Letters to the Editor

Should baseline-dependent cut-offs really be used to define disease improvement in juvenile idiopathic arthritis? And few other considerations

Rheumatology key message

- Analysis of covariance should be favoured to responder analysis based on current baseline-dependent cut-offs for JIA improvement.

Sir, In the recently published guideline of the European Medicines Agency on JIA [1], the different versions of the Juvenile Arthritis Disease Activity Score (JADAS) are quoted as valid primary end points to evaluate drug efficacy. Several sets of cut-offs are available to classify patients according to their disease activity status using the JADAS [2, 3]. In order to define disease improvement, cut-offs exist also for the change score (the difference between the JADAS value at baseline and follow-up) [3, 4].

An interesting example is the article by Horneff and Becker [4], in which cut-offs for the JADAS10 change score depending on groups of JADAS10 baseline values were developed. They assumed that 'the seriously ill will regard only a considerable decrease in JADAS as an improvement, while less ill patients will perceive a less substantial decrease as an improvement'.

They concluded that the higher the baseline values, the greater the cut-off that satisfactorily separates patients whose disease will improve from those whose disease will not: for baseline JADAS10 groups [5,15), [15,25) and [25,40), the cut-offs were, respectively, 4, 10 and 17. Therefore, in a clinical trial, the responders' rate would have to be determined accordingly in each subgroup defined by the baseline values.

However, it is a statistical fact that regardless of the correlation between the baseline and the outcome, the change score can itself be correlated with the baseline [5]. This phenomenon is called regression to the mean. To illustrate this, consider the following experiment.

One thousand patients with JADAS10 at baseline following a normal distribution with mean (s.d.) 15 (7) were simulated, using figures on the same scale as Horneff and Becker's paper [4]. The disease of the first 500 patients was supposed to improve after treatment, and the corresponding JADAS10 was simulated at follow-up using a normal distribution with mean (s.d.) 5 (7), independently of their initial baseline value. The disease of the last 500 patients was supposed not to improve, and their JADAS10 at follow-up was simulated using a normal distribution with mean (s.d.) 25 (7), still independently of their baseline value.

Fig. 1A shows the scatter plot of the baseline vs the outcome, where patients improving are depicted in black, while patients not improving are depicted in red. It clearly appears that there is no relationship between the baseline and the outcome, as simulated. Moreover, using a similar procedure to the one of the authors, as represented by the continuous horizontal line, a single cut-off for the JADAS10 at follow-up can be determined to discriminate efficiently the red from the black dots independently from the initial baseline groups; for example, <10, [10, 20], >20.

In Fig. 1B, however, the same patients are represented by plotting their baseline value against their change score, and a clear unguenuine correlation appears. Increasing cut-offs that separate patients improving from those not improving can easily be defined by group of baseline values, although there was no initial correlation between the baseline and the outcome.

This is attributable to the fact that the same variable (JADAS10 at baseline) is used both to define baseline severity and to compute the end point (JADAS10 at baseline minus JADAS10 at follow-up). Horneff and Becker's analysis [4] being performed in a similar fashion, even if the rationale of defining specific cut-offs for different disease activity states might have a clinical relevance, it cannot be ruled out that their set of cut-offs stems from the same phenomenon.

In order to define a score of disease improvement accounting for the relationship between the JADAS10 at follow-up and baseline, a logistic regression with improvement status at follow-up as end point could be fitted using the JADAS10 at both baseline and outcome. Such an approach would also allow integration of other covariates. The probability of improvement would then be directly given by the formula of the logistic regression. The complete methodology is illustrated in the field of rheumatology with the case of the DAS28 discussed by Collignon [6] (see references therein for a more extensive description).

One drawback of such scores is that they are sometimes designed using studies that do not permit identification of the cause of the variation of the score between baseline and outcome. In a single-armed trial, there is often no possible distinction between the treatment effect, the natural course of the disease or even the within-patient variation.

In any case, if the treatment effect is expected beforehand to differ between groups of baseline values, the trialist would be expected to investigate this through sensitivity analyses; for example, by fitting models accounting for the baseline-by-treatment interaction and by performing subgroup analyses defined by the baseline values.
Finally, the best practice remains to avoid responder analyses and to prefer an analysis of covariance (ANCOVA) of the JADAS10 at follow-up adjusted for all covariates deemed necessary, such as the JADAS10 at baseline. Indeed, dichotomizing a continuous score into responders and non-responders can lead to a substantial increase in sample size and to a loss of information [7]. If necessary, as pointed out in the European Medicines Agency Points To Consider on Multiplicity Issues In Clinical Trials [8], a supportive responder analysis could still be used to assess clinical benefit on a more interpretable scale once statistical significance has been shown for the continuous end point.

Acknowledgements

The Authors are thankful to Professor Stephen Senn from the Luxembourg Institute of Health and Professor Dr Norbert Benda from the Bundesinstitut für Arzneimittel und Medizinprodukte for their fruitful feedback on this letter. The views expressed in this article are the personal
views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its committees or working parties.

Funding: No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this manuscript.

Disclosure statement: The authors have declared no conflicts of interest.

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Revised version accepted 31 August 2016
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Advance Access publication 29 August 2016

Spondyloarthritis associated with familial Mediterranean fever: successful treatment with anakinra

SiR, FMF is an autosomal recessive, autoinflammatory disorder, with mutations in the MEFV gene. The clinical presentation is characterized by recurrent episodes of fever associated with abdominal, chest, joint and muscular pain [1, 2]. Colchicine is a safe daily treatment that can prevent both the recurrence of FMF attacks and the occurrence of inflammatory amyloidosis, but is usually ineffective in spondyloarthritis (SA) [2]. Patients with FMF and arthralgia can fulfill SA criteria, including sacroiliitis, enthesitis, inflammatory back pain mostly without spinal abnormalities at imaging and they are negative for HLA B27 [3, 4]. The recombinant IL-1 receptor antagonist anakinra has also been used in FMF patients unresponsive or intolerant to colchicine therapy [2, 5]. Anakinra has been tried for the treatment of isolated SA with modest efficacy in comparison with treatment with an anti-TNF inhibitor [6, 7]. We report here upon the efficacy of anakinra treatment in a patient displaying SA associated with FMF, and propose a literature review.

A 22-year-old North African man, presenting at our reference centre, had had typical FMF since childhood, with abdominal and thoracic pain accompanied by fever. Written informed consent was obtained from the patient. The diagnosis of FMF was genetically confirmed with the identification of a M694I homozygous mutation in MEFV. Daily colchicine treatment (1.5 mg/day) was successful in reducing/abolishing crises. For the past 2 years, he complained of daily inflammatory lower back pain and bilateral buttock pain, which occurred between FMF attacks. Lumbar movements were not limited (Schober’s test 10 + 4 cm); chest expansion was +3 cm. Bilateral calcaneal enthesopathy in ankles was identified, and the BASDAI score was 5/10. The diagnoses of both FMF and SA in this patient were established on the basis of Tel-Hashomer criteria and ASAS criteria, respectively.

On admission, the laboratory findings revealed an elevated CRP concentration (18 mg/l, normal range <5 mg/l). He was negative for HLA B27 but had typical radiological findings of SA that were confirmed by bilateral sacroiliitis on MRI (Fig. 1). Axial SA was diagnosed, and he started therapy with a combination of NSAIDs and colchicine, increased to a dose of 2 mg/day. There was no improvement in lower back pain, buttock pain, frequency of FMF attacks and inflammatory syndrome during an 18-month treatment period. Injection of steroid into the sacroiliac

Rheumatology key message

- Anakinra could be an effective treatment for colchicine-resistant patients with both spondyloarthritis and FMF.