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Goal-directed therapy for RA in routine practice is associated with improved function in patients with disease duration up to 15 years

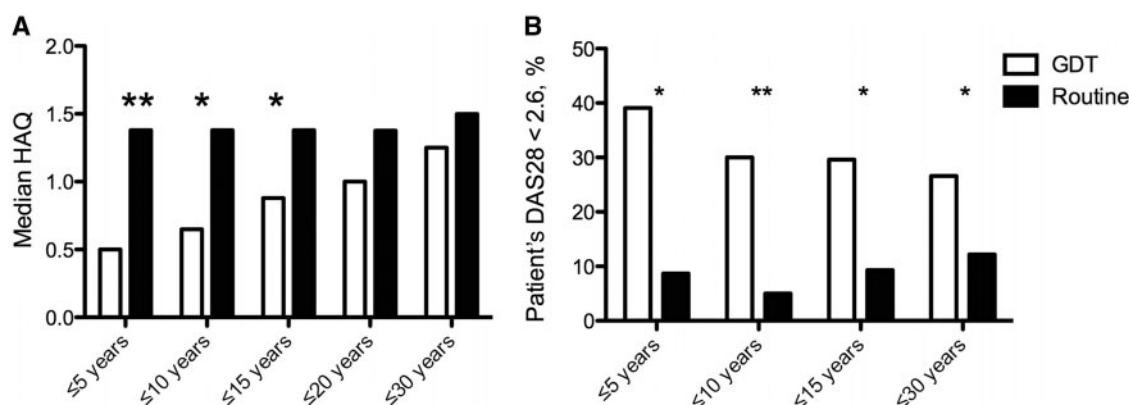
SIR, Improved therapies have dramatically increased our ability to suppress RA disease activity. Short-term goal-directed therapy or treat-to-target, central to the management of hypertension and diabetes, may be the next step to increase effectiveness of RA therapy, although recent recommendations for treat-to-target strategies acknowledge the limited data from routine care (RC) [1]. Nevertheless, inducing remission is a logical short-term goal in RA [2, 3]. Patients receiving DMARDs and achieving low disease states have less joint damage progression [4, 5]. Patient preferences for therapy outcomes consistently identify their priorities as reduced pain and maintenance of function [6, 7]. Our RA Centre service routinely uses goal-directed therapy (GDT) strategy, short-term goal DAS-28 remission (DAS-28 < 2.6). After 2 years, we tested if this strategy improved patient function, comparing RA Centre outcomes with those of clinics in the same hospital not using this strategy.

An RC group of consecutive patients recruited from clinics where treatment aimed to reduce signs and

symptoms with no precise goal, was compared with a matched sample of RA Centre patients, the GDT group. The Guy's Hospital Research Ethics Committee approved the study and patients gave informed consent. Patients with RA (ACR 1987 revised criteria) [8] over the age of 18 years were recruited for assessment, with no disease- or comorbidity-related exclusion criteria. Groups were matched within disease duration ± 2 years, age ± 5 years and sex. Rheumatologists treating the RC group were not aware of the patient DAS-28 score. HAQ-Disability Index (DI) was not used to guide treatment in either clinic. RC patients were assessed on a single occasion with joint counts and global disease activity performed by a research nurse not involved in therapy decisions. Fisher's exact tests were used for categorical data, and Wilcoxon signed rank sum tests for paired continuous data, almost all non-normally distributed. Multiple logistic regression assessed clinical factor contributions to achieving remission, and multivariable linear regression assessed influences on HAQ. Analyses were performed using SPSS 15.0 and Graph Pad Prism 5.

Ninety patients were recruited to the RC group and data compared with that collected contemporaneously from matched GDT patients. More GDT patients received combination DMARDs (12 vs 3%, $P=0.048$) but not biologics (20 vs 13%, $P=0.32$). Multiple regression analysis identified DAS-28, age, disease duration and pain VAS as independent predictors of HAQ-DI, with the highest contribution from DAS-28. Patients in the GDT group with disease duration up to 15 years showed significantly improved function compared with RC, with increasingly large differences in patients with shorter disease duration (Fig. 1A). Significantly more GDT patients achieved remission at all disease duration periods (Fig. 1B). Multiple logistic regression including all patients (disease duration up to 30 years) showed males were less likely to achieve remission [odds ratio (OR) 0.3; 95% CI 0.1, 0.8], and patients without erosions were more likely to achieve

Fig. 1 Goal-directed therapy increases the numbers of patients in remission and reduces HAQ in patients up to disease duration of 15 years. **(A)** Median HAQ is significantly lower in the GDT group at a range of disease durations. **(B)** Remission was defined by DAS-28 < 2.6; increased numbers of patients were in remission at all disease durations in the GDT group. * $P < 0.05$, ** $P < 0.01$.



remission (OR 2.9; 95% CI 1.1, 8.2). In patients with disease duration up to 15 years, only GDT was influential in achieving remission (OR 5.7; 95% CI 1.5, 21.7).

This study of outcomes in routine hospital clinics using standard medication regimens shows that a DAS-28 goal-directed strategy is associated with significantly improved function for patients with disease duration up to 15 years. DAS-28 remission achievers had significantly better HAQ scores compared with non-achievers. DAS-28 remission rates were significantly better in the GDT group with RA >15 years, but HAQ scores were not better. This may reflect clinical trial results, where patients with longer disease duration have smaller HAQ improvements despite similar DAS-28 improvements [9]. Secondly, GDT patients with disease up to 5 years, receiving 2 years of GDT, achieved much higher remission rates (39%) compared with RC patients (9%).

We assessed unselected patients attending routine outpatient clinics. As such, these results are relevant to general rheumatology clinic populations. In contrast to most studies of goal-directed therapy studying early arthritis, our patients had longer disease duration. We also demonstrate the challenges of achieving remission in unselected populations. Many patients declined increases in therapy or had co-morbidities preventing intensified therapy. Our patients were not selected by consenting to a treatment protocol, and therapy decisions were the usual consensus of rheumatologist advice, assessed from the patient's perspective. The concept of patient acceptable symptom state (PASS) may explain this reluctance. A large study of RC patients, with a mean disease duration of 7.6 years, showed that the DAS-28 score cut-off for PASS status was 4.05 [10]. Additionally, in the UK, biologic therapy is only available for patients with DAS-28 > 5.1. In conclusion, a goal-directed or treat-to-target strategy can be successfully utilized in RC to achieve higher remission rates, and is associated with better function in patients with early and medium disease duration. HAQ-DI for patients in remission was significantly lower than those not in remission, suggesting that DAS-28 remission is a relevant goal to improve function.

Rheumatology key message

- Treating to target in RA in routine practice is associated with improved function.

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Nicola J. Gullick¹, Stephen P. Oakley¹, Amir Zain¹, Terence Gibson¹, Tim Jones¹, Alan Mistlin¹, Jonathan D. Rees¹, Gabriel S. Panayi¹ and Bruce W. Kirkham¹

¹RA Centre, Guy's and St Thomas' NHS Foundation Trust, London, UK.

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Correspondence to: Bruce W. Kirkham, Department of Rheumatology, 4th Floor Tower Wing, Guy's Hospital, Great Maze Pond, London SE1 9RT, UK.

E-mail: bruce.kirkham@gstt.nhs.uk

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Streptococcal hypersensitivity reloaded: severe inflammatory syndrome in Behçet's disease following 23-valent polysaccharide *Streptococcus pneumoniae* vaccine

SIR, Infections with *Streptococcus pneumoniae* are a significant cause of morbidity and mortality in patients with autoimmune inflammatory rheumatic diseases. The European League Against Rheumatism (EULAR) recommends the 23-valent polysaccharide pneumococcal vaccine (23-PPV) in patients with inflammatory rheumatic diseases, including Behçet's disease (BD) [1]. Pneumococcal vaccine safety was tested in RA, juvenile arthritis and SLE [2] and no significant local or systemic adverse events and disease flares were reported.

We have recently implemented the EULAR recommendations in our outpatient service by systematically vaccinating patients with autoimmune inflammatory rheumatic diseases if they are treated with immunosuppressive agents. Subsequently we have observed four patients with BD who developed severe local reactions to the first application of 23-PPV at the injection site as well as a severe systemic inflammatory response. No systemic adverse reactions were observed in patients of our service who received 23-PPV for autoimmune conditions other than BD.

The clinical features of the four patients are summarized in Table 1. The three male patients fulfilled the criteria for BD and the female patient had an incomplete phenotype of BD with oral ulcers, oligoarthritis and HLA-B51 genotype positivity. The mean disease duration of BD was 9.5 years. All of the patients had been vaccinated against influenza and tetanus without complication, one also had received hepatitis A and tick-borne encephalitis vaccines without adverse reactions. The local adverse reaction to the 23-PPV originating from different charges was similar in all of the patients and developed ~4–8 h after the injection, with pain, redness and local swelling (spreading ~15 cm from the injection site); urticarial lesions were not observed. Whereas the local symptoms resolved completely after ~1 day in the female patient, the three males developed a severe systemic inflammation with malaise, high fever, chills and vomiting. Leucocyte counts increased to a maximum of $20.5 \times 10^9/l$ and the CRP to

385 mg/l. All symptoms resolved in a few days with local cooling, paracetamol, anti-inflammatory non-steroidal drugs and i.v. fluids. In one patient, the initially diffuse swelling at the injection site, which extended from the acromion to the elbow, turned into a profound pseudofolliculitis, prior to complete resolution (supplementary figure).

There are several possible explanations for this severe adverse reaction. Pneumovax 23 is the currently licensed pneumococcal polysaccharide vaccine. A 0.5 ml dose of this vaccine contains 25 µg of polysaccharides from the 23 most prevalent or invasive pneumococcal types in isotonic saline, plus 0.25% phenol as preservative. Minor local injection reactions are frequently observed, whereas the incidence of severe vaccine-related systemic adverse events is low. Phenol is used in many vaccines as a preservative with low immunogenic properties. It is therefore unlikely that phenol contributed to the adverse reactions.

BD is considered an autoinflammatory multisystem disease. An overreacting immune system with neutrophil hyperfunction, also described as pathergy, is frequently encountered. For pathergy testing, a sterile needle is used to obliquely penetrate the skin, provoking a local induration after 48 h. Pathergy-like inflammatory reactions can also be triggered by insults such as trauma, arthrocentesis or surgery, and then affect organs other than the skin [3]. However, three of the reported patients here had negative pathergy testing.

In patients with BD, elevated antibody titres directed against streptococci in the oral flora have been detected and skin hypersensitivity against streptococci has been included in the Japanese diagnostic criteria for BD [4]. An immune reaction to one or several of the 23 polysaccharides by pre-existing anti-streptococcal antibodies or an IgE-mediated anaphylactic reaction could therefore explain some symptoms of the patients, although the time course and the clinical features make the latter pathomechanism unlikely. The systemic inflammatory reactions in our cohort contrast to reports of local BD symptoms that occurred after streptococcal antigen exposure [5]. This divergence may be accounted by the obvious difference in the streptococcus species, as well as by different amounts of antigen and route of exposure. Interestingly, the mildest reaction was observed in the patient with incomplete BD who only received ibuprofen. To what extent etanercept, abatacept or AZA further influenced the symptoms in the other three patients remains speculative at this point.

More recently, BD has been proposed as an autoinflammatory disease secondary to an aberrant activation of the inflammasome, a complex modular structure that activates IL-1β [6]. In this context, it is interesting to note that 23-PPV can activate toll-like receptors (TLRs) 2 and 4 as known triggers of sterile inflammation [7]. TLR triggering by 23-PPV components with subsequent inflammasome activation via IL-1β in a predisposed host could explain the rapid onset of the adverse reaction, the occurrence of high fever and the neutrophilic nature of the systemic inflammatory response. Our observations may also