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Reply

To the Editor:

Dr. Ruperto and colleagues are quite right to defend the combined use of infliximab and methotrexate in children with JRA. Indeed, while their study failed to demonstrate statistically significant efficacy at the primary end point, it is widely agreed that the combination works. I doubt that any rheumatologists treating children will change their practice based on the results of this study, and that of course is my point.

Their argument that D-penicillamine and auranofin proved inefficacious in JRA holds little merit, since despite the early industry-supported studies suggesting efficacy in adults and children (including those conducted by some of the authors of the study by Ruperto et al) (1,2), these compounds were recognized to be ineffective in adults before the trial showing lack of efficacy in children (3–5).

Despite the improvement represented by recent US FDA and EU regulations requiring trials of new agents in children (6,7), industry-sponsored investigation must always be interpreted cautiously. The study design in which only those children who respond to an agent are entered into the randomized trial to determine if they experience a disease flare when the agent is replaced by placebo may be ethically necessary, but it is fundamentally flawed.

There are limited patient and personnel resources in pediatric rheumatology. As argued by Morgan DeWitt et al, in a perfect world all medications would be fully studied in each of the subgroups of the several distinct diseases grouped under the heading of juvenile idiopathic arthritis, each of which probably has a distinct natural history and pathogenesis. However, we clearly lack the patient numbers and resources to accomplish this. When investigators, patients, and allied health personnel devote their time to participating in a study, their time is equally occupied whether the study is a clinical trial conducted for registration purposes by a pharmaceutical company or an independent investigator-initiated trial. The pharmaceutical company-initiated trials in pediatric rheumatology have added little to our understanding of the basic science of these diseases. Scientific understanding which will promote a better future for children with rheumatic diseases is where the excellent resources of PRINTO, CARRA, and PRCSG and the limited resources of pediatric rheumatologists should be dedicated.

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MEK/ERK pathway inhibitors as a treatment for inflammatory arthritis might result in the development of lupus: comment on the article by Thiel et al

To the Editor:

We read with interest the article by Thiel et al describing the role of the MEK/ERK pathway in murine collagen-induced arthritis (1). We are concerned with the idea of using MEK/ERK inhibition as a potential treatment for rheumatoid arthritis and other inflammatory diseases, as the authors suggest. The authors did not cite any of the work that clearly indicates a role for reduced MEK/ERK signaling in T cells in the pathogenesis of lupus.

MEK/ERK pathway signaling regulates, at least in part, the expression of the chief “maintenance” DNA methylation enzyme, Dnmt1 (2). T cells from lupus patients have defective MEK/ERK pathway signaling, which results in reduced Dnmt1 expression and global T cell DNA hypomethylation (3). As a result, a number of methylation-sensitive genes, such as *TNFSF7* (CD70), *ITGAL* (CD11a), *PERF* (perforin), and *CD40LG* (CD40L), are overexpressed in lupus T cells (4,5). The MEK/ERK signaling defect in lupus T cells is proportional to disease activity (3). Moreover, treating T cells with MEK/ERK pathway inhibitors results in reduced Dnmt1

expression, and overexpression of the same methylation-sensitive genes similar to T cells from lupus patients (6,7). CD4+ T cells treated with MEK/ERK pathway inhibitors become autoreactive in vitro, as demonstrated by their ability to respond to syngeneic antigen-presenting cells without antigen and their ability to induce immunoglobulin production in coculture with autologous B cells (6,7). In addition, T cells treated with selective MEK/ERK inhibitors induced anti-double-stranded DNA antibody production when injected into syngeneic mice similar to T cells treated with DNA methylation inhibitors (6,8). The lupus-inducing drug hydralazine is a MEK/ERK pathway inhibitor (6). T cells treated with hydralazine showed reduced DNA methylation, were autoreactive in vitro, and were capable of inducing autoimmunity in vivo upon adoptive transfer into mice (6,9). Therefore, the data demonstrate a pathogenic role for defective MEK/ERK pathway signaling in lupus. We would caution that using MEK/ERK pathway inhibitors as a treatment in patients with inflammatory arthritis might result in the development of a lupus-like disease.

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Reply

To the Editor:

We thank Drs. Sawalha and Richardson for their comments. I would like to emphasize that the main purpose of this article, using the MEK inhibitor as a tool, was to delineate the role of the MEK/ERK pathway in this mouse model of rheumatoid arthritis (RA), and to argue that MEK is as integral to inflammatory processes as are the JNK and p38 MAP kinase pathways. The potential safety implications for clinical use, including the concerns by the authors of the letter, certainly would be explored in depth if this were to be pursued as a potential therapeutic approach for human RA. We did, however, investigate the effects of MEK inhibition on CD11a expression in our animal models following prolonged dosing with the MEK inhibitor.

While certainly not an exhaustive evaluation of the potential issues noted by Drs. Sawalha and Richardson, we found no evidence of CD11a up-regulation on splenocyte CD4+, CD8+, or B cell subpopulations. We were also surprised, to be honest, and as noted in the article, that animals treated for long periods of time with the MEK inhibitors were not globally immunosuppressed; in fact, we could not show that they were immunocompromised in any way. This was surprising and encouraging in light of the significant literature demonstrating the suppressive effects of MEK inhibition on a variety of leukocyte types in vitro, but, more importantly, illustrates that in vitro phenomena do not always translate to the whole organism.

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Identity of single-nucleotide polymorphisms used in a clinical pharmacogenetic model to predict the efficacy of methotrexate monotherapy: comment on the article by Wessels et al

To the Editor:

We were very interested to read the article by Wessels et al (1), which describes a clinical pharmacogenetic model that may predict response to methotrexate therapy in patients with recent-onset rheumatoid arthritis. The model incorporates sex, rheumatoid factor status, smoking status, Disease Activity Score, and 4 polymorphisms in the adenosine monophosphate deaminase (*AMPDI*), aminoimidazole carboxamide ribonucleotide transformylase (*ATIC*), inosine triphosphate pyrophosphatase (*ITPA*), and methylenetetrahydrofolate dehydrogenase (*MTHFD1*) genes. We agree that this approach of using a “pharmacogenetic index” based upon a cumulative effect of multiple polymorphisms and clinical factors may prove to be the best predictive model for a number of drugs,