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CASE BASED REVIEW

# Targeting very early systemic sclerosis: a case-based review

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## Abstract

It is unknown whether treatment in very early/early systemic sclerosis (SSc) can affect long-term outcomes. A case-based review was conducted (i) to assess the effect of rituximab (RTX) in very early SSc and (ii) to explore how many clinical trials in SSc targeted early disease and whether treatment of these patients led to better clinical outcomes. We identified cases of very early SSc from our department and performed a search in MEDLINE and Scopus databases for clinical trials in SSc during 2005–2018. Two cases are reported where RTX was administered within 24 months from the appearance of Raynaud's. In the first case, there was an improvement in interstitial lung disease as indicated by the improvement in pulmonary function tests and the regression of changes in high-resolution chest computed tomography. In the second case, a good clinical response in skin fibrosis was observed. The review revealed the following: (i) only one-third of the studies were specifically designed to target early disease, (ii) there is confusion related to disease duration definition across SSc clinical trials but an obvious trend towards improvement was evident during the past years, (iii) the question of whether early implementation of therapy may lead to better clinical outcomes cannot be definitely answered based on existing data and (iv) there is still a very low level of incorporation of the new classification criteria in SSc trials. This review suggests that there may be a window of opportunity in SSc and highlights the need for clinical trials targeting very early/early disease.

**Keywords** Systemic sclerosis · Scleroderma · Early systemic sclerosis · Rituximab

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## Introduction

Systemic sclerosis (SSc) carries the highest standardized mortality ratio among all systemic rheumatic diseases [1]. In most cases it is diagnosed when fibrotic manifestations are already evident, such as sclerodactyly or skin thickening. However, it is well known that SSc is a slowly progressive disease where immune dysregulation, autoantibody formation and vasculopathy precede the development of fibrosis by years [2, 3]. A significant progress towards early diagnosis of the disease was made a few years ago with the introduction of the new criteria which enable the diagnosis of SSc prior to the development of overt fibrotic manifestations [4]. Based on these new criteria we can identify subjects at the "pre-scleroderma" stage, which carry an increased probability of progressing to SSc, or diagnose patients with SSc at a very early stage. This early diagnosis could lead to early institution of treatment and hopefully better outcomes [5]. Despite being able to correctly diagnose patients with SSc very early, we still lack therapeutic guidelines for these patients. Treatment of SSc remains organ based, mainly

targeting overt fibrotic manifestations such as skin and lung fibrosis [6]. So far, we do not know whether treatment given very early in the disease course, prior to the establishment of fibrosis, is able to favorably affect long-term outcomes.

During the past years there has been significant progress regarding the treatment of SSc [7]. Our group, among others, has shown that B cell depletion therapy may improve skin thickening and SSc-related interstitial lung disease (ILD) [8–21]. A large-scale multicenter study from the European League against Rheumatism Scleroderma Trial and Research group also reported encouraging results, thus supporting the use of rituximab (RTX) in SSc [22], even though a small randomized placebo-controlled study failed to confirm or reject potential efficacy of RTX in the disease [23]. All studies assessing the clinical efficacy of B cell depletion therapy in SSc recruited patients with established disease fulfilling the old ACR criteria [24]. In our previous studies we found that patients with shorter disease duration had a better clinical response to RTX. We report two cases where RTX was administered very early in the disease process (less than 24 months from the appearance of Raynaud's) exhibiting clinical efficacy regarding lung and skin fibrosis. These cases raise several questions of whether there is a window of opportunity in SSc and whether we have the necessary tools to identify patients with SSc at an early stage. Even though the introduction of the new criteria for SSc was a significant step forward, there is still the major problem of how disease duration is defined. Defining disease duration based on the first non-Raynaud's manifestation is nowadays the most accepted approach, but still there is a lot of controversy and confusion. Furthermore, in order to target very early in the pathophysiologic process, intervention should be as close as possible to the first disease manifestation which in almost all cases is Raynaud's. However, the potentially vital information of duration since Raynaud's onset is not frequently reported in clinical trials. This is why we reviewed all clinical trials in SSc during the past 14 years in an effort to answer the following questions: (i) how many clinical trials in SSc targeted early disease and whether treatment of patients with early disease led to better clinical outcomes, (ii) how was disease duration defined in SSc clinical trials and whether data on duration since Raynaud's onset were provided and (iii) whether the new SSc criteria, specifically designed to allow early diagnosis, have been incorporated in clinical trials throughout the past 5 years.

## Patients and methods

### Patients

We retrospectively reviewed our patients' medical records to identify patients who fulfilled the 2013 ACR/EULAR classification criteria [4] for SSc and had received treatment with RTX within 24 months from the appearance of Raynaud's. According to local guidelines, since RTX is an off-label treatment for SSc, all patients gave written informed consent and an ethics committee approval (Patras University Hospital, Patras, Greece) was obtained for each case. RTX was administered using the classic rheumatoid arthritis (RA) scheme (1 g on days 0 and 14) and repeated every 6 months. We identified two cases where RTX was administered very early in the disease course and present each one individually. Written informed consent for publication was obtained for each case.

### Methods

#### Search strategy

A search in published studies indexed in MEDLINE and Scopus databases was performed from Jan-2005 to Dec-2018. In both databases, the Clinical Trial and English language filters were activated and the terms "systemic sclerosis treatment" used. The query submitted in MEDLINE translates into: ("scleroderma, systemic"[MeSH Terms] OR ("scleroderma"[All Fields] AND "systemic"[All Fields]) OR "systemic scleroderma"[All Fields] OR ("systemic"[All Fields] AND "sclerosis"[All Fields]) OR "systemic sclerosis"[All Fields]) AND ("therapy"[Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields])) AND Clinical Trial[ptyp]. A manual search of the reference lists of recent reviews was subsequently performed regarding the disease and the time period studied.

#### Eligibility criteria

Studies were included if they evaluated adult patients with systemic sclerosis and fulfilled the following:

(1) concerned treatment modalities with compounds systemically administered, (2) were prospective trials in inception and design, (3) did not concern extension or follow-up of previous studies or registry analysis, (4) presented data for clinical endpoints assessing skin and/or lung fibrosis, such as MRSS and PFTs (5) recruited at least ten patients and (6) were in English language.

Only prospective studies were included in the analysis, and not retrospective ones or studies based on registries, because only in prospective studies the investigators actually choose which patients to treat. Moreover, we focused on the fibrotic component of the disease and included only studies that reported clinical endpoints assessing skin and/or lung fibrosis because fibrotic manifestations appear early on the disease course and are typically associated with SSc diagnosis. Our aim was to explore whether the Rheumatology

research community prioritizes targeting of early disease and if there is a trend towards earlier implementation of therapy during the past years.

### Data extraction and statistical analysis

A data extraction form was designed and was used to extract the following information: last name of the first author, year of publication, treatment regimen, number of patients with SSc enrolled, demographic data of the cohorts (age and sex), disease subtype (diffuse or limited cutaneous), baseline pulmonary function tests (FVC, DLCO) and MRSS, follow-up duration regarding clinical endpoints, disease duration, disease duration definition, criteria implemented for systemic sclerosis classification.

## Results

### Case 1

A 56-year-old Caucasian female was referred to the Rheumatology Clinic from the Pulmonary Department of our institution in February 2012. She had a 1-year history of dyspnea on moderate exertion, a non-productive cough and already carried a diagnosis of "interstitial pneumonia with autoimmune features". She reported typical Raynaud's that first appeared 18 months ago; moreover, she had minor difficulties in swallowing and symptoms of gastroesophageal reflux during the past year. On physical examination she had a few telangiectasias on her face and neck and puffy hands but had no sclerodactyly and no skin thickening in any part of her body. Bibasilar crackles were clearly evident and capillaroscopy showed an early, active scleroderma pattern. Routine blood tests were normal but serologic studies revealed positive anti-centromere antibodies. A recent high-resolution chest computed tomography (HRCT) revealed extensive ground-glass lesions. Pulmonary function tests (PFTs) showed a normal FVC (82% of the predicted value) but a significantly decreased DLCO (44%). A detailed cardiac ultrasound was normal, with no evidence of pulmonary arterial hypertension (PAH). A clinical diagnosis of SSc was made; of note, this patient did not fulfill the old SSc classification criteria, the only SSc criteria available at that time, since she had no skin thickening. However, retrospective application of the new criteria was diagnostic for SSc with a score of 14 (3 points for each of positive specific auto-Abs and Raynaud's and 2 points for each of the following: puffy fingers, telangiectasias, capillaroscopy and ILD). ILD was clearly the most clinically significant disease manifestation. Considering the worsening of clinical symptoms, the extent of lung involvement on HRCT and the low DLCO, we proposed a therapeutic intervention. A course of RTX was administered in April 2012 using the classic RA scheme. In October 2012, 6 months following treatment, the patient had no cough and reported dyspnea only on severe exertion. Her PFTs had improved (FVC 94% and DLCO 55%). A new chest HRCT was performed which showed an obvious improvement as depicted in Fig. 1. Based on this favorable clinical response, continuation of treatment with RTX was

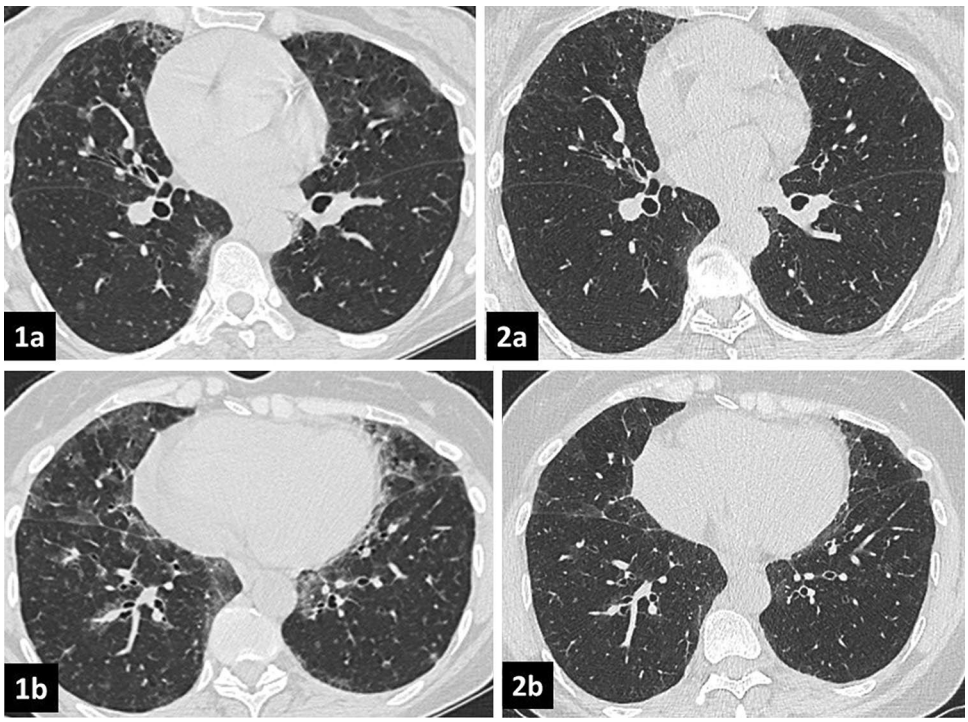


**Fig. 1** Regression of ILD following early implementation of RTX. Corresponding pre- (**1a**–**1b**) and post-treatment (**2a**–**2b**) HRCT images of the mid (**a**) and lower (**b**) lung zones. There is definite improvement with marked resolution of ground glass and reticular opacities. Furthermore, the peripheral fine reticulations and tiny subpleural nodules are almost imperceptible in the post-treatment images

decided. One year later (April 2013) the patient was stable and no longer reported dyspnea. On physical examination she had puffy hands but no skin thickening. Two years later (April 2014) the patient reported no respiratory symptoms and her PFTs had stabilized (FVC 91%, DLCO 53%). Her hands were no longer puffy and no skin thickening was evident. Since the patient had significantly improved while on B cell depletion treatment we chose to continue RTX as a maintenance treatment at a lower dose (1 g every 6 months) also taking into account that she had borderline low total IgG levels. She remained on that treatment for 3 years until April 2017. During this period of maintenance treatment, she remained free of respiratory symptoms and had stable PFTs. PFTs throughout treatment period are diagrammatically depicted in Fig. 2. The patient during the 5-year period of follow-up reported occasional episodes of Raynaud's, but did not develop any ischemic ulcers or skin thickening. Her mild dysphagia and symptoms of gastroesophageal reflux persisted despite proper dietary/lifestyle modifications and continuous proton pump inhibitor therapy. The patient underwent annual cardiac ultrasounds with no evidence of PAH.

## Case 2

A 27-year-old Caucasian female was first referred to our clinic in March 2013. She had a 1-year history of Raynaud's and a 3-month history of arthralgias in the small joints of the hands. On physical examination she had puffy hands but no sclerodactyly or skin thickening. Serologic tests revealed positive anti-Scl70 antibodies and capillaroscopy showed an early active scleroderma pattern. A diagnosis of SSc was made; retrospective application of the new SSc criteria was diagnostic of SSc with a score of 10 (3 points for each: positive specific auto-Abs and Raynaud's and 2 points for each of the following: puffy fingers and capillaroscopy). She had no cough or dyspnea on exertion despite being a hard-working young woman who travelled a lot and exercised regularly by running several kilometers daily. PFTs revealed a normal FVC (98%) but a slightly decreased DLCO (70%). Chest HRCT revealed only subtle ground-glass opacities of the lower lobes and cardiac ultrasound was normal. She denied any symptoms suggestive of gastroesophageal reflux and had no dysphagia or any other gastrointestinal symptom. Three months later, at her next visit to the clinic (June 2013), she reported malaise and worsening of her arthralgias; she could no longer exercise on a daily basis as she used to. On physical examination she had mild sclerodactyly with an MRSS of 2. At her next appointment (October 2013), her disease had clearly evolved. She had skin thickening of fingers (a score of 2 for each side), hands, forearms, feet and legs (a score of 1 for each) with a total MRSS of 12. The patient reported a sense of "squeaking" at both her Achilles tendons. Indeed, tendon friction rubs were evident. The evolution of the disease caused major psychological distress; she had to be seen by a psychiatrist and was placed on antidepressant therapy. Her main concern was the impact of the disease on her physical appearance and her ability to work, travel and exercise. Taking into account the rapid evolution of skin thickening and the presence of tendon friction rubs as poor prognostic signs, we discussed with the patient treatment options including methotrexate, mycophenolate and RTX. Following a joint decision of the treating physician and the patient, a course of RTX was administered in October 2013. Three months following treatment (January 2014) the patient had improved. She reported no malaise or arthralgias and her MRSS had decreased to 8 (fingers, hands, forearms, feet—a score of 1 for each). Six months

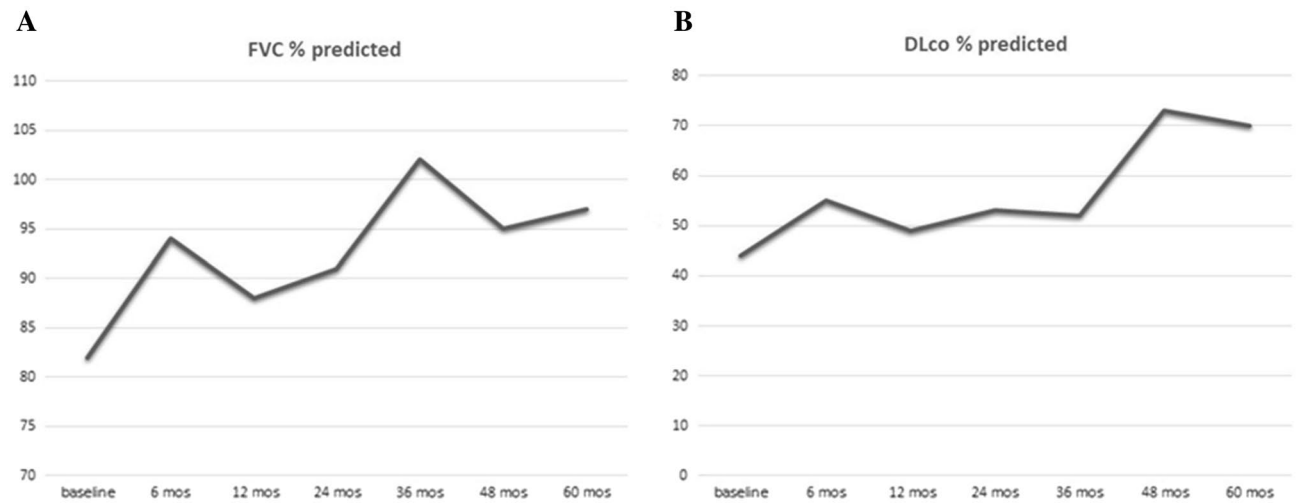


**Fig. 2** PFTs during RTX treatment. Increases in both FVC (**a**) and DLCO (**b**) during RTX treatment can be seen

following treatment (April 2014), the patient reported a major improvement. She was able to run long distances daily and had stopped antidepressants. Skin thickening had resolved; she only had mild sclerodactyly with an MRSS of 2. Notably, tendon friction rubs had disappeared. Based on this favorable clinical response we continued RTX treatment using the RA scheme until April 2017. Throughout this period, the patient remained in a steady clinical condition. She had only mild sclerodactyly and denied any respiratory or gastrointestinal symptoms; no ulcers developed during the disease course. She was fully functional; she got a job promotion and had to be more energetic than she already was. The patient received 8 consecutive RTX courses in total, with the last one administered in April 2017. RTX was no longer continued since the patient wished to conceive and start a family. Treatment was well-tolerated with only one episode of mild skin infection that was treated with antibiotics administered orally. She was last seen in September 2018 in stable clinical condition and no evidence of relapse.

## Review

### Study selection

The search strategy yielded a total of 647 articles from databases and manual search, which were screened according to title and/or abstract. From the remaining 89 articles after screening, we were able to retrieve full text in all but one article. Exclusions were due to non-prospective design ($n=10$), follow-up of previous studies ($n=3$) and low number of patients recruited according to inclusion criteria ($n=2$). In total, 73 articles met initial inclusion criteria for our study and were subjected to data extraction. A flowchart depicts the stages of article screening and selection (Fig. 3). The full list of articles analyzed is presented in Supplemental Data.

### Study characteristics

The total number of patients analyzed was 3078 cases, with each cohort ranging from 10 cases to 326 cases. The patient population comprised mostly females (76%) belonging to the diffuse subtype of the disease (85.4%). Less than half of the studies (43.8%) were randomized comparative studies, while the rest were mostly observational open-label cohort studies. Over 30 therapeutic regimens were administered in the studies analyzed. We extracted data about mean values of disease duration from 58 studies, concerning 2164 patients; in 15 studies mean values of disease duration were not reported. The total weighted mean disease duration (adjusted to the number of patients in each study) was 38.55 months. A subanalysis of weighted disease duration according to the publication year was conducted. We identified 25 studies with 1050 patients and a weighted mean disease duration

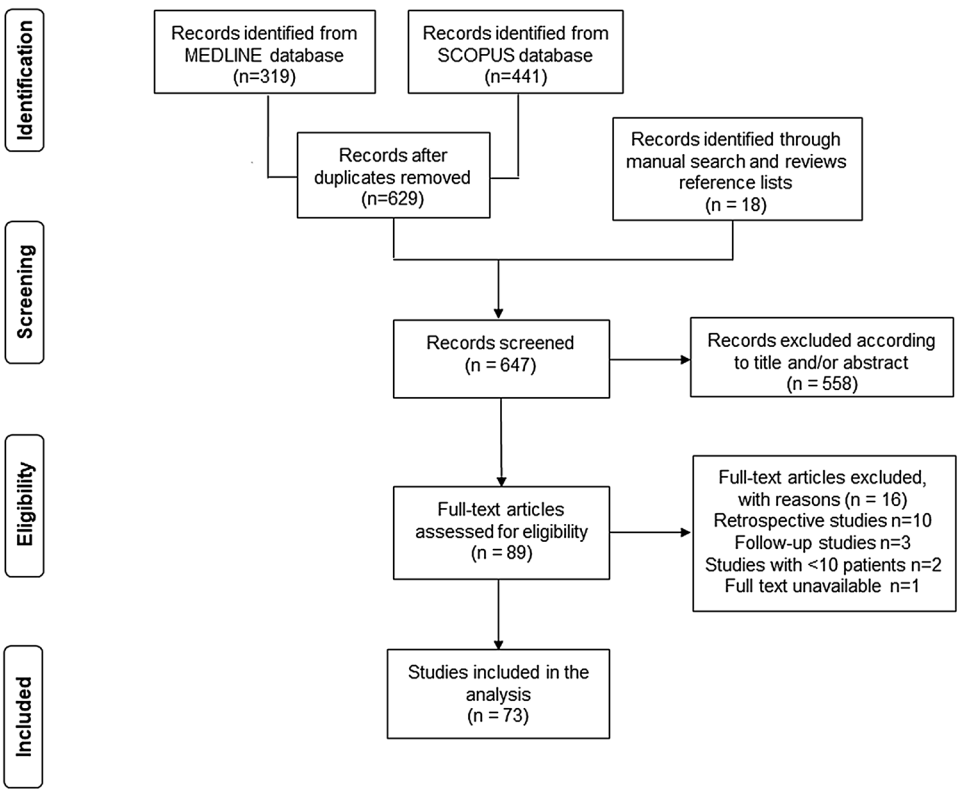


**Fig. 3** Flowchart of the review

of 39.21 months for years 2005–2009. For year groups 2010–2014 and 2015–2018, 18 studies (515 cases) and 15 studies (599 cases) yielded a weighted mean disease duration of 42.27 and 34.19 months, respectively. Baseline total weighted mean MRSS was 21.54 (data from 52 studies and 2121 cases).

We also explored in how many studies researchers chose and recruited early (< 36 months disease duration) or very early (< 18 months disease duration) patients with SSc. Of the 73 studies analyzed, only 24 studies (32.9%) recruited early cohorts and of those, only 4 studies recruited patients with very early disease. Stratification of these data according to the publication year of each study is depicted in Fig. 4. We next focused on studies that did not specifically target early disease ($n = 49$) and explored whether disease duration associated with clinical outcomes. We identified such an analysis only in 13 studies. In 8/13 studies there was no difference regarding outcomes according to disease duration. Nevertheless, in 4/13 studies investigators reported better outcomes in patients with shorter disease duration with only one study showing the opposite.

These data show that the typical SSc patient recruited in clinical trials throughout the past 14 years had an average disease duration of 38 months which is more than 3 years, the threshold generally used for defining early SSc. Considering that the mean MRSS score was more than 20, we can conclude that the majority of patients in clinical trials had full-blown, established disease. Only one-third of the studies were designed to target early disease. We expected to detect a trend towards more studies targeting early disease with time, but this was not evident in our analysis. The vast heterogeneity of the clinical trials included in our analysis did not allow us to answer the key question of whether studies targeting early disease (disease duration < 36 months) had better clinical outcomes compared to studies which did not apply strict entry criteria related to disease duration.

### Significant heterogeneity in disease duration definition

Our analysis found an obvious lack of a common disease duration definition across studies. Four separate definitions were identified: (1) "From first non-Raynaud's symptom" (49.3%), (2) "From disease diagnosis" (11%), (3) "From skin thickening onset" (5.5%) and (4) "From first symptom" (11%). The rest of the studies (23.2%) presented no clear definition in their manuscript for disease duration in their cohorts (Fig. 5a). The stratification of the studies according to year of publication showed a tendency for greater consistency regarding the definition used in recent years, since most studies published from 2015 and onwards use the definition "From first non-Raynaud's symptom" which is currently the most accepted definition (Fig. 5b). Our analysis clearly depicts the controversy and confusion related to disease duration definition in SSc. Despite the progress made during the past 3 years there is still room for improvement.

### Duration since Raynaud's onset

Raynaud's phenomenon is the first disease manifestation in almost all SSc patients. In the articles studied we managed to extract data regarding the duration since Raynaud's onset only in nine studies (12.3%). In 8/9 studies publication date was in 2015 or afterwards. These data indicate that the vast majority of studies does not report a potentially critical information such as duration since Raynaud's onset.

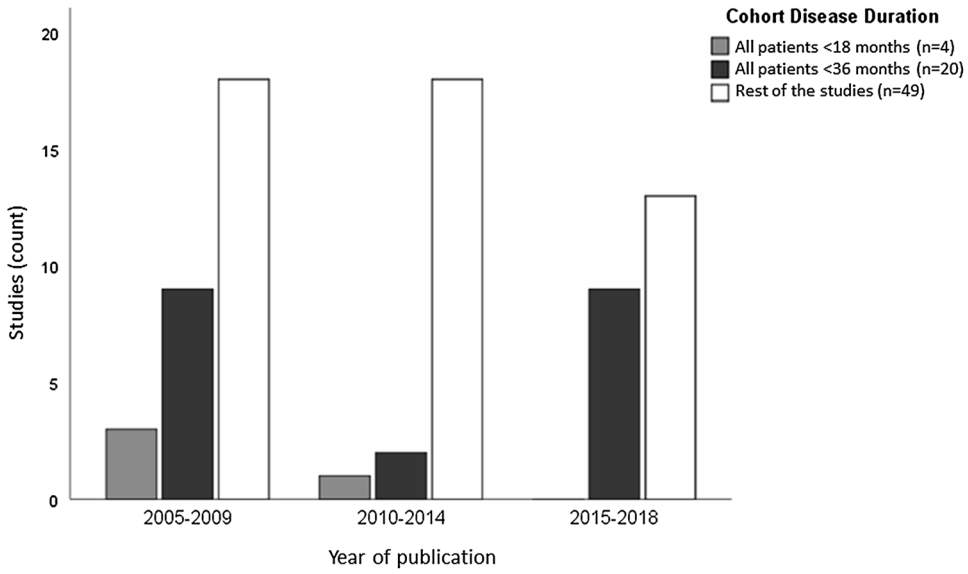


**Fig. 4** Studies that recruited early (< 36 months disease duration) or very early (< 18 months disease duration) patients with SSc stratified according to the publication year

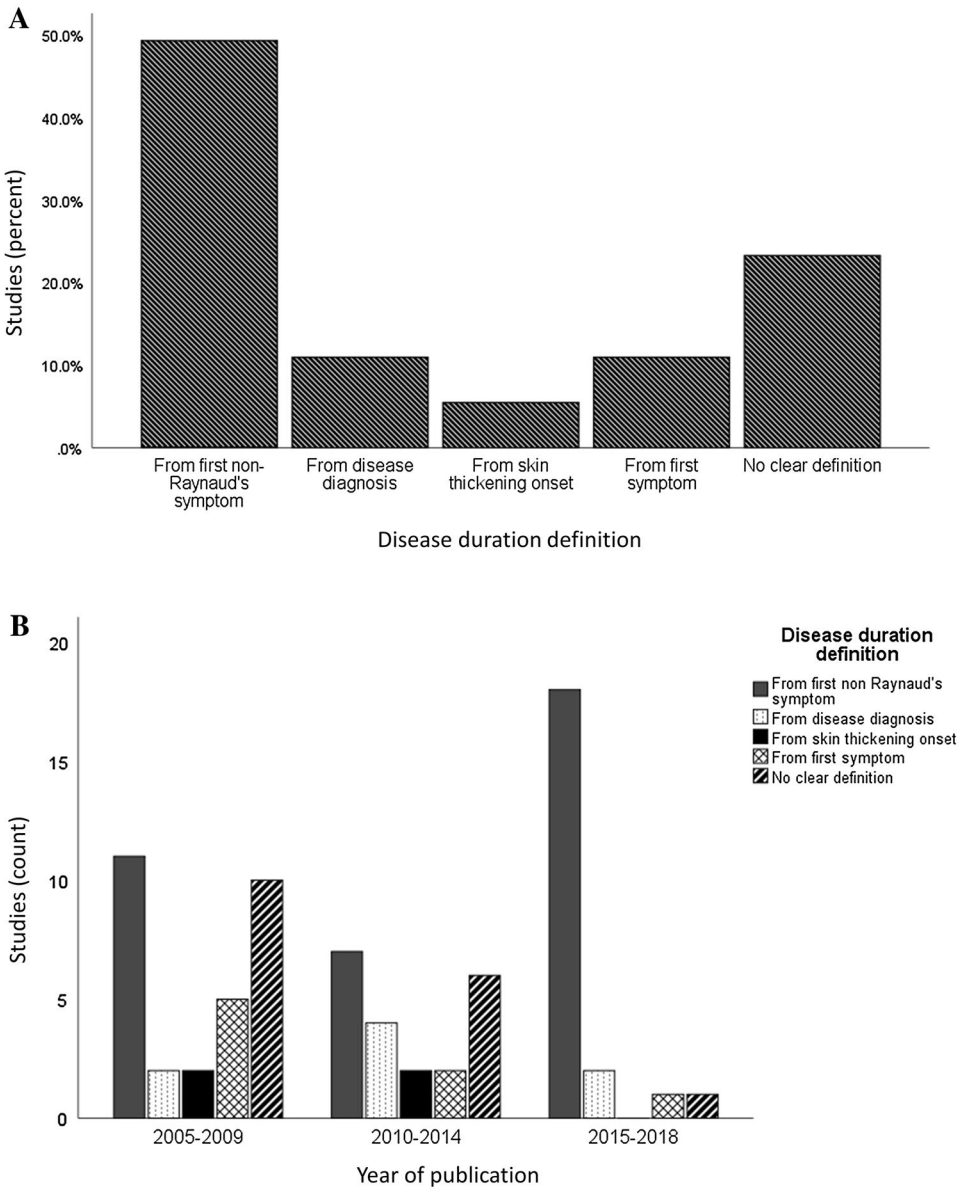


**Fig. 5** Significant heterogeneity in disease duration definition (**a**). A tendency for greater consistency regarding the definition used in recent years can be seen (**b**)

### Implementation of the new ACR/EULAR criteria for disease classification

A separate analysis of all articles published from 2014 until 2018 was performed to explore the incorporation of the new 2013 ACR/EULAR classification criteria. We identified only 6 studies (25%) incorporating the new criteria, all published in 2016 or afterwards (Fig. 6). Our analysis shows a low level of implementation of the new criteria in clinical studies, but this may be partially explained by the short time interval since the publication of the new criteria.

## Discussion

Despite having the proper tools to accurately identify patients with SSc very early in the disease course, a "wait and see" approach is still used in everyday clinical practice by implementing therapy only when fibrotic manifestations are clearly evident. The pathophysiology of SSc is extremely complex; however, it is generally accepted that autoimmunity/immune dysregulation and vasculopathy are the primary events that eventually trigger the fibrotic process [25]. Based on this pathogenetic model, one can

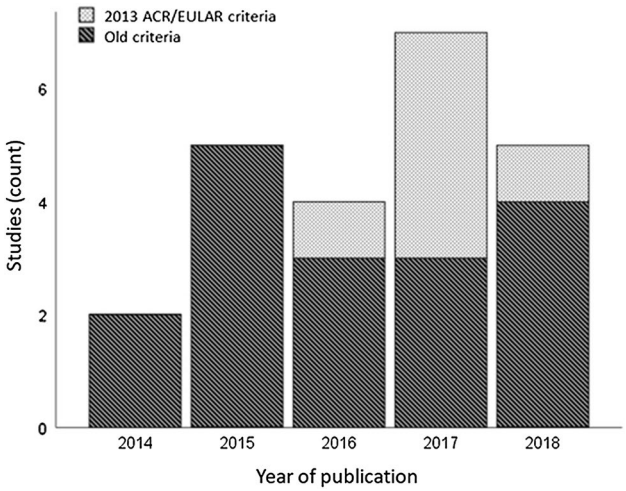


**Fig. 6** Low level of implementation of the new criteria in SSc clinical studies

hypothesize that a therapeutic intervention very early in the disease course, prior to the appearance of fibrotic manifestations, could potentially alter the natural course of the disease and might prevent permanent organ damage [26, 27]. We should emphasize, however, that clinical evidence for this is lacking since no study so far has targeted patients with very early disease, prior to the development of overt fibrosis. Moreover, a significant problem in targeting early disease is the lack of reliable predictors of disease progression. Therefore, targeting early disease carries the risk of overtreating patients that would not progress even with no treatment.

Rituximab is a chimeric monoclonal antibody that targets and depletes B cells. It was originally designed to treat B cell lymphomas but now is an established therapy for many systemic rheumatic diseases [28]. The obvious effect of a B cell depleting therapy would be the reduction of circulating autoantibodies with potential pathogenetic involvement. However, ignoring the antibody-independent roles of B cells in immune function could overlook other possible aspects of RTX effect. B cell cytokine downregulation and T cell pool modifications have been proposed as mechanisms of immune regulation following RTX administration [29]. In SSc, a B cell hyper-activated phenotype has been found in both animal models and humans [26]. Researchers have reported increased B cell activating factor (BAFF) in the serum of patients and altered B cell homeostasis in peripheral blood, with reduced, though activated, memory B cells and reduced B regulatory cells [30–32]. In addition, aberrations regarding critical molecules in B cell signaling process, such as co-receptors CD19 and CD22, have been also found [33–35]. Pathogenic autoantibodies and profibrotic cytokines IL-6 and TGF-β production, along with a direct cell to cell contact mechanism, may form the link between B cells and fibroblast activation in SSc [36]. RTX could disrupt this link through B cell depletion. Interestingly, studies of patients' response to treatment with RTX showed a downregulation of fibroblast collagen gene expression and upregulation of Dickkopf-1, a critical inhibitor of the Wnt pathway which is highly activated in scleroderma skin [37, 38].

In the cases presented, we had the chance to implement therapy, in the form of B cell depletion, very early in the disease course of two patients with a favorable clinical response. In the first case, there was an improvement in ILD, as indicated by the increase in PFTs and the regression of changes in HRCT, and in the second case we saw a good clinical response in skin fibrosis. Both these cases provide evidence in favor of a "window of opportunity" in SSc. It is clear that evidence provided from two cases cannot be considered powerful. However, the theoretical background and rationale in targeting very early disease is solid. The "hit early and hard" approach has already been tested and proven feasible and effective in other rheumatic diseases such as rheumatoid arthritis [39–41]. It is important to stress out that treatment implementation was decided with patients' approval based on significant disease deterioration. *Primum non nocere* is a fundamental principle of medical care, and physicians should always exercise caution regarding appropriate patient selection. In addition, the natural history of the disease should always be taken into consideration when assessing treatment efficacy, in order to avoid mislabeling spontaneous improvement or lack of progress as treatment effects. Therefore, we propose that large-scale, controlled clinical trials assessing the efficacy of RTX (or other immune based therapy such as mycophenolate) in patients with very early disease are highly needed.

The case-based review led to several conclusions of potential significance. The most important one is that the majority of patients recruited in clinical trials throughout the past 14 years do not have early disease. Only one-third of the studies were specifically designed to target early disease; the number of studies targeting early disease did not show any increasing trend with time. The key question of whether early implementation of therapy may lead to better clinical outcomes cannot be definitely answered based on existing data. As the therapeutic targets for treating SSc with biologic and/or antifibrotic drugs are expanding, there is an emerging need for the determination of the time that the initiation of specific therapy is more likely to be effective. Properly designed mechanistic and controlled studies with tight inclusion criteria in pre-defined SSc subpopulations, for instance those with recent disease onset, might provide the evidence for interventions with advanced therapies in very early stages of the disease.

Data analysis also clearly depicted the confusion related to disease duration definition across SSc clinical trials.

These controversies make interpretation of data reported in studies even more difficult than already is based on the heterogeneity and systemic nature of the disease. However, an obvious trend towards improvement in this area was evident throughout the past few years.

The review showed that duration since Raynaud's onset is rarely reported in clinical trials. This may be a vital piece of information especially if we move towards early implementation of therapy in the future. Finally, our analysis showed a very low level of incorporation of the new criteria in SSc trials. Even though this may be explained by the fact that the new criteria were recently published, we cannot exclude the possibility that some investigators still choose to use the old criteria which are certainly more straightforward and easy to apply.

**Author contributions** DD conceived the concept of the review, recruited patients, performed data interpretation and participated in the design, drafting and revision of the review. KM performed data acquisition, analysis and interpretation and participated in the design, drafting and revision of this review. PK participated in image analysis and contributed to the design and revision of the review. DB, TD and LS participated in study design and data interpretation and contributed to the revision of the review. All authors read and approved the manuscript.

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## Compliance with ethical standards

**Conflict of interest** KM has received registration fee coverage for domestic medical congress from Roche. DB has received travel and accommodation expenses coverage for domestic medical congress from Roche.

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