



Iron replacement in inflammatory bowel diseases: an evolving scenario

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Iron deficiency anemia (IDA) represents the most common extra-intestinal complication in patients with chronic inflammatory bowel diseases (IBD) [1, 2]. Iron deficiency (ID), even without anemia, negatively impacts on patients' quality of life, and is associated with the development of various comorbidities and an increased risk of hospitalization [3]. Thus, timely correction of ID, before anemia develops, is a major goal in IBD patients.

Historically, oral iron salts (typically ferrous sulfate) have been generally considered the standard first-line therapy for IDA, especially when anemia is mild and/or paucisymptomatic. The recommended daily dose for adults with ID is 100 to 200 mg of elemental iron. Although oral iron salts are safe, relatively inexpensive and widely accessible, their use is associated with several gastrointestinal adverse effects (AEs), such as nausea, constipation, diarrhea, and abdominal pain that can arise in up to 30–70% of patients [4]. Such AEs are particularly relevant in IBD patients, as they already have a damaged intestinal mucosa [5] and lead to premature discontinuation of oral iron in more than half of the subjects [6]. This compromises efficacy, since only a small amount (10–20%) of traditional oral iron formulations is absorbed in the duodenum, and consequently a prolonged intake (at least 3–6 months) is needed to normalize hematopoietic status and replenish iron stores, which in turn is essential to prevent short-term recurrence of ID/IDA. As a matter of fact, a number of reasons may argue against the use of oral iron in IBD. First, non-absorbed iron (near 80% of ingested doses) may further damage the intestinal mucosa through a direct toxic effect due to the production of reactive oxygen species [ROS] [7]. The residual iron has also been demonstrated to

be able to modify the gut microbiome, thereby promoting local inflammation [8, 9]. Moreover, recent experiments in anemic mice have shown that a 2-week treatment with low doses of ferrous sulfate induced an increased expression of several inflammatory markers, including C-reactive protein and Interleukin-6 [10]. Local and systemic inflammation may further hamper intestinal iron absorption via the up-regulation of hepcidin, the key regulator of iron homeostasis [11–13]. Indeed, some studies have reported a worsening of disease activity scores in IBD patients treated with oral iron [5].

In recent years, iron replacement therapy has been revolutionized by the introduction of novel intravenous (IV) iron preparations (e.g., ferric carboxymaltose) [14]. These “third-generation” formulations allow the rapid correction of ID with few administrations (e.g., just one or two infusions 1-week apart) and have a reassuring safety profile [14]. However, at least for the moment, they can be administered only in hospital setting, causing patients' discomfort and loss of working days. Of note, despite optimal correction of ID, anemia tends to recur in more than 50% of IBD patients within 10–12 months [15], resulting in the need of repeated infusions. While the long-term safety of repeated high-dose IV iron infusions in terms of susceptibility to infections or ROS generation remains to be fully evaluated, this approach has become increasingly popular and implemented in clinical guidelines [16].

Nevertheless, the development of newer oral iron preparations designed to increase absorption and decrease gastrointestinal AEs has led to reconsider the use of oral iron in IBD patients. One of these innovative preparations is “sucrosomial” iron (SI), which is a source of ferric pyrophosphate protected by a phospholipid bilayer membrane plus a sucrose matrix [17]. Based on in vitro experiments, it has been postulated that SI absorption takes place through a yet not fully elucidated mechanism based on the formation of vesicle-like structures able to bypass the conventional iron absorption pathway mediated

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by divalent metal transporter-1 (DMT-1) [18]. Moreover, SI administration in a mouse model of IDA did not induce hepcidin increase or any inflammatory response [10].

In this issue of *Internal and Emergency Medicine*, Abbati and co-workers investigated the effects of low-dose SI (30 mg/day for 12 weeks) in 30 uncomplicated IBD patients with mild anemia and ID (Hb levels 11.0–11.9 g/dl in females and 11.0–12.5 g/dl in males; transferrin saturation <20%) [19]. At the end of treatment, patients had a mean Hb increase of 0.7 g/dl, while in about 30% the mean Hb increase was >1 g/dl. Although the hematological response was mild, it was statistically significant and could be considered relevant in view of the low dose and the very low frequency of gastrointestinal AEs. Indeed, more than 80% of patients completed the scheduled treatment. SI treatment was also associated with a significant increase of transferrin saturation (from 11 to 17%). While this study is limited by the small sample size, the results are in accordance with other published case series [17]. Besides SI, other novel oral compounds (e.g. ferric maltol) have been proven effective in IBD patients unresponsive or intolerant to traditional oral iron salts [3, 20]. The use of the latter compounds is also under critical reevaluation, in light of the impressive advance in our knowledge of pathophysiology of iron deficiency [14]. Indeed, recent elegant studies in non-anemic ID women have shown that low doses of ferrous sulfate given on alternate days were as effective as the classical daily schedule and much better tolerated [21] [22]. While daily iron doses increased hepcidin for up to 24 h [21], the alternate day regimen allowed sufficient time for hepcidin return to baseline, hence optimizing fractional iron absorption and reducing gastrointestinal exposure to unabsorbed iron, ultimately leading to improved tolerance [22].

In summary, iron replacement therapy with oral compounds is facing a new era after decades of stagnation. Regarding IBD, larger trials, including patients with clinical features less selected as compared to the trial by Abbati et al., are needed to clarify whether or not new preparations and regimens will be actually viable alternative to current protocols. If the benefits suggested by the study of Abbati et al. will be confirmed, the future approach to mild IDA could change in several areas beyond gastroenterology.

Compliance with ethical standards

Conflict of interest FB and GM declare that they have no conflict of interest. DG declares fees for participation in advisory boards for La Jolla Pharmaceutical, Silence Therapeutics, and Novartis, and has received lecture fees from Vifor Fresenius Medical Pharma.

Statement of human and animal rights This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent None.

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