ARD Online First, published on December 19, 2012 as 10.1136/annrheumdis-2012-202657

CONCISE REPORT

Outcomes of patients with systemic sclerosis-associated polyarthritis and myopathy treated with tocilizumab or abatacept: a EUSTAR observational study

Muriel Elhai,[1] Marine Meunier,[1] Marco Matucci-Cerinic,[2] Britta Maurer,[3] Gabriela Riemekasten,[4] Tifenn Leturcq,[1] Raffaele Pellerito,[5] Carlos Alberto Von Mühlen,[6] Alessandra Vacca,[7] Paolo Airo,[8] Francesca Bartoli,[2] Ginevra Fiori,[2] Maria Bokarewa,[9] Valeria Riccieri,[10] Mike Becker,[4] Jérôme Avouac,[1] Ulf Müller-Ladner,[11] Oliver Distler,[3] Yannick Allanore,[1] on behalf of EUSTAR (EULAR Scleroderma Trials and Research group)

For numbered affiliations see end of article.

Correspondence to
Professor Yannick Allanore, Service Rhumatologie A, hôpital Cochin, 27 rue du faubourg St Jacques, Paris 75014, France; yannick.allanore@cch.aphp.fr

OD and YA contributed equally.

Received 11 September 2012
Revised 27 November 2012
Accepted 28 November 2012

ABSTRACT

Objective To evaluate the safety and effectiveness of tocilizumab and abatacept in systemic sclerosis (SSc)-polyarthritis or SSc-myopathy.

Methods 20 patients with SSc with refractory polyarthritis and seven with refractory myopathy from the EUSTAR (EULAR Scleroderma Trials and Research) network were included: 15 patients received tocilizumab and 12 patients abatacept. All patients with SSc-myopathy received abatacept. Clinical and biological assessments were made at the start of treatment and at the last infusion.

Results After 5 months, tocilizumab induced a significant improvement in the 28-joint count Disease Activity Score and its components, with 10/15 patients achieving a EULAR good response. Treatment was stopped in two patients because of inefficacy. After 11 months' treatment of patients with abatacept, joint parameters improved significantly, with 6/11 patients fulfilling EULAR good-response criteria. Abatacept did not improve muscle outcome measures in SSc-myopathy. No significant change was seen for skin or lung fibrosis in the different groups. Both treatments were well tolerated.

Conclusions In this observational study, tocilizumab and abatacept appeared to be safe and effective on joints, in patients with refractory SSc. No trend for any change of fibrotic lesions was seen but this may relate to the exposure time and inclusion criteria. Larger studies with longer follow-up are warranted to further determine the safety and effectiveness of these drugs in SSc.

INTRODUCTION

Joint involvement is common and disabling in systemic sclerosis (SSc).[1 2] Of patients with SSc, 46–97% complain about joint stiffness or pain, and up to 30% exhibit inflammatory clinical signs.[1 2] Moreover, ultrasound shows that a large proportion of patients with SSc exhibit synovitis (~50%) and tenosynovitis (~1/3), respectively.[3] Myopathy is also common in SSc, with a prevalence ranging from 16% to 81%; clinical presentations are broad and vary from myalgias to muscle weakness.[4]

No specific treatment is available for articular and muscle involvement in SSc and the use of low doses of oral corticosteroids in association with methotrexate is generally recommended, by analogy with rheumatoid arthritis (RA) in polyarthritis, and the use of steroids in myopathy.[2 4] As major improvements in the treatment of RA using biological agents have been achieved in recent years, there is also a rationale for using some of these targeted treatments, such as anti-interleukin 6 (anti-IL-6) or cytotoxic T lymphocyte antigen 4-immunoglobulin (CTLA4-Ig), in SSc, although no trial has yet been performed. IL-6 appears to be overexpressed in both the skin and serum of patients with SSc,[5–8] and it may induce collagen production by normal dermal fibroblasts and promote differentiation of dermal fibroblasts into myofibroblasts.[9 10] Furthermore, the contribution of IL-6 to dermal fibrosis, but also to lung fibrosis, has been demonstrated in murine SSc models.[11–13] Associations between high CTLA4 sera levels and SSc have also been reported.[14] These molecular targets are of interest since there is accumulating evidence suggesting that T cells have a key role in SSc pathogenesis, which are also predominantly inflammatory cells in SSc myopathy.[4 15] Consequently, it is worth studying the clinical effect on SSc of tocilizumab, a humanised anti-IL-6 receptor antibody, and abatacept, a recombinant CTLA4Ig fusion protein that selectively modulates costimulation resulting in downregulation of T cell activation. Therefore, we analysed the EULAR Scleroderma Trials and Research (EUSTAR) database to determine the off-label use of tocilizumab and abatacept in refractory polyarthritis or myopathy associated with SSc and performed a prospective multicentre observational study to assess the safety and effectiveness of these biological agents.[16]

METHODS

By interrogating the EUSTAR network in June 2011, 20 patients with SSc with active polyarthritis and insufficient response to disease-modifying anti-rheumatic drugs (DMARDs) and seven patients with active myopathy refractory to DMARDs and

To cite: Elhai M, Meunier M, Matucci-Cerinic M, *et al*. *Ann Rheum Dis* Published Online First: 18 December 2012 doi:10.1136/annrheumdis-2012-202657

cyclophosphamide were included.[16] All patients fulfilled American College of Rheumatology criteria for SSc. Patients received tocilizumab or abatacept upon the decision of their doctor in routine practice: 15 patients received tocilizumab at 8 mg/kg/month, and 12 patients abatacept at 10 mg/kg/month. All patients with SSc-myopathy received abatacept. Clinical and biological data were collected at the start of treatment and before the last infusion. The characteristics of the patients and outcome parameters were all derived from the online Minimal Essential Data Set and have already been reported in detail.[1 16 17]

Clinical data were as follows: age, sex, disease duration, cutaneous subtype, presence of digital ulcers, lung involvement (pulmonary fibrosis and/or abnormal respiratory function tests (forced vital capacity <75% predicted and/or carbon monoxide transfer <70% predicted), heart involvement (according to EUSTAR standards[16 17]), modified Rodnan total skin score, swollen and tender joint counts, morning stiffness, visual analogue scale articular pain score, 28-joint count Disease Activity Score (DAS28) score, Health Assessment Questionnaire Disability Index (HAQ-DI) and treatment received (steroids, DMARDs). Biological tests included routine blood tests, erythrocyte sedimentation rate, C-reactive protein, creatine kinase (CK) level, liver enzymes, cholesterol level and antibodies (anti-Scl-70, anticentromere, rheumatoid factor, anti-cyclic citrullinated peptide, anti-U1 ribonucleoprotein (RNP) and anti-J01). In patients with myositis, visual analogue scale for disease activity, assessed by the doctor, and manual muscle strength were documented. Side effects were recorded. All data analyses were performed using MedCalc V.9.2.1.0. Data were presented as median (IQR) for continuous variables and numbers (percentages) for categorical variables. Data were statistically analysed using the Wilcoxon test for comparison between two continuous variables. A p value < 0.05 was considered statistically significant.

RESULTS

Fifteen patients with SSc-arthritis were treated with tocilizumab; median age was 56 (45–61) years and disease duration 5 (4–9) years. About two-thirds of the patients were co-treated with low-dose steroids and 60% received methotrexate. Previous treatments included rituximab (three patients), immunosuppressant drugs other than methotrexate (four patients), abatacept (one patient) and anti-tumour necrosis factor α (TNFα; two patients). Five patients with SSc-arthritis received abatacept; median age was 53 (39–64) years and disease duration 13 (11–16) years. Previous treatments included immunosuppressant drugs for two patients and for one patient both anti-TNFα and tocilizumab. Seven patients (median age 55 (47–63) years, disease duration 7 (2–8) years) received abatacept because of refractory myopathy. Muscle biopsy had been performed in five cases and showed inflammatory infiltrates in all cases, together with necrosis in two patients. Anti-Jo1 and U1 RNP antibodies were detected in three patients (43%) and one patient (14%), respectively. Six had pulmonary involvement and none had heart involvement. Five (71%) were treated with steroids (low dose for all, except one who received a dose of 60 mg/day) and DMARDs. Two were also treated with cyclophosphamide. Among these patients, six also had refractory polyarthritis and were included in the analysis of articular outcomes after treatment with abatacept. The patient's characteristics are shown in table 1.

Articular outcome

At baseline, patients treated with tocilizumab had a high disease activity (median DAS28 score of 5.2 (3.9–6.1)). After 5 months, the DAS28 score and all articular parameters, except HAQ-DI, decreased significantly with a median decrease of 2.7 in the DAS28 score (table 2). Ten patients (67%) fulfilled good EULAR response criteria, whereas four (27%) were moderate responders. Steroids were stopped in two patients and the dose was reduced in three patients. Treatment with tocilizumab was well tolerated, only one patient complained of one episode of slight nausea after the first infusion without recurrence despite the continuation of treatment. In one patient, treatment was stopped at the fourth infusion for 2 months because of an

Table 1 Main characteristics of SSc-arthritis and SSc-myopathy patients at baseline

	Tocilizumab	Abatacept	
Characteristics	**SSc-arthritis (n = 15)**	**SSc-arthritis (n=5)**	**SSc-myopathy (n=7)**
Female n (%)	13 (86.7)	5 (100)	5 (71.4)
Diffuse cutaneous subtype n (%)	8/13 (61.5)	3/5 (60)	3/7 (42.9)
History of digital ulcer n (%)	3/15 (20)	3/5 (60)	3/7 (42.9)
ACR 1987 criteria for RA	10/11 (90.9)	5/5 (100)	0/7
Antibodies			
Anti-Scl-70	10/13 (76.9)	3/5 (60)	3/7 (42.9)
Anticentromere	1/13 (7.7)	2/5 (40)	2/7 (28.6)
RF	3/8 (37.5)	4/5 (80)	0/7
Anti-CCP antibodies	3/8 (37.5)	4/5 (80)	0/7
Pulmonary involvement			
FVC <75% predicted	2/13 (15.4)	1/5 (20)	1/7 (14.3)
TLCO <70% predicted	5/13 (38.5)	3/5 (60)	6/7 (85.7)
Pulmonary fibrosis	4/13 (30.8)	0/5	6/7 (85.7)
Ongoing co-treatments			
Methotrexate	8/14 (57.1)	1/5 (20)	2/7 (28.6)
Steroids (low dose ≤10 mg/day)	11/15 (73.3)	3/5 (60)	5/7 (71.4)*

Values are n (%) unless stated otherwise.
*Low dose for all except one with 60 mg/day.
ACR, American College of Rheumatology; Anti-CCP, anti-cyclic citrullinated peptide antibody; FVC, forced vital capacity; RA, rheumatoid arthritis; RF, rheumatoid factor; SSc, systemic sclerosis; TLCO, carbon monoxide transfer factor.

Table 2 Outcomes of patients with SSc-polyarthritis treated with tocilizumab and abatacept

	Tocilizumab (n=15)			Abatacept (n=11)		
	Baseline	Last infusion	p Value	Baseline	Last infusion	p Value
Follow-up (months)	5 (3–11.5)			11 (6–16.5)		
Modified Rodnan skin score	15 (4.5–24.0)	12.0 (3.8–16.3)	0.109	5 (2.3–14.5)	5 (2.3–15.3)	1.000
Tender joint count (/28)	9.0 (6.3–14)	1.5 (0–4)	0.001	6 (3.3–10)	1 (0–2)	0.002
Swollen joint count (/28)	4 (2–9.3)	0 (0–0)	<0.001	3 (0.5–4)	0 (0–0)	0.008
Morning stiffness (min)	60 (30–90)	25 (0–30)	0.008	60 (29.3–105)	15 (11.3–30)	0.004
VAS articular pain score (/100)	80 (48.3–86)	25 (20–56.8)	0.031	43 (20.8–51.3)	20 (4–31.3)	0.014
CRP	8.2 (2.6–15)	1.0 (0.6–3.1)	0.010	5.2 (5–9)	4 (2.3–8)	0.641
DAS28 score	5.2 (3.9–6.1)	2.8 (2.2–3.4)	<0.001	4.5 (3.5–5.0)	2.3 (1.2–3.4)	0.001
HAQ-DI score (/3)	1.3 (1–2.4)	1 (0.6–1.9)	0.055	1.1 (0.9–1.2)	0.4 (0.3–0.8)	0.063
Delta DAS28		2.7 (1.5–3.1)			1.7 (0.9–2.4)	
EULAR good responders, n (%)		10 (66.7)			6 (54.5)	

Data are presented as median (IQR) unless stated otherwise.
CRP, C-reactive protein; DAS28, 28-joint count Disease Activity Score; HAQ-DI, Health Assessment Questionnaire Disability Index; SSc, systemic sclerosis; VAS, visual analogue scale.

increase in liver enzymes and was restarted when transaminases returned to normal with subsequent good liver tolerance. In two patients, tocilizumab was stopped because of inefficacy after 3 months.

At baseline, patients treated with abatacept had a moderate disease activity with DAS28 score of 4.5 (3.5–5.0). After 11 months, there was a significant decrease in disease activity with a decrease in both DAS28 score and other articular parameters (except C-reactive and HAQ-DI). Six patients (55%) were good EULAR responders, whereas two patients (18%) were moderate responders. Steroids were stopped in two patients. The steroid dose was reduced in five patients. Treatment was maintained in all patients. Side effects were as follows: in the group with associated myopathy, one patient reported headache after each infusion and three infections occurred (two episodes of bronchitis in one patient treated with antibiotics and one herpes simplex virus infection). There was no significant change in skin or lung fibrosis with either abatacept or tocilizumab. Additional clinical data are reported in table 2.

Muscular outcome

In patients with SSc-myopathy, after a follow up of 18 months, myopathy tended to improve, but the results were not statistically significant. Outcomes are shown in table 3.

DISCUSSION

The data of this observational study suggest that tocilizumab and abatacept are safe and effective approaches to improving joint involvement after 5–11 months in refractory SSc-arthritis.

Inflammatory joint involvement is a heavy burden in SSc with no standard treatment.[2] Despite the advent of biological agents in RA and a subsequent rationale for their use in SSc,[2 5–15] targeted treatments have not yet been developed in SSc. One short report suggested some efficacy of anti-TNFα agents on inflammatory joint involvement in SSc.[18] However, their use is limited by the risk of exacerbation of lung fibrosis.[19] Our study suggests that patients with SSc, with refractory arthritis may benefit from tocilizumab or abatacept as do patients with RA. Both treatments were associated with a significant decrease in DAS28 score after 5 and 11 months. About two-thirds of patients with SSc could be classified as good responders. Interestingly, both treatments allowed reducing or stopping steroids, which are known to increase the risk of renal crisis in SSc. A trend towards a decrease in HAQ-DI was seen, although not reaching significance. This may be related to features other than articular involvement that were previously identified to affect the HAQ-DI score—for example, dermal thickness, age or raised platelet count.[20] The efficacy on joints was partly explained by some overlap with RA, as reflected by the prevalence of anti-cyclic citrullinated peptide in the cohort. However, all

Table 3 Outcomes of the seven patients treated with abatacept for refractory myopathy

Outcomes	Baseline	Last visit	p Value
Follow-up (months)	18 (12–23.5)		
Rodnan skin score	5 (2–19.8)	5 (2–19.3)	0.949
TLCO <70% predicted, n (%)	6 (85.7)	5 (71.4)	1.000
FVC <75% predicted, n (%)	1 (14.3)	1 (14.3)	1.000
VAS of myopathy disease activity assessed by doctor (/100)	28 (7.5–43)	12 (0–26.3)	0.125
VAS of myopathy disease activity assessed by patient (/100)	57 (25–83)	19 (0–85)	0.700
Muscle strength assessed by MMT (%)	92 (42–95)	92 (76–100)	0.663
CK level	456 (166–1800)	192 (109–402)	0.625
Delta CK		56 (−162–1632)	
CRP	5 (5–15.8)	5 (4–5)	0.875

Data are presented as median (IQR) unless stated otherwise.
CK, creatine kinase; CRP, C-reactive protein; FVC, forced vital capacity; MMT, manual muscle testing; TLCO, carbon monoxide transfer factor; VAS, visual analogue scale.

patients fulfilled American College of Rheumatology criteria for SSc and almost all had antibodies specific to SSc. To date, there is only case report on treating two patients with SSc (without inflammatory joint disease) with tocilizumab.[21] Contrary to our results, dermal fibrosis improved in both these patients, which was confirmed by histological assessment. However, lung fibrotic changes were unchanged.[21] It has to be emphasised that neither of these studies was designed to detect the effects of tocilizumab and abatacept on fibrosis in view of their sample size; their selection of patients, which was not stratified according to disease duration; their duration of follow-up and their outcome criteria.

Treatment with abatacept was associated with a trend towards improvement of refractory myopathy, but this was not statistically significant. Two hypotheses might be derived from this observation: the number of patients included might have been too small to reach significance or abatacept might be effective only on joint involvement. Study of a larger number of cases with EUSTAR network support is expected to clarify the effect of abatacept on myopathy.[16] Our study should be interpreted within its limitations, such as the lack of monitoring of radiological changes. In addition, despite all the efforts made by EUSTAR to homogenise the care of patients with SSc, the participation of several centres might have introduced some heterogeneity in their assessment.

Our study suggests that tocilizumab and abatacept do have the potential to improve the outcome of SSc-related arthritis. These results underline the need for larger prospective studies with a longer follow-up and radiological monitoring to better assess the safety and effectiveness of these drugs in SSc, and to facilitate also the off-label use of these drugs in selected patients.

Author affiliations
[1]Rheumatology A Department, Paris Descartes University, Cochin Hospital, Paris, France
[2]Department of Biomedicine, Section of Rheumatology, Florence, Italy
[3]Department of Rheumatology, University Hospital of Zurich, Zurich, Switzerland
[4]Department of Rheumatology and Clinical Immunology, German Rheumatology Research Centre, A Leibniz Institute, Charity University Hospital, Berlin, Germany
[5]Division of Rheumatology, "Ordine Mauriziano" Hospital, Torino, Italy
[6]Rheuma Clinic of Rheumatic Diseases, Porto Alegre, Brazil
[7]Chair and Unit of Rheumatology, University Clinic A.O.U. of Cagliari, Monserrato, Italy
[8]Rheumatology and Clinical Immunology Unit, Spedali Civili and University of Brescia, Brescia, Italy
[9]Rheumatology and Inflammation Research, Institute of Medicine, Sahlgrenska Hospital, University of Gothenburg, Gothenburg, Sweden
[10]Rheumatological Unit, Department of Internal Medicine and Clinical Specialities, University of Rome 'Sapienza', Rome, Italy
[11]Department of Rheumatology and Clinical Immunology, Justus-Liebig University Giessen, Kerckhoff Clinic Benekestrasse 2, Bad Nauheim, Germany

Contributors All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the version. ME had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study conception and design: ME, MM, OD, YA. Acquisition of data: ME, MM, MM-C, BM, GR, TL, RP, CAvM, AV, PA, FB, GF, MBo, VR, MBe, JA, UM-L, OD, YA. Analysis and interpretation of data: ME, OD, YA.

Disclosure ME, MM, MM-C, BM, GR, TL, RP, CAvM, AV, PA, FB, GF, MBo, VR, MBe, JA, YA: none, UM-L: speaker and adviser to BMS and Roche/Chugai; OD had consultancy relationship and/or has received research funding from Actelion, Bayer, Pfizer, Ergonex, BMS, Sanofi-Aventis, Sinoxa, United BioSource Corporation, Medacs, Biovitrium, Boehringer Ingelheim Pharma, Novartis, 4 D Science and Active Biotec for investigation of potential treatments of scleroderma and its complications.

Funding Funded in part by an unrestricted educational grant to EUSTAR by EULAR.

Competing interests None.

Ethics approval CPP ile de France 3.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Avouac J, Walker U, Tyndall A, *et al*. Characteristics of joint involvement and relationships with systemic inflammation in systemic sclerosis: results from the EULAR Scleroderma Trial and Research Group (EUSTAR) database. *J Rheumatol* 2010;37:1488–501.
2 Avouac J, Clements PJ, Khanna D, *et al*. Articular involvement in systemic sclerosis. *Rheumatology (Oxford)* 2012;51:1347–56.
3 Elhai M, Guerini H, Bazeli R, *et al*. Ultrasonographic hand features in systemic sclerosis and correlates with clinical, biological and radiographic findings. *Arthritis Care Res (Hoboken)* 2012;64:1244–9.
4 Ranque B, Authier FJ, Berezne A, *et al*. Systemic sclerosis-associated myopathy. *Ann N Y Acad Sci* 2007;1108:268–82.
5 Scala E, Pallotta S, Frezzolini A, *et al*. Cytokine and chemokine levels in systemic sclerosis: relationship with cutaneous and internal organ involvement. *Clin Exp Immunol* 2004;138:540–6.
6 Hasegawa M, Sato S, Fujimoto M, *et al*. Serum levels of interleukin 6 (IL-6), oncostatin M, soluble IL-6 receptor, and soluble gp130 in patients with systemic sclerosis. *J Rheumatol* 1998;25:308–13.
7 Gurram M, Pahwa S, Frieri M. Augmented interleukin-6 secretion in collagen-stimulated peripheral blood mononuclear cells from patients with systemic sclerosis. *Ann Allergy* 1994;73:493–6.
8 Feghali CA, Bost KL, Boulware DW, *et al*. Mechanisms of pathogenesis in scleroderma. I. Overproduction of interleukin 6 by fibroblasts cultured from affected skin sites of patients with scleroderma. *J Rheumatol* 1992;19:1207–11.
9 Duncan MR, Berman B. Stimulation of collagen and glycosaminoglycan production in cultured human adult dermal fibroblasts by recombinant human interleukin 6. *J Invest Dermatol* 1991;97:686–92.
10 Gallucci RM, Lee EG, Tomasek JJ. IL-6 modulates alpha-smooth muscle actin expression in dermal fibroblasts from IL-6-deficient mice. *J Invest Dermatol* 2006;126:561–8.
11 Saito F, Tasaka S, Inoue K, *et al*. Role of interleukin-6 in bleomycin-induced lung inflammatory changes in mice. *Am J Respir Cell Mol Biol* 2008;38:566–71.
12 Kitaba S, Murota H, Terao M, *et al*. Blockade of interleukin-6 receptor alleviates disease in mouse model of scleroderma. *Am J Pathol* 2012;180:165–76.
13 Yoshizaki A, Yanaba K, Ogawa A, *et al*. Immunization with DNA topoisomerase I and Freund's complete adjuvant induces skin and lung fibrosis and autoimmunity via interleukin-6 signaling. *Arthritis Rheum* 2011;63:3575–85.
14 Sato S, Fujimoto M, Hasegawa M, *et al*. Serum soluble CTLA-4 levels are increased in diffuse cutaneous systemic sclerosis. *Rheumatology (Oxford)* 2004;43:1261–6.
15 O'Reilly S, Hügle T, van Laar JM. T cells in systemic sclerosis: a reappraisal. *Rheumatology (Oxford)* 2012;51:1540–9.
16 Meier FM, Frommer KW, Dinser R, *et al*. Update on the profile of the EUSTAR cohort: an analysis of the EULAR Scleroderma Trials and Research Group Database. *Ann Rheum Dis* 2012;71:1355–60.
17 Walker UA, Tyndall A, Czirják L, *et al*. Clinical risk assessment of organ manifestations in systemic sclerosis: a report from the EULAR Scleroderma Trials and Research Group Database. *Ann Rheum Dis* 2007;66:754–63.
18 Lam GK, Hummers LK, Woods A, *et al*. Efficacy and safety of etanercept in the treatment of scleroderma-associated joint disease. *J Rheumatol* 2007;34:1636–7.
19 Allanore Y, Devos-François G, Caramella C, *et al*. Fatal exacerbation of fibrosing alveolitis associated with systemic sclerosis in a patient treated with adalimumab. *Ann Rheum Dis* 2006;65:834–5.
20 Clements PJ, Wong WK, Hurwitz EL, *et al*. Correlates of the disability index of the health assessment questionnaire: a measure of functional impairment in systemic sclerosis. *Arthritis Rheum* 1999;42:2372–80.
21 Shima Y, Kuwahara Y, Murota H, *et al*. The skin of patients with systemic sclerosis softened during the treatment with anti-IL-6 receptor antibody tocilizumab. *Rheumatology (Oxford)* 2010;49:2408–12.

Outcomes of patients with systemic sclerosis-associated polyarthritis and myopathy treated with tocilizumab or abatacept: a EUSTAR observational study

Muriel Elhai, Marine Meunier, Marco Matucci-Cerinic, et al.

Ann Rheum Dis published online December 19, 2012
doi: 10.1136/annrheumdis-2012-202657

Notes