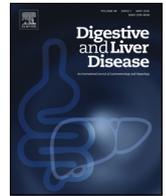




Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld



Alimentary Tract

Therapy experiences and preferences among patients with anemia: Results of a cross-sectional survey among Italian patients with inflammatory bowel disease

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ARTICLE INFO

Article history:

Received 13 March 2017
Received in revised form 16 June 2017
Accepted 28 June 2017
Available online xxx

Keywords:

Anemia
Ferric carboxymaltose
IBD
Preference
Survey
Treatment

ABSTRACT

Background: Anemia represents one of the most common and often the least treated complications of inflammatory bowel disease (IBD).

Aims: Our study investigates experiences and preferences concerning anemia treatment in patients with IBD.

Methods: IBD patients previously diagnosed with anemia were invited to participate in an anonymous survey between July and September 2015, which assessed demographic and clinical data, and experiences regarding anemia treatment.

Results: A total of 118 IBD patients were invited to participate in the study, of which 100 (85%) were included in the analysis. Seventy-five percent of patients reported a high personal burden related to intravenous therapy, while the majority of companions (76%) declared a moderate burden. The increased importance assigned to the possibility of a single session treatment was significantly associated with age (Beta = 0.01; p = 0.03), working status (Beta = 0.02; p = 0.04), anemia severity (severe vs. mild, Beta = 0.42; p = 0.03), and intravenous treatment (Beta = 0.44; p = 0.001).

Conclusions: Most patients reported a high personal and a moderate companions' burden. Having the possibility of effective single dose intravenous therapy was of great importance. Patients' perspective provides key information for evaluating the indirect costs of anemia treatment in IBD which, according to the health technology assessment approach, could be useful in a patient centered decision making process.

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1. Introduction

Inflammatory bowel disease (IBD) represents a chronic, systemic disorder associated with extra intestinal manifestations, complications, and other autoimmune disorders and has a significant impact on individual's health-related quality of life [1,2].

The possibility for chronic relapses in these patients leads to decreased work ability and productivity. Besides having a notable impact on patients and their families, IBD burdens the whole society, not just by increasing the costs of health services, but also affecting the economy as a whole [3,4].

Among the broad spectrum of systemic manifestations of IBD, anemia is one of the most frequent [1], but also one of the least recognized complications and, unfortunately, despite its dramatic impact on quality of life, is often the least treated one [5]. A reduced hemoglobin level is directly associated with physical and mental disabilities [6,7] which often lead to decreased quality of life and

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<http://dx.doi.org/10.1016/j.dld.2017.06.015>

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work ability, as well as an increased number of hospital admissions [8].

The current standard of care for anemia involves iron supplementation which can be administered orally or intravenously, with a wide variety of preparations. Patients with IBD often do not tolerate oral formulations and intravenous iron is considered a safe and effective alternative [9]. Intravenous ferric saccharate is usually considered the standard IV supplementation and it is typically administered as a slow push injection or a slow infusion in doses of 100–200 mg, requiring multiple outpatient visits and repeated intravenous access to reach its therapeutic target. Recently, alternative products, which differ in pharmacokinetic properties and safety profiles, have become available for use in clinical practice: iron gluconate (lower single doses), iron isomaltoside and ferric carboxymaltose (higher single doses) [10]. Among them, only the latter is currently available in the Italian hospital outpatient services.

Observational studies investigating iron supplementation therapy have shown a positive correlation between an increase in hemoglobin levels and improvements in cognitive function and quality of life [6,7].

However, both oral and intravenous iron supplementations are associated with a frequent occurrence of adverse effects. The occurrence of side effects can be reduced by increasing patient involvement in the treatment selection process, which is of great importance for obtaining greater comfort and adherence to therapy [11].

This issue is particularly relevant in chronic diseases such as IBD [12]. In a study by Baars et al., 81.0% of interviewed patients (1067 in total) considered it very important to be actively involved in the decision-making process when treating anemia as a comorbidity [13].

The introduction of innovative drugs with a better therapeutic profile, but at higher costs, poses great challenges for the development and implementation of guidelines and treatment protocols for anemia [11,14]. Within this context, the evaluation of patients' experiences and preferences represents a preliminary step to an informed process which should improve collaboration between patients and their healthcare professionals by providing patients' participation at decision-making consultations and their involvement in all stages of the decision process [15].

The main aim of our study was to investigate the impact of anemia treatment in IBD patients, in terms of perceived personal burden and days off work. Furthermore, the study aimed to explore treatment toxicity and preferences regarding anemia treatment in order to improve the disease management and better understand IBD patients' needs.

2. Material and methods

2.1. Study population

Patients previously diagnosed with IBD and currently in follow up in one of the IBD referral hospitals in the Lazio Region were invited to participate in an anonymous survey between July and September 2015. Patients were considered eligible if they were: affected by IBD, suffered from anemia as comorbidity, and had received at least one treatment for anemia (oral or IV).

All participants were asked to complete a questionnaire aiming to investigate preferences for anemia treatment and its perceived impact. The questionnaires were administered by volunteers of the association "AMICI LAZIO Onlus" in the IBD ambulatory care units of the hospitals. Uncompleted questionnaires (one or more questions unanswered) were excluded from the analysis.

2.2. Questionnaire survey

A self-compiled questionnaire was specifically designed by a working group represented by a public health physician, a gastroenterologist and a nurse from an IBD unit, and one representative of "AMICI Lazio Onlus" (Supplementary material 1).

The survey included 22 questions aimed to collect information from the following domains:

- Demographic characteristics (age, gender, education level, working status, city of residence).
- Clinical features (type and extent of disease).
- Characteristics concerning anemia and its therapy (hemoglobin level, frequency of diagnosis, type of treatment).
- Type and frequency of adverse events experienced during oral and intravenous therapy.
- Patient experiences with the current standard of care for IV anemia treatment (intravenous ferric saccharate): number of infusions, setting in which the on-going treatment is performed, independence during the treatment, time taken to receive the therapy (absence from workplace), therapy burden on patient's/companion's life and preferences for single session administration.
- Four additional questions were asked of patients who had experiences with ferric carboxymaltose, in order to provide data regarding its use and information on comfort, efficacy, and tolerability in respect to other treatments.

2.3. Statistical analysis

A descriptive analysis was conducted to report demographic and clinical characteristics of the included patients, along with their experiences and preferences for anemia treatment. Comparison of patients demographics and clinical data in respect to the perceived importance of a single-dose intravenous therapy was evaluated using the t-test for unpaired samples, one-way analysis of variance (ANOVA) or Pearson correlation test, as appropriate. A linear regression model was set up to test the association between the independent and explanatory variables.

Independent variables were determined by the perceived importance of a single administration of an intravenous therapy by using a visual analog scale with levels of agreement to the statement ranging from one to ten, while explanatory variables were determined using univariate analysis (variables with a p value <0.25 were included in the model, retaining those with p values <0.05). For the purpose of multivariate analysis the variable working status was dichotomized as "employed" and "not employed".

Statistical analyses were performed using IC Stata 14 for MAC, and the results reporting the p values <0.05 were considered statistically significant.

3. Results

A total of 118 IBD patients were invited to participate in the study; of those 102 met the inclusion criteria, but only 100 patients were included in the final analysis (two subjects were excluded because they left the questionnaire uncompleted).

3.1. Demographic and main clinical characteristics of the included patients

Mean age of the respondents was 39.2 ± 11.8 years and women accounted for 67% of them. Almost all respondents were residents of Rome, highly educated individuals, with a large proportion employed (47%) or self-employed (20%) (Table 1).

Table 1
Questionnaire responses (n = 100).

Gender (%)	Male	33.0
	Female	67.0
Age (mean ± SD)		39.2 ± 11.8
City of residence (%)	Roma	95.0
	Latina	4.0
	Aquila	1.0
	Elementary school/uneducated	0.0
Level of education (%)	First grade secondary school	1.0
	Second grade secondary school or vocational education	79.0
	Graduate and postgraduate	20.0
	Student	13.0
Working status (%)	Employed	47.0
	Self-employed	20.0
	Retired	8.0
	Seeking for job	12.0
	Ulcerative colitis	63.0
	Crohn's disease	14.0
Disease type (IBD) ^a (%)	Indeterminate colitis	23.0
	Remission	53.0
	Active mild-moderate	45.0
Disease state (IBD) (%)	Active moderate-severe	2.0
	Mild	8.0
	Moderate	54.0
Anemia diagnosis (%)	Severe	38.0
Number of anemia diagnosis (mean ± SD)		8.3 ± 6.5
Type of treatment (%)	Oral ^b	59.0
	Intravenous ^b	82.0
Number of intravenous infusions (mean ± SD)		16.3 ± 7.9
Need to be accompanied to receive the treatment (%)	Autonomous	34.1
	Parent	30.5
	Child/children	1.2
	Spouse/partner	34.1
Importance given to the single-session intravenous therapy (mean ± SD)		9.8 ± 0.5
Previous experiences with ferric carboxymaltose (%)		8
Rating for ferric carboxymaltose (mean ± SD)	Comfort	8.6 ± 0.5
	Efficacy	9.0 ± 0
	Safety (adverse effects)	9.6 ± 0.5
	Overall rating	9.1 ± 0.4

^a Inflammatory bowel disease.
^b Percentage from the entire sample.

The majority of subjects suffered from ulcerative colitis (63%), while only 14% from Crohn's disease, and the remaining 23% from indeterminate colitis. Almost all patients were either in clinical remission or their disease activity was mild or moderate. Only 2% of the patients were in a moderate or severe clinical state of disease (Table 1).

3.2. Characteristics of anemia and its treatment

Oral therapy was administered in 58% of the respondents while intravenous in 82% (93% of them received it more than ten times, with an average of 16 ± 8 infusions) (Table 1).

Concerning the diagnosis of anemia, 54% had moderate anemia with hemoglobin levels between 9 and 11 g/dl. Eight percent of patients suffered from mild anemia, while 38% had severe anemia, with hemoglobin levels less than 9 g/dl. For most patients, anemia was a recurrent and persistent issue: almost 40% of respondents were diagnosed with anemia at least ten times; in 41% of these patients a need for both oral and intravenous iron supplementation was apparent.

Concerning oral therapy, 22 out of 58 patients (38%) discontinued treatment due to the onset of adverse effects; the percentage of the patients discontinuing treatment while on intravenous iron was lower (15%). Distribution of adverse effects by type of anemia treatment is shown in Table 2.

Table 2
Adverse effects which constrained to interrupt the therapy, by type of anemia treatment.

Adverse effects	Oral (N = 58) n (%)	Intravenous (N = 82) n (%)
Patients constrained to interrupt the anemia treatment due to the onset of one of the following adverse effects	22 (37.9%)	12 (14.6%)
Disease exacerbation	12 (54.5%)	4 (33.3%)
Nausea/vomiting/dyspepsia	4 (18.2%)	6 (50%)
Various changes in bowel habits	5 (22.8%)	–
More than one symptom	1 (4.5%)	–
Rashes/urticaria/allergy	–	2 (16.7%)

3.3. Patients' experience with current intravenous therapy

Only one third of patients receiving intravenous therapy, all in hospital settings, were autonomous. The same percentage of respondents declared the need to be accompanied by spouse (34%) or parent (30%), rarely by children (1%) (Table 1).

Key findings about the absence from work (in hours) and burden related to intravenous treatment from the perspective of the patient and the companion (if present) are presented in Table 3. Around 67% of the patients and 76% of their companions were absent from their workplace for one day due to the need for intravenous therapy, while 24% and 9% of patients and their companions, respectively, declared no impact of therapy on their absence from

Table 3
Percentage of time loss and burden for patients and companions.

		Patients (accompanied and not, %)	Companions (all categories, %)
Time (hours)%	0	24.4	9.2
	1–3	4.8	1.8
	3–5	3.7	13.0
	>5	67.1	76.0
	Total	100.0	100.0
Burden	Light	0.0	6.4
	Moderate	24.7	76.6
	High	75.3	17.0
	Total	100.0	100.0

work. Approximately 9% of patients and 15% of their companions had to take 1–5 h off work because of hospital treatment.

Around 75% of patients reported a high personal burden and a moderate companions' burden. Moreover, all patients who reported the burden of a companion to be light or moderate rated the highest value of personal burden.

Consequently, patients considered the possibility to have a single-session administration of intravenous therapy to be highly important (mean \pm SD = 9.8 \pm 0.5; range 8–10). Eighty-seven percent of patients rated the highest value as answer (10/10).

3.4. Patients' experiences with ferric carboxymaltose

After evaluating the experience with ferric carboxymaltose through the question "Have you ever received a ferric carboxymaltose intravenous treatment?" only 8% of the patients responded affirmatively. Among these subjects the overall view was highly positive (mean \pm SD = 9.1 \pm 0.4; range 9–10), as well as perceived comfort of route of administration (mean \pm SD = 8.5 \pm 0.5; range 8–9), tolerability (mean \pm SD = 9.5 \pm 0.5; range 9–10), and efficacy (mean \pm SD = 9.0 \pm 0; range 9–9).

3.5. Results of the univariate and multivariate analyses

The importance given to the possibility of obtaining the supplementation therapy in a single session, although high in the overall sample, was significantly higher among female patients (9.9 vs. 9.6; $p < 0.01$) and tended to increase proportionally with age ($\rho = 0.23$; $p = 0.02$) and number of infusions ($\rho = 0.20$; $p = 0.05$) (Supplementary Table S2).

Moreover, another interesting although not statistically significant ($p = 0.08$) association was observed between working status and the importance given to a single session therapy, which was reported to be highest among workers with respect to unemployed patients. Additionally, those who had experience with ferric carboxymaltose treatment reported an even greater but not significant importance ($p = 0.29$) (Supplementary Table S2).

Table 4
Results of multiple regression analysis.

Dependent variable: single-session therapy	Coefficient, crude (CI 95%)	p Value ^a	Coefficient, adjusted (CI 95%)	p Value
Independent variables				
Age	0.01 (0.001–0.018)	0.02	0.01 (0.001–0.016)	0.032
Working status	0.18 (–0.025 to 0.392)	0.08	0.187 (0.005–0.369)	0.044
Anemia severity				
Mild	(ref.)	/	(ref.)	/
Moderate	0.55 (0.194–0.898)	0.003	0.297 (–0.051 to 0.645)	0.093
Severe	0.72 (0.362–1.085)	0.000	0.42 (0.035–0.799)	0.033
Intravenous therapy	0.60 (0.363–0.824)	0.000	0.44 (0.180–0.698)	0.001

The bold values represent statistically significant findings.

^a $p < 0.05$.

Multiple regression analysis showed that variables significantly associated with an increased importance given to the possibility of a single session treatment were: age (Beta = 0.01; $p = 0.03$), working status (workers respect to the unemployed persons, Beta = 0.02; $p = 0.04$), anemia severity (severe vs. mild, Beta = 0.42; $p = 0.03$), previous intravenous treatment (Beta = 0.44; $p = 0.001$) (Table 4).

4. Discussion

This study, conducted in IBD patients affected by anemia, gives a picture of the main patients' experience and preferences concerning one of the most frequent extra intestinal complications associated with their disease. The above findings confirm that anemia is a great issue for IBD patients; with most of them being affected by moderate or severe recurrent anemia often requiring IV treatment [16–18].

The nature and frequency of reported adverse events of IV treatment were generally in accordance with other previously published studies [19–22]. They were reported in higher percentages for oral rather than IV therapy, indicating that 22/58 (38%) patients on oral therapy had to discontinue it due to the onset of adverse effects, especially disease exacerbation, while discontinuation occurred in only 12/82 (15%) patients on IV treatment. Therefore, an advantage of implementing IV therapy in IBD was proven, as suggested also by the guidelines for treating anemia in these patients [23].

The present study also examined absence from work due to the need to receive iron supplementation in hospital, representing a significant loss of time in terms of a "whole day absence" from work (>5 h). In addition, intravenous therapy in approximately two thirds of patients (67%) required accompaniment, with clear implications in terms of productivity and everyday functioning of their caregivers. These findings add relevant information regarding the additional impact of anemia treatment to the indirect costs of an already impairing chronic disease, which has been widely studied in the literature [24–27]. Viazis et al. reported that more than half of Greek patients with IBD (57%) needed to take time off work, due to problems related to their disease or due to the need to visit an outpatient clinic. The days off work ranged from 1 to 20 per year and around 40% of patients reported having a limited working capability due to the onset of IBD symptoms [28]. Similar results were found by Blomqvist and Ekbohm in the Norwegian population [29]. However, the aforementioned papers refer to the principal disease, while updated information on work time lost due to the treatment of one of its more frequent comorbidity (anemia), will be useful for future economic evaluations.

Patients from our study sample had a high level of perception of the burden of treating anemia. The multivariate analysis confirmed the higher implication of a multiple session treatment especially in the working population, since being employed was principally associated with preferences towards single-dose treatment. However, it should be clearly stated that the overall opinion

was generally highly positive (none of the respondents gave a score below 8/10).

Currently, patients are not familiar enough nor have much experience with high-dose iron treatments [30]. Similarly, our findings confirmed a low percentage (8%) of IBD patients who had experienced ferric carboxymaltose treatment, reporting overall satisfaction, especially regarding tolerability, as well as for the effectiveness and comfort, as already shown in the literature [21,31].

Some limitations need to be taken into account. Considering the rather small sample size and the fact that the majority of the study participants were residing in Rome, extrapolation of the results to the general population requires some caution. Furthermore, the more represented disease type in this survey was ulcerative colitis, which is somehow surprising, as anemia has been described to be more common in Crohn's disease. We believe that the higher number of patients with ulcerative colitis who responded to the questionnaire might be due to the higher prevalence of ulcerative colitis with respect to Crohn's disease within the general population. Finally, the classification of disease state and anemia severity was based only using subjective patient reported outcomes.

Considering the growing emphasis on providing patient-focused health care and ensuring patient involvement in the design of health services, the collaboration with one of the most representative association of IBD patients in Central Italy represents one of the main strengths of this paper, thus providing a valuable source of information collected directly from the patients. Since anemia is closely associated with the quality of life of IBD patients, their perspective on various treatments and active participation in the decision-making process represents a crucial step. The patient's involvement will not only contribute to managing adverse effects, adherence and effectiveness, but it also has the potential to provide more room for patient's preference. Although patients' perspectives should be considered in addition to the evaluation of disease epidemiology, safety and effectiveness of the technology, as well as its organizational, ethical and economic impact, patients' views are often lacking and are rarely included in the Health Technology Assessment [32].

5. Conclusions

The survey conducted among the IBD patients and members of the association "AMICI Lazio Onlus" makes an important contribution in defining the patient's experience and perspective related to various strategies for treating anemia. Considering the importance of active involvement of the patients in the decision making process, this kind of patient-centered approach, provides valuable information for a further fully comprehensive evaluation of new therapeutic options.

Having the possibility for an effective intravenous therapy, administered in a single dose is of great importance to patients. Besides obvious benefits in terms of dosage adjustment, complications management and work productivity, this kind of approach shows a positive influence both on their family members, and indirectly on the whole society.

Conflict of interest

None declared.

Funding source

The project has been carried out with an unrestricted grant by Viphor Pharma, Italy.

Acknowledgements

The authors would like to thank the volunteers of the "Amici Lazio Onlus", one of the main regional IBD patients associations founded with the scope to help IBD patients and their families in managing disease and its complications, for their support in the realization of the survey and in the process of data entry of the paper questionnaires.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.dld.2017.06.015>.

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