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Is there a role for TNF- α antagonists in the treatment of SSc?

EUSTAR expert consensus development using the Delphi technique

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of interest, see page S44.

ABSTRACT

Objective: To obtain experiences and expert opinion on treatment of SSc patients with TNF- α antagonists.

Methods: An investigation was carried out among the EUSTAR centres into their expertise on use of TNF- α antagonists. Assessment forms on the frequency of TNF- α inhibitor use were distributed to EULAR Scleroderma Trials and Research Group (EUSTAR) centres. Afterwards, a three round Delphi exercise was performed to obtain expert consensus on the use of TNF- α inhibitors in SSc.

Results: Seventy-nine centres returned information on use of TNF- α antagonists in SSc patients. A total of 65 patients were treated with TNF- α inhibitors in 14 different centres. Forty-eight of the 65 patients treated with TNF- α inhibitors improved. Improvement was mainly seen in patients with arthritis, whereas the effects on fibrosis varied. In the first round of the subsequent Delphi approach, 71 out of 79 experts stated that they would use TNF- α antagonists in SSc. Arthritis was suggested as an indication for TNF- α antagonists by 75% of the experts. However, after the third stage of the Delphi exercise, the acceptance for the off-label use of TNF- α antagonists decreased and 59% recommended that TNF- α antagonists should not be used or only used in clinical trials in SSc patients, while 38% of the experts suggested the use of TNF- α antagonists for arthritis associated with SSc.

Conclusions: Most of the experts do not recommend the routine use of TNF- α antagonists in systemic sclerosis. Arthritis might be a potential indication in SSc, although controlled clinical trials with TNF- α antagonists are needed before general recommendations can be given.

Introduction

Numerous studies have shown that TNF- α plays an important role in the pathogenesis of autoimmune inflammatory diseases, and inhibition of TNF- α signalling has become an important therapeutic strategy for the treatment of diseases such as rheumatoid arthritis, spondylarthropathies and Crohn's disease (1, 2). In contrast to these inflammatory diseases, the role of TNF- α in fibrotic disease entities is uncertain. *In vitro* studies demonstrate convincingly that TNF- α inhibits the production of extracellular matrix proteins in fibroblasts and is a powerful inducer of matrix metalloproteinases (MMPs), and thus, inhibition of TNF- α could worsen fibrosis (3, 4). On the other hand, inhibition of TNF- α has been shown to ameliorate fibrosis in experimental *in vivo* models (5-7). However, these animal models do not fully resemble the situation in systemic sclerosis (SSc) (8), as most often these models show a highly inflammatory component. Skin fibrosis induced by bleomycin, for example, is strongly dependent on the infiltration of inflammatory cells with subsequent activation of fibroblasts by pro-fibrotic

cytokines such as interleukin-4 (IL-4) and IL-13 (9). In contrast, inflammatory infiltrates are sparse and often limited to early stages in SSc patients and the fibrosis might progress in the absence of evident inflammation due to endogenous or cytokine-driven activation of SSc fibroblasts with persistently increased collagen release even in the absence of inflammation (10).

Recent case series raised the question, whether TNF- α antagonists might be of benefit for the treatment of SSc. Bosello *et al.* reported on the outcome of four patients with SSc and secondary erosive arthritis treated with TNF- α antagonists (11). Treatment with TNF- α antagonists for 6 months improved arthritis in all patients. One of the patients achieved even an ACR 70 response, two an ACR 50 response, and one an ACR 20 response. In addition, a decrease of the modified Rodnan skin score (mRSS) was noticed in all patients with a reduction of more than 50% in 3 patients. Furthermore, the authors reported that fingertip ulcers, which were present in three patients, healed in two patients and improved in the third patient (11). These results are supported by other case-series and case-reports. Indeed, there are increasing numbers of publications on the use of TNF- α antagonists in patients with SSc indicating a wide-spread use of these agents (12-17). Recent analyses from the EUSTAR database and from other cohorts showed a striking level of radiologic hand involvement in patients with SSc (18), which might require the use of anti-arthritic molecular targeted therapies such as TNF- α antagonists. TNF- α antagonists have also been used successfully for other inflammatory driven fibrotic diseases such as eosinophilic fasciitis (19, 20). On the other hand, treatment with TNF- α antagonists was associated with fatal exacerbation of fibrosing alveolitis and with infectious complications in patients with SSc (21, 22). Similarly, TNF- α antagonists have been associated with fibrosing alveolitis in patients with RA (23). Overall, the benefits of TNF- α antagonists in the treatment of SSc are unclear, in particular because the results of open-label studies have to be interpreted with

caution because of the spontaneous regression of the mRSS and because of the remarkable inter-individual variability in the course of skin fibrosis in SSc patients (24-27).

We therefore performed an international investigation among members of the EUSTAR study group for SSc to address the following questions: Are TNF- α antagonists currently used for the treatment of SSc? What were the outcomes of these patients? Is there a consensus about special subgroups of SSc patients that might benefit from treatment with TNF- α antagonists?

Methods

Assessment of the use of TNF- α antagonists in SSc

All EUSTAR (www.eustar.org) scleroderma centres were asked to report patients with TNF- α inhibitor use using a structured assessment form (28). The assessment form was either given directly to the representatives of these centres or send via e-mail from the EUSTAR office to the EUSTAR centres. The form assessed the number of patients treated with TNF- α antagonists at the specific centre and which type of TNF- α antagonist (infliximab, etanercept or adalimumab) was given. Centres that had used TNF- α antagonists were asked, whether the patients improved, remained unchanged or worsened according to the physicians' judgment. Centres, which had treated SSc patients with TNF- α antagonists, were also asked, whether they would use TNF- α antagonists again for the treatment of SSc, to give the reasons for their decision and specify the subgroup of SSc patients they would treat with TNF- α antagonists. Centres, that had not treated SSc patients with TNF- α antagonists, were asked which clinical situations would be an indication for use of TNF- α antagonists in SSc patients and if so, to specify them. All information was kept anonymous.

Three-stage Delphi approach

The Delphi method is a consensus methods for medical and health service research (29, 30). In contrast to expert panels and to consensus development conferences, participants can offer their opinions independently in the Delphi

procedure without the bias problems of face-to-face meetings. Moreover, participants can change their opinion in consecutive stages of the process, based on the systematic feedback from the results of the previous Delphi rounds.

Prior to the Delphi exercise a non-systematic literature search on preclinical and clinical effects on fibrosis of TNF- α and its inhibition was performed. The results of this literature search were presented to the centres before the Delphi exercise was started and was repeated before each round. Arthritis was defined as described in reference (31). Centres were also informed about the results of the assessment prior to the first Delphi stage. For the first of the three-stage Delphi exercise, EUSTAR centres were asked to list potential indications for the use of TNF- α antagonists in patients with SSc. The respondents had the possibility to comment on their choice in a free text field. In addition, centres were asked whether they had experience with TNF- α antagonists in patients with SSc, and whether they would in general recommend the use of TNF- α antagonists.

For stage 2 of the Delphi exercise, 5 statements were developed based on the results of the first round: 1) I recommend using TNF- α inhibitors for treatment of fibrosis in SSc; 2) I recommend using TNF- α inhibitors in patients with late, treatment-resistant SSc; 3) I recommend using TNF- α inhibitors in patients with early inflammatory SSc; 4) I recommend using TNF- α inhibitors in SSc patients with associated arthritis; 5) I recommend using TNF- α inhibitors for SSc only in a controlled setting in randomised controlled trials; 6) I do not recommend using TNF- α inhibitors for treatment of SSc patients at all. Participants were asked to vote for one of these recommendations. Participants were aware of the reports from EUSTAR experts on SSc outcomes from round 1 when voting on the recommendations, and results from the non-systematic literature review before round 1 were also shown again before each round. For stage 3 of the Delphi exercise participants were shown the results of the previous round and were then asked to repeat the voting on the recommendations.

Results

Use of TNF- α antagonists in SSc

Seventy-nine of the 136 (58%) centres of the EUSTAR study group returned the assessment form on the use of TNF- α antagonists in SSc. Fourteen of the 79 responding centres (18%) had treated a total of 65 SSc patients with TNF- α antagonists. Of the 65 patients treated with TNF- α antagonists, 30 (46%) received infliximab, 29 (45%) etanercept and 6 (9%) adalimumab.

Of the 65 patients treated with TNF- α antagonists, 48 (74%) patients were reported by the EUSTAR experts to improve upon TNF- α antagonists (Table I). In 41/48 responders, arthritis associated with SSc improved under treatment with TNF- α antagonists according to the judgment of the treating physician. In 6 patients, fibrosis regressed and 8 patients experienced other benefits such as reduction of dose of corticosteroids, less fatigue, improvement of tendinopathy or myositis, reduction of dysphagia and improvement of alveolitis and calcinosis.

In 7 of the 65 treated patients (11%), disease was reported to worsen during treatment with TNF- α antagonists. In all of these patients, fibrosis progressed. In addition, a lupus-like reaction was noticed in 2 patients (3%). The disease remained unchanged in 10 (15%) SSc patients treated with TNF- α antagonists.

Delphi based recommendations

on the use of TNF- α antagonists in SSc

In the first round of the Delphi approach, most experts stated that they would recommend the use of TNF- α antagonists for the treatment of certain manifestations of SSc. Of the 14 centres with experience with TNF- α antagonists in SSc patients, 11 (79%) stated that they would use TNF- α antagonists again. As an indication for the use of TNF- α antagonists in SSc patients, all 11 centres defined arthritis secondary to SSc. One expert suggested that in addition to patients with secondary arthritis, patients with very early disease might also benefit from treatment with TNF- α antagonists.

Of the 65 centres that had not used TNF- α antagonists for the treatment of

Table I. Outcome of 65 SSc patients with TNF- α antagonists as judged by the treating physician.

	Total number of SSc patients / percentage	Manifestation improved / worsened
Improvement	48 / 74%	• Arthritis • Fibrosis • Alveolitis • Fatigue • Myositis • Tendinopathy • Dysphagia • Calcinosis • Reduction of corticosteroids
Unchanged	10 / 15%	
Worsening	7 / 11%	• Fibrosis
Side effects	2 / 3%	• Lupus-like reaction

SSc patients, 5 (6% of the participating centres) were not in favour of a possible indication for TNF- α antagonists in SSc as TNF- α has not been demonstrated convincingly to play a role in pathogenesis of fibrosis. Most of these experts argued that there might be a role for TNF- α antagonists in the very early stages of SSc before any fibrotic changes become clinically evident, whereas TNF- α antagonists might be harmful and exert pro-fibrotic effects in later, non-inflammatory stages of SSc with endogenous activation of SSc fibroblasts. Experts from the remaining 60 centres (76% of the participating centres) that had not treated SSc patients with TNF- α antagonists before would treat some clinical subgroups of SSc patients with TNF- α antagonists (Table II), in particular those with arthritis or overlap to rheumatoid arthritis (45 centres, 75%). Fourteen centres (23%) stated that they would treat early and highly inflammatory stages of SSc. Eight (13%) experts would try TNF- α antagonists in SSc patients with severe diffuse disease unresponsive to other treatments. Other suggested indications for TNF- α antagonists were generalised morphea (3 centres, 5%), pulmonary fibrosis or alveolitis (3 and 2 centres, 5% and 3%, respectively), pulmonary arterial hypertension (2 centres, 3%), severe Raynaud's disease (3 centres, 5%), myositis (1 centre, 2%) and enthesopathy (1 centre, 2%).

Fifty-eight centres completed the next two rounds of the three-stage Delphi-exercise (Table III). Twenty-nine

centres (50%) suggested that TNF- α antagonists should only be used in randomised controlled trials and would not use TNF- α inhibitors off-label for any manifestation of SSc. Five centres (9%) did not recommend the use of TNF- α antagonists at all. Twenty-two centres (38%) stated that they would use TNF- α antagonists for the treatment of polyarthritis in SSc patients. Other indications including fibrotic manifestations and early inflammatory SSc received a low number of votes. There was no difference in their recommendations between centres that had used TNF- α antagonists and those that had not.

Discussion

The present study reports the results of an international investigation distributed to the members of EUSTAR being experts in SSc diagnosis and treatment and subsequent Delphi based consensus on the use of TNF- α inhibitors in SSc. In the first round of the Delphi exercise, 94% of the participating centres stated that they had either already treated or would treat certain SSc patients with TNF- α antagonists. Interestingly, after discussion and re-rating during the Delphi process, the acceptance for TNF- α antagonists decreased and 59% of the experts recommended the use of TNF- α antagonists only within randomised controlled trials or did not recommend the use of TNF- α antagonists at all. The major reason for this decreased acceptance was that early inflammatory stages of SSc were no longer considered as a possible indication.

Indeed, there is good preclinical evidence that antagonists of TNF- α can prevent fibrosis under inflammatory conditions, while TNF- α antagonism has profibrotic effects in non-inflammatory conditions. For example, antagonists of TNF- α prevent fibrosis in animal models, in which a strong inflammatory component at the initial stages is an important trigger for the later development of fibrosis (reviewed in 8). However, when inflammatory conditions and cellular inflammatory infiltrates are absent as for example in *in vitro* models, TNF- α exerts direct antifibrotic effects on matrixproducing cells and inhibition of this process favours fibrosis (8). The reason why reviewers changed their opinion might be that patients with SSc are often not seen by expert centres in their very early inflammatory disease stages due to the delayed time from the first unspecific symptoms to the diagnosis of SSc. Most patients attend a physician late in the course of the disease, when fibrosis becomes clinically manifested. In disease stages with clinically evident fibrosis, prominent inflammatory infiltrates are absent in most patients and the increased release of extracellular matrix is mediated by an autonomous activation of resident fibroblasts (10). Thus, the therapeutic window for an anti-inflammatory treatment of SSc patients with TNF- α antagonists might be missed in most cases due to the delay in diagnosis (32).

The indication named most often in all three rounds of the Delphi approach was polyarthritis. Arthritis occurs in approximately 16% of patients with SSc, and it can be erosive in 10–41% of the patients (18). Although randomised controlled trials investigating the use of TNF- α antagonists in SSc are lacking, several reports suggest that SSc patients with severe arthritis might benefit from TNF- α antagonists (11–16). Consistently, several EUSTAR experts also reported positive responses of arthritis to TNF- α antagonists. Thus, first evidence indicates that arthritis in SSc patients might respond to treatment with TNF- α antagonists. Accordingly, 22/59 experts recommended the use of TNF- α antago-

Table II. Suggested indications for the treatment of SSc patients with TNF- α antagonists in the first round of the Delphi exercise.

Suggested indication for TNF- α antagonists in SSc patients	Percentage of participants
• arthritis / overlap to rheumatoid arthritis	75%
• early and highly inflammatory stages of SSc	23%
• severe diffuse disease unresponsive to other treatments	13%
• generalised morphea	5%
• pulmonary fibrosis	5%
• alveolitis	3%
• pulmonary arterial hypertension	3%
• severe Raynaud's disease	5%
• myositis	2%
• enthesopathy	2%

Table III. Voting of Delphi stage 2 and 3 on the recommendations for the use of TNF- α inhibitors in SSc patients.

	Delphi 2	Delphi 3
I recommend using TNF α inhibitors for treatment of fibrosis in SSc	2	0
I recommend using TNF α inhibitors in patients with late, treatment resistant SSc	0	1
I recommend using TNF α inhibitors in patients with early inflammatory SSc	3	1
I recommend using TNF α inhibitors in SSc patients with associated arthritis	12	22
I recommend using TNF α inhibitors for SSc only in a controlled setting in randomised controlled trials	32	29
I do not recommend using TNF α inhibitors for treatment of SSc patients at all	8	5
Total votes	57	58

nists for SSc patients with associated arthritis. However, at the same time, 29/59 experts recommended the use of TNF- α antagonists only in a controlled setting in randomised controlled trials. The most likely explanation for this result is the unclear risk of adverse events and the potential profibrotic effects (see below), which must be balanced against the beneficial effects on arthritis.

In contrast to arthritis, beneficial effects of TNF- α antagonists on fibrosis were reported only in few SSc patients and almost as many patients experienced a progression of fibrosis, while on TNF- α antagonists. This is further underlined by an SSc patient with polyarthritis and fibrosing alveolitis, who showed a fatal progression of lung fibrosis under treatment with adalimumab and azathioprine with progressive dyspnea and CT changes (21). Although the assessment form in this study was not designed to analyse the outcome of fibrosis, progression of fibrosis might reflect the

natural course of the disease, the relatively high number of patients with progression might be counted as a warning sign, and fibrosis needs to be specifically addressed in future clinical trials on TNF- α antagonists, even if designed to target SSc-associated polyarthritis. Accordingly, only very few centres would recommend the use TNF- α antagonists for fibrosis. Other disease manifestations mentioned by the participants to improve in single cases such as dysphagia are rather unlikely to be driven by TNF- α -dependent mechanisms and might reflect the natural course of the disease.

It needs to be strongly emphasised that data on clinical efficacy of TNF- α antagonists in this study should not be over-interpreted. This study was not designed as an interventional trial to assess disease outcomes. This would have required capturing a number of pre-defined primary and secondary outcome measures such as the modified Rodnan skin score, tender and swollen

joint counts in patients with arthritis together with x-ray and ultrasound joint erosion scores, ulcer burden, pulmonary function tests and HRCT as well as other parameters such as duration of treatment with TNF- α antagonists, mean time to improvement, multivariate analysis on parameters that predict response and on parameters that predict side effects, analysis in subgroups such as patients with limited and diffuse SSc. This was out of scope of the present study and needs to be addressed in future randomised controlled trials. Furthermore, out of 136 centres, only 79 centres participated in the first round of the Delphi exercise, and 58 centres in the 2nd and 3rd round. This is a limitation in a consensus study. The reasons for centres not to participate remain speculative, but one possibility is that those centres had not used TNF- α antagonists for their SSc patients or that TNF- α antagonists were not readily available for SSc patients in their respective countries. There are also intrinsic limitations to the Delphi technique itself. The Delphi technique simply reflects the opinion of the experts participating in the exercise. This expert opinion is not necessarily the truth, and depends on the experience and familiarity of the experts with the topic of the consensus. This further underlines the need for data from randomised controlled trials with TNF- α antagonists in SSc.

In summary, most EUSTAR experts recommend the use of TNF- α antagonists only in randomised controlled clinical trials and discourage the off-label use in individual patients outside of clinical trials. Arthritis is considered as a manifestation that might respond to TNF- α antagonists and response of SSc-arthritis to TNF- α antagonists should be investigated in more detail. In contrast, other manifestations of SSc such as fibrosis are not anticipated to benefit clearly from treatment with TNF- α antagonists. However, although these recommendations are based on consensus of the EUSTAR experts, randomised controlled trials with TNF- α antagonists in SSc are needed to determine a potential role for TNF- α antagonists in the treatment of SSc.

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Disclosure of interest

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