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LETTER

Letter to the Editor Regarding 'Iron Formulations for the Treatment of Iron Deficiency Anemia in Patients with Inflammatory Bowel Disease: A Cost-Effectiveness Analysis in Switzerland'

Manuel Muñoz · Walter Reinisch

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Dear editor,

We read with interest the recent publication by Aksan et al. that compared the cost-effectiveness of iron products (ferric carboxymaltose [FCM], iron isomaltoside [IIM], iron sucrose [IS], and oral iron) when administered to inflammatory bowel disease (IBD) patients with iron deficiency anemia (IDA) in a Swiss setting [1]. The cost-effectiveness assessed the additional cost per additional responder (hemoglobin [Hb] normalization or increase of at least 2.0 g/dl) and concluded that FCM was the superior choice in Switzerland and would save costs for healthcare payers. In our opinion, the underlying methodology for comparison of the intravenous (IV) iron preparations in this analysis has several weaknesses, and the authors' conclusion needs to be re-considered.

The Hb and body weight parameters for calculation of the iron dose were obtained from two randomized controlled trials with FCM conducted in international non-Swiss-specific IBD populations [2, 3], and in one of the trials the Hb cut-off for anemia was 10.0–11.0 g/dl [3], which is lower than recommended for adult non-pregnant IBD patients in the current clinical guideline [4]. Furthermore, the Hb and body weight data were provided as mean values with standard errors (SE) instead of standard deviations (SD). The resulting Hb of 9.6 (0.1) g/dl and body weight of 66.6 (0.7) kg used in the analysis are thus low and have an apparent narrower range than expected for a broad real-world heterogenous IBD population with IDA. A European survey of anemia management in IBD patients in routine practice reported a higher mean Hb value of 10.5 g/dl in a cohort of 79 Swiss IBD patients [5]. The mean body weight for a Swiss IBD population is probably also higher than the one in the present analysis considering that around 11.0% of IBD patients in Switzerland are obese with a body mass index of 30.0 kg/m^2 or higher [6]. Moreover, in a Scandinavian observational study with IIM treatment in gastroenterology patients with IDA, the mean (SD) Hb in the IBD group of 100 patients was 10.8 (1.4) g/dl and the mean (SD) body weight was 75.4 (17.4) kg [7].

The base case analysis demonstrated cost savings with FCM driven by a lower dose of iron compared to IIM and by a reduced number of infusions compared to IS; however, the cost

Manuel Muñoz and Walter Reinisch are co-first authors.

M. Muñoz (✉)
Department of Surgical Specialties, Biochemistry and Immunology, School of Medicine, University of Malaga, Málaga, Spain
e-mail: mmunoz@uma.es

W. Reinisch
Department of Internal Medicine III, Division of Gastroenterology & Hepatology, Medical University of Vienna, Vienna, Austria
e-mail: walter.reinisch@meduniwien.ac.at

comparisons were done using different methods to calculate the iron need. The iron dose for FCM was calculated with the Ganzoni formula as recommended in the Swiss label [8], while the iron doses for IIM and IS were obtained from the simplified dosing table with reference to the European Crohn's and Colitis Organisation (ECCO) anemia guideline [4]. This is an unexpected approach considering that the Swiss labels for IIM and IS also offer the possibility of using the Ganzoni formula to estimate the iron need [9, 10]. In addition, there is no simplified dosing table in the Swiss label for IS [10]. From a clinical perspective, it should be noted that the Ganzoni formula underestimates the iron requirements in IBD patients with IDA [3, 11], and the simplified dosing table is recommended in the clinical guideline when estimating the iron need for any IV iron therapy [4]. The simplified dosing table, however, was not present in the Swiss FCM label dated from August 2020 and at the time of the analysis by Aksan et al. The use of the Ganzoni formula for FCM resulted in a lower iron dose and consequently fewer infusions for total dose administration and reduced costs compared to the higher iron doses for IIM and IS that were obtained from the simplified dosing table. Thus, the different dose calculation methods contributed to a favorable outcome for FCM, i.e., lower costs. The correct approach would have been to use the same method for calculation of the dose for all three IV iron preparations, and the Ganzoni formula is an option in all three Swiss labels for FCM, IIM, and IS [8–10]. When using the same dose calculation method for all IV iron preparations, as done in the scenario analysis with the Ganzoni formula in the present analysis, FCM was less costly than IS, but more costly than IIM. The changed outcome versus IIM was due to fewer infusions per patient for full IIM dose administration compared to FCM. This opposite result in cost for FCM versus IIM compared to the base case analysis, now in favor of IIM, was not mentioned in either the discussion or in the conclusion. The cost advantage of IIM over FCM by saving of infusions has also been reported in other cost comparison analyses in IBD patients [12–14].

The efficacy comparisons of the iron treatments in this analysis were based on calculated Hb responses using odds ratios from a previous network meta-analysis (NMA) in IBD patients with IDA to obtain the percent values for IIM, IS, and oral iron relative to FCM [15]. This NMA had several limitations as it compared the IV iron preparations based on data from clinical trials that differed markedly in design regarding baseline characteristics, efficacy endpoint definition, method for calculating the iron need, administered IV iron dose, and treatment duration [16, 17]. The number of patients contributing with data for each iron drug in the analysis also differed considerably [15]. The results in the NMA demonstrated no statistically significant difference in efficacy between the IV iron formulations, although there was a trend for better efficacy with FCM compared to IIM and IS [15]. It should be noted that efficacy was compared based on Hb response rates for the IV iron formulations at different doses; the mean dose for FCM was $> 50.0\%$ higher than that for IIM [15]. Hb change is a more clinically informative measure of efficacy than response rate, and it allows for dose-adjusted comparisons. A recently published observational study that directly compared the treatment effects of FCM and IIM in IBD patients with IDA at equal doses showed similar Hb efficacies and a non-significant trend for a greater response with IIM compared to FCM treatment [18].

Given the multitude of choices of iron drugs today, cost-effectiveness comparisons are valuable tools to help decide the optimal treatment for patients, clinicians, and payers. The present cost-effectiveness analysis by Aksan et al. comes along with multiple biases in favor of FCM for both cost and efficacy and therefore should be interpreted with caution.

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