Patients’ own ability to assess activity of their rheumatoid arthritis

Sir, Increasingly patients are able to access their Rheumatology Department via nurse-led Rheumatology helplines and, due to the overbooking of our clinics and the long distances patients have to travel to attend, there clearly is a potential for departments to develop a telephone follow-up service for patients with rheumatoid arthritis (RA). Published work on Rheumatology telephone follow up concentrates on a doctor-rather than nurse-led service [1] and we have been unable to find any literature on patients’ ability to assess their own disease activity on the telephone, although there is work on patients’ assessment of Disease Activity Score (DAS) using a mannequin [2]. We therefore undertook a pilot study to assess this fact. We chose DAS28 as a measure of disease activity as it is a validated score for both the early and the established RA [3] and has been shown to be sensitive to change [4].

Patients attending the nurse consultant, nurse specialist and the specialist registrar clinics at Worcestershire Royal Hospital over the summer of 2005 with a diagnosis of RA were invited to participate in this study. They were asked to count the number of their tender and swollen joints using only verbal clues as to which joint, and then gave a numerical global health assessment from 0–100. The health care practitioner (HCP) then undertook a standard DAS28 assessment with global health assessment measured on a visual analogue scale and later calculated both the scores. Changes in medication and investigations requested were also noted.

A total of 50 patients were recruited (of which 32 were female; age: mean and median 59 yrs; range 31–83). The disease duration ranged from 6 months to 32 yrs with a mean of 12 and a median of 11 yrs. Of the 50 patients, 39 were on one disease modifying drug (DMARD), six were on two and five on none. Two patients were also taking an anti-TNF therapy.

The results of verbal DAS28 (vDAS28) and standard DAS28 were distributed normally with a mean vDAS28 score of 4.2 with a range of 0.46–8.54, and a mean DAS28 of 3.99 with a range of 0.76–6.68. The correlation between the scores was good with an R value of 0.895. Bland Altman plot analysis did not suggest whether the patients were more or less likely to overestimate DAS28 score at differing levels of disease activity.

Interestingly vDAS28 correlated best with verbal tender joint count, $R = 0.729$, and least well with actual swollen joint count, $R = 0.294$, whereas DAS28 correlated best with global health assessment, $R = 0.681$, and least well with actual swollen joint count, $R = 0.46$. Verbal tender joints correlated relatively poorly with actual tender joints, $R = 0.57$, as did verbal swollen joints with actual swollen joints, $R = 0.46$.

Ten patients were prescribed an increase in medication at the clinic, seven were to start, restart or increase methotrexate, two were to start leflunomide and one to start sulphasalazine. One patient was advised a reduced dose of oral steroid and one, a reduced dose of methotrexate due to mildly deranged liver function tests. An abdominal ultrasound and a pulmonary function test were requested.

These results suggest that it may be possible for patients to assess their own disease activity and that vDAS28 could form a part of a nurse-led telephone follow-up consultation. There are limitations to this study in that patients might have had non-verbal clues and the HCP may not have looked at inter-observer error. We also recognize the limitations of DAS28 as an assessment tool, particularly in patients who have a predominantly lower limb disease. However, we intend to assess the vDAS28 further by contacting patients the day before they attend our nurse-led anti-TNF clinic and if there is a good correlation between the vDAS and standard DAS at the clinic visit, we will aim to offer the alternate mode of consultation through the telephone. Such a strategy would require dedicated clinic slots for patients who are identified as needing more detailed assessment, investigations or a change in therapy. Funding for such clinics would also need to be identified by healthcare commissioners.

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Polymorphisms of the FCRL3 gene in a Spanish population of systemic lupus erythematosus patients

Sir, Receptors for the Fc portion of IgG (FcγRs) are essential mediators of the inflammatory effect of immune complexes and cytotoxic antibodies [1, 2]. FcγRs are candidate genes to the susceptibility to autoimmune disease. A new family of FcRs, FcR-like (FcRL) or FcR homologous (FcRH) genes, with similarity in structure and sequence to the classical FcR genes, has been recently identified [3]. They map in the chromosomal region 1q21–32, which has showed evidence of linkage with systemic lupus erythematosus (SLE) and other autoimmune diseases [4, 5]. A very recent study reported an association of the FCRL3 gene with several autoimmune diseases [6]. The aim of this study was to investigate the association of the FCRL3 and SLE in a large cohort of SLE Spanish patients.

We analysed a Spanish Caucasian case-control panel consisting of 520 SLE patients meeting the American College of Rheumatology (ACR) criteria for SLE [7, 8], and recruited from five Spanish hospitals. Samples were obtained from subjects after they provided written informed consent. The study was approved by all local ethical committees of the corresponding hospitals. A total of 540 matched blood and bone marrow donors were included as healthy controls. Among the patients, 59.9% had anti-dsDNA antibodies, 35.9% developed lupus nephritis and 37.5% were DRB1*03 positive. No significant differences in the frequency of the different alleles of the three polymorphisms studied were observed among the patient groups or the control groups from different cohorts. Hence, we combined all cohorts to form a SLE case-control group, which was used in further analyses. The control study population was found to be

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in the Hardy–Weinberg equilibrium for all the polymorphisms studied.

Table 1 shows the distribution of genotypes and alleles of the three FCRL3 polymorphisms studied in SLE patients and controls. As described previously [6], the concordance between the polymorphisms fcr3_3 and fcr3_6 was almost total, and so they both are referred to as fcr3_3 Single Nucleotide Polymorphism (SNP) hereafter. There was a significant deviation in the distribution of the fcr3_3 genotypes between the patient and the control groups (P = 0.047 by chi-square test on a 3 × 2 contingency table). We tested the hypothesis of a recessive model of inheritance for the proposed causal allele fcr3_3 C. Frequency of homozygous CC was higher in SLE patients (18.5 vs 14.3% in the control group), but the difference did not reach statistical significance (P = 0.06). No statistically significant differences in the distribution of fcr3_4 genotypes were detected to compare SLE patients and controls (P = 0.8 by chi-square test on a 3 × 2 contingency table). Also no significant differences in the distribution of the allelic frequencies were observed to compare SLE patients and controls in any case. Table 1 shows data for the three most common fcr3_3/4/6 haplotypes (frequency > 5%) found in our population. A significantly higher frequency of the CGA haplotype was found among patients (15.7 vs 12.4%, P = 0.04, OR = 1.32, 95% CI 1.00–1.75).

No significant differences in the distribution of these polymorphisms were observed when comparing individuals with vs without anti-dsDNA antibodies, having vs not having lupus nephritis and DRB1*03 positive vs negative (data not shown).

Validation of genetic association studies requires replication using independent data set in order to search for functional variants relevant to disease etiology [9]. Results of the present work cannot completely confirm the recent finding that FCRL3 is associated with SLE [6]. We found a different genotype distribution of the proposed causal variant among SLE patients and controls. Although our results for CC genotype were not statistically significant (statistical power < 78% to detect an OR = 1.49), they showed the same trend as the Japanese study.

In fact, odds ratios (ORs) (1.36 vs 1.49) were very similar in both studies. The finding that no significant differences in the fcr3_3 allelic frequencies does not discard a recessive model as that proposed by Kochi et al. [6]. To analyse the haplotype distribution, we found that the CGA haplotype was the only FCRL3 haplotype that seemed to be associated with SLE. Of note, the study by Kochi et al. [6] did not perform haplotype analysis in SLE, but both haplotypes bearing the fcr3_3 C allele were associated with RA with similar OR. According to our results, the presence of the fcr3_3 C allele in neutral and risk haplotypes would discard the fcr3_3 C allele as the only SLE associated variant. Genetic heterogeneity, due to variability not only in the frequency of alleles but also in diverse effects of linkage disequilibrium for other important genetic markers, seems to be the most likely cause of the discrepancies between ours and the previous results. In fact, the frequency of CAA haplotype was higher in Caucasian (31% in European American and 26% in Spanish) than in Japanese controls (19% < P < 0.0001 in both cases), whereas the frequency of the CGA haplotype was similar in Spanish (12.4%), Japanese (14%) and European American (14%, P < 0.05) populations. In conclusion, our results suggest that the FCRL3_3 SNP does not play a major role in SLE susceptibility in Spanish population. Potential association of the FCRL3 gene cannot be excluded.

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Deficient activity of von Willebrand factor-cleaving protease in thrombotic thrombocytopenic purpura in the setting of adult-onset Still's disease

SIR, Adult-onset Still’s disease (AOSD) is a systemic autoimmune disorder of unknown aetiology and pathogenesis, characterized by high spiking fever, a salmon-pink evanescent rash and polyarthritis. Although the aetiology and pathogenesis of this disease are not fully understood, several lines of evidence suggested that immunological mechanism play important roles in the pathogenesis [1].

Thrombotic thrombocytopenic purpura (TTP) is a potentially life-threatening disorder characterized by haemolytic anaemia, consumptive thrombocytopenia, disturbance of consciousness, fever and renal damage. A major breakthrough in the understanding of the pathogenesis of TTP is the discovery of deficient activity of the von Willebrand factor-cleaving protease (vWF-CP), a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS)-13 [2–4]. Severe ADAMTS13 deficiency is an important pathogenetic factor for many cases of classical TTP. TTP is occasionally associated with various systemic autoimmune diseases such as systemic lupus erythematosus and Sjogren’s syndrome [5, 6]. However, TTP is rarely reported occurring with AOSD. Here, we describe the first case report of AOSD that developed TTP with the detection of diminished ADAMTS-13 activity.

A 23-yr-old woman with a 4-yr history of AOSD was admitted to our hospital complaining of nausea, vomiting and gross haematuria. Since her onset of AOSD, the patient had had three exacerbations of spiking fever and polyarthritis in the past. She was administered prednisolone for recurrent spiking fever and polyarthritis at another hospital. Though D-penicillamine and methotrexate were also used at one point, they were discontinued owing to adverse effects. At the time of this current admission, renal function (serum creatinine was 0.7 mg/dl) and platelet count (36 10^4/l) were normal. However, her disease activity and polyarthritis had not been well-controlled with prednisolone only. She first visited our clinic in 1998, and three weeks after prednisolone was tapered from 15 to 14 mg/day, severe polyarthritis and low-grade fever appeared, and she was admitted to Tokyo Women’s Medical University Aoyama Hospital in May 2000 (Fig. 1).

**FIG. 1.** Clinical course. Onset of AOSD: spiking fever, salmon-pink evanescent rash and polyarthritis repeatedly appeared as the dose of corticosteroid was decreased. These symptoms were ameliorated with increasing dose of corticosteroid. Just before the onset of TTP, prednisolone dose was tapered from 15 to 14 mg/day, symptoms of AOSD appeared and serum ferritin level increased. Onset of TTP: after the treatment with high-dose corticosteroid and plasma exchange, anaemia, thrombocytopenia, liver function and renal dysfunction were rapidly ameliorated. PSL: prednisolone; MTX: methotrexate; D-Pc: D-penicillamine; Hb: haemoglobin; Plt: platelet; LDH: lactic acid dehydrogenase.