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The effect of rituximab on systemic sclerosis: A systematic review and meta-analysis

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Abstract---Background: Skin fibrosis is a complication of the multifaceted and difficult condition known as systemic sclerosis (SSc). The interstitial lungs disease (ILD), which is a common consequence, has a worse prognosis. Although debates concerning its effectiveness and toxicity, cyclophosphamide is regarded as the gold standard for treating this condition. Furthermore, research employing the medication rituximab (RTX) has indicated that this treatment option could be beneficial. Objectives: The goal of this research was to evaluate the available scientific data on the impact of RTX on SSc. Methods: Clinical trials (CTs) investigating the application of RTX in SSc, published up to 2022, and were included in a systematic review (SR). Using methodical searching in academic databases employing a predetermined research methodology, the articles were located. SCIENCE DIRECT, SCOPUS, SCIELO, LILACS, PUBMED, , COCHRANE, WHOLIS, EMBASE, PAHO, and WEB OF SCIENCE were among the resources examined. A manually searching was done as well. Through using Jadad score, the Risk of Bias Tool (RoB 2.0), and the Risk of Bias in Non-Randomized Trials - of Treatments tools, the technical quality of the articles was assessed (ROBINS-I). Utilizing Review Manager, a meta-analysis of the randomized CTs had been carried out. Results: According to the current systematic review, ten CTs had been included. Seven of them weren't randomized, while three of them were. At some point during the follow-up, the forcing vital capacity (FVC) of five patients improved significantly. Based on the improved Rodnan skin scoring, eight researches on skin demonstrated statistically significant changes. The meta-analysis discovered RTX's beneficial effects in SSc, with lung disease

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statistically significant. Conclusion: Rituximab is a viable therapy option for SSc-related cutaneous fibrosis as well as ILD.

Keywords---Interstitial lung disease, Rituximab, Systemic sclerosis, Systematic review, cutaneous fibrosis.

Introduction

Skin fibrosis and internal organs involvements are symptoms of the autoimmunity connectively tissues diseases systemic sclerosis (SSc), which is characterized by vascular dysfunctions and extensive collagen deposition (1-3).

B cell disorders are a component of this complex illness, however the pathophysiology of SSc is not fully known. Substantial disability and mortality are linked to the condition. A typical medical manifestation is pulmonary dysfunction. Dyspnea and coughing are delayed indications, but a thorough CT study reveals that 40–50% of individuals had interstitial lungs lesions, and 10–20% of all individuals will eventually experience respiratory distress (4). The two primary reasons for mortality in SSc are intermittent lungs disease (ILD) and pulmonary artery hypertensions (PAH). There are several clinical manifestations, including restricted inflammatory disease and widespread systemically sclerosis, with varying degrees of internal organs failure, based on the level of skin involvements (5, 6).

The therapeutic significance of traditional immunosuppressant drugs has not been established, and their impacts have been relatively small. Initially widespread SSc skin symptoms can be treated with methotrexate (7). The European Leagues Against Rheumatisms (EULAR) recommends using cyclophosphamide as part of the therapy for SSc-associated ILD (CYC) (8, 9). Furthermore, this medication has been linked to teratogenic effects, gonadal insufficiency, suppressions of the bones marrow, and infections (10, 11). Additionally, the CYC impact diminished a few months after termination in the initial SSc pulmonary research (12). Mycophenolate mofetil (MMF), which has been proven in certain trials to stabilize lungs functions, has been suggested as a substitute for the initiation and maintenance of the immunosuppressive therapy (13). Additional tailored immunotherapies have lately been researched. B cells elimination treatment (CD20) and hematopoietic stem transplants have both produced positive outcomes (14, 15).

Monoclonal chimerics antibodies targeting CD20, rituximabs (RTX), deprives periphery B lymphocytes. It was initially authorized in 1994 for the therapy of sluggish non-Hodgkin lymphoma (16). Recently, RTX has been employed off-label to treat immune-mediated illnesses like multiple sclerosis, autoimmune hemolytics anemias, immunological thrombocytopenic purpuras, and systemically autoimmunity rheumatics diseases other than rheumatoid arthritis as well as transplantation rejections (17). Its usage in SSc has already been suggested due to mounting data about the involvement of B lymphocytes in SSc (18).

The fragilities of present therapy, the fatality and incapacitating effects of SSc-ILD, and the fresh findings in favor of RTX therapy justify the significance of this study (19). As a result, the objective of this research was to look into the data from experimentations that assessed how rituximab affected individuals with systemic sclerosis' respiratory and cutaneous functions.

Methods

Guidelines and registrations

This study was carried out according to a study methodology (6) as well as the Recommended Reporting for Systematic Reviews and Meta-Analyses (PRISMA) criteria (20).

Eligibility criteria

Inclusion criteria

The primary data sources were included if they matched the eligibility requirements: (P) research on systemic sclerosis sufferers who were identified by the ACR/EULAR (2013) (21) and/or Leroy categorization for SSc (22); Assessment of ILD and pulmonary fibrosis; C placebo or other treatments; O randomized clinical studies (RCT) and non - randomized clinical studies (non RCT); S (Non-RCT).

Exclusion criteria

The Systematic Review did not include evaluations, case studies, abstractions, theses, or even other forms of observational studies.

Resources of data and bibliography searches

Up until 2022, the datasets EMBASE, SCIELO, PAHO, LILA CS, SCIENCE DIRECT, COCHRANE, WHOLIS, SCOPUS, WEB OF SCIENCE, and PUBMED were searched separately first by authors MMVFC, ACFN, IDSFP, and IDTA. The keywords "CLINICAL TRIAL" and "SYSTEMIC SCLEROSIS" or "SCLERODERMA SYSTEMIC" and "RITUXIMAB" were used in the selection method. A manually searching was done as well.

Without regard to publishing date restrictions, the initial choice concentrated on the titles and abstracts. The papers were posted on the Rayyan portal (23) for readers to peruse the titles and abstracts. At this step, duplicated headings and other items that were not specifically mention the topic of interest were eliminated. This stage was separately completed by three reviewers (MMVFC, ACFN, and IDSFP), and questions were answered by a fourth investigator (KPMA). The papers that satisfied the requirements were sent for a thorough perusal (secondly staging). The investigators (MMVFC, ACFN, and IDSFP) chose the studies that would be considered for the assessment after reading the full publications. Underneath the direction of a fourth investigator, the disagreements or questions were clarified (KPMA).

Collecting Data

Publishers, year of publishing, research site, kind of analysis, sampling size and age, patient factors, length of treatment, treatment plan, follow-up period, key variables, and key findings were all taken from the chosen papers.

The data was gathered and managed individually by two reviewers (MMVFC and IDTA), who then entered them into an EXCEL® worksheet. Questions were answered by the third reviewer (KPMA).

Risk of bias evaluation

The Jadad score was used to rate the randomized clinical studies' methodological quality. Five questions make up the Jadad score, which evaluates three variables: randomization, blinding, and descriptions of withdrawals and failures (24). The hazard of bias instrument (RoB 2.0) was used in the randomized clinical trials to evaluate the risk of bias. The sufficient randomness generating, allocation concealment, participation and personnel blinding, blinding outcomes evaluation, biased reporting, and other elements of bias were all evaluated using the risk of bias instrument. The danger of bias was classified as being low, high, or ambiguous (25).

The "Risk of Bias in Non-Randomized Trials - of Treatments" instrument (ROBINS-I) (26) was used to assess non-RCTs. The following categories of disciplines are available: [1] lower risk of bias [2] moderately risk of bias [3] seriously risk of bias [4] severe risk of bias [5] and [1] insufficient data. The scientific quality of the experiments (RCTs and Non-RCTs) was evaluated separately by three experts (KPMA, VHOS, and ACFN), and any discrepancies were settled with the assistance of the fourth investigator (GP).

Dataset synthesis and assessment

The pre and post-interventional assessment' means and standard deviations were retrieved. These variables were used to determine the variance delta (△) and variance standard deviations for the intervention and control cohorts. Findings from the data statistic were shown using standardized mean differences (SMD) between the categories (interventions and controls). Subsequently, the chi-square and I2 statistical measures were used to determine the measurement of heterogeneity. The random effects modeling was used to determine the cumulative effect size of the investigations. Utilizing Review Manager 5.3, all analyses were carried out.

Results

The databases first searching produced an aggregate of 2790 publications. 1784 publications were added to the total after duplication was eliminated. By using the titles and abstracts, they were evaluated. The eligibility of the remaining 23 papers was subsequently evaluated using their whole contents. Thirteen publications were disqualified since they failed to meet the requirements for

eligibility or because they failed to address the research issue. There was only one article found by manually searching. Figure 1 displays a flowchart for PRISMA.

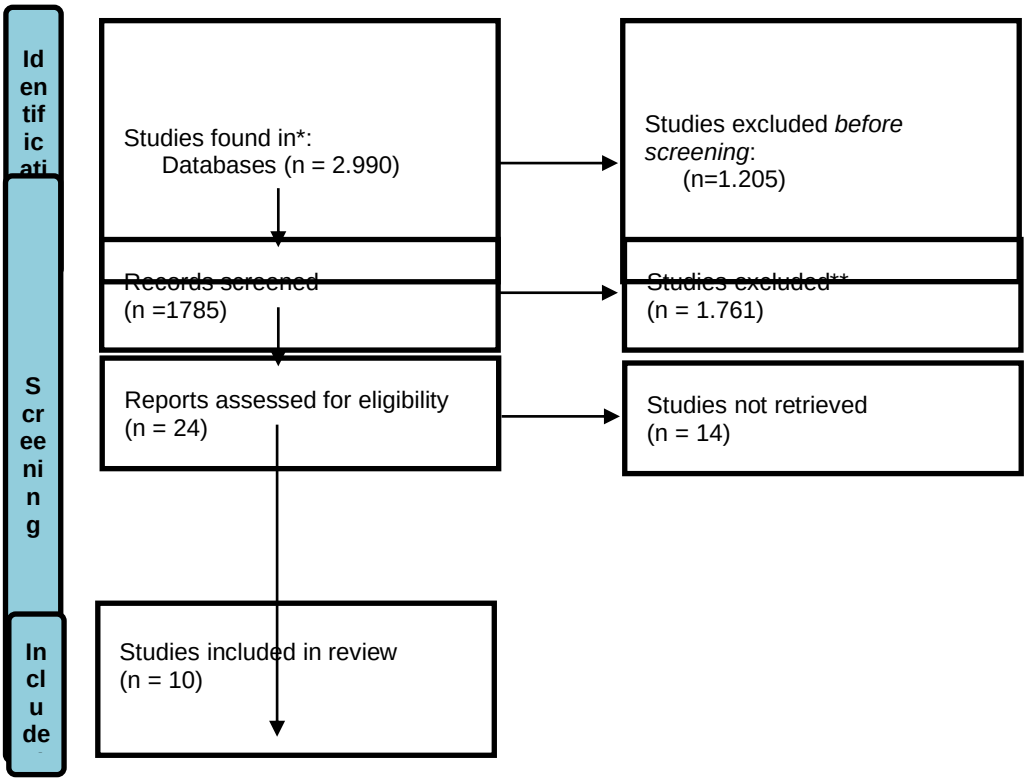

Figure (1): PRISMA chart of the included studies

Ten items in overall satisfied the criteria for inclusion. Three of these investigations (9, 27, 28) were RCTs, while seven (3, 12, 29-33) were Non-RCTs.

SSc was determined to exist in patients based on ACR/EULAR and/or LeRoy guidelines.

RCTs

There were 90 SSc individuals who participated in the study overall. The experiments were carried out in India, Greece, and the Netherlands. 14 to 60 individuals made up the sample sizes. The range of ages was 32.3 to 68.5. The majority of participants were women (85.4 percent). The follow-up period lasted between six months and two years (Table 1 and 2).

Table 1 Data from randomized clinical trials summarized in authors, site of the study, samples characterizations, RTXs schemes and follow-up, adverse events and main findings:

Authors (years)	**Site of the study**	**Randomizations**	**Samples (Totally / RTXs / Controls)**	**Age (Minimum-Maximum/ Mean ± SD)**	**Females (%)**	**Follow-up duration**	**RTXs schemes**
Daoussis et al. (2010) (27)	Greece	Randomized	14/ 8/ 6	**Control Group:** 47.7–68.5/ 56 **RTX group:** 41.0–66.5/ 53	85.7	One year	Two RTXs rounds. Every phase included four 375 mg per m2 of bodily area injections given once every week for six months.
Boonstra et al. (2017) (9)	Netherlands	Randomized	16/ 8/ 8	**Control Group:** 36.6 ± 4.3 **RTX group:** 44.5 ± 5.6	87.5	Two years	Single 1000 mg RTXs consolidating therapy once, after six months, and two infusions of 1000 mg spaced two weeks later.
Sircar et al. (2018) (28)	India	Randomized	60/ 30/ 30	**Control Group:** 36.50 ± 9,73 **RTX:** 34.67 ± 8.13	83	Six months	Two 1000 mg RTX pulses given intravenously at Zero & fifteen days, and then 1000 mg of RTX given as standard treatment at six months.

Table 2 AE findings of the RCT studies included:

	AE findings		**Skin – mRSS**		**Lungs - FVC (%)**		**Tomographic analysis**	**Jadad scoring**
Daous	Detect		**Skin -**		**Lung -**		Detected	3

sis et al. (2010) (27)	ed		**mRSS**		**FVC (%)**			
		Timing	**Control grouping**	**RTXs grouping**	**Control grouping**	**RTXs grouping**		
		Starting	11.5 ± 2.16	13.5 ± 6.9	86.0 ± 19.6	68.1 ± 19.7		
		One year	9.7 ± 3.4	8.4 ± 6.5 (+)	81.7 ± 20.7	75.6 ± 19.7 (+)		
Boonstra et al. (2017) (9)	Detected		Skin - mRSS		Lung - FVC (%)		Detected	3
		Timing	**Control grouping**	**RTXs grouping**	**Control group**	**RTXs grouping**		
		Starting	14.0 ± 3.8	16.4 ± 4.4	92.0 ± 6.1	97.9 ± 6.6		
		One year (Δ)	- 1.8	- 3.6	+ 0.3	+ 4.7		
		Two years (Δ)	- 1.9	- 5.3	- 1.4	+ 4.0		
Sircar et al. (2018) (28)	Detected	**Timing**	**Control grouping**	**RTXs grouping**	**Control grouping**	**RTXs grouping**	Not detected	3
		Starting	23.83 ± 9.28	21.77 ± 9.86	59.25 ± 12.96	61.30 ± 11.28		
		Six months	18.33 ± 7.69 (+)	12.10 ± 10.14 (+)	58.06 ± 111.23	67.52 ± 13.59		

All three publications employed FVC respiratory functional testing and lungs diffusion capacities for carbon monoxide to evaluate lungs fibrosis and monitor therapy responses. Highly resolution computed tomography was only employed by Boonstra et al. (2017) (9) and Daoussis et al. (2010) (27). Additionally, forceful expiratory volumes in one second were employed by Daoussis et al. (2010) (27).

(FEV1). The improved Rodnan skin scoring (mRSS) and histopathological examination of skin fibrosis were utilized in the research to assess the cutaneous fibrosis.

Through making comparisons among the preliminary evaluations and the assessment at twelve months, Boonstra et al. (2017) (9) have used Goh eligibility requirements for analysis in relation to the pulmonary fibrosis computed tomography assessment, demonstrating a transformation in the lungs cells directly affected proportion: 1.6 percent in the RTX cohort and + 2.8 percent in the placebo cohort (p = 0.28). Using the scoring given by Warrick et al. (1991), Daoussis et al. (2010) (27) observed that CT ratings were the same for all participants in the RTX cohort at starting and at four months; a non-statistically significantly increase was observed for the control group (34).

Regarding side effects, Sircar et al. (2018) mentioned 2 deaths: one case developing serious pulmonary arterial hypertensions five months after the trial's conclusion (in the RTX cohort), as well as another participant in the healthy controls evolved scleroderma renal catastrophes and passed away three months just after sixth daily dosage of CYC. Boonstra et al. (2017) (9) revealed one death (placebo cohort) because of disease advancement. Nevertheless, the side effects associated with RTX groupings included lung infections, breast cancer, and aberrant cervical histopathology culminating to hysterectomy, anemia from heavy menstruation, pancytopenia, and digitally ulceration. To the RTX, two investigations found very minor side effects (9, 28).

The standard of the randomized clinical trials was evaluated using the Jadad scale. Five questions make up this scoring, which evaluates three elements: randomization, blinding, and the explanation of withdrawal and failures. Following examination, it was noted that all three papers received three points, with blinding issues constituting the primary issues (Table 3). Table 4 provides evaluations of the two publications for each Rob 2.0 category in relation to the evaluation of the probability of bias from Randomized trials.

Table 3 RCTs' technical designs using the JADAD scale (2005) ranked in decreasing order.

	Was the research characterized as being random?	**Was the randomized technique suitable?**	**Was the research referred to as blinding?**	**Was the blinding techniue suitable?**	**Was there an explanation of departures and dropouts?**	**Overall rating**
Daoussis et al. (2010) (27)	1	1	0	0	1	3
Boonstra et al. (2017) (9)	1	0	1	0	1	3

Sircar et al. (2018) (28)	1	1	0	0	1	3

The studies conducted by Boonstra et al. (2017) (9) and Sircar et al. (2018) (28) had minimal levels of bias, according to an analysis of the risk of bias. But at the other side, several problems were found in the randomization method and in the departures from the targeted interventions in the study conducted by Daoussis et al. (2010) (27) (Table 4).

Table 4 Risk of bias in RCTs (Rob 2.0)

	Randomized technique	**Intentional errors in treatments**	**Absent outcomes information**	**Outcomes evaluation**	**choice of data reported**	**Total bias**
Daoussis et al. (2010) (27)	Some concerns	Some concerns	Weak	Weak	Weak	Some concerns
Boonstra et al. (2017) (9)	Weak	Weak	Weak	Weak	Weak	Weak
Sircar et al. (2018) (28)	Weak	Weak	Weak	Weak	Weak	Weak

NRCTs

There were 128 SSc individuals who participated in the study. Three investigations were conducted in Belgium, two in Italy, one in Greece, and one in the United States, among other locales. Patient sampling ranged in size between 8 and 51. The participants' ages ranged from 28.3 to 69. The majority of cases were women (64.4 percent). The duration of the follow-up period was 24 weeks to 86 months (Table 5 and 6).

Table 5 Data from randomized clinical trials summarized in authors, site of the study, samples characterizations, RTXs schemes and follow-up:

Authors (years)	**Site of the study**	**Samples (Totally / RTXs / Controls)**	**Age (Minimum - Maximum / Mean ±**	**Females (%)**	**Follow-up duration**	**RTXs schemes**

			SD)			
Bosello et al. 2010 (29)	Italy	9/9/0	**RTXs group:** 40.9 ± 11.1	88,9	36 months	Two injections of 1000 mg, spaced two weeks apart.
Smith et al. 2013 (32)	Belgium	8/8/0	**RTXs group:** 49.0–69.0/ 38.0	37,5	24 months	After six months, receive another 1000 mg in two separate treatments spaced by two weeks.
Smith et al. 2010 (31)	Belgium	8/8/0	**RTXs group:** 49.0–57.0	37.5	24 weeks	Two injections of 1000 mg, spaced two weeks apart.
Melsens et al. 2017 (12)	Belgium	17/17/0	**RTXs group:** 36.0–69.0/ 51.0	35,3	24 months	After six months, receive another 1000 mg in two separate infusions spaced by two weeks.
Lafyatis et al. 2009(30)	USA	15/15/0	**RTXs group:** 32.0–57.0/ 45.8	86.66	Twelve months	1000 mg, given twice, 2 weeks separated.
Bosello et al. 2015 (33)	Italy	20/20/0	**RTXs group:** 41.4 ± 13.1	85	86 months	Two injections of 1000 mg, spaced two weeks apart.
Daoussis et al. 2017 (3)	Greece	51/ 33/ 18	**Control Group:** 52.11 ± 16.10 **RTXs group:** 54.3 ± 14.33	80.39	Seven years	at least two RTX phases. Each six months, four cycles of 375 mg per m2 of body area administered every week made up every phase.

Table 6 AE findings of the NRCTs studies included:

	AE findings		**Skin – mRSS**	**Lungs - FVC (%)**	**Tomographic analysis**
Bosello et al. 2010 (29)	Detected	**Timing**	**Skin - mRSS**	**Lung - FVC (%)**	Detected
		Starting	21.1 ± 9.0	91.6 ± 20.7	
		Three months	15.2 ± 6.0	Not reported	
		Six months	12.0 ± 6.1(+)	Not reported	
		One year	7.0 ± 4.0	Not reported	
		18 months	7.0 ± 3.5	Not reported	
		Two years	5.0 ± 2.0	Not reported	
		Three years	4.0 ± 1.4	96.8 ± 18.9	
Smith et al. 2013 (32)	Detected	**Timing**	**Skin - mRSS**	**Lungs - FVC (%)**	Detected
		Starting	24.8 ± 3.4	92.8 ± 8.6	
		Three months	19.4 ± 5.4(+)	88.5 ± 12.9	
		Six months	14.3 ± 3.5(+)	88.3 ± 9.3	
		One year	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	
		Two years	13.6 ± 5.6(+)	84.7 ± 13.3 (+)	
Smith et al. 2010 (31)	Detected	**Timing**	**Skin - mRSS**	**Lungs - FVC (%)**	Detected
		Starting	24.8 ± 3.4	83.9 ± 8.1	
		One year	19.4 ± 5.4(+)	81.0 ± 17.7	
		Two years	14.3 ± 3.5(+)	77.0 ± 9.8	
Melsens et al. 2017 (12)	Detected	**Timing**	**Skin - mRSS**	**Lungs - FVC (%)**	Detected
		Starting	25.5 ± 6.0	93.5 ± 11.3	
		Three months	18.6 ± 6.5 (+)	90.7 ± 11.6	
		Six months	14.6 ± 6.2 (+)	93.3 ± 13.4	
		One year	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	
		Two years	12.6 ± 5.1(+)	90.5 ± 16.3	
Lafyatis et	Detected	**Timing**	**Skin - mRSS**	**Lungs - FVC (%)**	Detected

al. 2009 (30)		**Starting**	20.6 ± 4.4		89.2 ± 10.8		
		Six months	20.2 ± 5.5		92.7 ± 10.3		
		One year	21.1 ± 5.2		Not reported		
Bosello et al. 2015 (33)	Detected	**Timing**	**Skin - mRSS**		**Lungs - FVC (%)**		Detected
		Starting	22.3 ± 9.5		87.4 ± 19.5		
		Six months	14.4 ± 8.4(+)		89.0 ± 17.		
		One year	11.2 ± 7.5(+)		90.7 ± 17.9 (+)		
		Two years	9.95 ± 6.0(+)		89.9 ± 21.2		
		Three years	8.1 ± 5.2(+)		94.0 ± 16.1		
		Four years	9.8 ± 7.2(+)		95.6 ± 20.7		
Daoussis et al. (2017) (3)	Detected	**Timing**	**Control grouping**	**RTXs grouping**	**Control grouping**	**RTXs grouping**	Detected
		Starting	17.78 ± 9.48	14.72 ± 10.52	Detected	80.6 ± 21.21	
		One year	15.78 ± 9.89	8.83 ± 7.83 (+)	Detected	83.02 ± 19.05	
		Two years	13.72 ± 9.67 (+)	5.93 ± 5.15 (+)	Detected	86.9 ± 20.56 (+)	
		Three years	15.53 ± 9.53(+)	4.53 ± 5.29 (+)	Detected	Not reported	
		Four years	13.64 ± 8.56(+)	5.37 ± 8.34 (+)	Detected	Not reported	
		Seven years	Not reported	Not reported	Detected	91.69 ± 14.81	

(+) statistically significant

All publications employed FVC pulmonary functions tests, lung diffusion capacities carbon monoxide, and highly-resolution computerized tomography for lungs fibrosis evaluations and the clinical outcome follow-up. Additionally, overall lung capacities and forceful expiratory volume in one second were employed in several publications (FEV1). Most papers employed the modified Rodnan skin scores (mRSS) or biopsies and immunohistochemistry analyses to assess cutaneous fibrosis.

Bosello et al. (2015) (33) employed the criterion put forward by Kazerooni et al. [34] for the computed tomography assessment of pulmonary fibrosis, with no appreciable change in the computed tomography values. It was determined by Lafyatis et al. (2009) (30) and Melsens et al. (2017) (12) that cases' CT scans did not demonstrate the development of new tumors or lung disease. The outcomes of the tomographic lungs analyses carried out on their cases were not reported by Smith et al. (2010) (31), Smith et al. (2013) (32), or Bosello et al. (2010) (29). Table 4 contains information on the advancement of mRSS and FVC.

Mortality was found in four non-RCTs. In their 2015 investigation, Bosello et al. (33) documented two fatalities (cardiovascular involvements). One fatality from sepsis was documented by Smith et al. (2013) (32). (Port veins catheters infections after coronary bypass surgeries). Yet another fatality from sepsis (central venous catheter infections following cardiac bypass surgery) and one mortality from pancreatic cancer were both documented by Melsens et al. (2017) (12). In the RTX cohort of the trial by Daoussis et al. (2017) (3), there were 5 fatalities recorded: three from respiratory distress, one from lung cancer, and one during sleep.

Breasts, prostates, and pancreatic cancers, herpetic zosters, ulcers infections, respiratory diseases, tooth abscesses, fever without a contagious emphasis, coronary bypass surgery, nosocomial infections, urinary infections, hospital admissions for breathlessness, and kidney and liver disaster from scleroderma were among the seriously complications.

Table 7 provides the evaluations of the cases reviewed by ROBINS-I with respect to the estimation of the danger of bias from NRCTs. Three studies were found to have a low risk of bias (12, 31, 32), three to have critical bias (3, 33) and (30), and one to have substantial bias (29). It is important to note that ambiguity and incomplete information were the assessments' most troublesome categories (Table 7).

Table 7 Risk of bias in Non-randomized control trials (ROBINS-I)

	Confounding	Patients collection	Categorization of treatments	Intentional errors in treatments	Inadequate information	Outcomes evaluation	Categorized published data	Total judgments
Bosello et al. (2010) (29)	Serious	Weak	Weak	Weak	Weak	Weak	Weak	Serious
Smith et al. (2013) (32)	Weak	Weak	Weak	Weak	Weak	Weak	Weak	Weak
Smith et al. (2010) (31)	Weak	Weak	Weak	Weak	Weak	Weak	Weak	Weak
Melsens et al. (2017) (12)	Weak	Weak	Weak	Weak	Weak	Weak	Weak	Weak
Lafyatis et al. (2009) (30)	Critical	Weak	Weak	Weak	Weak	Weak	Weak	Critical
Bosello et al. (2015) (33)	Weak	Weak	Weak	Weak	Weak	Weak	Weak	Critical
Daoussis et al. (2017) (3)	Serious	Weak	Weak	Weak	Critical	Weak	Weak	Critical

Meta-analysis of rituximab's impacts on the skin and lungs

The three randomized controlled studies were involved in the meta-analysis, and the findings for respiratory and cutaneous conditions following the follow-up periods are shown (6 to 12 months). The results shown in Fig. 2 indicate that the use of rituximab has a favorable and significant impact on pulmonary functions (SMD 0.66 (Compelled Vital Capacity - FVC); 95 percent CI 0.23 to 1.09; p = 0.003). Low heterogeneity was discovered in this study (I2 = 0%; p = 0.69).

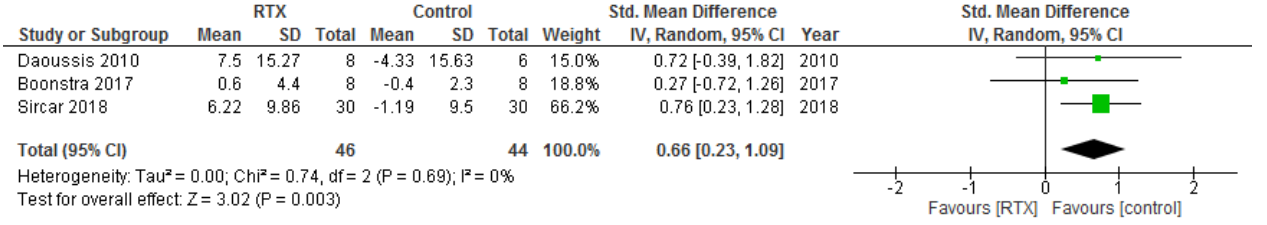

Fig. 2 Lung (FVC) Rituximab Consequences (RCTs)

Concerning the skin outcomes, positive findings were seen for the use of rituximab with a skin fibrosis decrease (SMD 0.40 (modification Rodnan skin scoring - mRSS); 95 percent CI − 0.92 to 0.11; p = 0.12); even if researchers did not identify any substantial differences between the experimentally and controlled grouping). Moderate heterogeneity was detected (I2 = 43%; p = 0.28) (Fig. 3).

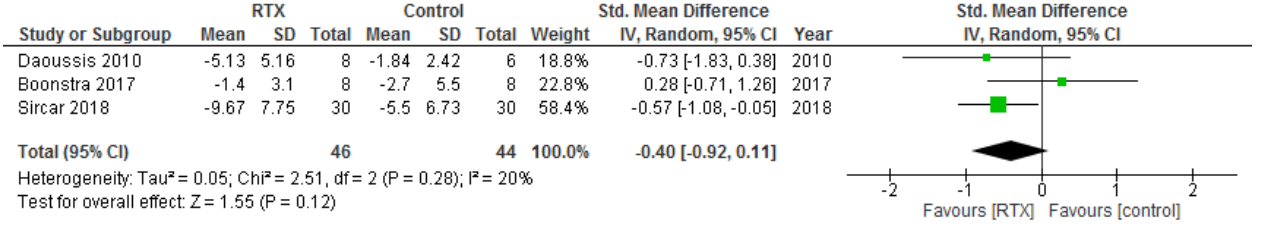

Fig. 3 Rituximab Side Effects - Skin (RCTs)

Discussion

This systematic review confirmed that the administration of RTX for SSc-associated ILD typically resulted in non-statistically substantial improvements. The usage of rituximab has been shown to improve skin fibrosis and lungs functions in cases with systemic sclerosis, according to the findings of a meta-analysis, although only the lung results showed a meaningful impact. The limited sample size in this meta-analysis might have had an impact on the findings. Additionally, the papers in this SR showed that there were few diagnostic tests with included participants, no blinding, varying RTX treatment plans, and the use of a variety of criteria to assess the therapeutic efficacy.

Two investigations that provided guidance for treating SSc-associated ILD with CYC in accordance with EULAR guidelines were rated as having excellent quality by the Jadad scoring (7, 24). Due to the fact that the two publications comprised of the EULAR methodology were randomized, double-blind, placebo-controlled, and multicentric investigations, they received the highest scoring possible (5 points). According to Tashkin et al. (2006), oral CYC therapy for a year led to a modest but considerable improvements in FVC and overall lungs capacity (35). On the other hand, Hoyles et al. (2006) discovered no appreciable increase in computerized tomographic and FVC in the CYC cohort (36).

When contrasting these investigations to those that were a part of the systematic review, it is clear that the majority of the investigations used computed tomography of the chest as secondary sources and used FVC as the primary outcome. The Controlled trials that included in the current meta-analysis scored less poorly (3 points) on the Jadad scale and had some issues with ROB 2's risk of bias assessment.

This systematic review discovered that the administration of RTX resulted in, in eight of the 10 trials, significantly statistical improvements at a certain time throughout follow-up for SSc cutaneous involvements (3, 27, 29, 33) (12, 31, 32). In the meta-analysis, positive findings were seen for the use of rituximab in the decrease of epidermal fibrosis, despite the fact that researchers did not find any statistically significant differences from the control cohort. The publications that were part of the meta-analysis employed various RTX strategies, scored worse on Jadad (3 points), and had some weaknesses in the risk of bias assessment on ROB 2.

Methotrexates (MTX), which has been shown in two researches to improve the revised Rodnan skin scoring (mRSS) but whose consequences on other tissues are unknown, is recommended by the EULAR as the golden treatments recommendations for SSc cutaneous fibrosis (37, 38). The trials were randomized, scored between three and five on the Jadad score, employed a placebo as the control cohort, and measured the mRSS.

According to Van Den Hoogen et al. (1996), more SSc individuals responded effectively to MTX than to a placebo (37). Pope et al. (2001) found that MTX use was preferable to placebo, but the differences between the groupings were deemed to be small (38). Furthermore, it is crucial to note that, from the perspective of patients care, the consumption of this medicine can result in liver damage, pancytopenia, teratogenesis, and lungs injuries although the EULAR's guidelines for its usage (39).

Mild infusions responses were the predominant side effects linked to the use of RTX in SSc, along with sepsis, urinary tract infections, lung diseases, herpes zosters, and cardiovascular involvements. Additionally, deaths were identified in four investigations (3, 28, 33) (12, 32).

IRRs are frequent during infusions, particularly if no premeditations are administered. Besides IRRs, infections are the most frequent side consequence (40). Unfortunately, about 10% of individuals had serious infusion

responses. While supportive care and stopping RTX can usually reverse adverse effects, serious repercussions of infusions responses have also been noted, involving pulmonary and cardiovascular problems (41).

With the exception of individuals with T cell insufficiency due to Human immunodeficiency virus, no increases in the frequencies of solid tumors or lymphomas have been seen in cases receiving RTX when it comes to the risk of malignancy (41). According to this viewpoint, the patterns of AEs associated with the administration of RTX for these disorders are similar to that identified in this SR, employing RTX in SSc.

The manifestations of SSc, a chronic condition with various presenting patterns, severely interfere with everyday life and lower quality of life (42, 43). The main issues are the traditional skin stiffening, which limits daily activities, particularly manual activities, and the heavy symptoms load (44). Depressive symptoms, discomfort, and exhaustion are also frequent. Ailments of the internal organs and unexpected illness progression, particularly the diffused type, are additional concerns (45). People with SSc must spend numerous years controlling the symptoms of a complicated and progressing disorder because the disease is identified in earlier to middle life and has no known cure (46). As a result, individuals with systemic sclerosis could experience an increase in pleasure and quality of life thanks to better skin and pulmonary functions metrics, which will also help them with their biggest criticisms.

The majority of the included papers were not randomized clinical trials (NRCT), there were varying RTX therapy regimens, and there were multiple indicators used to assess the therapeutic efficacy, which presented challenges for performing this analysis.

Comparable to the current research, a recently systematic review and meta-analysis conducted by Tang et al. (2020) focused on the effectiveness and safety characteristics of Rituximab in SSc cases as well as adverse outcomes. This analysis looked at the advancement in cutaneous fibrosis and pulmonary functions affiliated with the use of RTX. Additionally, they did not simply consider clinical trials and employed an alternative methodology to assess the psychometric properties of Randomized trials and NRCTs and the risk of bias (the Newcastle – Ottawa scaling) (1).

The improved Rodnan skin scoring demonstrated a long-term increase, according to Tang et al (mRSS). Forcing Vital Capacity (FVC) and Diffusing Capability of the Lungs for Carbons Monoxides (DLCO) measurements of pulmonary functions showed no change. At six months, 9.70 at twelve months, and 10.93 at two years, the ΔmRSS was 7.00. Δ FVC: - 0.69 at six months, -2.62 at twelve months, and -0.67 at twenty-four months. The ΔDLCO was -2.39 at six months, 3.28 at twelve months, and -0.79 at twenty-four months. Rituximab-related adverse reactions were documented at an incidence of 12% (1). This analysis seeks to validate these findings by adding more reliable information to the meta-analysis, which only considered RCTs and offered suggestions for further research.

Conclusion

Rituximab is a medicine that needs to be further researched since it has been generating rising interest in the scientific communities as a significant option to the management of multiple sclerosis. After carefully examining the data in our evaluation, we have come to the conclusion that rituximab is a potential therapy option for SSc-related cutaneous fibrosis and ILD. In patients who had systemic sclerosis, RTX treatment improved skin changing and pulmonary functions, with notable differences for the lungs outcomes, according to the meta-analysis of the three RCTs. Therefore, greater sample sizes and investigations with appropriate methodology must be carried out to reach a more conclusive result. The current study advises the performance of randomized, double-blind, crossover, multicenter trials with an adequate number of participants and a clearly defined follow-up period. These studies should also standardize the treatment regimens for the RTX and control groups as well as the clinical techniques for evaluating the severity of the illness and the effectiveness of the treatments. These investigations will show how RTX behaves when used to treat systemically sclerosis, enabling clinicians to make well-informed judgments about its application in SSc and enabling patients to take advantage of this novel treatment approach.

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