Potential efficacy of T and B lymphocyte-targeted therapies on articular involvement of patients with rheumatoid arthritis and systemic sclerosis overlap syndrome. Results from a 2-centre series of 19 cases

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Abstract

Objective

To analyse in routine practice the efficacy of targeted therapies on joint involvement of patients with rheumatoid arthritis/systemic sclerosis (RA/SSc) overlap syndrome.

Methods

This was a retrospective analysis of medical records of two academic centres over a 10-year period. Joint response to targeted therapies was measured according to EULAR criteria based on Disease Activity Score (DAS)-28. In addition, changes in CRP level and glucocorticoid consumption were recorded.

Results

Nineteen patients were included. Methotrexate (n=11) and hydroxychloroquine (n=4) were the most used first-line treatments. Targeted therapies were frequently used (n=14). Tocilizumab was the most selected therapy (n=8), then rituximab (n=5), abatacept and anti-tumour necrosis factor (n=4). Twenty-one treatment sequences were assessed, including 18 with EULAR response criteria. Responses were "good" or "moderate" in 100% (4/4) of patients treated with abatacept, 80% (4/5) with rituximab, 40% (2/5) with tocilizumab, and 25% (1/4) with anti-TNF. T and B lymphocyte-targeted therapies (abatacept, rituximab) resulted more frequently in a "good" or "moderate" response compared to cytokine inhibitors (tocilizumab, etanercept, infliximab) with a significant decrease in DAS-28 at 6 months (-1.75; p=0.016) and a trend to a lower consumption of glucocorticoids.

Conclusion

In patients with RA/SSc overlap syndrome refractory to conventional synthetic-DMARDs, T and B lymphocyte-targeted therapies seem to be a promising therapeutic option to control joint activity.

Key words

biologic DMARDs, rheumatoid arthritis, systemic sclerosis, overlap syndrome, joint involvement

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Introduction

Rheumatoid arthritis (RA)/systemic sclerosis (SSc) overlap syndrome is a rare and understudied association. Szücs *et al*. published the largest series of 22 patients in 2007 (1). While the frequency of joint involvement is estimated at 30% in patients with SSc, RA could affect 6% of them (2). RA-specific antibodies such as rheumatoid factors (RF) and anti-cyclic citrullinated peptide (anti-CCP) are found in 25% and 9% of patients with SSc, respectively (3). Immune dysregulation, a shared pathogenesis of RA and SSc, could be the target of effective treatment in both diseases (4). Only open-label studies evaluating biologic disease modifying anti-rheumatic drugs (bDMARD) have reported encouraging results regarding the impact of tocilizumab, abatacept and rituximab on joint involvement in SSc (5, 6). In 2021, the DESIRES clinical trial reported the efficacy of B-cell targeted therapy (rituximab) on skin fibrosis related to SSc (7). The management of these patients is therefore not standardised.

Given the limited number of publications and the absence of a current consensus on the management of RA/SSc overlap syndrome, we aimed to analyse in routine practice the efficacy of targeted therapies on joint involvement of patients with RA/SSc overlap syndrome.

Patients and methods

We conducted a retrospective study in the rheumatology and internal medicine departments of two French academic centres: Rouen University Hospital and Caen University Hospital. Inclusion criteria were patients aged > 18 years, fulfilling 2010 ACR/EULAR criteria for RA (8) and 2013 ACR/EULAR criteria for SSc (9), who had received one or more DMARD. Patients without antibodies specific to RA (RF or anti-CCP) were excluded. The sequence of targeted therapies used was recorded for each patient. The response for each treatment line was defined as "good", "moderate" or "none" according to EULAR criteria for therapeutic response in RA (10). DAS-28 was calculated at baseline and at first medical re-evaluation after month 6 (M6). In the absence of DAS-28, three criteria, namely therapeutic maintenance for more than 12 months, joint ultrasonography (US) assessment revealing no synovitis and discontinuation of glucocorticoid therapy, were required for a "good" treatment response.

As secondary endpoints, CRP level and glucocorticoid consumption were recorded at baseline and at first medical re-evaluation after M6.

Patients were identified by reviewing the medical records of all patients managed during 2010-2020 in our two centres. At Rouen University Hospital, we performed a search via semantic query involving Normandy Clinical Data Warehouse (11) according to the keywords "rheumatoid arthritis" and ["scleroderma" or "CREST"]. At Caen University Hospital, a search was performed via the anonymised local registry of SSc for patients with the modality "joint symptoms (arthralgia or arthritis)".

Data collection

Clinical, biological and imaging data were retrieved from medical records. The immunological profile of patients with RA and SSc was defined according to the presence of the following autoantibodies: RF, anti-CCP, anti-nuclear, anti-soluble nuclear antigens, anti-centromere, anti-topoisomerase I, anti-PM/Scl and anti-RNAPolIII. Joint US data, when available, were collected, including the presence of synovitis and tenosynovitis exhibiting a significant Power Doppler signal (score ≥2).

Statistical analysis

As the sample size was limited, we did not perform statistical analysis to compare the targeted therapies. We used a Wilcoxon signed rank test for paired data to compare outcomes on DAS-28, CRP and glucocorticoid consumption between cytokine inhibitors (tocilizumab, etanercept, infliximab) and lymphocyte-targeting therapies (rituximab, abatacept). A p-value of <0.05 was considered statistically significant. We used the statistical software R through the graphical user interface pvalue.io.

Ethics

This study has been approved by the Institutional Review Board of Rouen University Hospital concerning research on existing data (no. 2021-56).

Results

Twenty-two patients (median age 61 (±6.5) years) fulfilling inclusion criteria were identified. Three patients were excluded due to the absence of RF and anti-CCP in their sera. Finally, 19 patients were included. Patients' characteristics are summarised in Table I.

Eighteen patients (95%) initially received conventional synthetic background therapy (csDMARD). Methotrexate was the most used first line csDMARD (n=11), while eight patients received another drug, namely hydroxychloroquine (n=4), leflunomide (n=2), azathioprine (n=1) or mycophenolate mofetil (n=1). Five patients (26%) did not receive targeted therapy and had therapeutic maintenance with methotrexate for a mean of 4.2 years. Fourteen patients (74%) received at least one line of bDMARD.

We identified 21 treatment sequences (20 with bDMARD; 1 with targeted synthetic DMARD). Tocilizumab was the most selected therapy (n=7), then rituximab (n=5), abatacept and anti-tumour necrosis factor (anti-TNF) (n=4, respectively), and tofacitinib (n=1). Considering only the period 2016-2021, tocilizumab and abatacept were the most frequently selected therapies (7 and 3, respectively), then rituximab (n=2). More than half of the patients received a single line of targeted therapy (8/14). Six patients required a second line due to primary failure at first re-evaluation (n=4), intolerance (n=1) or secondary escape (n=1).-

Seventeen sequences were evaluated for treatment efficacy according to EULAR response criteria. Two sequences of tocilizumab were stopped early due to side effects (One case of worsening of interstitial lung disease on respiratory function and one case of vomiting). One sequence (rituximab) was considered as "good" due to therapeutic maintenance for at least 36 months, joint US assessment showing no disease activity and discontinuation of glucocorticoid therapy at 12 months. In our sample, a "good" or "moderate" response rate was observed in 100% (4/4) of patients with abatacept, 80% (4/5) with rituximab, 40% (2/5) with tocilizumab, 25% (1/4) with anti-TNF. One patient treated with tofacitinib had a EULAR response considered as "good".

In the lymphocyte inhibitor group, mean DAS-28 decreased significantly by 1.75 points (p=0.016). Mean glucocorticoid consumption decreased by

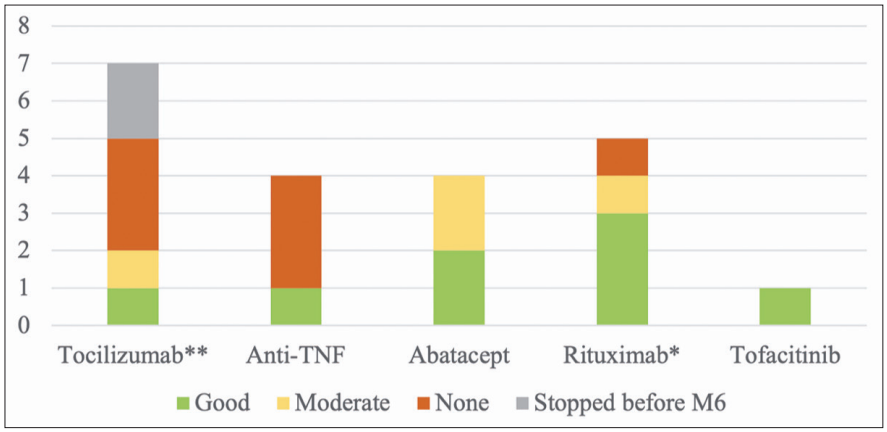

Fig. 1. Joint response to targeted therapy according to EULAR criteria or efficacy criteria based on therapeutic maintenance.
*response according to efficacy criteria as defined in the text: rituximab (n = 1).
**two sequences stopped before M6 could not be evaluated.
M6: month 6 of follow-up on treatment.

Table I. Characteristics of the population of 19 patients with rheumatoid arthritis/systemic sclerosis overlap syndrome.

General characteristics	NA	
Age at diagnosis (years)	0	60 [52; 67]
Time to RA /SSc diagnosis (years)	0	4 [0; 9]
Sex (female)	0	84%
Joint involvement at diagnosis		
Arthralgia	0	100%
Synovitis	0	90%
DAS-28 CRP	7	4.56 [3.93; 5.69]
Synovitis (B-mode ultrasound scan)	6	100%
Tenosynovitis (B-mode ultrasound scan)	6	46%
Joint hyperaemia (Doppler-mode ultrasound scan)	6	77%
Biological and immunological data at diagnosis		
CRP (mg/l)	0	15 [0; 24.5]
Rheumatoid factor	0	84%
Anti-CCP	1	68%
Anti-CCP (UA/ml)	1	43 [5; 272]
Anti-centromere antibody	0	42%
Anti-topoisomerase I antibody	0	21%
Anti-RNA polIII antibody	0	16%
Anti-PMScl antibody	0	5%
csDMARD used as first line treatment before targeted therapy* (number of patients)		
Methotrexate	0	11
Hydroxychloroquine	0	4
Leflunomide	0	2
Azathioprine	0	1
Mycophenolate mofetil	0	1

Quantitative data are expressed as median [interquartile]. Qualitative data are expressed as percentage. Anti-CCP: anti-cyclic citrullinated peptide; CRP: C-reactive protein; DAS-28: Disease activity score-28; NA: not available; RA: rheumatoid arthritis; SSc: systemic sclerosis.
*1 patient received bi-therapy (methotrexate plus hydroxychloroquine) as first-line treatment.

4.62 mg per day (p=0.054). Mean CRP decreased by 4.71 mg/l (p=0.59). In the cytokine inhibitor group, mean DAS-28 decreased by 0.77 points (p=0.36). Mean glucocorticoid consumption decreased by 1.33 mg per day (p=0.79). Mean CRP decreased by 6.5 mg/l (p=0.5). These data are summarised in Table II.

Table II. Outcomes of joint involvement in patients receiving targeted therapies.

	NA	M0	M6/M12	Δ mean	*p*
Cytokine inhibitors (tocilizumab, etanercept, infliximab)					
Joint					
DAS-28* (n=9)	0	6.32 (±1.01)	5.40 (±1.69)	-0.912	0.13
DAS-28 CRP (n=9)	0	5.91 (±1.32)	5.14 (±1.71)	-0.773	0.36
CRP (mg/L) (n=9)	0	26.9 (±19.4)	20.4 (±27.9)	-6.50	0.5
Glucocorticoids (mg/d) (n=9)	0	10.5 (±12.9)	9.17 (±12.4)	-1.33	0.79
Lymphocyte inhibitors (abatacept, rituximab)					
Joint					
DAS-28 CRP (n=8)	1	5.30 (±1.36)	3.55 (±1.53)	-1.75	**0.016**
CRP (mg/L) (n=8)	1	17.0 (±17.7)	12.3 (±19.9)	-4.71	0.59
Glucocorticoids (mg/d) (n=8)	1	7.25 (±5.26)	2.62 (±2.83)	-4.62	0.054

All data are quantitative and expressed as means (± standard deviation).
*DAS-28 ESR used to evaluate tocilizumab, DAS-28 CRP used to evaluate etanercept and infliximab.
CRP: C-reactive protein; DAS-28: Disease Activity Score-28; ESR: erythrocyte sedimentation rate; NA: not available.

Discussion

In this retrospective, two-centre, 10-year multi-departmental study, we identified 22 patients who fulfilled both RA and SSc classification criteria. This sample size is similar to that of the largest series reported in the literature (1). Patients with SSc may have inflammatory joint manifestations and mimic RA fulfilling EULAR classification criteria. We therefore excluded patients without specific RA antibodies to limit selection bias. We used a semantic search method in a health data warehouse, which was more efficient than analysis by coding, to capture all RA/SSc patients followed at Rouen University Hospital. As published studies on this topic are rather old, the present work is the first to analyse the efficacy and tolerance of targeted therapies in a well-documented population of 14 patients. Until now, open-label studies evaluating the joint response of bDMARD in SSc patients used various and heterogeneous criteria (5, 6). We used EULAR criteria to assess therapeutic response in the majority of patients since DAS-28 items are widely used in routine clinical practice. Lymphocyte-targeted therapies (abatacept, rituximab) led more frequently to a better (good or moderate) response than cytokine inhibitors (8/9 *vs*. 3/9) with a higher decrease of DAS-28. Moreover, glucocorticoid consumption tended to decrease with lymphocyte inhibitors while the daily dose remained stable with cytokine inhibitors.

In this respect, our results are consistent with recent data from the DESIRES trial confirming the potential interest of rituximab in the management of SSc (7).

However, since 2016, tocilizumab is the most used first-line treatment. The publication in the same year of the results of the faSScinate trial that showed, as a secondary endpoint, a better maintenance of forced vital capacity with tocilizumab in a context of pulmonary involvement in SSc (12), may have guided practitioners' choices. Furthermore, the reported cases of acute ILD possibly induced by anti-TNF agents in patients with SSc may explain the lower use of this bDMARD class (13). Finally, the more frequent selection of tocilizumab since 2016 might also be explained by the encouraging results observed in early studies in autoimmune diseases, but not subsequently confirmed in phase III trials such as in Sjögren's syndrome (14). Therefore, the lack of efficacy of tocilizumab in RA/SSc overlap syndrome supports data from previous studies, including those obtained in rhupus syndrome for which T and B lymphocyte-targeted therapies seem to be a relevant therapeutic option unlike anti-cytokine biologics (15).

The main limitations of this study are related to its retrospective nature and its small sample size. Our statistical results should be interpreted with caution. CRP remained elevated with tocilizumab due to two patients having a follow-up CRP of between 50 and 60 mg/l, which may suggest another cause of CRP elevation at reassessment or poor compliance. All the other patients had a decrease of CRP below 5 mg/l. This may have led to a measurement bias. It was not relevant to perform statistical analysis to compare targeted therapies, given the small number of patients. In the absence of a recommendation, the assessment and follow-up of patients may have varied between centres and practitioners depending on their medical specialty.

In conclusion, among the treatments used in routine practice to improve joint involvement in RA/SSc overlap syndrome refractory to csDMARDs, T and B lymphocyte-targeted therapies seem to be a relevant option.

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