sacroiliac joints can also be used as an “objective” finding in nonradiographic axSpA to improve specificity and to increase confidence in the diagnosis. High “inflammatory activity” as visualized on the MRI of the sacroiliac joint has been shown to predict conversion of nonradiographic axSpA to ankylosing spondylitis (radiographic axSpA) (Bennett AN, McGonagle D, O’Connor P, Hensor EM, Sivera F, Coates LC, et al. Severity of baseline magnetic resonance imaging–evident sacroiliitis and HLA–B27 status in early inflammatory back pain predict radiographically evident ankylosing spondylitis at eight years. Arthritis Rheum 2008;58:3413–8).

It has also been shown that high CRP levels and a “positive” MRI scan of the sacroiliac joints (i.e., showing inflammation) can to some extent predict the response to tumor necrosis factor α (TNFα) inhibitors (Lord PA, Farragher TM, Lunt M, Watson KD, Symmons DP, Hyrich KL. Predictors of response to anti-TNF therapy in ankylosing spondylitis: results from the British Society for Rheumatology Biologics Register. Rheumatology [Oxford] 2010;49:563–70). For these reasons, the European Medicines Agency has made either of these findings a prerequisite for allowing treatment with TNFα inhibitors in patients with nonradiographic axSpA.

We realize that in several parts of the world, it is expensive to order MRI scans of the sacroiliac joints as part of a routine investigation. In these situations, determination of the CRP level is a less expensive alternative, but it may miss identification of patients with nonradiographic axSpA and normal CRP levels who may have active inflammation on the MRI scan and hence may have a worse prognosis. In addition, we should not forget that these understandable restrictions still prevent a significant proportion of patients with normal CRP/MRI results but a disease burden similar to that of patients with increased CRP levels/abnormal MRI results from being treated optimally.

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Half-life and safety of canakinumab in pediatric patients: comment on the article by Ilowite et al

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To the Editor:

We read with great interest the report by Ilowite et al, summarizing the results of a trial investigating the efficacy and safety of rilonacept in the treatment of systemic juvenile idiopathic arthritis (JIA) (1). We believe a statement made in the article is incorrect and needs clarification.

In the Discussion section, the authors stated the following about the circulating half-life of rilonacept: "Rilonacept could offer an alternative [context: to canakinumab], with its circulating half-life of 8.6 days, in contrast to the long biologic activity of canakinumab (236 days), which could be a disadvantage in the setting of an SAE [context: serious adverse event]."

This statement, however, does not seem fully consistent with the published literature. In adults with cryopyrin-associated periodic syndromes (CAPS), the mean terminal half-life of canakinumab was demonstrated to be 26 days, with the terminal half-life in pediatric CAPS patients found to be similar to that in adults (2). Pharmacokinetic properties of canakinumab are similar in the CAPS and systemic JIA pediatric populations (2). From a pharmacokinetic standpoint, based on the known 26-day half-life of canakinumab, 5–6 half-lives is 130–156 days, a range that encompasses another relevant efficacy end point, the median time to worsening in the adapted American College of Rheumatology Pediatric criteria level in the withdrawal arm (placebo) of the phase III study from which the 236-day data point was derived (3–6).

While extensive postmarketing and phase IV surveillance data are not yet available, there has been no indication in the available safety data that the 26-day half-life of canakinumab is problematic in the management of serious adverse events.

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Reply
To the Editor:

We would like to thank Dr. Brunner and colleagues for their thoughtful comments. While we disagree that the statement they quote is wrong, we agree that further clarification is warranted.

In the Discussion section of our report, we tried to highlight the differences in circulating half-life of the 3 available interleukin-1 inhibitors: anakinra (1) with the shortest, canakinumab (2) with the longest, and rilonacept (3) with a half-life in-between those of the other 2 agents. The short half-life of anakinra results in the need for daily painful injections which may not be preferred by patients, their families, and/or the prescribing physicians. Conversely, the relatively long half-life of canakinumab has the advantage of infrequent monthly injections; however, some clinicians are concerned that the persistent higher drug levels may complicate the clinical course and treatment of a patient with a serious adverse event, particularly infection. We continue to believe that this is an issue that routinely impacts prescribing practices.

Confusion may stem from our use of the term “biologic activity” when referring to canakinumab’s prolonged efficacy demonstrated in withdrawal studies, and comparing this pharmacodynamic property of the drug with the pharmacokinetics of rilonacept. Comparison of the biologic activities of the 2 drugs would have been preferred, but no withdrawal studies with rilonacept in patients with systemic JIA have been performed, making this impossible.

We understand that there are no robust data at this time to demonstrate whether our concerns regarding patients who are receiving canakinumab and have a severe infection are valid, and we await results from future postmarketing and phase IV safety surveillance studies. Until then, pediatric rheumatologists must make treatment decisions based on the information available. Considerations of agent half-lives, both pharmacokinetic and pharmacodynamic, will and should influence prescribing practices.

The RAPPORT investigators, in addition to Dr. Ilowite, are Kristi Prather, MPH, Yuliya Lokhnygina, PhD, Laura E. Schanberg, MD, Melissa Elder, MD, PhD, Diana Milojevic, MD, James W. Verbsky, MD, PhD, Steven J. Spalding, MD, Yukiko Kimura, MD, Lisa F. Immundo, MD, Marilynn G. Panaro, MD, David D. Sherry, MD, Stacey E. Tarvin, MD, Kathleen O’Neil, MD, Lawrence S. Zemel, MD, James D. Birmingham, MD, Beth S. Gottlieb, MD, MS, Michael L. Miller, MD, PhD, Natasha M. Ruth, MD, MS, Carol A. Wallace, MD, Nora G. Singer, MD, and Christy I. Sandborg, MD.

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