

## CORRESPONDENCE



## Adalimumab in Juvenile Rheumatoid Arthritis

**TO THE EDITOR:** Lovell et al. (Aug. 21 issue)<sup>1</sup> report that adalimumab seems to be effective in the treatment of children with juvenile rheumatoid arthritis. However, interpretation of their results is difficult, given the medication-withdrawal design of the trial. During the open-label lead-in phase, patients who had a response to the drug were preselected and children who could not tolerate it were excluded. The double-blind phase was therefore enriched with patients who had a response to the drug, and the treatment effects observed may be larger than those seen in an unselected population.

The evaluation of safety also raises some concerns. Since all the patients initially received adalimumab, how can we rule out a carryover effect that might have masked the true incidence of adverse events?<sup>2</sup>

The authors highlight the ethical issues associated with denying active treatment during a double-blind phase of placebo-controlled trials in pediatric populations. However, failure to appropriately estimate the potential benefit and side effects might be of even more concern.

We believe that the assertion that “the open-label lead-in approach is generalizable to clinical practice” must be considered with caution.

Paolo Sfriso, M.D.

University of Padua  
35128 Padua, Italy  
paolo.sfriso@unipd.it

Francesca Ravaioli, Ph.D.

Italian Medicine Agency  
00144 Rome, Italy

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**TO THE EDITOR:** Anti-tumor necrosis factor (TNF) therapy with etanercept, a soluble TNF receptor, has become a valid treatment option in children with polyarticular juvenile rheumatoid arthritis who have not had a response to at least one disease-modifying antirheumatic drug.<sup>1,2</sup> We strongly believe that trials of biologic treatments should enroll patients who have had an inadequate response or intolerance to etanercept, which remains the most effective and safe anti-TNF therapy in children with juvenile rheumatoid arthritis.<sup>3</sup> Unfortunately, in their study of the role of adalimumab in children with polyarticular-course juvenile rheumatoid arthritis, Lovell et al. considered as eligible for enrollment only children who did not have an adequate response to nonsteroidal anti-inflammatory drugs, and they stratified these patients according to methotrexate use. Moreover, there is some evidence of an increased risk of serious infections and a dose-dependent risk of tumors among patients treated with infliximab and ada-

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limumab.<sup>4</sup> These findings, which were not considered in the trial,<sup>3</sup> should also be taken into account. We suggest that adalimumab should be carefully restricted to patients who have not had a response to combined therapy with methotrexate and etanercept.

Andrea Taddio, M.D.

Federico Marchetti, M.D.

Institute of Child Health  
34100 Trieste, Italy  
ataddio@yahoo.it

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**TO THE EDITOR:** Lovell and colleagues conclude that adalimumab appeared to be efficacious in children with polyarticular-course juvenile rheumatoid arthritis. Immunogenicity is emerging as an important problem in treatment with monoclonal antibodies.<sup>1</sup> Lovell and colleagues report that approximately 16% of the patients had anti-adalimumab antibodies, which did not seem to interfere with the efficacy of adalimumab. This incidence is higher than the 5% incidence among adults with rheumatoid arthritis, reported by Abbott Laboratories.<sup>2</sup> We wonder which method was used to detect these antibodies, since the use of different methods hampers the comparison of results.<sup>1</sup> The findings of Lovell and colleagues are in accordance with those of our study, in which anti-adalimumab antibodies were detected in 17% of the patients with rheumatoid arthritis after 6 months of treatment.<sup>3</sup> In our study, however, the presence of these antibodies was associated with low or undetectable serum adalimumab levels and a reduced clinical response, which was also observed in Crohn's disease.<sup>4</sup> Therefore, it would be interesting to know more details about the relationship among anti-adalimumab antibodies, serum adalimumab levels, and the American College of Rheumatology Pediatric response.

Mirjam K. de Vries, M.D.

Irene E. van der Horst-Bruinsma, M.D., Ph.D.

VU University Medical Center  
1081 HV Amsterdam, the Netherlands  
mk.devries@vumc.nl

Gerrit Jan Wolbink, M.D., Ph.D.

Sanquin Research  
1066 CX Amsterdam, the Netherlands

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**THE AUTHORS REPLY:** A major advantage of the randomized medication-withdrawal design is that it minimizes exposure to placebo. Enrollment of patients with juvenile idiopathic arthritis (formerly called juvenile rheumatoid arthritis) in the placebo group of a traditional randomized, controlled trial can have long-lasting effects. For example, a median of 9 years after enrollment in one trial, the patients with juvenile idiopathic arthritis who had received 6 months of placebo instead of sulfasalazine had significantly more joints with active arthritis, lower scores for overall well-being, and fewer periods of inactive disease and clinical remission while they were not receiving medication.<sup>1</sup> Sulfasalazine had only a moderate benefit in the original randomized, controlled trial.

Much more effective treatments (e.g., anti-TNF biologic agents) are available or are being tested in randomized, controlled trials for juvenile idiopathic arthritis. The potentially negative effect of placebo in these trials could be even greater. We believe that a randomized medication-withdrawal study design provides the best balance of scientific rigor and well-being of subjects. The Food and Drug Administration has approved three biologic agents for use in juvenile idiopathic arthritis on the basis of medication-withdrawal trial design, and the guidelines of the European Medicines Agency describe the use of a withdrawal trial design in studies involving patients with juvenile

idiopathic arthritis ([www.emea.europa.eu/pdfs/human/ewp/042204en.pdf](http://www.emea.europa.eu/pdfs/human/ewp/042204en.pdf)).

We agree with Taddio and Marchetti that etanercept is a valid and important treatment option for children with juvenile idiopathic arthritis. However, direct-comparison studies of the anti-TNF agents in children with juvenile idiopathic arthritis are lacking, and the available studies have not shown clear differences in efficacy or safety among the anti-TNF agents in adults with rheumatoid arthritis.<sup>2-4</sup> Thus, we do not agree that trials of biologic treatments should be performed only in patients with juvenile idiopathic arthritis in whom treatment with etanercept has failed or that infliximab and adalimumab, as compared with etanercept, are associated with a higher risk of serious infections and malignant conditions. Testing the anti-TNF therapies in approximately similar populations of patients with juvenile idiopathic arthritis allows patients, parents, and physicians to make the decision about the use of these therapies. Our trial of adalimumab also provides information about the use or nonuse of methotrexate as background therapy in children with juvenile idiopathic arthritis.

The assay used for detection of anti-adalimumab antibodies in this trial was an enzyme-linked immunosorbent assay that has been used for more

than 11 years in the adalimumab-development program, and it has been accepted by regulatory agencies worldwide. In the study of juvenile idiopathic arthritis, serum adalimumab levels were slightly decreased if anti-adalimumab antibodies were detected; however, this patient population still showed a strong clinical response (unpublished data).

Daniel J. Lovell, M.D., M.P.H.

Cincinnati Children's Hospital Medical Center  
Cincinnati, OH 45229  
[daniel.lovell@cchmc.org](mailto:daniel.lovell@cchmc.org)

Nicolino Ruperto, M.D., M.P.H.

Istituto di Ricovero e Cura a Carattere Scientifico G. Gaslini  
16147 Genoa, Italy

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## Sorafenib in Advanced Hepatocellular Carcinoma

**TO THE EDITOR:** Llovet et al. (July 24 issue)<sup>1</sup> report that their study of sorafenib therapy in patients with hepatocellular carcinoma showed a higher overall incidence of treatment-related adverse events with sorafenib than with placebo (80% vs. 52%), although the difference was not noted to be significant. The availability of new therapies, with expected small variations in objective end points, has heightened awareness of the importance of the impact of treatment on patients' overall lives.<sup>2</sup> Besides the traditional end points (e.g., median overall survival and time to radiologic progression), quality of life has been acknowledged as an important issue in cancer clinical trials and clinical practice.<sup>3,4</sup> We think that an assessment of patients' quality of life would have provided important complementary information to be evaluated in the article.

Another concern might be the low incidence

in the study of grade 3 hypertension (2% in the sorafenib group vs. <1% in the placebo group). In a recent systematic review<sup>5</sup> of published clinical trials evaluating hypertension associated with sorafenib, the overall incidences of all-grade and high-grade hypertension were 23.4% and 5.7%, respectively.

Giancarlo Spinzi, M.D.

Silvia Paggi, M.D.

Valduce Hospital  
22100 Como, Italy  
[gispinz@tin.it](mailto:gispinz@tin.it)

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