

Managing iron deficiency and iron deficiency anemia in inflammatory bowel disease. The results of the “Gestiona hierro-EII” survey

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ABSTRACT

Introduction: iron deficiency anemia is a common and very relevant manifestation of inflammatory bowel disease (IBD). Although clinical practice guidelines have been published and updated on this subject, the management in the daily practice of this complication is far from optimal.

Objective: to determine the actual management, needs and limitations of anemia in IBD by means of a survey of gastroenterology specialists.

Material and methods: a self-administered telematic survey was carried out between April and May 2017 and was sent to SEDP members. The survey included four sections: participant demographics, monitoring, treatment and limitations/needs.

Results: a total of 122 evaluable surveys were received from all Spanish autonomous communities. Iron deficiency anemia is considered as a frequent manifestation of IBD and is monitored in all patients via the measurement of hemoglobin and ferritin. In the case of anemia, the survey respondents found it necessary to rule out the presence of IBD activity. However, only 14.8% prescribed intravenous iron when IBD was active. The required dose of intravenous iron is mainly calculated according to patient needs but only 33.1% of clinicians infused doses of 1 g or more.

Conclusions: the “Gestiona Hierro EII” survey on the management of anemia in IBD demonstrated a high quality of care, even though some aspects need to be improved. These included the prescription of intravenous iron for patients with disease activity, the use of high-dose intravenous iron and the implementation of algorithms into clinical practice.

Conflicts of interest: This survey was promoted by the SEDP and sponsored by Laboratorios Ferrer. The authors declare that the drafting of questions, submission and the subsequent development of the present articles were undertaken with complete independence. However, several authors, as well as the SEDP, have previously received funding from Ferrer and also from other companies related with to management of IBD and anemia.

Key words: Inflammatory bowel disease (IBD). Iron deficiency anemia. Iron deficiency. Survey.

INTRODUCTION

Anemia is a common complication or manifestation of inflammatory bowel disease (IBD). The prevalence varies among studies and between 10% and 75% of IBD patients have anemia according to the various reported series (1). The presence of anemia in IBD is highly relevant due to the associated poor quality of life, increased use of resources and more aggressive disease, since it is accompanied by increased hospitalization or surgery rates (2,3). Symptoms such as fatigue and asthenia, among others, seriously impair the quality of life in patients with IBD and are associated with anemia (4). Furthermore, anemia is often a marker in patients with Crohn’s disease (CD) and also occurs as a result of inflammatory activity. Furthermore, the presence of iron deficiency without anemia is also a factor associated with a poorer quality of life (5). Taking all of the above into account, it is hardly surprising that fatigue is considered as the primary goal of IBD treatment in 14% of patients (6). All this suggests that both anemia and iron deficiency are basic factors to be considered in the management of patients with IBD.

However, evidence shows that the treatment of anemia or iron deficiency in patients with IBD has room for improvement. In this respect, an ICURE population cohort study carried out in Uppsala found that only 46% of patients with anemia received treatment with iron or transfusions (7). Other studies confirm an under treatment of IBD-related

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anemia, including the German AnaemIBD Study performed in 55 German hospitals. This study found that only 43% of patients with anemia and IBD received treatment for anemia (8). A survey sent to member patients of the European Federation of Crohn's and Ulcerative Colitis Associations (EFCCA) showed that 33% of subjects with IBD and anemia did not receive treatment for anemia (9). The issue of under treatment not only affects adults but also the pediatric population (10).

Apart from under treatment, other aspects in the routine management of IBD-related anemia may also be improved. One example is the use of intravenous iron therapy. The consensus guidelines of the European Crohn's and Colitis Organisation (ECCO) recommend that intravenous rather than oral iron be used for the first-line treatment of anemia when IBD is clinically active (11). However, intravenous iron is only rarely used in clinical practice, which has seemingly not improved in recent years (12).

Information on the management and treatment of anemia in clinical practice is sparse in our setting. Based on the results of the REGIS study of anemia in patients hospitalized due to digestive conditions in Spain (13), it may be concluded that anemia is common in inpatients with IBD (54% in CD, 85% in ulcerative colitis [UC]), with on-treatment rates of 50% on admission and 45% at discharge. Therefore, it may be inferred that anemia is undertreated in our setting.

Due to all of the above, the "Gestiona Hierro-EII" project was devised. This study devised a specific online survey for SEPD members with the main goal of determining the current practice in the management of clinical issues related to iron deficiency and anemia in patients with IBD. The patients, treatment regimen and therapeutic alternatives were also taken into consideration, as well as the identification of opportunities and proposals for improvement.

MATERIALS AND METHODS

The "Gestiona Hierro-EII" initiative is a prospective observational project based on an online structured survey aimed at SEPD members. In order to develop the "Gestiona Hierro-EII" survey, a set of items related to the various aspects of the management of anemia and iron deficiency in IBD were devised. This included items regarding the perceptions, attitudes and experience of gastroenterologists and their perceived limitations and needs. Following an internal discussion process in three meetings, a dedicated expert committee reviewed the drafted items. The definitive survey included a total of 48 items and was structured with four dimensions. These included a general section with participant demographic data, monitoring aspects (criteria, parameters, times, etc.), anemia management (regimens, doses, administration routes, follow-up, etc.) and participant-perceived limitations/needs (delays, infrastructure, education, etc.).

Procedure

An invitation was sent by the SEPD to the practicing clinical members (1,561 at the survey baseline) via e-mail and posting information in the Society communication channels (web page, news bulletins, Info-SEPD magazine). Par-

ticipants were asked to complete the survey online using the *Formularios-SEPD* platform, from April 24 to May 22, 2017. All fully completed surveys obtained during the month were processed.

Statistical analysis

Quantitative variables are described as mean and standard deviation. Qualitative variables are shown in tables that include relative and absolute frequencies, both for the overall population and the subgroups established according to various variables (sex, age, time practicing, workplace, activity and specialist care of patients).

An inferential study of different qualitative variables was carried out using a homogeneity test based on the Chi-squared distribution when the expected values permitted; otherwise, the Fisher's exact test was applied. A p-value of 0.05 was regarded as significant for all statistical tests. The statistical analysis was performed using the SPSS 21.0 software package.

RESULTS

A total of 122 fully completed surveys were received and the response rate was almost 8%. Virtually all Spanish autonomous communities were represented. Among the participants, 51.6% were younger than 40 years of age, 84.4% worked in cities with over 50,000 inhabitants, 55.7% had less than ten years of experience in clinical practice, 69.7% worked at a public tertiary university hospital and 52.5% were female. Overall, 68% of respondents claimed to provide "specialist IBD care". However, this self-proclaimed status should be interpreted with caution as only 20.5% of participants worked in specialist IBD clinics or units and 50% cared for fewer than 50 IBD patients.

Iron deficiency anemia monitoring

Respondents considered that anemia or iron deficiency was a common finding in IBD that involved 34.1% of patients. Likely due to this fact, virtually all gastroenterologists (97.5%) considered that iron deficiency anemia should be monitored in all patients with IBD regardless of disease activity. Most specialists requested tests to assess the presence of inflammatory activity upon identifying iron deficiency anemia in a patient with IBD. In this regard, the most commonly ordered tests included C-reactive protein (90.8%), fecal calprotectin (89.1%) and colonoscopy (31.1%). Professionals with private practice ordered more colonoscopies than those that practiced exclusively in the public sector (45.9% vs 24.4%, $p < 0.05$).

All specialists assessed potential anemia in patients with CD or UC in remission, every 3-6 months in 85.1% of cases. Various laboratory tests were requested in order to identify anemia; hemoglobin and ferritin measurements were the most commonly used (Fig. 1). The use of hematocrit as an anemia marker was mainly used by specialists with more clinical practice experience (87.0% of specialists with over ten years of experience in practice vs 70.6%, $p < 0.03$). Anemia test selection does not seem to be influenced by center

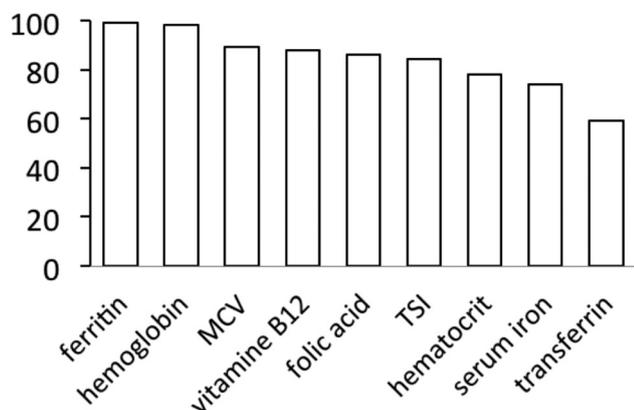


Fig. 1. Parameters requested in order to identify anemia in patients with IBD as a percentage of respondents. Most specialists requested more than one parameter; serum ferritin and hemoglobin levels were most commonly ordered (MCV: mean corpuscular volume; TSI: transferrin saturation index).

type, professional activity or the number of IBD patients ($p > 0.05$ for all cases). Therefore, only inferential observations will be provided where differences according to demographic characteristics were identified.

Treatment of iron deficiency anemia

Half of the participants chose to treat iron deficiency anemia when symptoms developed and the remaining participants only considered laboratory results and did not assess symptom burden (51.6% vs 48.4%). However, most practitioners in private practice treated anemia when symptoms were present (67.6% of private practitioners vs 44.7% of public practitioners, $p < 0.02$). With regard to lab parameters that were deemed essential to initiate iron therapy, ferritin was most commonly used (78.7%), followed by hemoglobin (70.5%) and transferrin saturation index (48.4%) or serum iron (32.8%). Hematocrit values were only used by 19.7% of participants, although more experienced professionals used hematocrit values more frequently (29.6% vs 11.8%, $p < 0.014$) for therapy onset. These results suggest that 63.9% of professionals prescribed iron therapy when the hemoglobin level was lower than 12 g/dl in females or 13 g/dl in males, and 73.8% did so after finding a low ferritin level, even with normal hemoglobin values.

The decision to use either oral or parenteral iron for treatment was often based on hemoglobin levels (84.4% of respondents), while only 68.9% of practitioners took IBD activity into account. In fact, only 13.1% failed to prescribe oral iron during a flare-up. Interestingly, 63.9% of gastroenterologists considered patient preferences and 31.1% factored in cost in order to prescribe either oral or intravenous iron therapy. There were no differences according to demographic characteristics.

Parameters considered during the follow-up of iron deficiency anemia mainly included hemoglobin (99.2% of respondents) and ferritin (95.1%), followed by transferrin saturation index (76.2%) and the mean corpuscular volume (74.6%).

The decision of which parameters should be used for monitoring anemia was influenced by the time spent in practice, and specialists with over ten years of clinical experience and those in the private sector used mean corpuscular volume ($p < 0.04$) and hematocrit ($p < 0.018$) values significantly more often. Most respondents monitored anemia every three months (67.2%). The most commonly used therapies for IBD-related iron deficiency anemia included oral iron followed by intravenous iron, and intramuscular iron was only prescribed by 4.9% of specialists.

Treatment with oral iron

An important aspect in the management of iron deficiency anemia with oral iron is treatment duration. Most practitioners administer iron until the laboratory parameters return to normal levels (ferritin in 50.8% of cases and hemoglobin in 12.3% of cases). However, 29.5% of participants prescribed oral iron for a fixed period of time regardless of the laboratory results. As per the recommendations for oral iron, fasting was not advised in 33.6% of cases. Patient experience and tolerance were considered when prescribing oral iron and the prescription of oral iron depended upon tolerability in 92.6% of gastroenterologists. How was oral iron intolerance considered? In this respect, 53.3% of participants considered intolerance when two formulations had been tried and when more than two oral iron formulations had been tried in 36.1% of cases. Treatment failure criteria were heterogeneous after oral iron therapy completion, as shown in table 1.

Treatment with intravenous iron

The reasons to prescribe intravenous iron are listed in table 2. The fact that most practitioners only prescribed intrave-

Table 1. Criteria used to determine the failure of oral iron therapy for iron deficiency anemia

	Frequency	Percentage
Hemoglobin decreased	25	20.5%
Hemoglobin remained unchanged	38	31.1%
Hemoglobin did not increase by at least 1 g/dl	59	48.4%

Table 2. Reasons quoted by respondents to prescribe intravenous iron for IBD-related iron deficiency anemia

	Frequency	Percentage
Oral iron intolerance	104	85.2%
Refractoriness to oral iron	87	71.3%
Severe anemia refractory to oral iron	83	68.0%
Severe anemia regardless of oral iron therapy	64	52.5%
Any anemia with disease activity	18	14.8%

nous iron when oral iron failed or was poorly tolerated, rather than as the first regimen, is an important finding. In addition, only 14.8% prescribed intravenous iron when IBD was active, as recommended by clinical practice guidelines.

Intravenous iron dosage was mainly calculated according to patient needs, using either Ganzoni's formula (38.5%) or the simplified ECCO formula (27.0%). However, 34.4% of participants used standard doses according to patient profiles. Furthermore, most (63.1%) considered that instruments to calculate intravenous iron requirements do not underestimate actual patient needs. The centers where intravenous iron were administered are listed in table 3.

On most occasions (90.2%), participants considered that the intravenous iron available in their hospital could provide an optimal coverage of patient needs. This is likely related to the fact that most professionals (81.1%) could prescribe high-dose iron therapy, whereas 12.3% could only prescribe low-dose therapy. There is a wide variability with regard to what is considered as a high-dose or low-dose therapy, which depends on the medicinal products available in each center. In spite of the facilities reported by participants regarding the use of intravenous iron, most (51.2%) prescribed repeated doses of 500 mg or up to 1 g in some cases. Whereas only 33.1% used single or repeated doses of 1 g or higher according to the requirements previously estimated. The reasons put forward to prescribe high-dose intravenous iron are listed in table 4.

Limitations and needs with regard to treatment with intravenous iron

A potential limitation in the use of intravenous iron is the waiting time for the infusion. In this regard, a positive experience was observed as 15.6% of participants said that they could administer intravenous iron immediately and 64.8% reported within one week. Delays of over two weeks were

Table 3. Units where intravenous iron was administered

	Frequency	Percentage
General day hospital	98	80.3%
IBD day unit	12	9.8%
Hospitalization area	6	4.9%
Hematology day hospital	4	3.3%
Other	2	1.6%

Table 4. Criteria used by respondents to prescribe high-dose intravenous iron for IBD-related iron deficiency anemia

	Frequency	Percentage
Patient convenience	83	68.0%
Day hospital streamlining	70	57.4%
Low-dose intravenous iron failure	63	51.6%
Poor venous access	59	48.4%

only reported by 3.3% of respondents. Other factors limiting the use of intravenous iron according to participants are listed in table 5.

The present survey revealed a limited use of high-dose intravenous iron for the treatment of IBD-related iron deficiency anemia. A potential limitation would be the fact that practitioners deemed it unnecessary. However, 97.5% of respondents positively valued the availability of a high-dose therapy. The possibility to resolve anemia with a single infusion was scored as "quite good" or "very good" in 95.9% of cases; also, there was a preference for the use of high-dose iron therapy.

The most relevant needs identified in order to improve the management of IBD-related iron deficiency anemia are listed in table 6. Most of these needs are unrelated to the epidemiological factors discussed. However, having available day hospital services was a need that was more commonly identified by those practicing outside a tertiary hospital. With regard to the need for clear clinical practice guidelines, 83.6% of participants thought that having diagnostic-therapeutic algorithms at hand would be "quite helpful" or "very helpful", and 40.2% said that they were not referring to guidelines but made decisions on a patient-by-patient basis.

Education needs

With regard to information and training, 84.4% of specialists considered information on the management of IBD-related anemia to be necessary. Overall, 54.9% of participants had not received any specific training during the last three

Table 5. Limiting aspects of intravenous iron indication for IBD-related iron deficiency anemia

	Frequency	Percentage
Prior tolerance	75	61.5%
Treatment cost	61	50.0%
Available infrastructure	54	44.3%
Poor venous access	59	48.4%
Fear of complications	48	39.3%
Patient clinical status	33	27.0%

Table 6. Aspects that respondents deemed necessary in order to improve the management of IBD-related iron deficiency anemia

	Frequency	Percentage
Clear clinical practice guidelines	99	81.1%
Courses to improve knowledge on the issue at hand	31	25.0%
More information	30	24.6%
Nursing staff availability	30	24.6%
Day hospital services availability	28	23.0%

years. The expressed need for training may be satisfied in many different ways and the preferred modalities included distance learning (47.6%), classroom training (21.4%) and a mixed approach. Only 11.7% of cases favored the provision of written self-study materials.

DISCUSSION

The SEPD-promoted “Gestiona Hierro-EII” project has clarified the current practice in the management of clinical issues related to iron deficiency and anemia in patients with IBD. The responses submitted by the 122 practitioners who completed the survey provided an insight into relevant aspects such as presentation in patients with active IBD, the use of high-dose intravenous iron, the use of algorithms in clinical practice and ongoing education needs. The demographic distribution of respondents is consistent with prior observations in other “Gestiona” programs, where the SEPD highlighted the current clinical management and the needs pertaining to digestive conditions (14-16).

There is virtually a unanimous consensus that anemia or iron deficiency is a significant condition in the setting of IBD, which should be monitored in all patients regardless of disease activity. IBD inflammatory activity is usually assessed via laboratory tests such as C-reactive protein or fecal calprotectin levels. Endoscopy has been relegated to a secondary role as expected in clinical practice as compared to a clinical trial setting. The diagnosis of anemia relies on abnormal hemoglobin or ferritin values, whereas hematocrit has been pushed to the background and is still used by more experienced specialists.

In order to prescribe iron for the treatment of iron deficiency anemia, it is important to note that all specialists require indicative laboratory tests, particularly ferritin or hemoglobin levels, even in the absence of symptoms. In this regard, 73.8% of specialists even recommend that iron deficiency anemia be treated when ferritin levels are low, regardless of hemoglobin values. Therefore, specialists are particularly aware of iron deficiency without anemia, which is known to have an impact on patient-perceived health status (5). This is relevant since international guidelines (11) stress the importance of reduced hemoglobin levels as a surrogate marker for anemia and recommend that it is monitored and managed during follow-up, with no specific mention of hypoferritinemia without anemia.

It is of note that the decision to use oral or parenteral iron for treatment is based on hemoglobin levels and almost one third of specialists do not consider IBD inflammatory activity. In fact, the current recommendation is that intravenous iron should be the first-choice therapy for iron deficiency anemia for patients with clinically active IBD (11).

The duration of iron therapy for IBD-related iron deficiency anemia is mainly dependent on laboratory tests, usually when ferritin levels return to normal. However, nearly one third of specialists prescribe treatment for a fixed prearranged length of time, regardless of laboratory parameters. These results were expected, since the guidelines recommend that a therapy for anemia should normalize hemoglobin levels and iron deposits, i.e., ferritin. A potentially debatable aspect is whether the patients’ opinion should be taken

into account with regard to quality of life. Since anemia and iron deficiency impair quality of life, the maintenance of therapy until quality of life has normalized might represent a potential therapeutic goal. In fact, reviews on this topic suggest that increases in hemoglobin levels should translate into an improved quality of life (17). However, deciding what is the goal of iron therapy is important, as its efficacy. Thus, response to treatment may range from 9% to 43% according to whether hemoglobin normalization or a hemoglobin level increase of 2 g/dl is chosen as the treatment goal (18). Most specialists monitor prescribed therapy via changes in hemoglobin and/or ferritin levels, which actually are the best markers available for iron response (19).

The results of the present survey identified delays or under treatment with regard to the use of intravenous iron, as was to be expected from the literature (7,12). These delays result from the fact that intravenous iron is rarely considered as a first-choice option or suitable for a flare-up. Furthermore, intolerance to oral iron develops once administered, which most often involves trials with different oral preparations. Other limiting factors are associated with the fear of complications. Intravenous iron must be always infused under safe conditions to prevent maximum infusion-related risks (20). However, according to recommendations, treatment with intravenous iron is an advisable strategy to resolve anemia and improve patient quality of life (21) with a favorable safety profile both for iron isomaltoside and iron carboxymaltose (22,23). The cost of newer intravenous iron preparations is also quoted as a limiting factor. In this regard, even though unit prices for newer products are certainly higher, the total treatment costs are lower. Before the advent of iron isomaltoside in our setting, savings per IBD patient were estimated at €948 with the use of iron carboxymaltose rather than iron saccharate (24).

The administration of intravenous iron products usually requires repeated doses of up to 1 gram. Currently, infusion strategies are being reconsidered due to the availability of intravenous iron treatments that allow effective, safe doses of two or more grams per infusion (19). The reasons for the reluctance to use high-dose intravenous iron cannot be determined from this survey. However, they are likely related to the stringent criteria for the use of intravenous iron therapy.

The “Gestiona Hierro-EII” survey also identified the needs perceived by specialists in order to improve the management of IBD-related iron deficiency anemia, bearing in mind that around 50% of participants had a total of 50 IBD patients under their care. The primary needs of respondents included improved infrastructures to streamline intravenous iron infusions, staff availability and particularly the availability of information. This is reflected by their needs for both clinical practice guidelines and enhanced education programs to keep them updated on the management of IBD-related anemia. Institutions such as the SEPD will play a key role in the latter point by offering gastroenterologists the necessary means to access up-to-date, ongoing training on the issue at hand.

Although interesting, the “Gestiona Hierro-EII” survey also has some limitations. The most important is related to the number of responses collected, which was low as expected. Therefore, most statistical analyses were not statistically

significant, likely due to an insufficient number of observations.

In summary, while the management of anemia and iron deficiency in IBD patients could be improved in our setting, the lack of understanding of the current practice makes it difficult to design optimization strategies or programs. Similarly, the identification of practitioner-perceived needs will improve the management of anemia in these patients by providing enhancement measures such as training programs, awareness campaigns, day hospital facilities for intravenous iron infusion and patient follow-up, etc. The "Gestiona Hierro-EII" project, based on the management of IBD-related anemia by SEPD gastroenterologists, revealed an adequate management with regard to this complex issue. However, room for improvement was also identified in aspects such as the use of intravenous iron for patients with active IBD, the use of high-dose intravenous iron with fewer infusions or the implementation of clinical practice algorithms.

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