disease despite receiving at least three different medications in addition to steroids. All patients at the start of anakinra treatment were receiving oral prednisolone with a median daily dose of 1 mg/kg (range 0.4–2 mg/kg), being steroid dependent and unable to wean further.

Six patients had excellent response to anakinra with resolution of both systemic and joint disease. Five patients achieved disease remission with 1 mg/kg anakinra, one patient required 2 mg/kg to achieve disease remission. One patient had continued disease activity despite 2 mg/kg anakinra. The laboratory markers also normalized rapidly in those six patients as shown in Table 1. Using the Core Set Criteria as an assessment tool, all variables were much improved after starting anakinra in six patients [7]. The prednisolone dose also reduced once anakinra was started to a median of 0.75 mg/kg/day at 1 month after starting anakinra and to a median value of 0 mg/kg/day at 6 months after starting anakinra. One patient had macrophage activation syndrome at presentation, also with a pericardial effusion and hepatosplenomegaly. Her systemic features failed to respond to immunoglobulin and cyclosporin but she had a rapid and dramatic response to anakinra. After 1 month on anakinra all her symptoms resolved and laboratory parameters had normalized. The patient who did not respond to anakinra had persistence of active arthritis despite increasing the dose to 2 mg/kg; she also had persistently raised inflammatory markers but no rash, fever, lymphadenopathy or other extra-articular manifestations of the disease.

One patient developed gastroenteritis with pre-renal failure requiring intraportal support 1 month after starting anakinra. One patient developed a chronic cough with clubbing 1 yr after starting anakinra. A lung biopsy showed resolving inflammatory changes secondary to adenovirus infection. She also developed varicella pneumonitis requiring hospital admission 2 yrs after starting anakinra. Three patients developed itch and/or erythema around the injection sites with one patient developing severe pain at the injection site requiring her to stop anakinra after 3 months. On stopping anakinra she subsequently had a flare of her disease with both systemic features and arthritis requiring further pulses of methylprednisolone.

In six out of seven patients with severe SOJIA, there was a rapid early improvement in systemic symptoms and joint disease. There were three serious infections but anakinra was continued in these patients. One patient stopped anakinra due to severe injection site pain. Irigoyen et al. [4] have demonstrated a good response to anakinra without serious side-effects in a case series of 14 patients. The results obtained in this case series support the use of anakinra as second-line therapy in children with SOJIA who have failed to respond to standard therapy. The small number of patients and the retrospective quality of the data collected limits our case series. We believe that in refractory cases of SOJIA, especially those with active systemic features, anakinra could prove a valuable addition to the therapeutic armamentarium.

## Table 1. Clinical and laboratory variables before and after treatment

<table>
<thead>
<tr>
<th></th>
<th>Pre-anakinra</th>
<th>1 month</th>
<th>3 months</th>
<th>6 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin (g/dl)</td>
<td>8.4 (7.2–10.1)</td>
<td>11.0 (8.8–12.4)</td>
<td>10.6 (8.6–13.4)</td>
<td>11.1 (9.2–12.6)</td>
<td>11.9 (9.5–14.4)</td>
</tr>
<tr>
<td>White cell count (×10⁹)</td>
<td>20.8 (12.9–50.4)</td>
<td>8.8 (5.5–13.4)</td>
<td>7.9 (4.6–10.7)</td>
<td>8.8 (4.2–12.9)</td>
<td>8.8 (5.3–10.0)</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>103 (28–155)</td>
<td>12 (11–38)</td>
<td>7 (5–12)</td>
<td>7 (5–12)</td>
<td>9 (7–12)</td>
</tr>
<tr>
<td>Childhood health assessment questionnaire (CHAQ)</td>
<td>2 (0–3.0)</td>
<td>0 (0–2.2)</td>
<td>0 (0–0.6)</td>
<td>0 (0–0.9)</td>
<td>0.5 (0–2.0)</td>
</tr>
<tr>
<td>Active joints</td>
<td>8 (0–16)</td>
<td>2 (0–7)</td>
<td>0 (0–34)</td>
<td>0 (0–4)</td>
<td>0 (0–20)</td>
</tr>
<tr>
<td>Restrictive joints</td>
<td>0 (0–6)</td>
<td>0 (0–12)</td>
<td>0 (0–1)</td>
<td>0 (0–10)</td>
<td>0 (0–27)</td>
</tr>
<tr>
<td>Patient global assessment (VAS)</td>
<td>5 (0–8)</td>
<td>0 (0–12)</td>
<td>0 (0–2)</td>
<td>0 (0–1)</td>
<td>0 (0–4)</td>
</tr>
<tr>
<td>Physician global assessment (VAS)</td>
<td>4 (2–9)</td>
<td>2 (0–5)</td>
<td>0 (0–2)</td>
<td>0 (0–1)</td>
<td>0 (0–6)</td>
</tr>
<tr>
<td>Prednisolone dose (mg/kg)</td>
<td>1 (0.4–2)</td>
<td>0.75 (0.2–1)</td>
<td>0.4 (0–0.1)</td>
<td>0 (0–0.25)</td>
<td>0 (0–0.25)</td>
</tr>
</tbody>
</table>

### Rheumatology key message

- Anakinra is a potentially effective therapy for children with SOJIA.

### Disclosure statement: The authors have declared no conflicts of interest.

**Comment on: An allograft inflammatory factor 1 (AIF1) single nucleotide polymorphism (SNP) is associated with anticentromere antibody positive systemic sclerosis**

SIR, We are interested to read the aforementioned article in your journal [1]. Allograft inflammatory factor 1 (AIF1) has now been studied in several diseases and its genomc sequence has been published widely. The authors claim to demonstrate a genetic association between a non-synonymous exonic substitution in AIF1 and systemic sclerosis. They suggest that this substitution is rs2269475 encoding a tryptophan to arginine substitution at amino acid residue 15, located in exon 4 of the AIF1 gene.
However, we believe this is erroneous for two reasons. First, rs2269475 has previously been described as a non-coding SNP in intron 4. Second, it is very unlikely that amino acid 15 will be found in the 4th exon of any gene. In addition to this, the authors reported they looked into another SNP, rs4711274. This SNP is located in intron 1 of the gene not intron 2 as stated. The association study may still be valid but rs2269475 does not represent an important functional change in AIF1 as the authors claimed.

Disclosure statement: The authors have declared no conflicts of interest.

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Comment on: An allograft inflammatory factor 1 (AIF1) single nucleotide polymorphism (SNP) is associated with anticitrulline antibody positive systemic sclerosis: reply

Sir, AIF1 rs2269475 polymorphism is a non-synonymous coding polymorphism in NCBI database (http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=2269475). The rs2269475 polymorphism causes a tryptophan to arginine amino acid substitution that is predicted to be damaging by Polyphen (http://genetics.bwh.harvard.edu/cg-bin/php/pph4dSNP.cgi). We regret the oversight in reporting the location of polymorphisms rs2269475 and rs4711274, which are in fact located on exon 3 and intron 1, respectively, of the AIF1 gene.

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Comment on: The pharmacogenetics of methotrexate

Sir, With interest, we have read the review by Hider and colleagues [1] on the pharmacogenetics of methotrexate (MTX) in patients with RA. In this letter, we would like to address an additional point of interest that is not discussed in their article:

We agree with the authors that the currently available pharmacogenetic data from association studies are inconclusive and do not allow us to draw definite conclusions about the relationship between genotype and treatment outcome in RA. Therefore, pharmacogenetic information has not yet established value with respect to the choice of drugs in RA treatment for the individual patient.

The authors report various single nucleotide polymorphisms (SNPs) related to the MTX mechanisms of action, which may influence the response to treatment. Their hypothesis that a combination of genotypes may be necessary to predict the individual response to MTX is of special importance. In addition, they emphasize that the effect of demographic and disease characteristics on treatment response should be investigated.

Recently, important progress has been made to predict the individual response to MTX treatment by our group, indeed combining multiple genes as well as non-genetic determinants of MTX response [2]. A clinical pharmacogenetic predictive model has been developed including eight genetic and non-genetic factors to categorize patients with early RA (n = 205) who started MTX monotherapy into three groups: non-responders with a low probability of response, patients with an intermediate probability of response and responders with a high probability of response to MTX monotherapy. The model for MTX efficacy consisted of the variables gender, RF and smoking status, the Disease Activity Score (DAS) at baseline and four polymorphisms in the adenosine monophosphate deaminase (AMPD1), 5-aminomimidazole-4-carboxamide ribonucleotide transformylase (ATIC), inosine triphosphate pyrophosphatase (ITPA) and methylenetetrahydrofolate dehydrogenase (MTHFD1) genes. The true positive and negative response rates were 95 and 86%, respectively. Sixty per cent of the patients were categorized into responders and non-responders with the use of this model.

This pharmacogenetic model has been validated in a small cohort, and will be further validated in an independent large cohort of early RA patients. Following validation, refinement and further improvement of the prediction model may be warranted.

In summary, personalized medicine using pharmacogenetic predictive models in common complex traits such as RA is becoming available and may have the potential to prove beneficial for individual RA patients.

Disclosure statement: The authors have declared no conflicts of interest.

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Comment on: The pharmacogenetics of methotrexate: reply

Sir, We thank Dr van der Kooij et al. [1] for their interest in our review and for highlighting their recently published study [2] examining the utility of a clinical pharmacogenetic model in