confirmed JIA diagnosis according to the ILAR criteria were included. All included patients had started MTX therapy between 1990 and 2006. All patients gave their informed consent. The study was approved by the Medical Ethics Committee of the UMCU. Patients had been systematically followed every 3 months using a standardized report form on disease activity. Similar profiles were observed in adult RA patients. From a clinical point of view, prediction of treatment response at only one time point (e.g. 6 months) is less informative because, at the next hospital visit, a substantial number of patients may become non-responders and vice-versa. Second, the snapshot approach only evaluates patients that are still available at the analysed time point and hence, ignoring dropouts or missing data. Often, missing data are not missing completely at random (MCAR) and could be related to the primary outcome, i.e. toxicity or intolerance. As a consequence, the estimators will be biased for the investigated SNP on treatment response.

Assessing the FPRP in snapshot approach pharmacogenetic studies may be helpful in detecting spurious findings. However, future pharmacogenetic studies in arthritis research should preferably evaluate the treatment response in a longitudinal way. Longitudinal analysis will allow us (i) to better characterize the different response profiles of patients (Fig. 1) and (ii) to perform sophisticated repeated measurement statistics that are not affected by the disadvantages of snapshot statistics. This method allows estimating the occurrence of response for a group as a whole over a certain period of time. This approach will generate clinically more relevant information because it will predict the long-term response characteristics of patients better and will reduce the risk of false-positive and -negative findings.

Rheumatology key message

- Longitudinal designs and repeated measures vs cross-sectional analysis prevent false-positive findings in MTX pharmacogenetics.

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**Is a 12-week trial sufficient to evaluate clinical responses to etanercept or MTX treatment in early RA?**

Sir, Treatment of RA during the early phase of disease appears to produce better control than treatment that is delayed until disease is more advanced [1–4]. Although clinical response to TNF inhibitors or MTX often occurs within the first days or weeks of treatment [5], some RA patients have a more delayed response to these agents [6]. Because decisions to continue or change therapies may be made at 12 weeks (as described in the TICORA [7] and BeSt [8] trials), it is unknown whether, and to what extent, some patients would respond if allowed to continue for a longer period of treatment. This question is particularly relevant since high-level responses, such as ACR50 and ACR70, may take up to 24–30 weeks to peak.

To determine whether more patients would respond during a treatment trial longer than 12 weeks, we evaluated ACR20, ACR50 and ACR70 responses and disease activity scores using 28 joints (DAS-28) at Week 26 in patients with early RA (ERA) who did not respond to
etanercept or MTX monotherapy after 12 weeks of treatment. This analysis focuses specifically on patients with ERA; its design is similar to a study of data from the recent trial of etanercept and methotrexate with radiographic patient outcomes (TEMPO) trial of a more heterogeneous RA population [6].

We conducted a retrospective analysis of data from patients in the multicentre, double-blind, randomized Phase 3 study of etanercept vs MTX in patients with ERA [5]. Patients aged ≥18 years, diagnosed with active RA within the previous 3 years, were randomized to receive etanercept 25 mg twice a week or MTX 7.5–20 mg once a week. This analysis, using descriptive statistics, evaluates response (R) or non-response (NR) at Week 26 according to whether patients achieved an ACR20 treatment response at Week 12. Non-responder imputation was used for missing ACR response data; DAS-28 results are reported as observed. All analyses were performed with SAS STAT system version 9.1 (SAS Institute, Cary, NC, USA).

This analysis includes 217 patients treated with MTX 7.5–20 mg and 207 patients treated with etanercept 25 mg. As previously described, baseline demographics were comparable in both groups [5].

Approximately one-third (63 of 185) of the patients who had not achieved an ACR20 response at Week 12 became ACR20 responders at Week 26, including 33% of etanercept patients and 35% of MTX patients (Fig. 1). Some Week 12 non-responders also achieved ACR50 (etanercept 12%, MTX 11%) or ACR70 (etanercept and MTX, both 2%) responses by Week 26 (Fig. 1).

Among the patients who did not achieve ACR20 at Week 12, but became ACR responders at Week 26, mean (s.d.) DAS-28 scores showed some improvement from baseline to Week 12: MTX 6.4 (1.2) at baseline and 5.5 (1.3) at Week 12; etanercept 6.6 (0.7) at baseline and 5.0 (1.0) at Week 12. DAS-28 scores showed additional improvement at Week 26: MTX 3.98 (1.1) and etanercept 4.2 (1.0).

In patients with ERA who did not achieve a clinical response after 12 weeks of etanercept or MTX monotherapy, about one-third went on to achieve significant clinical improvements when treatment was continued for an additional 14 weeks. While this might have been predicted for MTX, it is perhaps surprising in the case of TNF inhibitor therapy, as clinicians have become accustomed to rapid clinical responses with these agents.

Introduction of novel therapies, particularly TNF inhibitors, has elevated the overall goals of treatment for patients with RA, and the highest level of response is now sought. Among the slower responding patients, it is noteworthy that a small percentage of them did achieve higher levels of response (e.g. ACR50 and ACR70). In an analysis of patients from the TEMPO study, radiographic benefits were comparable between rapid and slower responders [6]. It is also possible that the slower responders may represent persons with more refractory disease. In conclusion, as has been seen in a more heterogeneous population of RA patients [6], 12 weeks of therapy with either etanercept or MTX appears to be too short a treatment trial to determine whether there will be a clinical response for an important subset of patients with ERA. This finding is important for clinicians, as guidelines for

![Fig. 1 Improvement in ACR response from Week 12 to Week 26.](https://example.com/fig1.png)

<table>
<thead>
<tr>
<th></th>
<th>ACR20</th>
<th>ACR50</th>
<th>ACR70</th>
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<tr>
<td><strong>Etanercept</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>25 mg bi-weekly</td>
<td>28/84 (33)</td>
<td>10/84 (12)</td>
<td>2/84 (2)</td>
</tr>
<tr>
<td>n (%) 95% CI</td>
<td>23, 43</td>
<td>5, 19</td>
<td>0, 6</td>
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<tr>
<td><strong>MTX</strong></td>
<td></td>
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<tr>
<td>7.5–20 mg weekly</td>
<td>35/101 (35)</td>
<td>11/101 (11)</td>
<td>2/101 (2)</td>
</tr>
<tr>
<td>n (%) 95% CI</td>
<td>25, 44</td>
<td>5, 17</td>
<td>0, 5</td>
</tr>
</tbody>
</table>

Responders were defined as patients who achieved at least an ACR20 response.
the use of TNF inhibitors in some countries consider 12 weeks as a sufficient time period to see a response [9].

Rheumatology key message

- RA patients may require >12 weeks to respond to etanercept or MTX therapy.

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Erdheim–Chester disease: report on a case and new insights on its immunopathogenesis

Sir, Erdheim–Chester disease (ECD) is a rare (approximately 350 published cases worldwide) non-Langerhans cell histiocytosis (LCH) characterized by tissue infiltration with CD68+ CD1a– foamy histiocytes. The disease almost invariably affects bones, causing the nearly pathognomonic osteosclerosis of the limbs. In addition, ECD patients frequently have extra-skeletal manifestations, including exopthalmos, xanthelasma, interstitial lung disease, retroperitoneal fibrosis, pituitary and hypothalamic infiltration and central nervous system and cardiovascular involvements [1–3]. IFN-α represents the best available treatment [4], but response to therapy varies among patients and according to the sites of involvement [5].

The aetiology is unknown. Similar to LCH [6], ECD lesions express a wide array of cyto-chemokines, which may orchestrate histiocyte recruitment and activation [7]. We describe here the release of cyto-chemokines potentially relevant to ECD pathogenesis by intra-lesional cells from a patient with skeletal and multi-organ involvements.

A 45-year-old man with a 10-year history of chronic renal failure due to renal polycystosis was admitted for