Do snapshot statistics fool us in MTX pharmacogenetic studies in arthritis research?

SIR, Recently, an interesting discussion was published in *Rheumatology* on discrepant literature results concerning MTX pharmacogenetics in RA [1–3]. This discussion was triggered by the paper of Lee et al. [2] introducing the concept of false-positive report probability (FPRP) in the field of arthritis research. The discussion focused on the discrepant results observed for single nucleotide polymorphisms (SNPs) in the *ATIC* gene (rs4673993 and rs2372536, both in linkage disequilibrium): the 347 C-allele [4, 5] and the G-allele [2, 6] were both associated with increased efficacy of MTX. Similar discrepancies for SNPs in the methylenetetrahydrofolate reductase (*MTHFR*) gene were reported in a meta-analysis earlier this year [7]. In trying to explain the discrepancy, Dervieux [1] pointed out the challenges and difficulties that researchers face when validating associations between low-penetrance genetic polymorphisms and complex phenotypes such as drug response. The discussion focused on differences between studies in the FPRP, differences in sample size or power, demographic dissimilarities among cohorts, environmental factors such as folate status, duration of disease and treatment duration.

We would like to argue that one of the most important reasons for discrepant studies is because of cross-sectional analysis, also called the snapshot approach. Most pharmacogenetic studies examine only one time point during (MTX) treatment. For instance, MTX response was assessed at 6 months in the European studies [4, 5] and after 50 months in the US cohorts [2, 6]. The snapshot approach suffers from several methodological flaws. First, the snapshot approach may not reflect the true response characteristics over the whole treatment phase. To illustrate this, we have plotted the typical treatment response patterns of patients with juvenile idiopathic arthritis (JIA; Fig. 1). From Figure 1 it becomes clear that treatment response can be roughly divided into three profiles: (A) patients who will respond to treatment at any time point between start of treatment and 1-year follow-up and will stay in remission (47%); (B) patients who shift back and forth from responder to non-responder (31%); and (C) patients who do not show any response during the first year of treatment (22%). This study was performed in the University Medical Centre Utrecht (UMCU), Wilhelmina Children’s Hospital, The Netherlands. Patients with a

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**Fig. 1** Responders and non-responders in 183 JIA patients following Paediatric American College of Rheumatology 30% (ACRped30) criteria in 3-month intervals up to the most recent visit after start of treatment with MTX.

Response is divided into three profiles: (A) patients who will respond towards treatment at any time point between start of treatment and 1-year follow-up and will stay in remission (47%); (B) patients who shift back and forth from responder to non-responder (31%); and (C) patients who do not show any response during first year of treatment (22%). t3, t6, t9, t12 = time points 3, 6, 9 and 12 months, respectively, after start of MTX treatment; mrv = most recent visit.
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.

References

Letters to the Editor

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