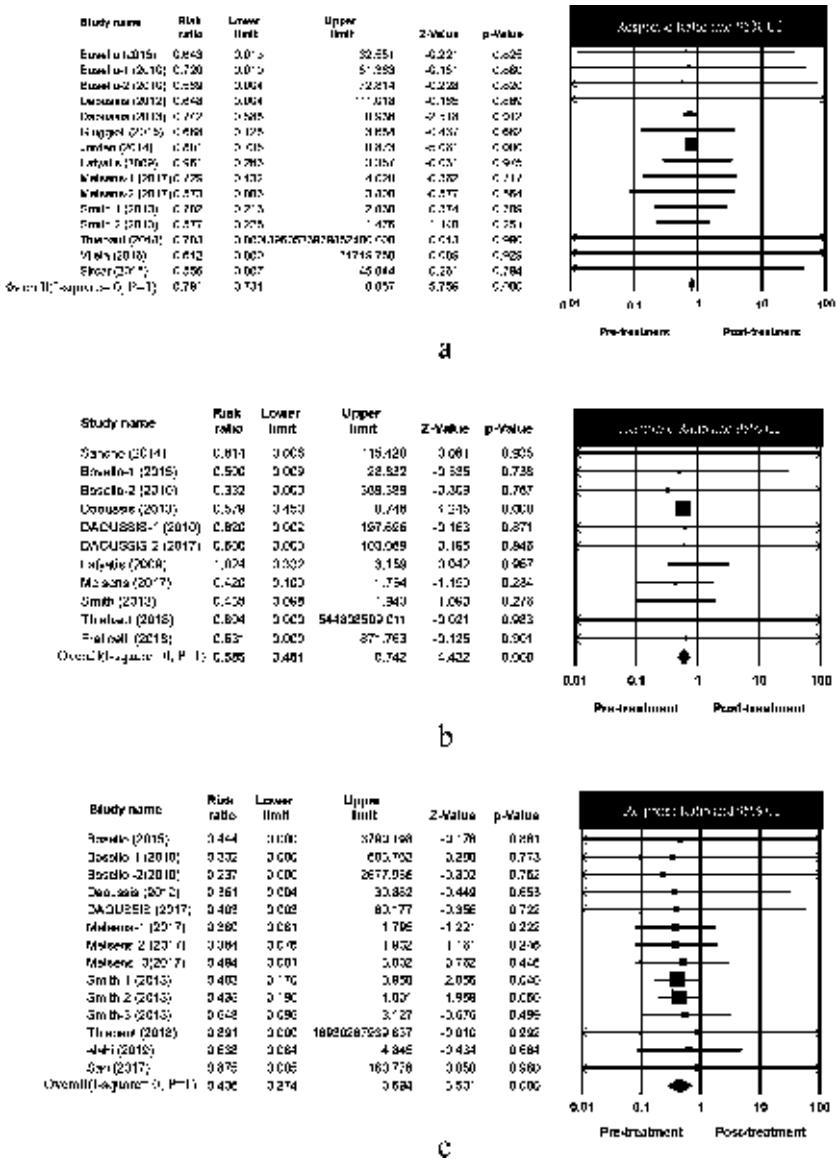


Fig. 2 Forest plot of response ratio for rituximab efficacy on mRSS of SSc patient at (**a**) 6 months, (**b**) 12 months, (**c**) 24 months' treatment

disagreement was resolved by discussion and reaching consensus. The following items were extracted: first author's name, year of publication, RTX regimen, primary and/or secondary clinical outcome, and adverse events.

Data synthesis and analysis (meta-analysis)

Statistical analysis was performed in the comprehensive meta-analysis software (CMA, version 2.2.064,

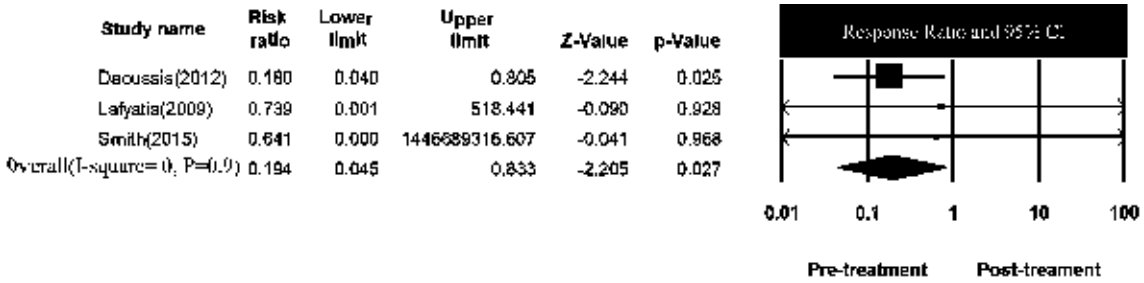


Fig. 3 Forest plot of response ratio for rituximab efficacy on MS of SSc patient at 6 months' treatment

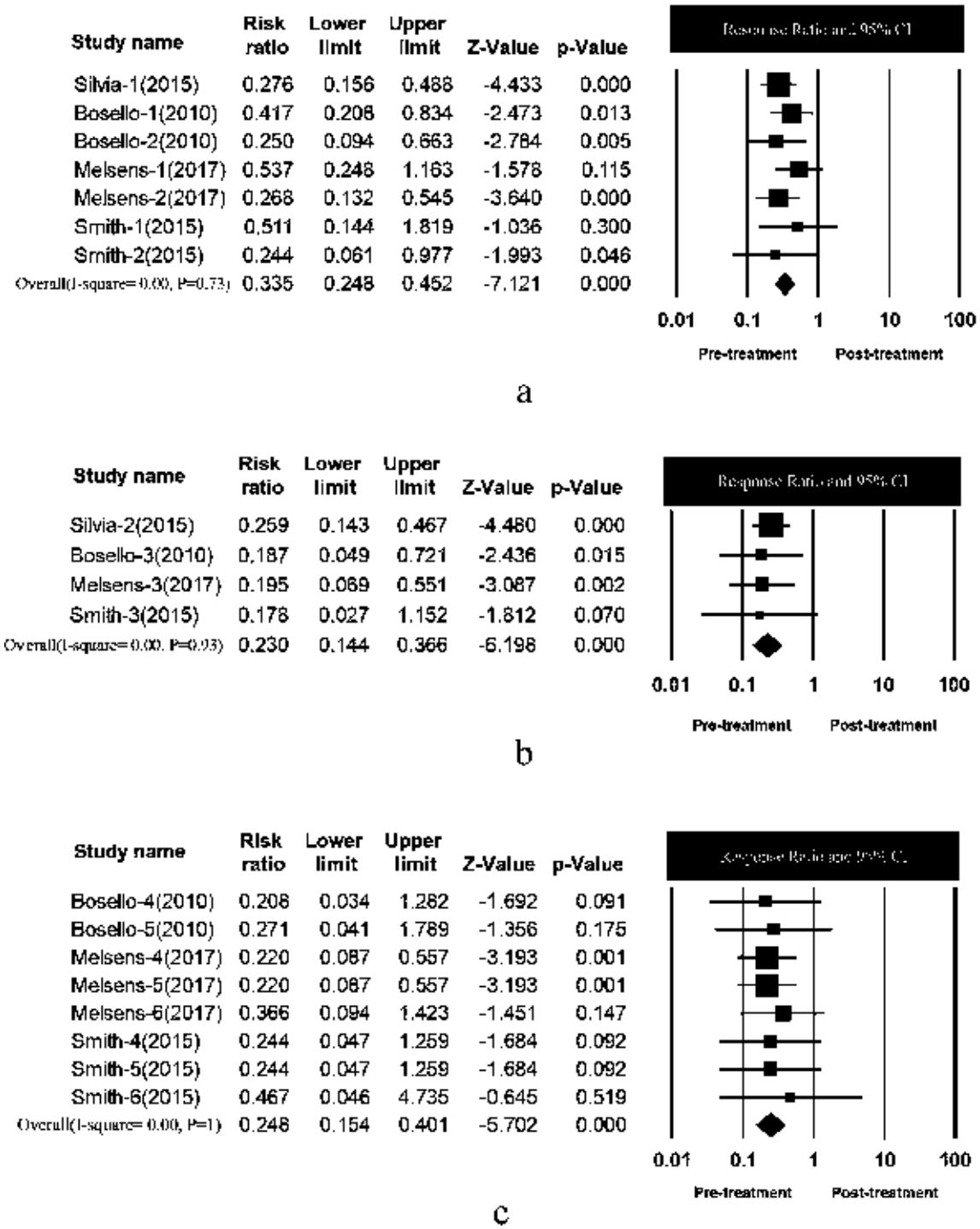


Fig. 4 Forest plot of response ratio for rituximab efficacy on DAS of SSc patient at (**a**) 6 months, (**b**) 12 months, (**c**) 24 months' treatment

Englewood, NJ, USA). The between-study variance was calculated by the DL (Der Simonian and Laird) estimator, which is the default option in several meta-analysis programs such as CMA [25]. To evaluate RTX efficacy in the patients, before and after RTX therapy, the data in all the parameters were collected to calculate the response ratio [26]. Moreover, the prevalence (risk ratio) was utilized to evaluate the safety profile. Effect sizes

Study name	Risk ratio	Lower limit	Upper limit	Z-Value	p-Value
Silvia(2015)	0.706	0.298	1.674	-0.790	0.430
Bosello(2010)	0.590	0.083	4.225	-0.525	0.600
Overall(I-square= 0, P=0.87)	0.686	0.311	1.512	-0.934	0.350

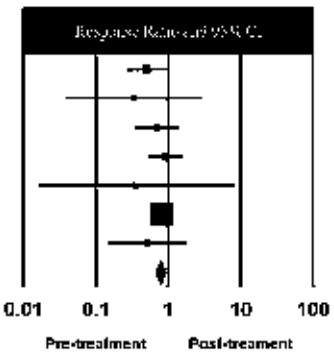
Fig. 5 Forest plot of response ratio for rituximab efficacy on severity index of SSc patient at 12 months' treatment

Fig. 6 Forest plot of response ratio for rituximab efficacy on HAQ-DI of SSc patient at (**a**) 6 months, (**b**) 12 months, (**c**) 24 months' treatment

Study name	Risk ratio	Lower limit	Upper limit	Z-Value	p-Value
Silvia-1(2015)	0.563	0.306	1.114	-1.634	0.102
Bosello-1(2010)	0.556	0.273	1.129	-1.625	0.104
Bosello-2(2010)	0.444	0.193	1.024	-1.904	0.057
Melsens-1(2017)	1.100	0.705	1.717	0.420	0.675
Melsens-2(2017)	0.900	0.542	1.495	-0.407	0.684
Smith-1(2015)	1.071	0.759	1.513	0.392	0.695
Smith-2(2015)	0.929	0.580	1.487	-0.309	0.758
Lafyatis-1(2009)	0.955	0.796	1.146	-0.494	0.621
Overall(I-square= 15, P=0.3)	0.922	0.809	1.052	-1.208	0.227

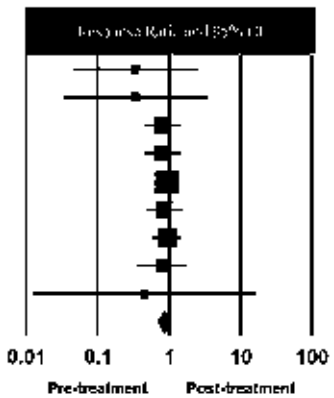
a

Study name	Risk ratio	Lower limit	Upper limit	Z-Value	p-Value
Silvia-3(2015)	0.500	0.269	0.931	-2.187	0.029
Bosello-3(2010)	0.333	0.039	2.841	-1.005	0.315
Melsens-3(2017)	0.700	0.350	1.401	-1.007	0.314
Smith-3(2015)	0.929	0.533	1.618	-0.261	0.794
Daoussis-2(2012)	0.364	0.016	8.029	-0.640	0.522
Lafyatis-2(2009)	0.821	0.681	0.989	-2.074	0.038
Daoussis-2(2010)	0.507	0.147	1.743	-1.079	0.281
Overall(I-square= 0, P=0.6)	0.782	0.665	0.921	-2.952	0.003



b

Study name	Risk ratio	Lower limit	Upper limit	Z-Value	p-Value
Bosello-4(2010)	0.333	0.045	2.444	-1.081	0.280
Bosello-5(2010)	0.333	0.033	3.326	-0.936	0.349
Melsens-4(2017)	0.800	0.456	1.403	-0.779	0.436
Melsens-5(2017)	0.800	0.456	1.403	-0.779	0.436
Smith-4(2015)	0.929	0.625	1.380	-0.367	0.714
Smith-5(2015)	0.857	0.477	1.542	-0.515	0.607
Smith-6(2015)	0.929	0.580	1.487	-0.309	0.758
elahi(2019)	0.793	0.358	1.759	-0.571	0.568
Daoussis-1(2012)	0.454	0.012	16.523	-0.430	0.667
Overall(I-square= 0, P=0.98)	0.851	0.689	1.052	-1.489	0.137



c

with 95% CI were calculated for dichotomous data, and pooled effect sizes were estimated via a fixed-effect model [27]. The presence of heterogeneity was examined via the X^2 test. The total variation across the studies which was due to heterogeneity rather than chance was indicated by the Q test with $p < 0.05$ and $I^2 > 50\%$. The potential publication bias was assessed via Begg's funnel plot method. When the funnel plot was asymmetric, the possibility of publication bias was evaluated by the trim-and-fill method in which the imputation of potentially missing studies (probably unpublished studies) yields a symmetric funnel plot. After imputation, if the overall effect size (adjusted effect size) was not significantly changed, publication bias was deemed to be unlikely to affect the pooled estimate of effect size [28].

Results

Included studies

The initial search strategy yielded 1024 publications. After removing 453 duplicates, the remaining articles were evaluated by screening their titles and abstracts, and 571 irrelevant articles were excluded in this stage due to the following reasons: non-RTX (49), non-SSc (158), other study types (reviews, letters to the editor, communications, case reports, in-vitro, animal) (339). Finally, 24 studies were selected based on the predefined inclusion and exclusion criteria. Fig. 1 presents the details of the online database search strategy. The main features of the studies included in the meta-analysis are given in Table 1.

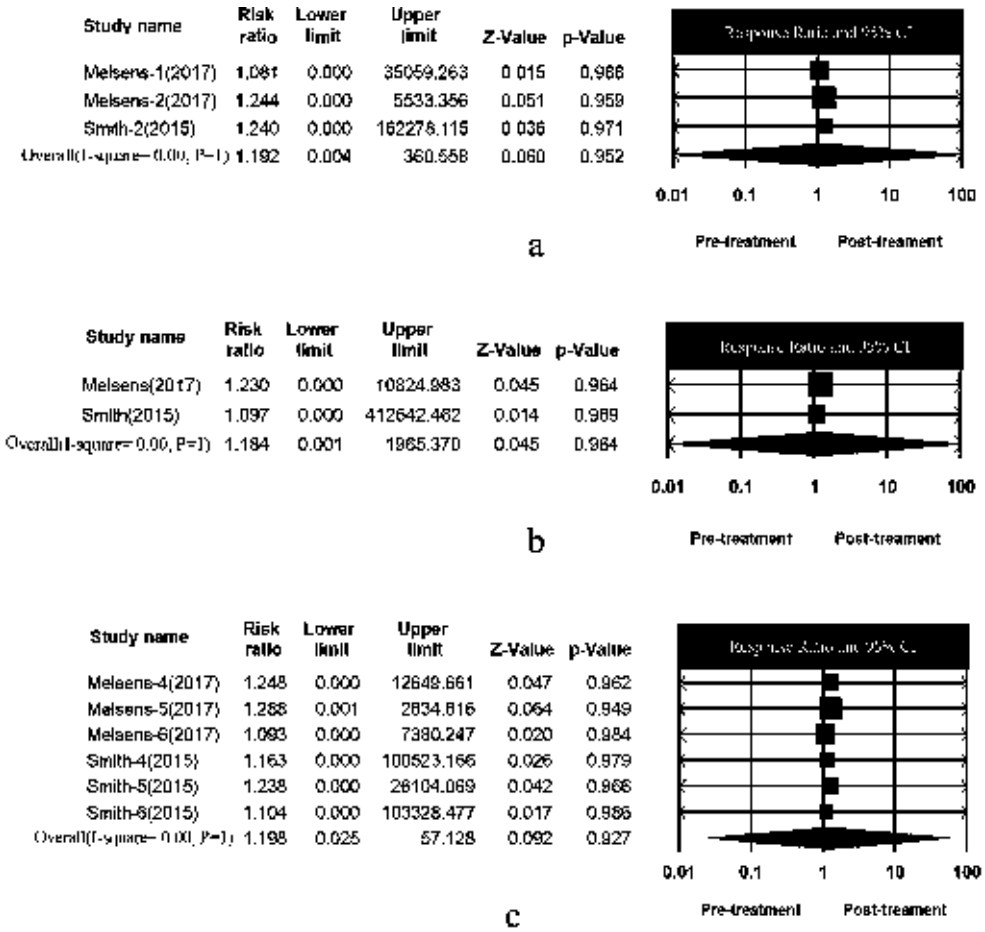


Fig. 7 Forest plot of response ratio for rituximab efficacy on SF-36 of SSc patient at (**a**) 6 months, (**b**) 12 months, (**c**) 24 months' treatment

Efficacy evaluation

Skin score and disease indices

Interestingly, the skin score improved over time in RTX-treated SSc patients. Fig. 2 displays that mRSS values significantly decreased to 0.8, 0.58, and 0.433 after 6, 12, and 24 months, in that order ($p = 0.000$ for all comparisons with respect to the baseline). After six months, the overall response ratio of MS equaled 0.2 (Fig. 3) ($p = 0.02$).

Based on Fig. 4, the activity index was significantly reduced during the follow-up (6 months: 0.33, 12

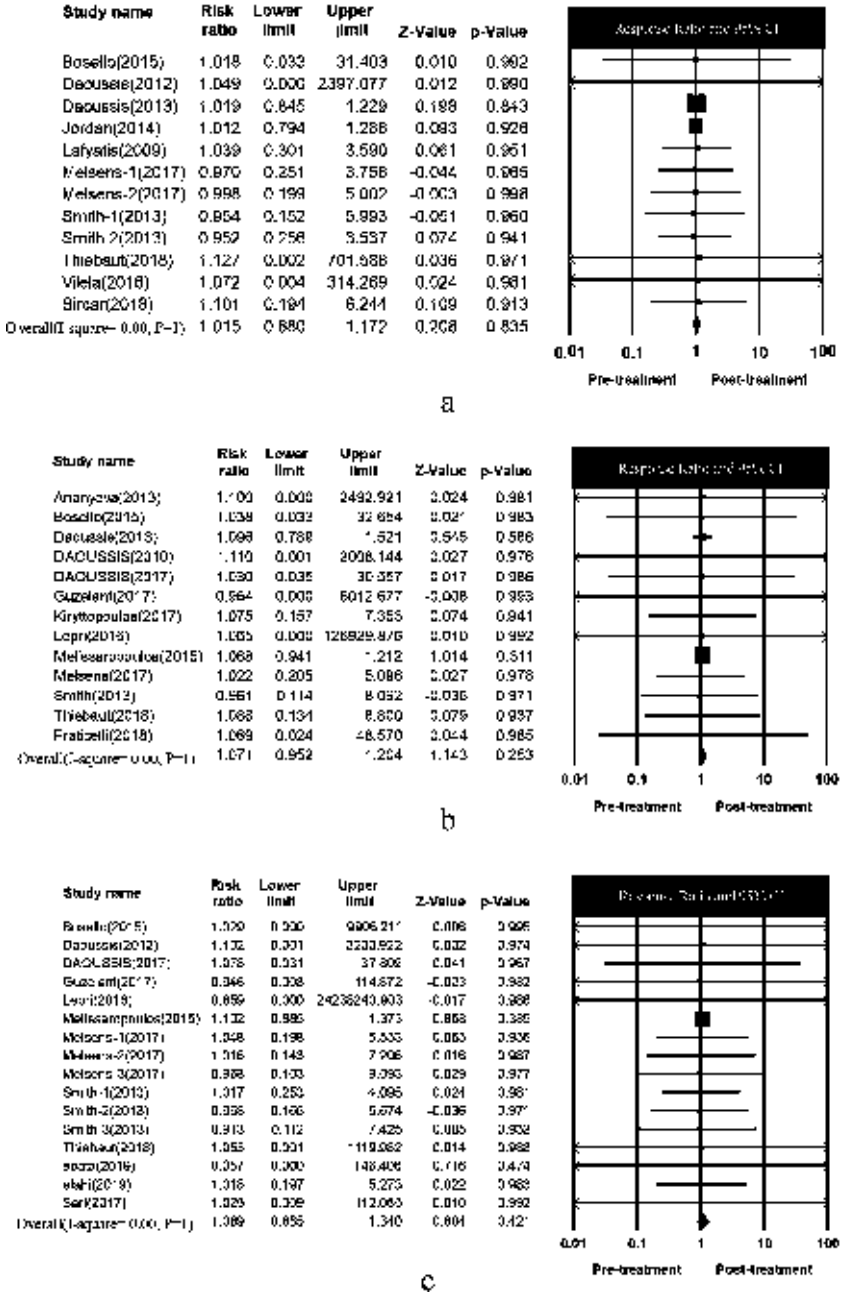


Fig. 8 Forest plot of response ratio for rituximab efficacy on FVC of SSc patient at (**a**) 6 months, (**b**) 12 months, (**c**) 24 months' treatment

months: 0.23, 24 months: 0.24, p = 0.000 for all the comparisons with respect to the baseline). However, the overall pooled estimate of the severity index at the final available follow-up equaled 0.68 (Fig. 5) (p = 0.35). The HAQ-DI value significantly decreased to 0.78 at 12 months (p = 0.003) and SF-36 was stabilized over the time of treatment (Figs. 6 and 7). The results demonstrated no significant heterogeneity.

Cardiopulmonary involvement

FVC and DLCO, as well as TLC and FEV, were measured to check the improvement of pulmonary function in patients with SSc. All the lung parameters remained stable during the follow-up with RTX (Figs. 8, 9, 10, 11). The parameters Cardiac involvement was assessed by LVEF and sPAP. Based on Figs. 12 and 13, both parameters were stabilized over time treatment with RTX.

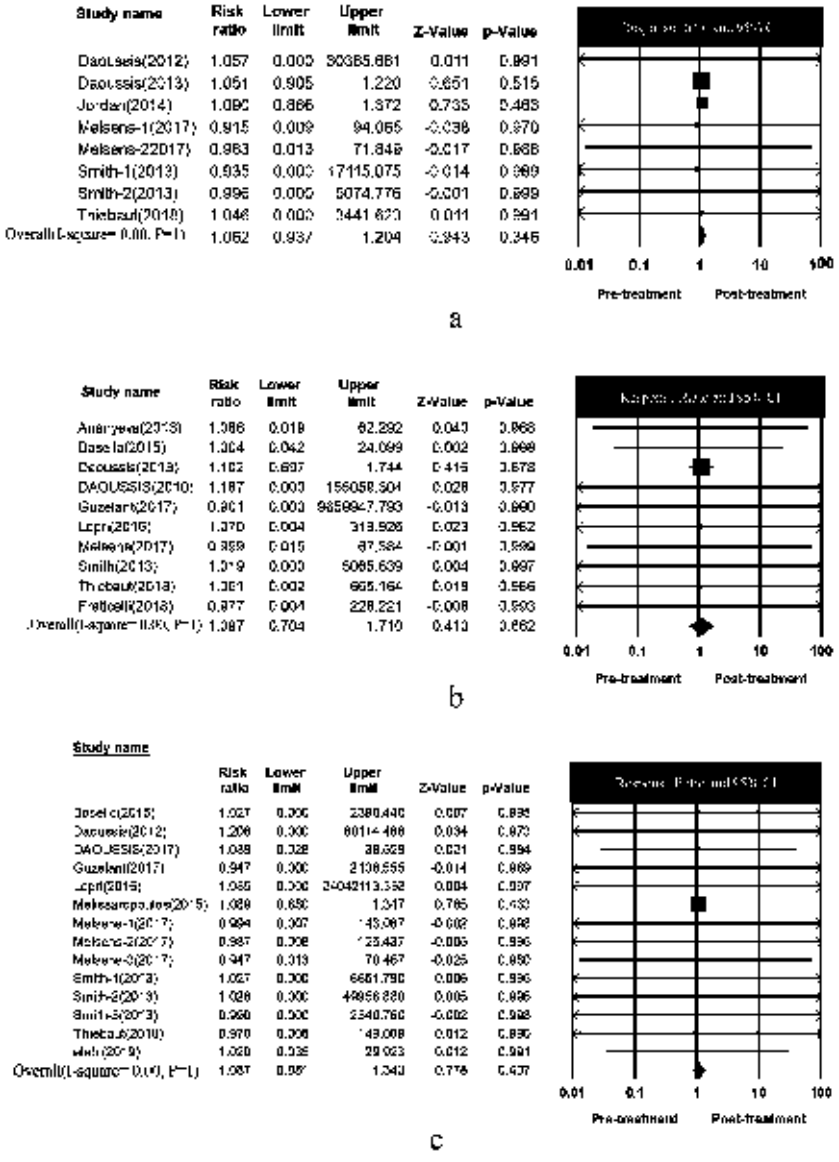


Fig. 9 Forest plot of response ratio for rituximab efficacy on DLCO of SSc patient at (**a**) 6 months, (**b**) 12 months, (**c**) 24 months' treatment

The level of infiltrating B cells, IgM, IgG, and IgA did not change during the RTX therapy (Figs. 14, 15, 16, 17). No significant heterogeneity was detected in the overall pooled estimates.

Safety profile

RTX's safety profile in SSc patients was also examined, and Fig. 18 presents the pooled data. The prevalence of induction death, cancer, infection, and infusion in RTX-treated SSc patients were 9, 5, 18 and 10%, respectively, and the result indicated no significant heterogeneity.

Publication bias

Funnel plots were utilized to examine the existence of publication bias in the present meta-analysis. A visual

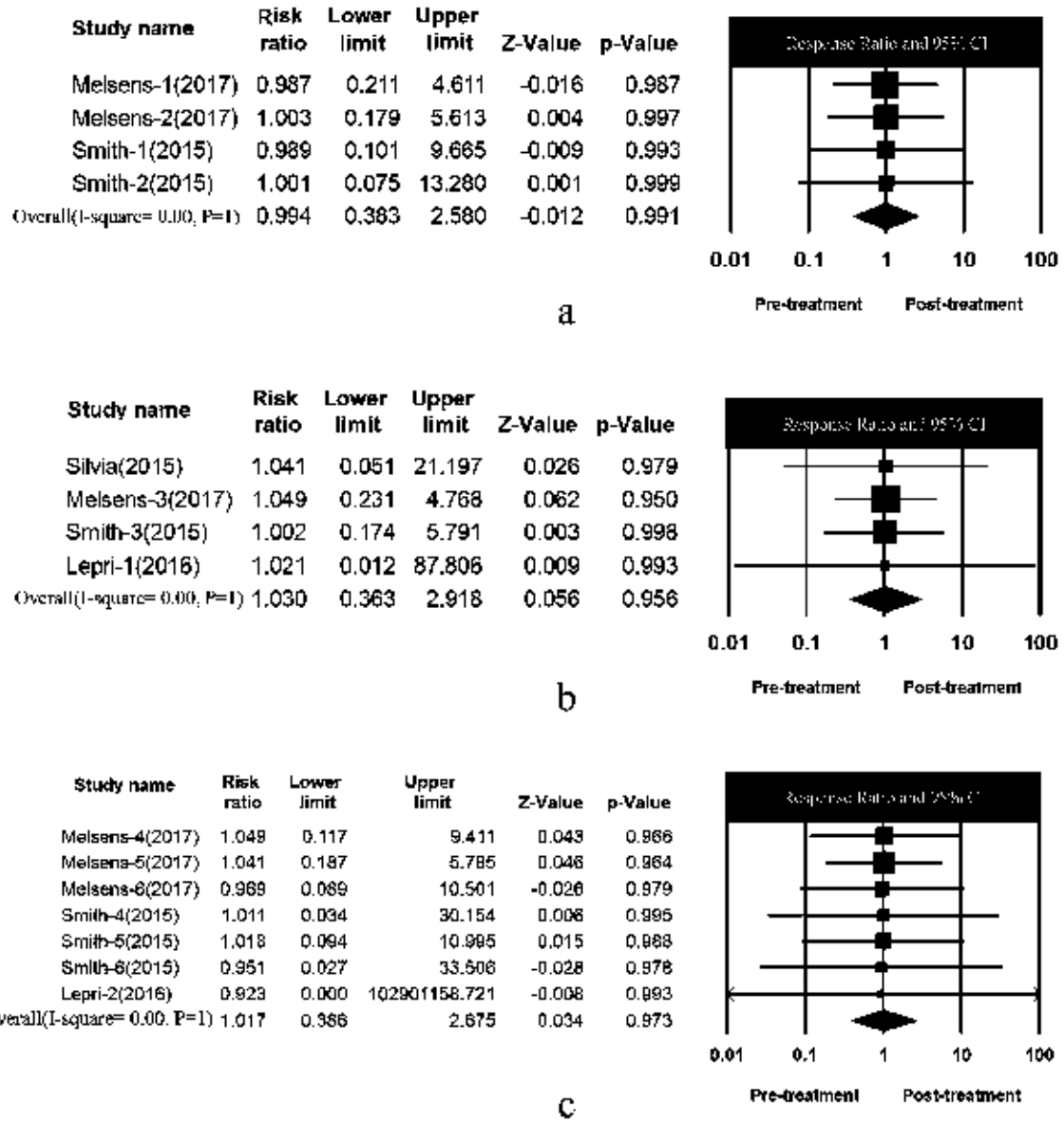


Fig. 10 Forest plot of response ratio for rituximab efficacy on TLC of SSc patient at (**a**) 6 months (**b**) 12 months (**c**) 24 months' treatment

inspection of the funnel plots (Figs. 19, 20, 21, 22, 23, 24, 25) demonstrates clear symmetry for all subgroup analyses.

Discussion

RTX has been recommended as a B-cell depletion drug to treat SSc patients, but contradictory data have been reported about its efficiency [38]. A meta-analysis was recently conducted to obtain accurate results about this issue, but the findings are not reliable due to heterogeneity, lost papers, and lack of the same central index in all the included articles [9]. Therefore, this is the first systematic review and meta-analysis to comprehensively evaluate the long-term clinical efficacy and safety profile of RTX on the quality of life of SSc patients.

According to the results, if RTX is administered to SSc patients, it will significantly reduce the skin score and disease activity that can lead to significant

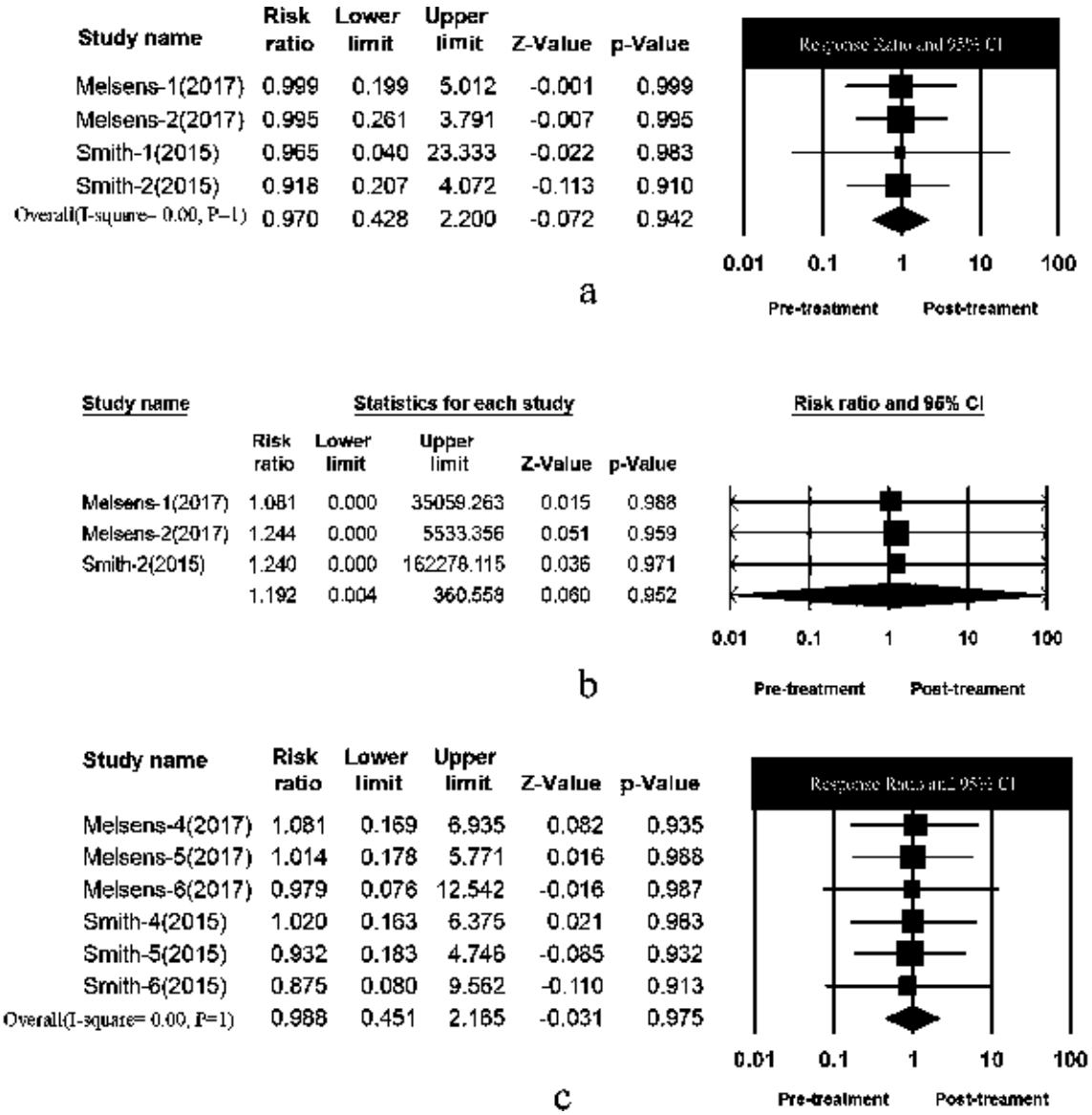


Fig. 11 Forest plot of response ratio for rituximab efficacy on FEV of SSc patient at (**a**) 6 months, (**b**) 12 months, (**c**) 24 months' treatment

improvements in the quality of life of these patients. It was also shown that internal organ involvement remains stable under treatment with RTX. RTX's safety profile in SSc patients was satisfactory because few RTX-related severe adverse events were recorded in the studies. Moreover, no heterogeneity or publication bias was found across the included studies.

In spite of the clear impact of RTX on reducing the circulating B cells, the mechanism of its action in connective tissue diseases is still vague. Treatment with RTX results in varying, but modest, changes in the levels of autoantibody. As a result, this mechanism does not seem to explain any therapeutic benefit in SSc patients. In recent research, RTX decreased B cells in most (but not all) synovial tissues of patients who had rheumatoid arthritis (RA) [40]. Although local B cell functions (e.g., cytokine secretion or antigen presentation) have been viewed as alternative mechanisms for RTX activity, the clinical response in RA patients was not associated with the degree of pretreatment B cell infiltration in synovial tissues [41]. Numerous clinical studies have been conducted to comprehensively evaluate the safety and efficacy and of this therapeutic agent in several involved tissues and organs. Concerning the application of RTX in SSc, cutaneous

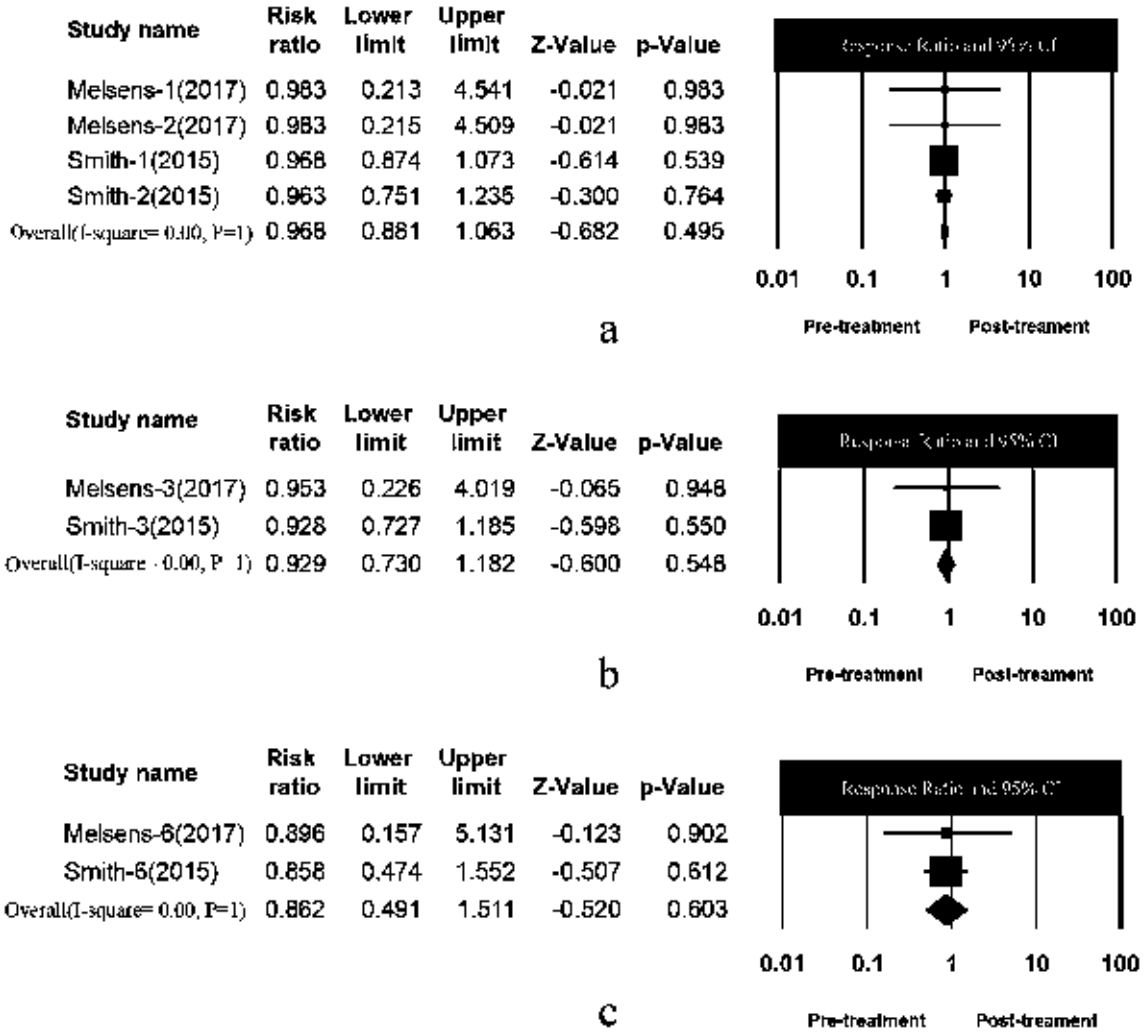


Fig. 12 Forest plot of response ratio for rituximab efficacy on LVEF of SSc patient at (**a**) 6 months, (**b**) 12 months, (**c**) 24 months' treatment

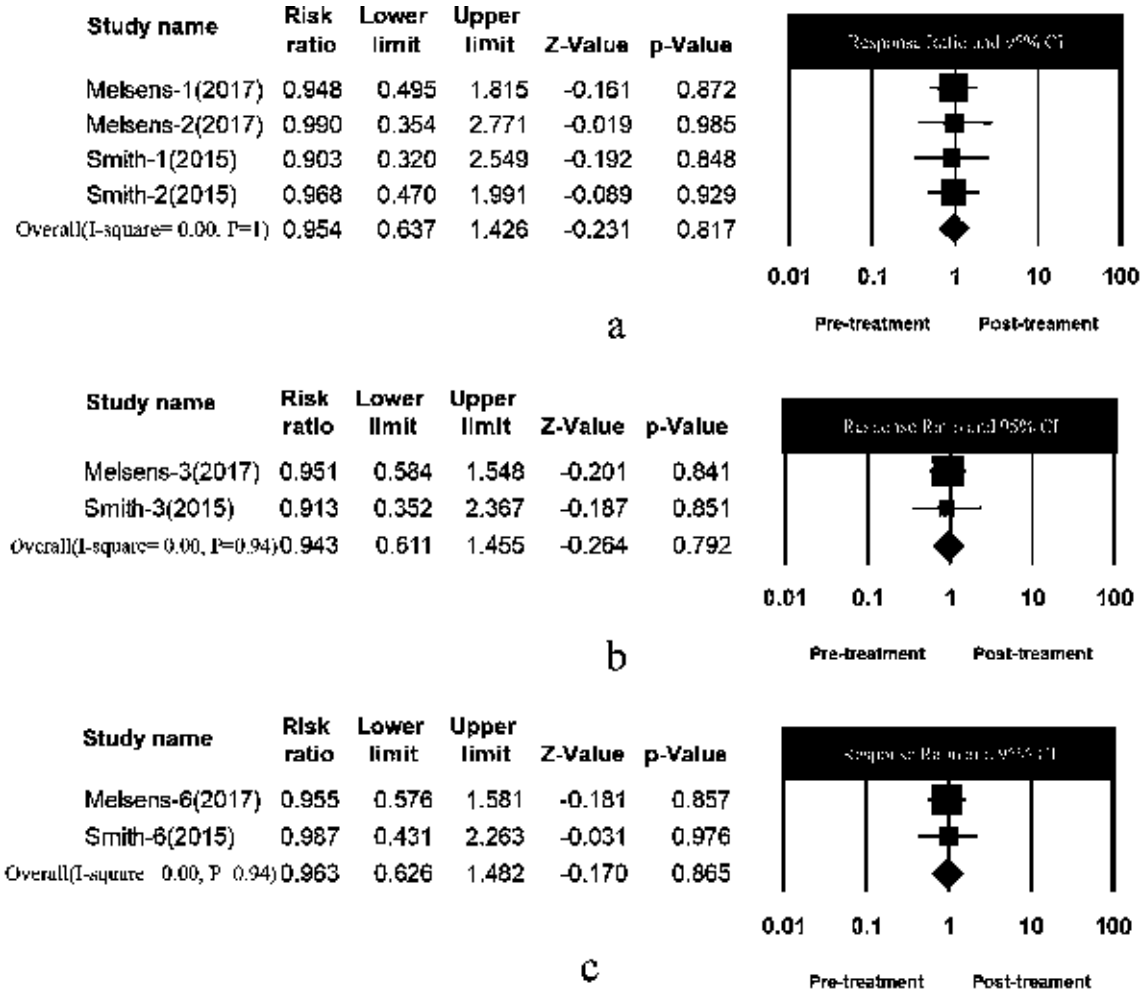


Fig. 13 Forest plot of response ratio for rituximab efficacy on sPAP of SSc patient at (**a**) 6 months, (**b**) 12 months, (**c**) 24 months' treatment

and pulmonary functions are often assessed as the primary research outcomes due to their significance for clinical mortality [42].

As previously mentioned, internal organ involvement remains stable under RTX treatment, which is in favor of a better prognosis. Based on previous studies, if no

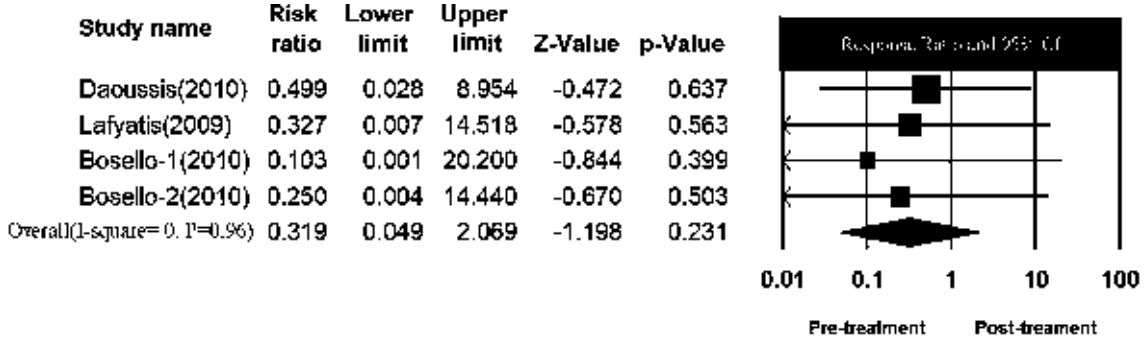


Fig. 14 Forest plot of response ratio for rituximab efficacy on B-cell of SSc patient at 6 months' treatment

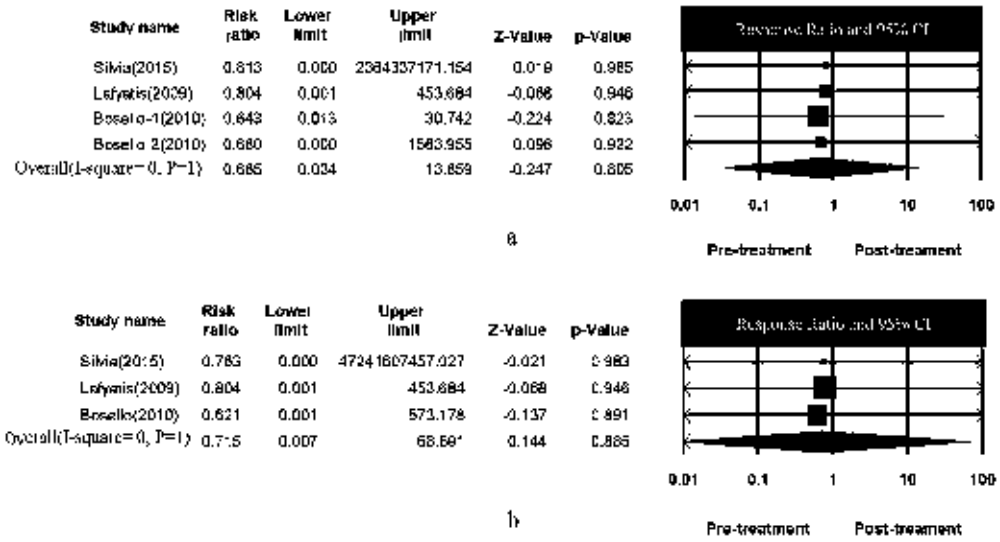


Fig. 15 Forest plot of response ratio for rituximab efficacy on IgM of SSc patient at (**a**) 6 months, (**b**) 12 months' treatment

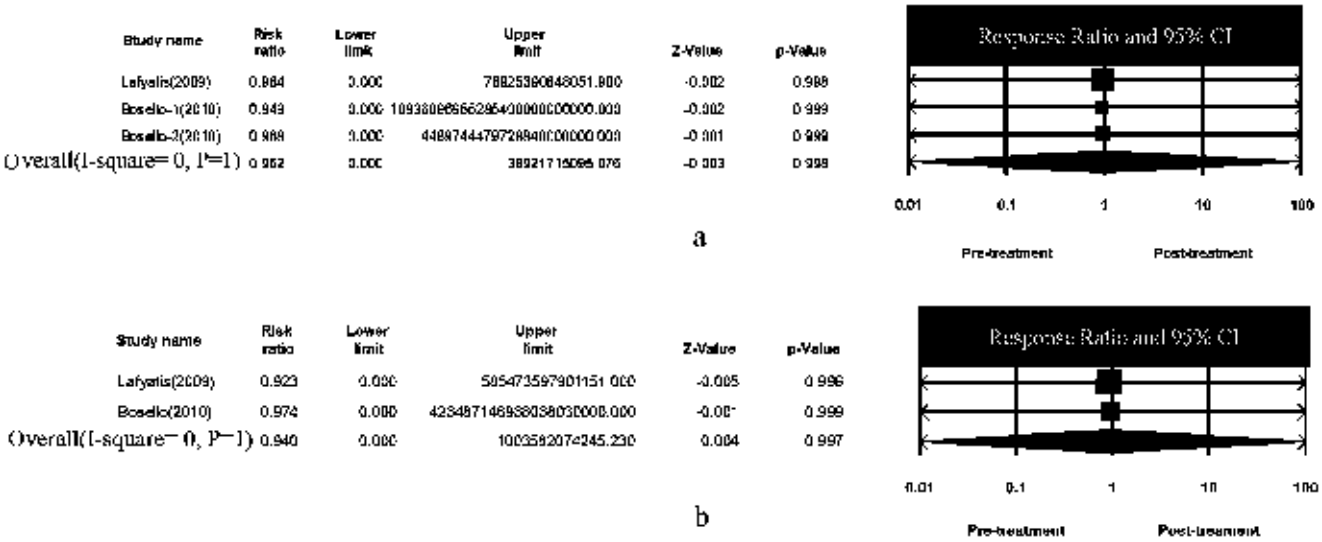


Fig. 16 Forest plot of response ratio for rituximab efficacy on IgG of SSc patient at (**a**) 6 months, (**b**) 12 months' treatment

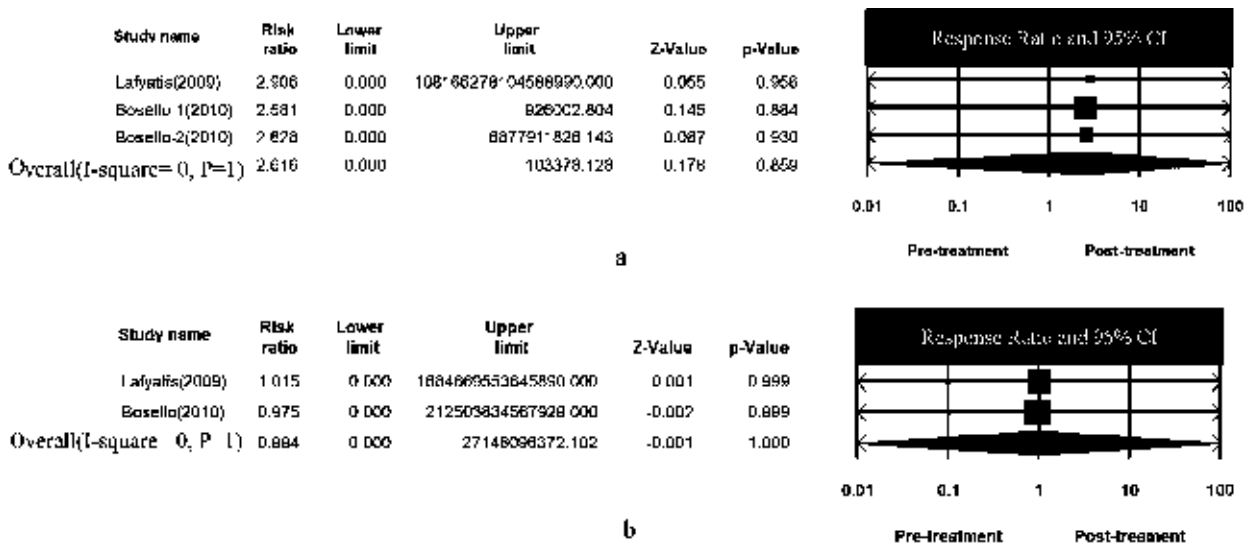


Fig. 17 Forest plot of response ratio for rituximab efficacy on IgA of SSc patient at (**a**) 6 months, (**b**) 12 months' treatment

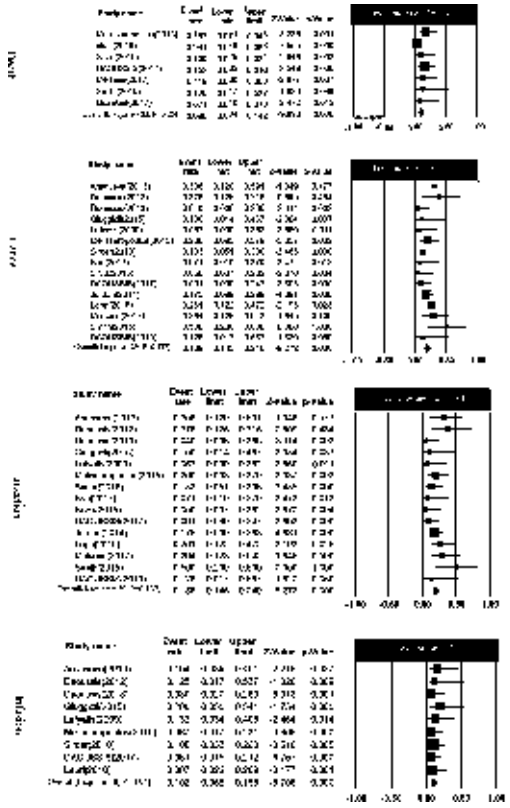


Fig. 18 Forest plot of prevalence rate of death, cancer, infection and infusion in rituximab-treated SSc patients at the end of follow-up

severe organ involvement happens within the first three years, patients will have a better nine-year cumulative survival (72 vs. 38%, $p < 0.0001$) [43]. All the results are consistent with previous studies [30, 31, 44], thereby confirming RTX's disease-modifying properties.

The mRSS is a validated surrogate marker [45] frequently adopted as an outcome measure in clinical trials [46]. Exacerbation of mRSS is associated with higher mortality and worsening of internal organ involvement. On the contrary, improvement of the skin score predicts favorable outcomes such as better survival [47]. Interestingly, despite changes in the skin score after treatment with RTX, a reduction in myofibroblast score was observed in these patients. These data indicate that a decline in myofibroblast score could be a preclinical indicator of improved scleroderma skin fibrosis [31].

It is notable that, although the mRSS significantly improved, the percentage of infiltrated B-cells in the skin and immunological markers remained stable; a point that should be investigated further via randomized controlled trials.

All the reported RTX-related adverse events are detailed in the present meta-analysis. The most frequently occurring adverse events are mild infusion-related reactions and infectious complications [33]. Nevertheless, patients who receive placebo demonstrated similar or even higher infection rates, suggesting that these adverse events could be associated with

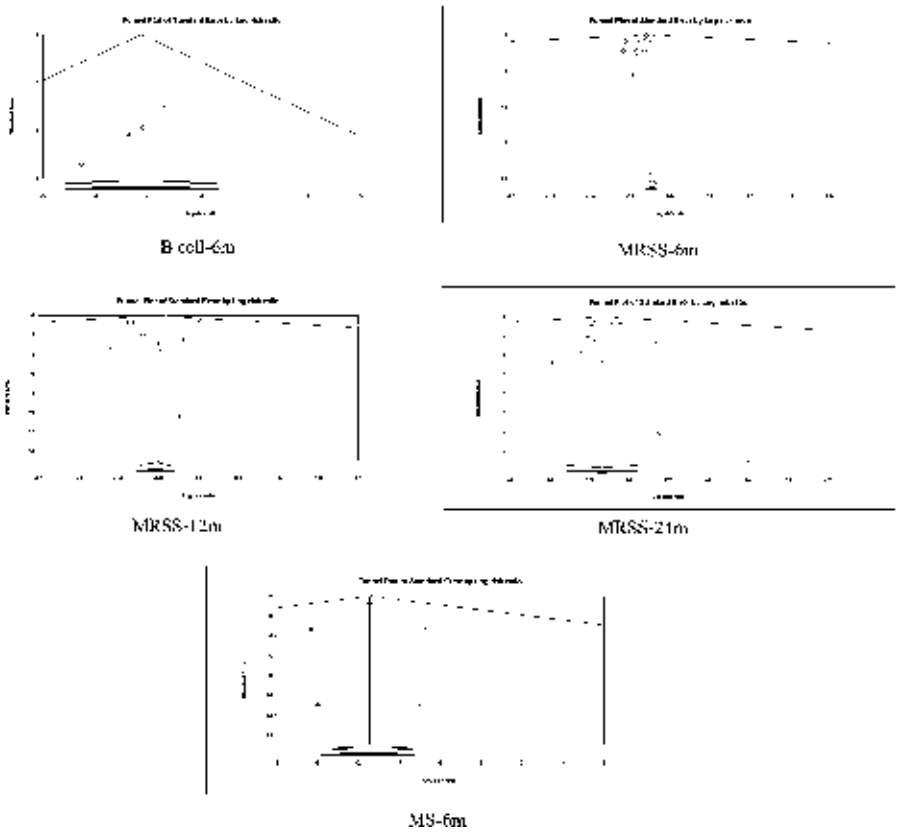


Fig. 19 Begg's funnel plots to explore the possibility of publication bias in the pooled estimate of rituximab efficacy on skin of SSc patient at different treatment months (m)

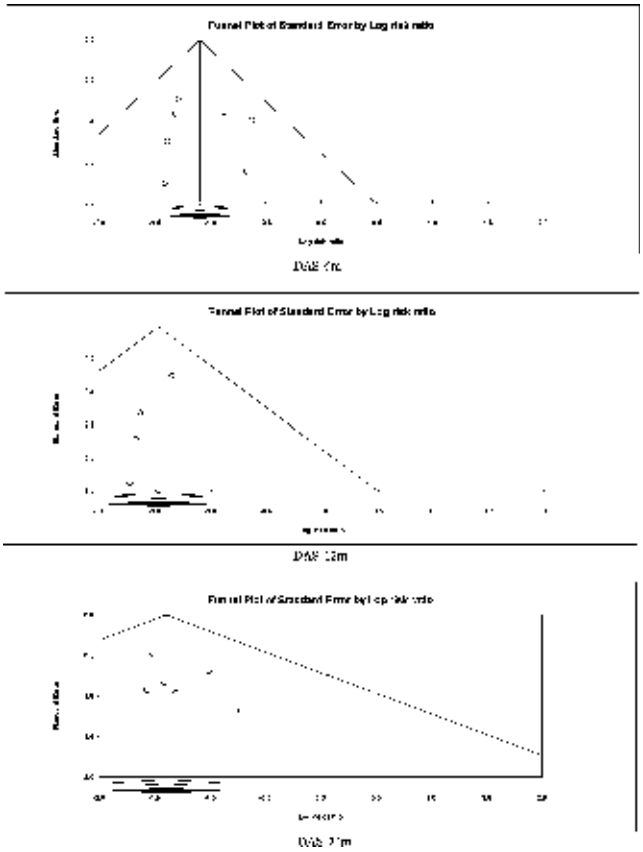


Fig. 20 Begg's funnel plots to explore the possibility of publication bias in the pooled estimate of rituximab efficacy on disease index of SSc patient at different treatment months (m)

DMARD co-treatment or the natural course of the disease [48].

Even though our results suggest that cutaneous function in patients with SSc can benefit from the clinical use of RTX, more clinical trials are required to elucidate how RTX can be applied in combination therapy and to optimize the combined treatment for better controlling lung involvement in patients with SSc [49]. For instance, the most recent data demonstrate that patients who are concomitantly treated with RTX and mycophenolate mofetil have a better outcome in terms of both skin and lung fibrosis, compared to patients who receive RTX alone [50].

We have shown RTX's safety and clinical efficacy, particularly for skin fibrosis, in SSc. Still, our study has a number of limitations. The open-label design and the small sample size of these studies are major limitations preventing us from drawing any firm conclusion as to the efficacy of RTX in SSc. Also, the patients' variable background and co-treatment options for them may make the comparison between studies difficult [34]. In addition, the diversity in RTX regiment and follow-up in different clinical centers may lead to the inconsistency of results. Finally, the available data on the parameters in conventional-therapy groups were inadequate. Unlike the RTX-treated group, it is not possible to generate pooled data during follow-up in the conventional-therapy group [19, 30, 50, 51]. These limitations motivate the initiation of a phase III prospective, randomized, double-blinded, placebo-controlled trial in SSc, which serves as the next step for proving the efficacy of B cell targeting on fibrotic manifestations in SSc.

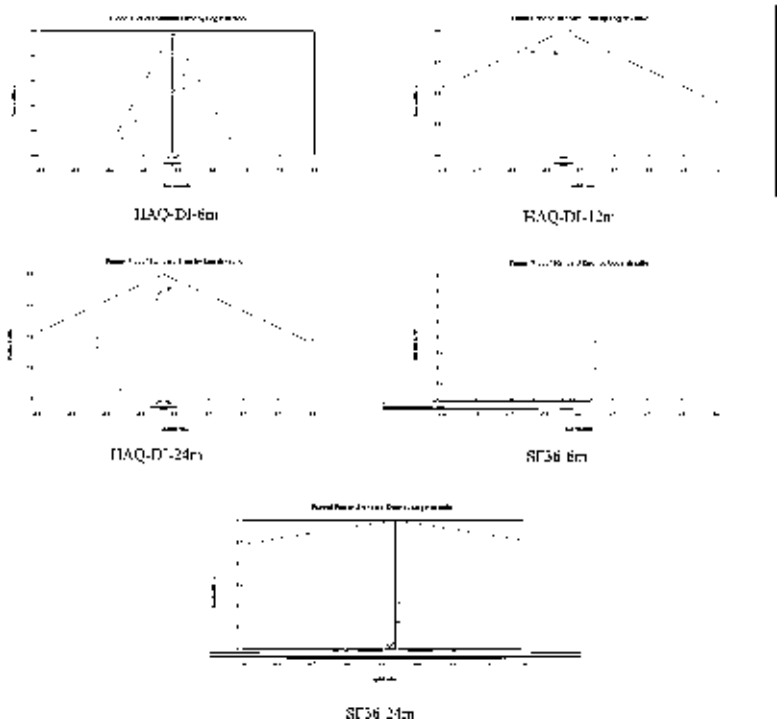


Fig. 21 Begg's funnel plots to explore the possibility of publication bias in the pooled estimate of rituximab efficacy on quality of life of SSc patient at different treatment months (m)

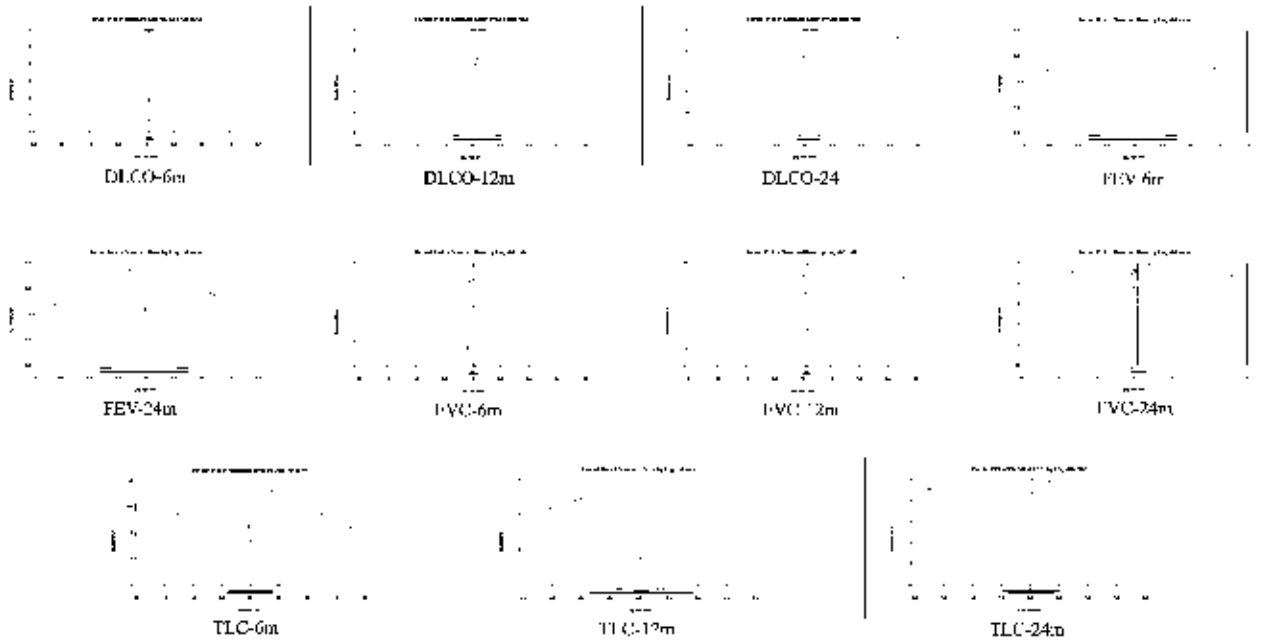
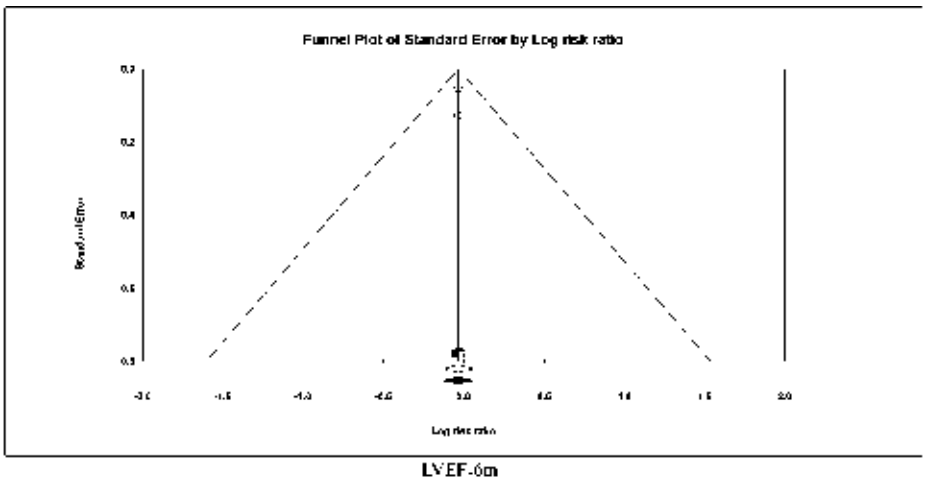
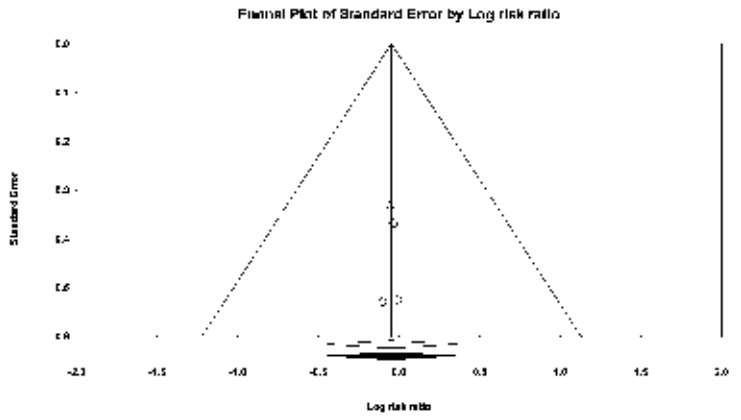


Fig. 22 Begg's funnel plots to explore the possibility of publication bias in the pooled estimate of rituximab efficacy on lung function of SSc patient at different treatment months (m)

Fig. 23 Begg's funnel plots to explore the possibility of publication bias in the pooled estimate of rituximab efficacy on heart function of SSc patient at different treatment months (m)



LVEF-6m



sPOP-6m

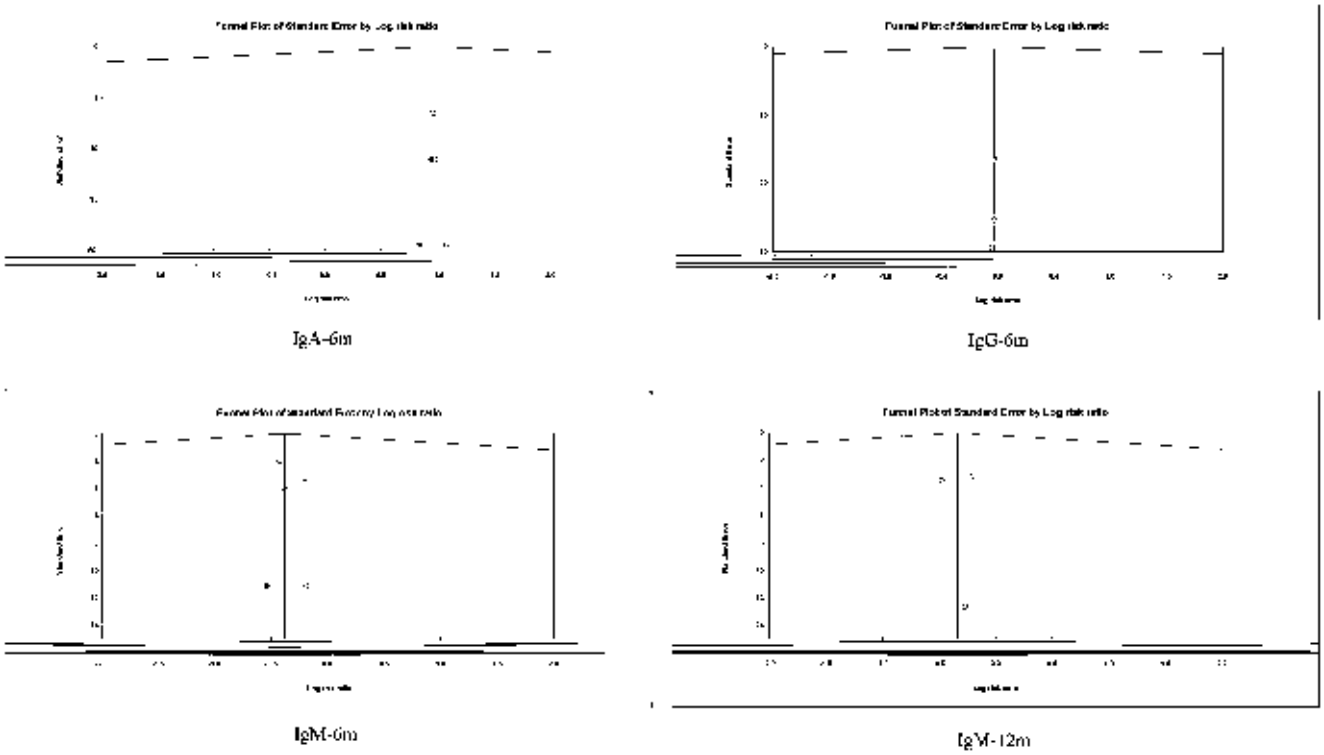


Fig. 24 Begg's funnel plots to explore the possibility of publication bias in the pooled estimate of rituximab efficacy on immunoglobulin factors of SSc patient at different treatment months (m)

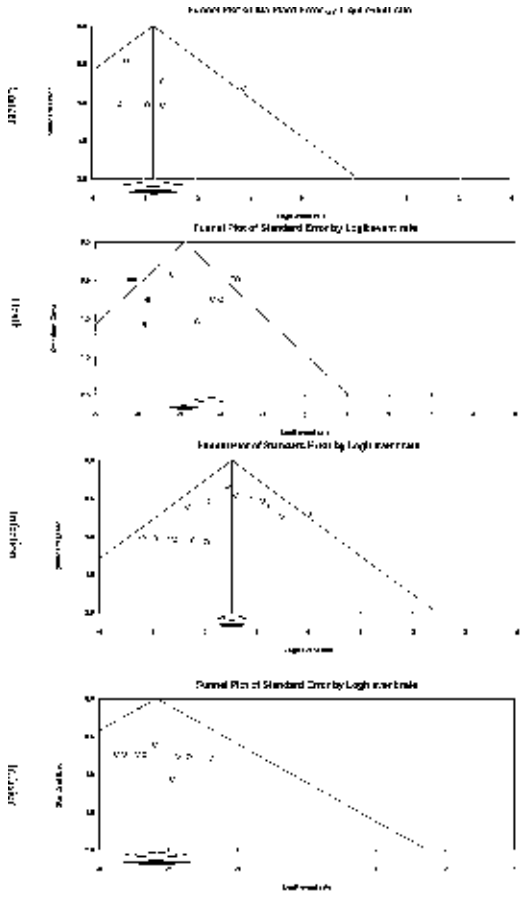


Fig. 25 Begg's funnel plots to explore the possibility of publication bias in the pooled estimate of rituximab efficacy on safety parameters of SSc patient at the end of follow-up

Conclusion

Based on our literature review, RTX is relatively safe and well tolerated, reduces the clinical skin score, significantly improves the quality of life, and may prove effective in stabilizing internal organ involvement in patients with SSc. Still, these promising results about RTX efficacy should be confirmed in large-scale and multicenter phase III randomized-controlled trials compared with matched-control SSc patients who do not receive RTX treatment.

Abbreviations PRISMA-P, preferred reporting items for systematic reviews and meta-analyses protocols; SSc, systemic sclerosis; ILD, interstitial lung disease; RTX, rituximab; mRSS, modified Rodnan Skin Score; FVC, forced vital capacity; DLCO, diffusing capacity of the lungs for carbon monoxide; TLC, total lung capacity; FEV, forced expiratory volume; sPAP, systolic pulmonary artery pressure; HAQ-DI, Health Assessment Questionnaire Disability Index; SF-36, short form 36; MS, Myofibroblast Score; DAS, Disease Activity Score; LVEF, left ventricular ejection fraction; Ig, immunoglobulin; DMARDs, disease modifying anti-rheumatic drugs

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Author contribution MM conceived of the study, participated in its design and coordination, and critically revised the manuscript. ZA had full access to all the data collection, analysis, interpretation, and drafted the manuscript. MA, ZM, NA were the study investigators and contributed to the process of data collection. All authors read and approved the final manuscript.

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Declarations

Disclosures None.

References

1. Denton CP, Khanna D (2017) Systemic sclerosis. Lancet 390: 1685–1699
2. Jordan S, Distler JHW, Maurer B, Huscher D, van Laar JM, Allanore Y, Distler O (2015) Effects and safety of rituximab in systemic sclerosis: an analysis from the European Scleroderma Trial and Research (EUSTAR) group. Ann Rheum Dis 74:1188–1194
3. Bosello S, De Santis M, Lama G, Spanò C, Angelucci C, Tolusso B, Sica G, Ferraccioli G (2010) B cell depletion in diffuse progressive systemic sclerosis: safety, skin score modification and IL-6 modulation in an up to thirty-six months follow-up open-label trial. Arthritis Res Ther 12:R54
4. Pittman N, Rawn SM, Wang M, Masetto A, Beattie KA, Larché M (2018) Treatment of small intestinal bacterial overgrowth in systemic sclerosis: a systematic review. Rheumatology 57:1802–1811
5. The L (2017) Systemic sclerosis: advances and prospects. Lancet (London, England) 390:1624
6. Daoussis D, Tsamandas A, Antonopoulos I, Filippopoulou A, Papachristou DJ, Papachristou NI, Andonopoulos AP, Liossis S-N (2016) B cell depletion therapy upregulates Dkk-1 skin expression in patients with systemic sclerosis: association with enhanced resolution of skin fibrosis. Arthritis Res Ther 18:118
7. Bosello SL, De Luca G, Rucco M, Berardi G, Falcione M, Danza FM, Pirronti T, Ferraccioli G (2015) Long-term efficacy of B cell depletion therapy on lung and skin involvement in diffuse systemic sclerosis. In: Seminars in arthritis and rheumatism vol 4. Elsevier, pp 428-436
8. Bellan M, Patrucco F, Barone-Adesi F, Gavelli F, Castello LM, Nerviani A, Andreoli L, Cavagna L, Pirisi M, Sainaghi PP (2019) Targeting CD20 in the treatment of interstitial lung diseases related to connective tissue diseases: a systematic review. Autoimmun Rev:102453
9. Tang R, Yu J, Shi Y, Zou P, Zeng Z, Tang B, Wang Y, Ling G, Luo M, Xiao R (2020) Safety and efficacy of Rituximab in systemic sclerosis: a systematic review and meta-analysis. Int Immunopharmacol 83:106389
10. Daoussis D, Liossis S, Tsamandas A, Kalogeropoulou C, Paliogianni F, Sirinian C, Yiannopoulos G, Andonopoulos A (2012) Effect of long-term treatment with rituximab on pulmonary function and skin fibrosis in patients with diffuse systemic sclerosis. Clin Exp Rheumatol 30:S17
11. Sircar G, Goswami RP, Sircar D, Ghosh A, Ghosh P (2018) Intravenous cyclophosphamide vs rituximab for the treatment of early diffuse scleroderma lung disease: open label, randomized, controlled trial. Rheumatology 57:2106–2113
12. Fraticelli P, Fischetti C, Salaffi F, Carotti M, Mattioli M, Pomponio G, Gabrielli A (2018) Combination therapy with rituximab and mycophenolate mofetil in systemic sclerosis. A single-centre case series study. Clin Exp Rheumatol 36:S142–S145
13. Sancho JA, Narváez J, Castellví I, Herrera S, Molina M, Castillo D, Rodríguez JO, De la Morena BI, Villarino MR, Pascual EV (2014) FRI0485 Long-term efficacy of rituximab in systemic sclerosis. A Spanish multicentric analysis. Ann Rheum Dis 73:563–563
14. Ananyeva L, Desinova O, Starovoytova M, Koneva O, Yutkina N, Onsyannikova O, Volkov A, Aleksandrova E (2013) SAT0198 Rituximab for the treatment of systemic sclerosis associated interstitial lung disease: a case series. Ann Rheum Dis 72:A648–A648
15. Daoussis D, Liossis S-N, Antonopoulos I, Markatseli T, Yiannopoulos G, Drosos A, Andonopoulos A (2013) THU0245 Rituximab has a beneficial effect on lung function and skin fibrosis in patients with systemic sclerosis. An open label study. Ann Rheum Dis 71:237–238
16. Guzelant G, Melikoglu M, Musellim B, Yilmaz D, Fresko I, Seyahi E, Hatemi G, Ugurlu S, Hamuryudan V (2017) AB0634 Rituximab in systemic sclerosis-interstitial lung disease, a case series of 18 patients. BMJ Publishing Group Ltd,
17. Melissaropoulos K, Daoussis D, Antonopoulos I, Markatseli T, Georgiou P, Yiannopoulos G, Drosos A, Andonopoulos A, Liossis S (2015) SAT0450 Rituximab in systemic sclerosis. Results of an up to seven years, open label, multicenter study with a follow-up of 89 patient-years. BMJ Publishing Group Ltd,
18. Kiryttopoulos P, Michailidis T, Papchianou E, Charalampidis M, Dimitriadis P, Agorastos A (2017) FRI0412 The positive effect of rituximab in pulmonary fibrosis of systemic sclerosis. BMJ Publishing Group Ltd,
19. Thiebaut M, Launay D, Riviere S, Mahévas T, Bellakhal S, Hachulla E, Fain O, Mekinian A (2018) Efficacy and safety of

rituximab in systemic sclerosis: French retrospective study and literature review. Autoimmun Rev 17:582–587
20. Lepri G, Avouac J, Airò P, Anguita Santos F, Bellando-Randone S, Blagojevic J, Garcia Hernàndez F, Gonzalez Nieto JA, Guiducci S, Jordan S (2016) Effects of rituximab in connective tissue disorders related interstitial lung disease. Clin Exp Rheumatol 34:181–185
21. Booth A, Clarke M, Dooley G, Ghersi D, Moher D, Petticrew M, Stewart L (2012) The nuts and bolts of PROSPERO: an international prospective register of systematic reviews. Syst Rev 1:2
22. Moradzadeh M, Aghaei M, Mehrbakhsh Z, Abdollahi N, Arab Bafrani Z (2018) Efficacy and safety of Rituximab therapy for patients with systemic sclerosis disease (SSc): systematic review and meta-analysis [CRD42018103751].
23. Wan X, Wang W, Liu J, Tong T (2014) Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol 14:135
24. Faul F, Erdfelder E, Lang A-G, Buchner A (2007) G* Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods 39:175–191
25. Veroniki AA, Jackson D, Viechtbauer W, Bender R, Bowden J, Knapp G, Kuss O, Higgins JP, Langan D, Salanti G (2016) Methods to estimate the between-study variance and its uncertainty in meta-analysis. Res Synth Methods 7:55–79
26. Lajeunesse MJ (2011) On the meta-analysis of response ratios for studies with correlated and multi-group designs. Ecology 92:2049–2055
27. Borenstein M, Hedges LV, Higgins J, Rothstein HR (2009) Converting among effect sizes. Introduction to Meta-analysis:45–49
28. Higgins JP, Thompson SG, Deeks JJ, Altman DG (2003) Measuring inconsistency in meta-analyses. Bmj 327:557–560
29. Lafyatis R, Kissin E, York M, Farina G, Viger K, Fritzler MJ, Merkel PA, Simms RW (2009) B cell depletion with rituximab in patients with diffuse cutaneous systemic sclerosis. Arthritis Rheum 60:578–583
30. Daoussis D, Liossis S-NC, Tsamandas AC, Kalogeropoulou C, Kazantzi A, Sirinian C, Karampetsou M, Yiannopoulos G, Andonopoulos AP (2010) Experience with rituximab in scleroderma: results from a 1-year, proof-of-principle study. Rheumatology 49:271–280
31. Smith V, Piette Y, Van Praet JT, Decuman S, Deschepper E, Elewaut D, De Keyser F (2013) Two-year results of an open pilot study of a 2-treatment course with rituximab in patients with early systemic sclerosis with diffuse skin involvement. J Rheumatol 40:52–57
32. Daoussis D, Melissaropoulos K, Sakellaropoulos G, Antonopoulos I, Markatseli TE, Simopoulou T, Georgiou P, Andonopoulos AP, Drosos AA, Sakkas L A (2017) multicenter, open-label, comparative study of B-cell depletion therapy with Rituximab for systemic sclerosis-associated interstitial lung disease. In: Seminars in arthritis and rheumatism vol 5. Elsevier, pp 625-631
33. Melsens K, Vandecasteele E, Deschepper E, Badot V, Blockmans D, Brusselle G, De Langhe E, De Pauw M, Debusschere C, Decuman S (2018) Two years follow-up of an open-label pilot study of treatment with rituximab in patients with early diffuse cutaneous systemic sclerosis. Acta Clin Belg 73:119–125
34. Giuggioli D, Lumetti F, Colaci M, Fallahi P, Antonelli A, Ferri C (2015) Rituximab in the treatment of patients with systemic sclerosis. Our experience and review of the literature Autoimmunity reviews 14:1072–1078
35. Sari A, Guven D, Armagan B, Kilic L, Erden A, Akdogan A (2017) AB0604 Rituximab experience in patients with longstanding systemic sclerosis-associated interstitial lung disease: a series of 14 patients. BMJ Publishing Group Ltd,
36. Elhai M, Boubaya M, Distler O, Smith V, Matucci-Cerinic M, Sancho JJA, Truchetet M-E, Braun-Moscovici Y, Iannone F, Novikov PI (2019) Outcomes of patients with systemic sclerosis treated with rituximab in contemporary practice: a prospective cohort study. Ann Rheum Dis 78:979–987
37. Ebata S, Yoshizaki A, Fukasawa T, Miura S, Takahashi T, Sumida H, Asano Y, Sato S (2019) Rituximab therapy is more effective than cyclophosphamide therapy for Japanese patients with anti-topoisomerase I-positive systemic sclerosis-associated interstitial lung disease. J Dermatol 46:1006–1013
38. Jordan S, Distler JH, Maurer B, Huscher D, Van Laar JM, Allanore Y, Distler O, group ERs (2014) Effects and safety of rituximab in systemic sclerosis: an analysis from the European Scleroderma Trial and Research (EUSTAR) group. Annals of the Rheumatic diseases:annrheumdis-2013-204522
39. Vilela VS, Maretti GB, Gama LMdS, Costa CHd, Rufino RL, Levy RA (2016) Rituximab for the therapy of systemic sclerosis: a series of 10 cases in a single center. Rev Bras Reumatol 56:458-463
40. Teng YO, Levarht EN, Hashemi M, Bajema IM, Toes RE, Huizinga TW, van Laar JM (2007) Immunohistochemical analysis as a means to predict responsiveness to rituximab treatment. Arthritis Rheum 56:3909–3918
41. Edginton S, Hitchon C, Froese W, El-Gabalawy H (2016) Effects of Rituximab and Infliximab treatment on carboxypeptidase B and its substrates in RA synovium. J Rheumatol 43:846–854
42. Sari A, Guven D, Armagan B, Erden A, Kalyoncu U, Karadag O, Bilgen SA, Ertenli I, Kiraz S, Akdogan A (2017) Rituximab experience in patients with long-standing systemic sclerosis–associated interstitial lung disease: a series of 14 patients. J Clin Rheumatol 23:411–415
43. Steen VD, Medsger TA Jr (2000) Severe organ involvement in systemic sclerosis with diffuse scleroderma. Arthritis Rheum 43:2437–2444
44. Smith V, Van Praet JT, Vandooren B, Van der Cruyssen B, Naeyaert J-M, Decuman S, Elewaut D, De Keyser F (2010) Rituximab in diffuse cutaneous systemic sclerosis: an open-label clinical and histopathological study. Ann Rheum Dis 69:193–197
45. Kumánovics G, Péntek M, Bae S, Opris D, Khanna D, Furst DE, Czirják L (2017) Assessment of skin involvement in systemic sclerosis. Rheumatology 56:v53–v66
46. Khanna D, Furst DE, Clements PJ, Allanore Y, Baron M, Czirjak L, Distler O, Foeldvari I, Kuwana M, Matucci-Cerinic M (2017) Standardization of the modified Rodnan skin score for use in clinical trials of systemic sclerosis. J Scleroderma Relat Disord 2:11–18
47. Gale SL, Trinh H, Mathew N, Jahreis A, Lin CJF, Sarsour K (2020) Characterizing disease manifestations and treatment patterns among adults with systemic sclerosis: a retrospective analysis of a US healthcare claims population. Rheumatol Ther 7:89–99
48. Cohen SB, Emery P, Greenwald MW, Dougados M, Furie RA, Genovese MC, Keystone EC, Loveless JE, Burmester GR, Cravets MW, Hessey EW, Shaw T, Totoritis MC (2006) 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 54:2793–2806
49. Saunders P, Tsipouri V, Keir GJ, Ashby D, Flather MD, Parfrey H, Babalis D, Renzoni EA, Denton CP, Wells AU (2017) Rituximab versus cyclophosphamide for the treatment of connective tissue disease-associated interstitial lung disease (RECITAL): study protocol for a randomised controlled trial. Trials 18:275

50. Elhai M, Boubaya M, Distler O, Smith V, Matucci-Cerinic M, Alegre Sancho JJ, Truchetet M-E, Braun-Moscovici Y, Iannone F, Novikov PI, Lescoat A, Siegert E, Castellví I, Airó P, Vettori S, De Langhe E, Hachulla E, Erler A, Ananieva L, Krusche M, López-Longo FJ, Distler JHW, Hunzelmann N, Hoffmann-Vold A-M, Riccieri V, Hsu VM, Pozzi MR, Ancuta C, Rosato E, Mihai C, Kuwana M, Saketkoo LA, Chizzolini C, Hesselstrand R, Ullman S, Yavuz S, Rednic S, Caimmi C, Bloch-Queyrat C, Allanore Y (2019) Outcomes of patients with systemic sclerosis treated with rituximab in contemporary practice: a prospective cohort study. Ann Rheum Dis 78:979–987

51. Daoussis D, Melissaropoulos K, Sakellaropoulos G, Antonopoulos I, Markatseli TE, Simopoulou T, Georgiou P, Andonopoulos AP, Drosos AA, Sakkas L, Liossis S-N (2017) A multicenter, open-label, comparative study of B-cell depletion therapy with Rituximab for systemic sclerosis-associated interstitial lung disease. Semin Arthritis Rheum 46:625–631