Is rituximab effective for systemic sclerosis? A systematic review and meta-analysis

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Abstract

Background: Systemic sclerosis (SSc) is a clinically complex and challenging disease, that leads to skin fibrosis. Its most frequent complication is interstitial lung disease (ILD), which leads to a worse prognosis. In this situation, cyclophosphamide is considered the gold standard for its treatment, despite the controversies regarding its efficacy and toxicity. However, studies using rituximab (RTX) have shown that this drug may be a promising therapeutic option.

Objectives: This paper objective was to analyze the scientific evidence on the RTX effects on SSc.

Methods: A systematic review (SR) was performed including clinical trials (CTs) on the use of RTX in SSc, published up to May 2020. The studies were identified through systematic searches in bibliographic databases using a predefined search strategy. The following databases were used: PUBMED, SCOPUS, SCIELO, LILACS, SCIENCE DIRECT, WEB OF SCIENCE, COCHRANE, WHOLIS, PAHO and EMBASE. Also, a manual search was performed. The methodological quality of the studies was determined using Jadad scale, Risk of Bias Tool (RoB 2.0) and Risk of Bias in Non-Randomized Studies - of Interventions tool (ROBINS-I). A meta-analysis of the randomized CTs was performed, using Review Manager.

Results: Ten CTs were included in this SR. Of these, three were randomized and seven were non-randomized. Five showed a statistically significant improvement in forced vital capacity (FVC) at some time during follow-up. Regarding the skin, eight studies showed statistically significant improvements according toa the modified Rodnan skin score. The meta-analysis found positive effects of RTX in SSc, with a statistical significance for lung disease.

Conclusion: Rituximab is a promising strategy for the SSc-associated ILD and cutaneous fibrosis treatment. PROSPERO registration number: CRD42019132018.

Keywords: Systemic sclerosis, Rituximab, Interstitial lung disease, Cutaneous fibrosis, Systematic review

Introduction

Systemic sclerosis (SSc) is an autoimmune connective tissue disease characterized by vascular dysfunction and excessive collagen deposition, resulting in skin fibrosis and internal organs involvement [1–4].

The SSc pathogenesis is not completely understood, but B cell abnormalities are part of this complex disorder [5, 6]. The disease is associated with significant incapacity and mortality [2]. Pulmonary involvement is a common clinical presentation. Dyspnea or cough are late signs, but systematic CT practice shows that about 40–50% of patients have interstitial lung lesions and 10–20% of all patients will develop respiratory failure [7]. Interstitial lung disease (ILD) and pulmonary artery hypertension (PAH) are the two major causes of death in SSc [4,

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8–10]. According to the skin involvement degree, there are different clinical presentations, especially limited systemic sclerosis and diffuse systemic sclerosis, with various extents of internal organ damage [1, 2].

Classical immunosuppressants have shown very modest effects and their clinical relevance is uncertain [7]. Methotrexate can be used as treatment for skin manifestations in early diffuse SSc [11]. Treatment for SSc-associated ILD is based on the European League Against Rheumatism (EULAR) recommendations, i.e. the use of cyclophosphamide (CYC) [2, 9, 12, 13]. However, this drug is associated with teratogenicity, gonadal failure, bone marrow suppression and infection [2]. Besides, within the first SSc lung study, the CYC effect decreased a few months after cessation [14]. Mycophenolate mofetil (MMF) has been suggested as an alternative for induction and maintenance of the imunosuppressive treatment and has been shown to stabilize lung function in some studies [14]. Recently, other immune-based, targeted therapies have been investigated. Hematopoietic stem cell transplantation and B cell depletion therapy (CD20) have shown good results [12, 15, 16].

Rituximab (RTX) is a monoclonal chimeric antibody against CD20 that depletes peripheral B cells. It was first approved for indolent non-Hodgkin lymphoma treatment in 1994. Over the last few years, RTX has been used off-label in transplant rejection and immune-mediated diseases such as multiple sclerosis, autoimmune hemolytic anemia, immune thrombocytopenic purpura, and systemic autoimmune rheumatic diseases other than rheumatoid arthritis [11]. Its use in SSc has been proposed because of the growing evidence about the B cells role in SSc [17].

The incapacity and mortality caused by SSc-ILD, the fragility of current therapies and the new evidence supporting treatment with RTX justifies the importance of this review. Therefore, the aim of this study was to analyze the evidence available in experimental studies that evaluated the rituximab effects on the pulmonary and skin function in patients with systemic sclerosis.

Methods
Protocol and registration
This review was conducted in accordance with a study protocol [18] and the Preferred Reporting for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [19]. The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) on 24 July 2019 (CRD42019132018).

Eligibility criteria
Inclusion criteria
Studies that met the following eligibility criteria were included: (P) studies performed on patients with systemic sclerosis, diagnosed using the ACR/EULAR (2013) [20] and/or Leroy classification for SSc [21]; (I) interventions with the use of rituximab; (C) placebo or other treatment; (O) analysis of ILD and pulmonary fibrosis; (S) randomized clinical trials (RCT) and nonrandomized (Non-RCT).

Exclusion criteria
Reviews, case reports, abstracts, thesis and other types of epidemiologic studies were excluded of the Systematic Review.

Information sources and literature search
The search was performed independently by the researchers MMVFC, ACFN, IDSFP and IDTA in the following databases: PUBMED, SCOPUS, SCIELO, LILACS, SCIENCE DIRECT, WEB OF SCIENCE, COCHRANE, WHOLIS, PAHO and EMBASE, until May 20th, 2020. The search strategy used was: ("RITUXIMAB") AND ("SCLERODERMA SYSTEMIC" OR "SYSTEMIC SCLEROSIS") AND ("CLINICAL TRIAL"). Also, a manual search was performed.

The first selection was focused on the title and abstract, with no limitations on the publication date. The articles were uploaded in Rayyan platform [22] for title and abstract reading. In this stage, all articles that did not directly address the subject of interest were excluded and duplicated titles were removed. Three reviewers (MMVFC, ACFN, IDSFP) did independently this step; doubts were clarified with the aid of a fourth researcher (KPMA).

The articles that met the criteria were directed to a full reading (second stage). After reading the complete articles, the researchers (MMVFC, ACFN, IDSFP) selected the articles to be included in the review. The discrepancies or doubts were resolved under the guidance of a fourth researcher (KPMA).

Data extraction
The following data were extracted from the selected articles: authors, year of publication, study location, type of study, sample size and age, patient characteristics, duration of intervention, therapeutic scheme, follow-up time, main variables and main results.

Two reviewers (MMVFC and IDTA) were responsible for extracting and managing the data independently, which were inserted into an EXCEL® spreadsheet; doubts were clarified with the help of the third researcher (KPMA).

Risk of bias assessment
The methodological quality of the randomized clinical trials was assessed using the Jadad scale. The Jadad scale consists of five questions that assess three factors:

randomization, blinding and withdrawals and dropouts description [23]. For the risk of bias assessment, the risk of bias tool (RoB 2.0) was applied in the randomized clinical trials. The risk of bias tool assessed the adequate random sequence generation, allocation concealment, participant and staff blinding, blinding outcome assessment, selective reporting, and other sources of bias. Regarding the classification, the risk of bias was assessed as low, high or unclear [24].

Non-RCTs were evaluated by the "Risk of Bias in Non-Randomized Studies - of Interventions" tool (ROBINS-I) [25]. Domains can be classified as [1]: low risk of bias [2]; moderate risk of bias [3]; serious risk of bias [4]; critical risk of bias; and [5] no information. Three researchers (KPMA, VHOS and ACFN) independently assessed the methodological quality of the studies (RCTs and Non-RCTs) and the differences were resolved with the help of the fourth researcher (GP).

Data analysis and synthesis

The means and standard deviations of the pre and post-intervention evaluations were extracted. With these values the variation delta ($\triangle$) and the variation standard deviations were calculated for the intervention and control groups. In the descriptive analysis, the results were presented by means of standardized mean differences (SMD) between the groups (intervention and control). Then, the assessment of heterogeneity was calculated using the chi-square and I^2 statistical tests. To calculate the total effect size of the studies, the random effects model was applied. All analyses were performed using Review Manager 5.3 [26].

Results

A total of 2790 articles were generated through the database first search. After duplicates were removed, the new total was 1784 articles. These were screened using the titles and abstracts. The full texts of the remaining 23 articles were then assessed for eligibility. Thirteen articles were excluded because they did not fulfill the eligibility criteria or did not answer the research question. Through manual search, only one article was included. Figure 1 shows the PRISMA flowchart.

Fig. 1 Selection of manuscripts for the systematic review
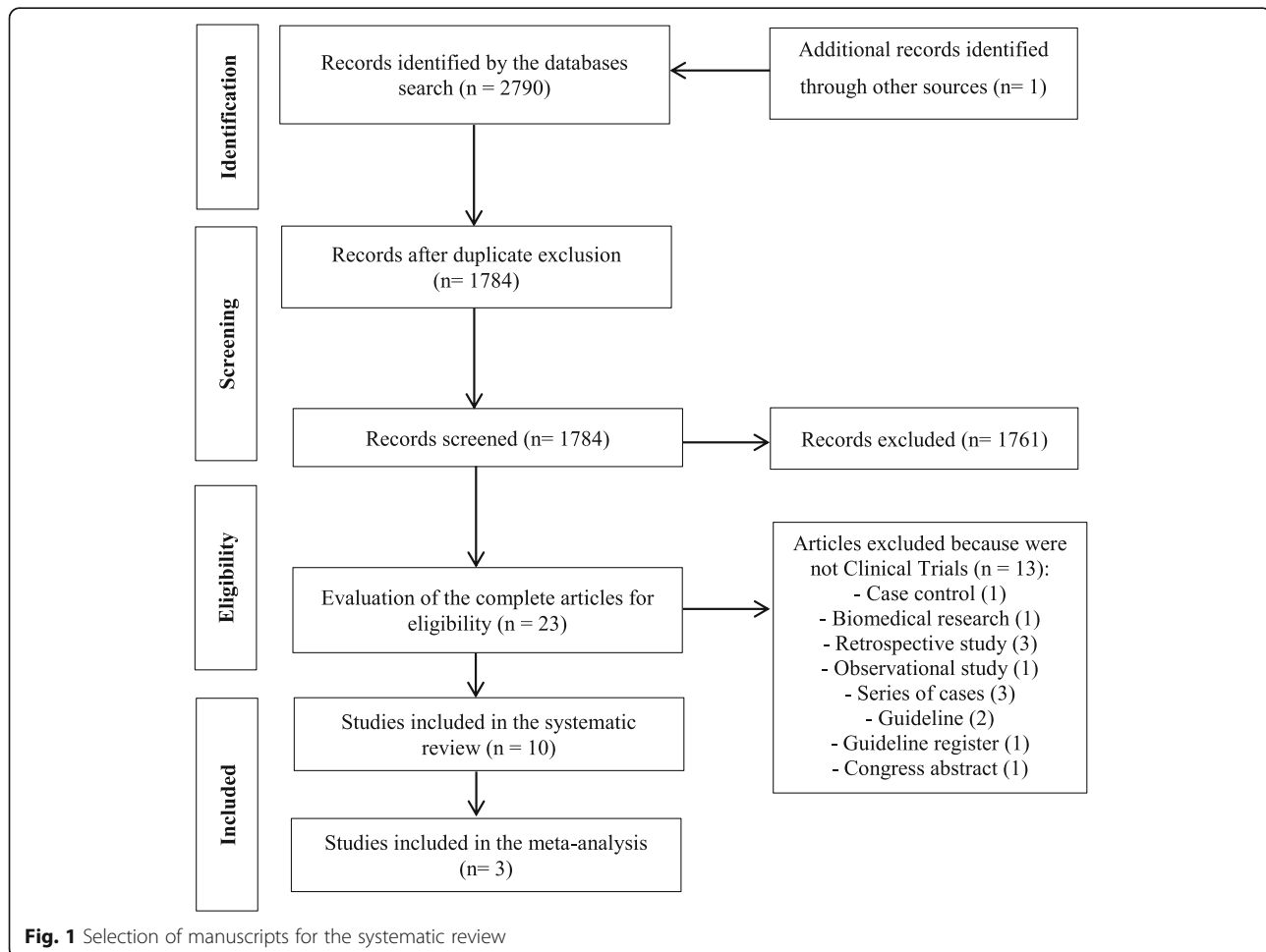
In total, 10 articles met the inclusion criteria. Of these studies, three were RCTs [17, 27, 28] and seven were Non-RCTs [5, 12, 16, 29–32]. Patients were confirmed to have SSc based on ACR/EULAR and/or LeRoy criteria.

RCTs

The total number of SSc patients included was 90. The studies were performed in Netherlands, Greece and India. Sample sizes ranged from 14 to 60 patients. The ages ranged from 32.3 to 68.5 years. Most of the patients were female (85.4%). The follow up time ranged from 6 months to 2 years (Table 1).

Regarding lung fibrosis assessments and the treatment response follow-up, all three articles used FVC pulmonary function tests and lungs diffusing capacity for carbon monoxide. Only Boonstra et al. (2017) and Daoussis et al. (2010) used high resolution computed tomography. Daoussis et al. (2010) also used forced expiratory volume in one second (FEV1). For the cutaneous fibrosis evaluation, the studies used the modified Rodnan skin score (mRSS) and histological assessment of skin fibrosis.

About the pulmonary fibrosis tomographic evaluation, Boonstra et al. (2017) used the Goh criteria for analysis, showing a change in the lung tissue affected percentage by comparing the initial analysis and the evaluation at 12 months: – 1.6% in the RTX group and + 2.8% in the placebo group ($p = 0.28$). Daoussis et al. (2010), using the score proposed by Warrick et al. (1991), reported that CT scores were identical at baseline and at 24 weeks in all patients in the RTX group; a non-statistically significant increase was reported in the control group [33].

About the adverse events, Boonstra et al. (2017) reported one death (placebo group) due to disease progression, and Sircar et al. (2018) reported two deaths: one patient developed severe pulmonary arterial hypertension 5 months after the completion of the trial (in RTX group) and another patient, in control group, developed scleroderma renal crises and died 3 months after the sixth dose of CYC. However, pulmonary infection, breast carcinoma, abnormal cervical histology leading to hysterectomy, anemia due to severe menstruation, pancytopenia and digital ulcers were the adverse events related to RTX groups. Two studies reported mild reactions to the RTX [27, 28].

The Jadad scale was used to assess the quality of the randomized controlled trials. This score consists of five questions that assess three factors: randomization, blinding, and the withdrawals and dropouts description. After the evaluation, it was observed that all three articles obtained 3 points and that the main problems were related to blinding (Table 2). Regarding the evaluation of the risk of bias from RCTs, Table 3 presents the assessments of the two articles for all Rob 2.0 domains.

Analyzing the risk of bias, the study by Boonstra et al. (2017) [27] and the one by Sircar et al. (2018) [28] had a low risk of bias. On the other hand, in the research carried out by Daoussis et al. (2010) [17] some concerns were observed in the randomization process and in the deviations from the intended interventions (Table 3).

Characteristics and study designs are available on Tables 1 below.

NRCTs

The total number of SSc patients included was 128. The studies were performed in several locations: three studies in Belgium, two in Italy, one in Greece and one in the USA. Sample sizes ranged from 8 to 51 patients. The ages ranged from 28.3 to 69 years. Most of the patients were female (64.4%). The follow up time ranged from 24 weeks to 86 months (Table 4).

Regarding lung fibrosis assessments and the treatment response follow-up, all articles used FVC pulmonary function tests, lungs diffusing capacity carbon monoxide and high-resolution computed tomography. Some articles also used total pulmonary capacity and forced expiratory volume in one second (FEV1). For the cutaneous fibrosis evaluation, most articles used the modified Rodnan skin score (mRSS) and/or biopsy and immunohistochemical analysis.

Regarding the tomographic evaluation of pulmonary fibrosis, Bosello et al. (2015) used the criteria proposed by Kazerooni et al. [34], with no significant change in the tomographic scores. Lafyatis et al. (2009) and Melsens et al. (2017) concluded that patients did not show new lesions or lung disease progression on CT. Smith et al. (2010), Smith et al. (2013) and Bosello et al. (2010) did not report the results of tomographic lung analyses performed on their patients. Data on the evolution of mRSS and FVC can be found in Table 4.

Four Non-RCTs reported deaths. The study by Bosello et al. (2015) reported two deaths (cardiovascular involvement). Smith et al. (2013) reported one death from sepsis (port vein catheter infection after coronary bypass surgery). Melsens et al. (2017) reported one death due to sepsis (central venous catheter infection after coronary bypass) and one death from pancreatic cancer. Five deaths were noted in the RTX group of the study performed by Daoussis et al. (2017): three of respiratory failure, one of lung cancer and one died while sleeping.

Regarding serious adverse events, there were some types of cancers (breast, prostate and pancreas), herpes zoster infection, ulcer infections, respiratory infections, dental abscess, fever without an infectious focus, coronary bypass, secondary infection, urinary infection, hospitalizations for hyperventilation and renal crisis from scleroderma.

Table 1 Summary of randomized clinical trial data according to author, country, sample characterization, RTX scheme and follow-up, adverse events and main results

Author (year)	Country	Randomization	Sample (Total / RTX / Control)	Age (Min-Max/ Mean +/− SD)	Female sex (%)	Follow-up	RTX scheme	AE	Outcomes		Skin - mRSS Control group	Skin - mRSS RTX group	Lung - FVC (%) Control group	Lung - FVC (%) RTX group	Tomographic analysis	Jadad score
Sircar et al. (2018)	India	Yes	60/ 30/ 30	CG: 36.50 ± 9,73 RTX: 34.67 ± 8.13	83	6 months	Two RTX pulses of 1000 mg at 0 and 15 days i.v, and 1000 mg of RTX after 6 months as maintenance therapy	Yes	Time	Start	23.83 ± 9.28	21.77 ± 9.86	59.25 ± 12.96	61.30 ± 11.28	No	3
										6 months	18.33 ± 7.69 (+)	12.10 ± 10.14 (+)	58.06 ± 111.23	67.52 ± 13.59		
Boonstra et al. (2017)	Netherlands	Yes	16/ 8/ 8	CG: 36.6 ± 4.3 RTX: 44.5 ± 5.6	87.5	2 years	1000 mg, two infusions, two weeks apart, and one 1000 mg RTX consolidation treatment once, after 6 months	Yes	Time	Start	14.0 ± 3.8	16.4 ± 4.4	92.0 ± 6.1	97.9 ± 6.6	Yes	**3**
										12 months (Δ)	- 1.8	- 3.6	+ 0.3	+ 4.7		
										24 months (Δ)	- 1.9	- 5.3	- 1.4	+ 4.0		
Daoussis et al. (2010)	Greece	Yes	14/ 8/ 6	CG: 47.7–68.5/ 56 RTX: 41.0–66.5/ 53	85.7	1 year	Two cycles of RTX. Each cycle consisted of four infusions of 375 mg per m² of body area, once a week, repeated after 6 months	Yes	Time	Start	11.5 ± 2.16	13.5 ± 6.9	86.0 ± 19.6	68.1 ± 19.7	Yes	**3**
										12 months	9.7 ± 3.4	8.4 ± 6.5 (+)	81.7 ± 20.7	75.6 ± 19.7 (+)		

* Data not reported in article; (+) statistically significant

Table 2 Methodological design evaluation of the RCTs according to the JADAD scale (2005), classified in descending order

	Was the study described as randomized?	Was the randomization method appropriate?	Was the study described asblinding?	Was the blinding method appropriate?	Was there a withdrawals and dropouts description?	Total score
Sircar et al. (2018)	1	1	0	0	1	3
Boonstra et al. (2017)	1	0	1	0	1	**3**
Daoussis et al. (2010)	1	1	0	0	1	**3**

Regarding the evaluation of the risk of bias from NRCTs, Table 5 presents the assessments of the studies evaluated by ROBINS-I. It was observed that 3 studies had a low risk of bias [30–32], 3 critical bias [12, 16, 29] and 1 serious bias [5]. It is worth noting that the most problematic domains in the evaluations were related to confounding and missing data (Table 5).

Meta-analysis of the effects of rituximab on the lung and skin

In the meta-analysis, the three RCTs were included and the results are presented for pulmonary and skin outcomes after the follow-up period (6 to 12 months). The data described in Fig. 2 point to a positive and significant effect on lung function with the rituximab use (SMD 0.66 (Forced Vital Capacity - FVC); 95% CI 0.23 to 1.09; $p = 0.003$). In this analysis, low heterogeneity was found ($I^2 = 0\%$; $p = 0.69$).

Regarding the skin outcome, although we did not detect any significant difference between the experimental and control group, favorable results were observed for the rituximab use with a skin fibrosis reduction (SMD – 0.40 (modified Rodnan skin score - mRSS); 95% CI – 0.92 to 0.11; $p = 0.12$). Heterogeneity was classified as moderate ($I^2 = 43\%$; $p = 0.28$) (Fig. 3).

Discussion

This SR verified that, for SSc-associated ILD, the RTX use led to, in most cases, a non-statistically significant improvement. However, the results obtained in the meta-analysis point to a positive effect of the rituximab use on the lung function and skin fibrosis in patients with systemic sclerosis, but the significant effect was detected only for the pulmonary outcome. The results of this meta-analysis may have been influenced by the small sample size. Besides, the studies in this SR revealed a small number of clinical trials with few included subjects, the absence of blinding, disparate RTX therapeutic schemes and the use of several different parameters to evaluate the treatment response.

Following the EULAR recommendations, two studies guided the treatment of SSc-associated ILD with CYC and were classified by the Jadad score as having high quality [13, 23]. The two articles included in the EULAR protocol obtained the maximum score (5 points) in addition to good methodological quality, as they were randomized, double-blind, placebo-controlled and multicentric studies. Tashkin et al. (2006) reported that one year of oral CYC treatment resulted in a slight but significant improvement in FVC and total lung capacity [35]. Conversely, Hoyles et al. (2006) found no significant improvement in FVC and computed tomography in the CYC group [36].

Comparing these studies with those included in this systematic review, it can be noted that, in most of the studies, FVC was used as the primary endpoint with computed tomography of the chest as a secondary analysis. The RCTs included in our meta-analysis have lower scores in Jadad (3 points) and have some frailty on evaluation of risk of bias in ROB 2.

Regarding cutaneous involvement in SSc, this SR found that the use of RTX led to, in eight of the ten studies, a statistically significant improvement at some point during follow-up [5, 12, 16, 17, 30–32]. In the

Table 3 Risk of bias in RCTs (Rob 2.0)

	Randomization process	Intended interventions deviations	Missing outcome data	Outcome measurement	Reported result selection	Overall bias
Sircar et al. (2018	Low	Low	Low	Low	Low	Low
Boonstra et al. (2017)	Low	Low	Low	Low	Low	Low
Daoussis et al. (2010)	Some concerns	Some concerns	Low	Low	Low	Some concerns

Table 4 Summary of non-randomized clinical trial data according to author, country, sample characterization, RTX scheme and follow-up, adverse events and main results

Author (year)	Country	Sample (Total/RTX/Control)	Age (Min-Max/Mean +/− SD)	Female sex (%)	Follow-up	RTX scheme	AE	Outcomes					Tomographic analysis
								Time	Skin - mRSS Control group	Skin - mRSS RTX group	Lung - FVC (%) Control group	Lung - FVC (%) RTX group	
Daoussis et al. 2017	Greece	51/33/18	CG: 52.11 ± 16.10 RTX: 54.3 ± 14.33	80.39	7 years	Two or more RTX cycles. Each cycle consisted of four infusions of 375 mg per m² of body area, once a week, repeated every 6 months.	Yes	Start	17.78 ± 9.48	14.72 ± 10.52	77.72 ± 18.29	80.6 ± 21.21	Yes
								12 months	15.78 ± 9.89	8.83 ± 7.83 (+)	77.18 ± 19.25	83.02 ± 19.05	
								24 months	13.72 ± 9.67 (+)	5.93 ± 5.15 (+)	77.59 ± 19.45	86.9 ± 20.56 (+)	
								36 months	15.53 ± 9.53(+)	4.53 ± 5.29 (+)		*	
								48 months	13.64 ± 8.56(+)	5.37 ± 8.34 (+)		*	
								7 years	*	*	61.11 ± 15.73 (+)	91.69 ± 14.81	
Bosello et al. 2015	Italy	20/20/0	RTX: 41.4 ± 13.1	85	86 months	1000 mg, two infusions, two weeks apart.	Yes	Start		22.3 ± 9.5		87.4 ± 19.5	Yes
								6 months		14.4 ± 8.4(+)		89.0 ± 17.	
								12 months		11.2 ± 7.5(+)		90.7 ± 17.9 (+)	
								24 months		9.95 ± 6.0(+)		89.9 ± 21.2	
								36 months		8.1 ± 5.2(+)		94.0 ± 16.1	
								48 months		9.8 ± 7.2(+)		95.6 ± 20.7	
Lafyatis et al. 2009	USA	15/15/0	RTX: 32.0–57.0/ 45.8	86.66	1 year	1000 mg, two infusions, two weeks apart.	Yes	Start		20.6 ± 4.4		89.2 ± 10.8	Yes
								6 months		20.2 ± 5.5		92.7 ± 10.3	
								12 months		21.1 ± 5.2		*	

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Table 4 Summary of non-randomized clinical trial data according to author, country, sample characterization, RTX scheme and follow-up, adverse events and main results *(Continued)*

Author (year)	Country	Sample (Total / RTX / Control)	Age (Min-Max/ Mean +/– SD)	Female sex (%)	Follow-up	RTX scheme	AE	Time	Skin - mRSS	Lung - FVC (%)	Tomographic analysis
Melsens et al. 2017	Belgium	17/17/0	RTX: 36.0–69.0/ 51.0	35,3	2 years	1000 mg, two infusions, two weeks apart and 1000 mg, two infusions, two weeks apart, after 6 months.	Yes	Start	25.5 ± 6.0	93.5 ± 11.3	Yes
								3 months	18.6 ± 6.5 (+)	90.7 ± 11.6	
								6 months	14.6 ± 6.2 (+)	93.3 ± 13.4	
								12 months	10.7 ± 3.5 (+)	95.6 ± 13.5	
								15 months	9.7 ± 3.5(+)	98.0 ± 13.7 (+)	
								18 months	9.8 ± 3.8(+)	95.0 ± 15.4	
								24 months	12.6 ± 5.1(+)	90.5 ± 16.3	
Smith et al. 2010	Belgium	8/8/0	RTX: 49.0–57.0	37.5	24 weeks	1000 mg, two infusions, two weeks apart.	Yes	Start	24.8 ± 3.4	83.9 ± 8.1	Yes
								12 weeks	19.4 ± 5.4(+)	81.0 ± 17.7	
								24 weeks	14.3 ± 3.5(+)	77.0 ± 9.8	
Smith et al. 2013	Belgium	8/8/0	RTX: 49.0–69.0/ 38.0	37,5	2 years	1000 mg, two infusions, two weeks apart and 1000 mg, two infusions, two weeks apart, after 6 months.	Yes	Start	24.8 ± 3.4	92.8 ± 8.6	Yes
								3 months	19.4 ± 5.4(+)	88.5 ± 12.9	
								6 months	14.3 ± 3.5(+)	88.3 ± 9.3	
								12 months	10.8 ± 4.6(+)	89.2 ± 13.7	
								15 months	10.0 ± 2.6(+)	94.4 ± 10.1	
								18 months	10.8 ± 2.6(+)	89.8 ± 12.0	
								24 months	13.6 ± 5.6(+)	84.7 ± 13.3 (+)	

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Table 4 Summary of non-randomized clinical trial data according to author, country, sample characterization, RTX scheme and follow-up, adverse events and main results *(Continued)*

Author (year)	Country	Sample (Total / RTX / Control)	Age (Min-Max/ Mean +/− SD)	Female sex (%)	Follow-up	RTX scheme	AE	Outcomes			Tomographic analysis
								Yes	Time	Skin - mRSS	Lung - FVC (%)	
Bosello et al. 2010	Italy	9/9/0	RTX: 40.9 ± 11.1	88,9	3 years	1000 mg, two infusions, two weeks apart.	Yes	Start	21.1 ± 9.0	91.6 ± 20.7	Yes
								3 months	15.2 ± 6.0	*	
								6 months	12.0 ± 6.1(+)	*	
								12 months	7.0 ± 4.0	*	
								18 months	7.0 ± 3.5	*	
								24 months	5.0 ± 2.0	*	
								36 months	4.0 ± 1.4	96.8 ± 18.9	

* Data not reported in article; (+) statistically significant

Table 5 Risk of bias in Non-RCTs (ROBINS-I)

	Confounding	Participants selection	Interventions classification	Intended interventions deviations	Missing data	Outcomes measurement	Reported results classification	Overall judgment
Daoussis et al. (2017)	Serious	Low	Low	Low	Critical	Low	Low	Critical
Bosello et al. (2015)	Critical	Low	Low	Low	Low	Low	Low	Critical
Lafyatis et al. (2009)	Critical	Low	Low	Low	Low	Low	Low	Critical
Melsens et al. (2017)	Low	Low	Low	Low	Low	Low	Low	Low
Smith et al. (2010)	Low	Low	Low	Low	Low	Low	Low	Low
Smith et al. (2013)	Low	Low	Low	Low	Low	Low	Low	Low
Bosello et al. (2010)	Serious	Low	Low	Low	Low	Low	Low	Serious

meta-analysis, although we did not detect any significant difference in relation to the control group, favorable results were observed for the rituximab use in skin fibrosis reduction. The studies included in the meta-analysis used different RTX schemes, have lower scores in Jadad (3 points) and have some frailty on the risk of bias evaluation in ROB 2.

According to the EULAR recommendations for SSc cutaneous fibrosis, methotrexate (MTX) is indicated as the gold standard for treatment, based on two studies indicating that this drug improves the modified Rodnan skin score (mRSS), but the effects on other organs have not been established [37, 38]. The studies were rated with scores 3 and 5 on the Jadad scale and were randomized, used a placebo in the control group and assessed the mRSS.
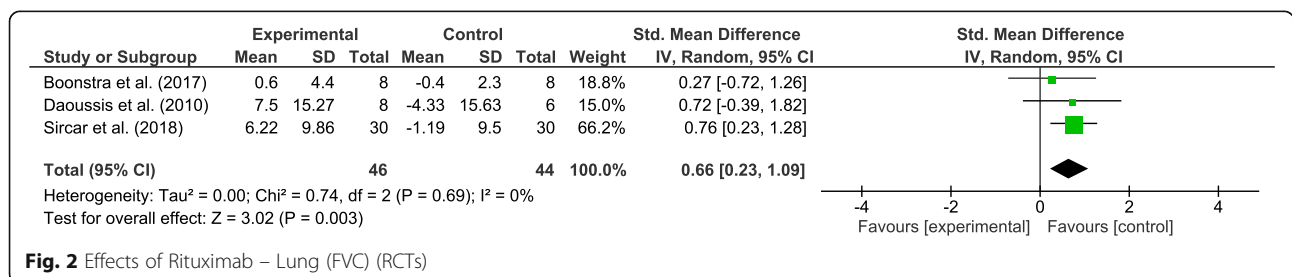
Van Den Hoogen et al. (1996) concluded that a greater number of SSc patients responded favorably to MTX compared to placebo [37]. The results of Pope et al. (2001) showed a favorable trend with the MTX use over placebo, but the differences between groups were considered subtle [38]. However, despite the EULAR recommendations for the MTX use, it is important to point out that, from the patient safety point of view, the use of this drug can cause liver toxicity, pancytopenia, teratogenesis and lung injury [39].
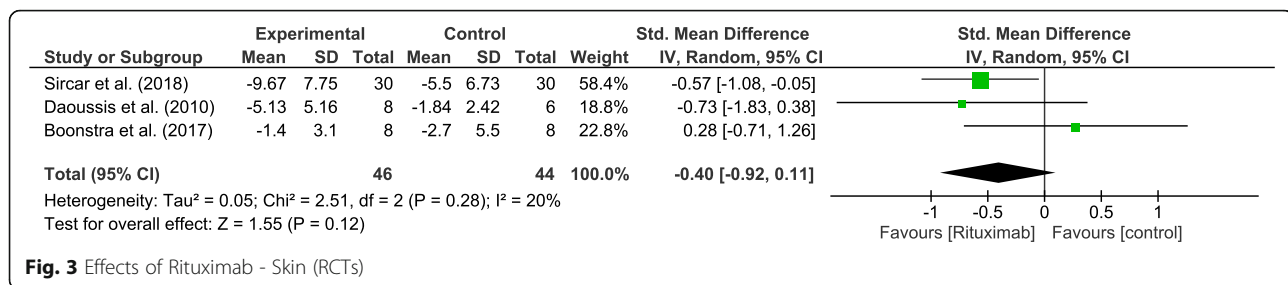
The main adverse events associated with the RTX use in SSc were mild infusion reactions, besides sepsis, urinary tract, pulmonary, herpes zoster and cardiovascular involvement. In addition, four studies reported deaths [12, 16, 28, 30, 32].

Infusion-related reactions (IRRs) are common, especially when no premedication is given. Infections are the most prevalent side effect next to IRRs [11]. However, severe infusion reactions occur in approximately 10% of patients. In most cases adverse events are reversible by interruption of RTX in addition to supportive care, but severe consequences of infusion reactions have been reported, including pulmonary and cardiovascular events [40].

Regarding the malignancy risk, no elevations in solid tumor or lymphoma rates have been observed in patients using RTX, except for patients with T cell deficiency in HIV infection [40]. From this perspective, the pattern of AEs of the RTX use in these diseases is like that found in this SR, using RTX in SSc.

As a chronic disease with different types of presentation, SSc symptoms significantly disrupt daily activities and diminish quality of life [41, 42]. The major complaints are the classic skin hardening that restricts everyday activities, especially manual ones, and the substantial symptom burden [43]. Fatigue, pain and depressive

Fig. 2 Effects of Rituximab – Lung (FVC) (RCTs)

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Study or Subgroup	Experimental			Control			Weight	Std. Mean Difference IV, Random, 95% CI	Std. Mean Difference IV, Random, 95% CI
	Mean	SD	Total	Mean	SD	Total			
Sircar et al. (2018)	-9.67	7.75	30	-5.5	6.73	30	58.4%	-0.57 [-1.08, -0.05]	
Daoussis et al. (2010)	-5.13	5.16	8	-1.84	2.42	6	18.8%	-0.73 [-1.83, 0.38]	
Boonstra et al. (2017)	-1.4	3.1	8	-2.7	5.5	8	22.8%	0.28 [-0.71, 1.26]	
Total (95% CI)			**46**			**44**	**100.0%**	**-0.40 [-0.92, 0.11]**	

Heterogeneity: Tau² = 0.05; Chi² = 2.51, df = 2 (P = 0.28); I² = 20%
Test for overall effect: Z = 1.55 (P = 0.12)

Favours [Rituximab]   Favours [control]

Fig. 3 Effects of Rituximab - Skin (RCTs)

symptoms are also common. Other complaints include unpredictable disease course, especially the diffuse form, and internal organs ailments [44]. Because SSc is diagnosed in early to middle age and has no cure, individuals with SSc face many years of managing the manifestations of a complex and progressive condition [45]. Thus, the improvement of parameters related to skin and pulmonary function may bring greater comfort and quality of life to patients with systemic sclerosis, relieving their main complaints.

The main difficulties in conducting this study were that most of the selected articles were not controlled clinical trials (NRCT), the disparate RTX therapeutic regimens and the use of several different parameters to evaluate the treatment response.

A recent systematic review with meta-analysis, performed by Tang at al. (2020), analyzed the improvement in cutaneous fibrosis and pulmonary function associated to the RTX use, similar to our study, however, the focus was on the safety and efficacy profile of Rituximab in SSc patients, as well as adverse events. Besides that, they did not include only clinical trials and used a different strategy to analyze risk of bias and the methodological quality of RCTs and NRCTs (the Newcastle – Ottawa scale) [46].

Tang et al. showed a long-term improvement in the modified Rodnan skin score (mRSS). Pulmonary function (using Forced Vital Capacity – FVC – and Diffusing Capacity of the Lungs for Carbon Monoxide – DLCO) remained stable. The ΔmRSS was: 7.00 at 6 months, 9.70 at 12 months, and 10.93 at 24 months. The ΔFVC: – 0.69 at 6 months, – 2.62 at 12 months, and – 0.67 at 24 months. ΔDLCO was: – 2.39 at 6 months, – 3.28 at 12 months, and – 0.79 at 24 months. The rate of Rituximab-related adverse events was 12% [46]. Thus, our review aims to ratify these results, bringing more accurate data in the meta-analysis, since it addressed only RCTs and provided guidance and recommendations for new studies.

Conclusion

Rituximab is a drug that has been causing growing interest in the scientific community as an important alternative for the sclerosis treatment and should be widely studied. Analyzing the results presented in our review, we can conclude that rituximab represents a promising strategy for the treatment of ILD and cutaneous fibrosis associated with SSc. The meta-analysis of the three RCTs identified that RTX use had a positive effect both on pulmonary function and on improving skin changes in patients with systemic sclerosis, with a significant difference for the lung outcome. However, studies with good methodological quality and larger sample must be performed to a more effective conclusion. The present study recommends that randomized, double-blind, crossover, multicenter trials should be performed, with an appropriate sample number and a well-defined follow-up time. Moreover, these trials should standardize the RTX and control group therapeutic regimens and the clinical methods of assessing the disease and treatment response. These studies will demonstrate the RTX behavior in the systemic sclerosis treatment, so that clinical decisions regarding its use in SSc are well-supported and patients can benefit from this new therapeutic option.

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Availability of data and materials
Not applicable.

Ethics approval and consent to participate
Ethical approval and informed consent are not necessary for this research, because it is a systematic review (use of secondary data).

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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