

Anaemia management in patients with inflammatory bowel disease: routine practice across nine European countries

Jürgen Stein^a, Palle Bager^b, Ragnar Befrits^c, Christoph Gasche^d, Maja Gudehus^e, Eric Lerebours^f, Fernando Magro^g, Fermin Mearin^h, Daniell Mitchell^e, Bas Oldenburgⁱ and Silvio Danese^j

Background and objectives Anaemia and iron deficiency (ID) are common complications in inflammatory bowel disease (IBD). In patients undergoing iron therapy, intravenous iron supplementation is recommended in preference to oral therapy. This study evaluated routine practice in the management of IBD-associated anaemia and ID to verify implementation of international treatment guidelines.

Materials and methods Gastroenterologists from nine European countries ($n=344$) were surveyed about their last five IBD patients treated for anaemia ($n=1404$). Collected information included tests performed at anaemia diagnosis, haemoglobin (Hb) levels and iron status parameters, the anaemia treatment given and, if applicable, the iron administration route.

Results Selection of diagnostic tests and treatment for IBD-associated anaemia varied considerably across Europe. Anaemia and iron status were mainly assessed by Hb (88%) and serum ferritin (75%). Transferrin saturation was only tested in 25% of patients. At diagnosis of anaemia, 56% presented with at least moderate anaemia ($Hb < 10$ g/dl) and 15% with severe anaemia ($Hb < 8$ g/dl). ID (ferritin < 30 ng/ml) was detected in 76%. Almost all patients (92%) received iron supplementation; however, only 28% received intravenous iron and 67% oral iron. Management practice was similar in 2009 and 2011.

Introduction

Anaemia, a common complication in inflammatory bowel disease (IBD), affects quality of life and triggers hospitalization and morbidity in IBD patients [1–3]. Iron deficiency (ID) is the main cause of IBD-associated anaemia [4,5] and is reported in 36–90% of patients [4–6]. Notably, even without anaemia, ID can impair physical performance [7].

Whereas iron stores are depleted (absolute ID) because of dietary restrictions, malabsorption and/or intestinal bleeding, inflammatory disease additionally affects the availability of iron for effective haematopoiesis by hepcidin-mediated sequestration of iron in the iron stores [7,8].

Given the high prevalence of ID and anaemia, regular assessment of iron status in all patients with IBD is recommended [4]. Diagnostic criteria for anaemia are the

Conclusion In clinical practice, most IBD patients received oral iron even though this administration route may aggravate the disease, and despite international guidelines recommending intravenous administration as the preferred route. The high frequency of ID suggests insufficient monitoring of iron status in IBD patients. There is a need to increase awareness and implementation of international guidelines on iron supplementation in patients with IBD. *Eur J Gastroenterol Hepatol* 25:1456–1463 © 2013 Wolters Kluwer Health | Lippincott Williams & Wilkins.

European Journal of Gastroenterology & Hepatology 2013, 25:1456–1463

Keywords: intravenous iron, iron deficiency, iron-deficiency anaemia, iron replacement therapy

^aInterdisciplinary Crohn Colitis Centre Rhein-Main, Frankfurt am Main, Germany, ^bDepartment of Hepatology and Gastroenterology, Aarhus University Hospital, Aarhus, Denmark, ^cDepartment of Gastroenterology, Karolinska University Hospital, Stockholm, Sweden, ^dDepartment of Gastroenterology and Hepatology, Medical University of Vienna, Vienna, Austria, ^eVifor Pharma, Glattpburg, Switzerland, ^fDepartment of Gastroenterology, Hospital Charles Nicolle, Rouen, France, ^gDepartment of Pharmacology and Therapeutics, Institute for Molecular Cell Biology, University of Porto, Porto, Portugal, ^hDepartment of Gastroenterology, Centro Médico Teknon, Barcelona, Spain, ⁱDepartment of Gastroenterology and Hepatology, University Medical Center Utrecht, Utrecht, The Netherlands and ^jDepartment of Gastroenterology, Istituto Clinico Humanitas, Milan, Italy

Correspondence to Jürgen Stein, MD, PhD, Interdisciplinary Crohn Colitis Centre Rhein-Main, Schifferstrasse 59, 60594 Frankfurt, Germany
Tel: +49 69 9055978 10; fax: +49 69 9055978 29;
e-mail: j.stein@em.uni-frankfurt.de

Received 14 June 2013 Accepted 10 August 2013

minimum haemoglobin (Hb) and haematocrit levels specified by the WHO [9]. Absolute ID can be diagnosed on the basis of low serum ferritin levels (< 30 ng/ml); however, acute-phase reactions or hepcidin-mediated iron sequestration may result in falsely normal or elevated ferritin levels [4,7,10]. A more accurate marker for the availability of sufficient iron is transferrin saturation (TSAT) greater than 16–20% [3,4,10,11].

Iron supplementation is recommended in all cases of iron-deficiency anaemia and should also be considered for cases of ID without manifest anaemia [3,4,10]. Whereas some patients may respond to oral iron supplementation, its effectiveness is limited by poor absorption, gastrointestinal adverse events [12,13] and potential exacerbation of IBD [5,14]. Randomized studies have shown that intravenous (i.v.) iron is at least

as effective as oral iron, delivers faster response rates and is better tolerated than oral iron [4,10,15–17].

This cross-sectional study evaluated routine practice in the diagnosis and treatment of IBD-associated anaemia and ID, and the implementation of anaemia treatment guidelines into practical management.

Materials and methods

Study populations

Gastroenterologists from nine European countries were selected at random to report data on their last five IBD patients treated for anaemia within the preceding 6 months. Experienced gastroenterologists were identified and contacted by a market research agency according to the following inclusion criteria: spending over 50% of working hours on patient care and personally seeing and treating more than 20 patients with gastrointestinal disorders per month including more than five IBD patients, at least three of whom had received treatment for anaemia. Data were collected in two waves: from June to September 2009 in France (FR), Germany (DE), Spain (SP), Switzerland (CH) and the United Kingdom (UK) (wave 1), and from August to September 2010 in Austria (AT), Italy (IT), The Netherlands (NL) and Sweden (SE) (wave 2).

An additional data set was collected in FR, DE, SP, CH and UK about 2 years after the first survey (June–August 2011). This data set was not included in the main analysis, but used only for comparison with the corresponding data set from wave 1 to assess whether routine medical practice changed over time.

Data collected from patient records

Patient data were collected online, with gastroenterologists using data from patient records to complete the survey. Demographic data included sex, age, weight, height, dietary habits, comorbidities and other conditions. Data on anaemia management covered the performed diagnostic tests, levels of Hb, ferritin and TSAT at the time of anaemia diagnosis and selected anaemia treatments. For all iron-treated patients, information on the iron administration route (oral, intramuscular, i.v.) and the type of specialist who initiated the treatment was collected. During wave 1 only, additional details on iron therapy including reasons for prescription were recorded. In wave 2, red blood cell (RBC) transfusions were evaluated in more detail.

To avoid perceived ambiguity in some questions posed in the first wave and to better reflect time frames reported by physicians in respect of the treatments provided, some questions were rephrased in the second wave. The question on 'current' anaemia treatment (wave 1) was extended to include 'current or last treatment' in wave 2 and the question as to whether a patient had 'ever' received RBC transfusion (wave 1) was limited to 'during the last 12 months' in wave 2.

Data collected in the physician self-reporting section

In the first wave, participating gastroenterologists were asked to characterize themselves by defining their own routine practice in terms of Hb cut-off levels applied for the diagnosis of anaemia and for the initiation of drug treatment, respectively, minimum target Hb levels for anaemia treatment in IBD patients and primary and secondary treatment objectives when prescribing an iron product.

Data analysis

Results are presented for individual countries and all nine countries combined. Alternatively, data from wave 1 or wave 2 countries only were combined as indicated. Where appropriate, patients not undergoing current treatment (wave 1 only) were censored from the analysis to allow better comparability of results of the two waves, as indicated. All collected data were subject to a plausibility check looking for dates and elapsed times that were not in chronological order or were inconsistent with other data, as well as incorrect units or test values with very high or very low results. In addition, randomly selected physicians (10% of all participants) were asked to complete the questionnaire a second time. Entries that did not pass the plausibility check or differed between first and second completion were verified by phone interviews.

As the number of patients receiving i.v. iron was low, specific information on the use of this supplementation route (e.g. reasons for choice of i.v. iron) was gathered from an extended patient sample. For this purpose, each gastroenterologist was asked to include up to two additional i.v. iron-treated patients when completing the survey. However, these additional patients were not included in any of the other analyses.

Results

Baseline patient characteristics

In total, 344 gastroenterologists participated, of whom 268 were hospital-based only. Seventy-six gastroenterologists in five countries (AT, FR, DE, SP, CH) were either entirely office based or both office and hospital based. Details on 1404 patients with IBD-associated anaemia (mean age 45 years) were reported (Table 1). There was an almost equal sex distribution in the patient population (men: 48%; range: 37–56%). A minority of patients presented with comorbidities such as metabolic disorders (8.5%; range: 1–14%), gastrointestinal disorders other than IBD (1.1%; range: 4–14%) or cardiovascular disorders other than chronic heart failure (3%; range: 1–10%). The average BMI was 24 (range: 22–25).

Assessment of anaemia and iron status in patients with inflammatory bowel disease

The diagnosis of anaemia was made or confirmed by assessment of Hb levels in 88% (range: 71–99%) of the

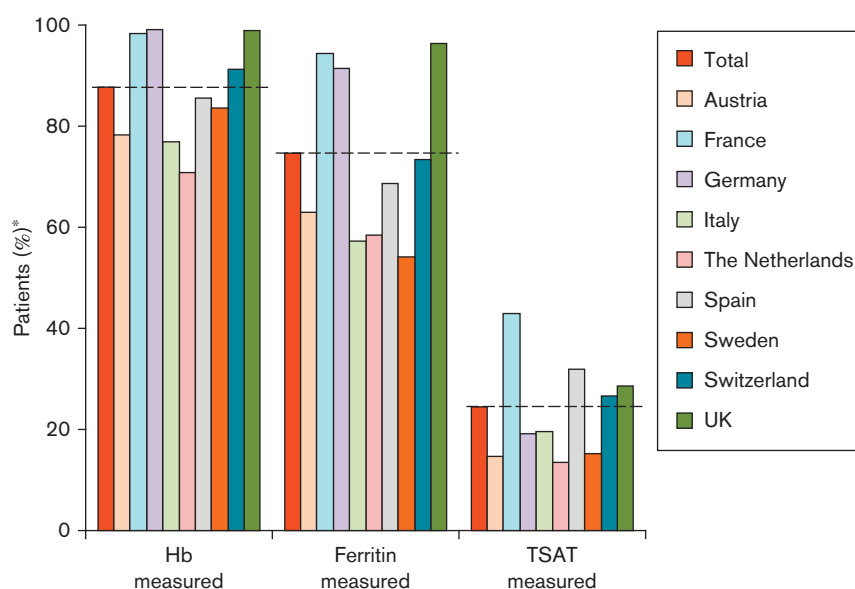
Table 1 Baseline patient characteristics

	FR	DE	SP	CH	UK	AT	IT	NL	SE	Total/mean
Patients (n) ^a	177	208	201	79	164	151	250	89	85	1404
Demographics										
Male (%)	46	43	56	52	37	52	54	40	51	48
Age (mean) (years)	39	45	50	41	39	43	52	41	47	45
Hb levels and iron status at diagnosis										
Hb (g/dl) ^a										
Mean	9.2	9.3	9.8	10.5	9.0	8.9	9.7	8.7	9.9	9.4
Median	9.4	9.6	10.1	10.8	9.0	9.0	10.0	8.7	9.9	9.7
Ferritin (ng/ml) ^a										
Mean	45.2	40.0	18.6	36.8	17.5	26.6	52.5	24.2	41.6	34.2
Median	20.0	15.5	12.0	12.0	11.0	14.0	13.0	12.0	10.5	13.0
TSAT (%) ^a										
Mean	17.7	22.6	18.9	9.8	22.2	12.3	30.6	16.8	11.3	19.8
Median	16.5	19.5	14.0	9.0	15.0	9.5	33.0	10.5	7.0	15.0

AT, Austria; CH, Switzerland; DE, Germany; FR, France; IT, Italy; NL, The Netherlands; SE, Sweden; SP, Spain; TSAT, transferrin saturation; UK, United Kingdom.

^aPatients without current treatment (only in wave 1) were censored from the analysis.

Fig. 1



Diagnostic tests used to assess/confirm anaemia and iron status in patients with inflammatory bowel disease-associated anaemia.

Gastroenterologists mainly tested haemoglobin (Hb) concentration and serum ferritin levels in their patients to assess/confirm anaemia. Transferrin saturation (TSAT) was only tested in 25% of patients. *Patients without current treatment (only in wave 1) were censored from the analysis. Hb, haemoglobin; TSAT, transferrin saturation. Dotted line indicates the total for all patients across countries.

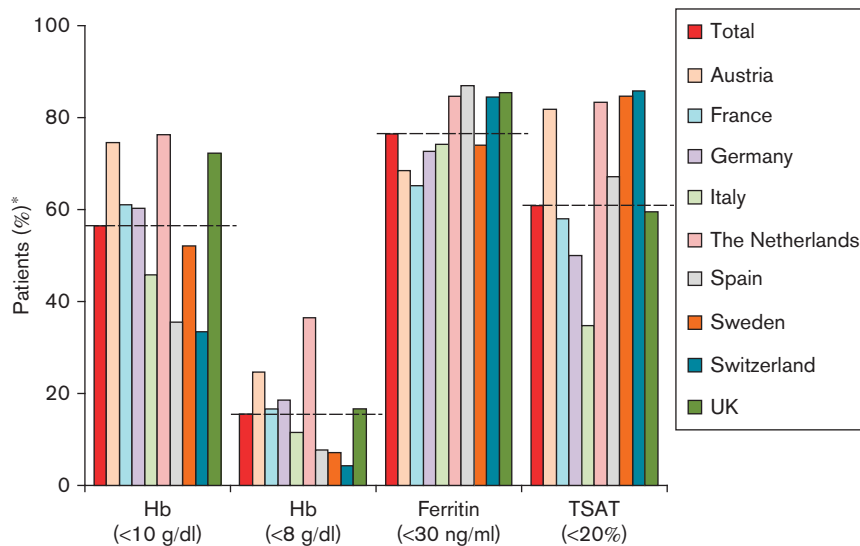
study population (Fig. 1). Percentages were highest in the UK, FR and DE, where Hb was tested in more than 98% of patients, and lowest in NL (71%), IT (77%) and AT (78%). Among entirely hospital-based gastroenterologists, Hb was less frequently assessed than by those at least partially office based (86.1 vs. 93.3%; $P < 0.001$).

The mean Hb at the time of anaemia diagnosis was 9.4 g/dl (range: 8.7–10.5 g/dl) (Table 1). Of those patients tested for Hb, a total of 56% (range: 33–76%) presented with moderate to severe anaemia (Hb < 10 g/dl [4,18]), which, according to current guidelines [4,10], is an absolute indication for i.v. iron (Fig. 2). Percentages varied across countries, being the highest in NL (76%), AT (75%) and

the UK (72%), and the lowest in CH (33%), SP (35%) and IT (46%). Severe anaemia (Hb < 8 g/dl [18]) was diagnosed in 15% of patients (range: 4–37%). Other tests performed to diagnose or confirm anaemia were haematocrit (76%; range: 45–99%) and RBC indices, such as mean corpuscular volume (78%; range: 45–100%).

Iron status assessment was mainly based on serum ferritin measurement (75%; range: 54–96%). As expected in an IBD patient population, a high percentage (76%; range: 65–87%) of patients presented with absolute ID (ferritin < 30 ng/ml [4]) and in half of the patients, serum ferritin was less than or equal to 13 ng/ml (median value; Table 1). Mean serum ferritin at initial diagnosis

Fig. 2



Proportion of patients with low levels of haematologic parameters at diagnosis of anaemia. More than half of the patients (56%) presented with at least moderate anaemia (Hb < 10 g/dl) at the time of diagnosis and 15% with severe or life-threatening anaemia (Hb < 8 g/dl). Ferritin (< 30 ng/ml), indicating insufficient iron stores, was detected in 76% and TSAT (< 20%), indicating insufficient available iron for effective erythropoiesis, in 61% of tested patients. *Patients without current treatment (only in wave 1) were censored from the analysis. Hb, haemoglobin; TSAT, transferrin saturation. Dotted line indicates the total for all patients across countries.

was 34 ng/ml (range: 18–53 ng/ml). TSAT, a marker for iron availability, was tested only in a quarter of patients (25%; range: 13–43%). Of all nine countries, FR had the highest percentage of patients tested for TSAT (43%), followed by SP (32%) and the UK (29%), whereas TSAT assessment was uncommon in NL (13%) and SE (15%). Mean TSAT of tested patients was 19.8% (range: 9.8–30.6%). Among tested patients, 61% (range: 35–86%) had TSAT less than 20%, indicating absolute or functional ID [19], and in half of the patients TSAT was 15% or less (median value; Table 1). The rates of iron status assessment were comparable for hospital-based and office-based gastroenterologists (ferritin 74.1 vs. 76.3%, TSAT 23.9 vs. 26.8%).

Treatment of anaemia and iron deficiency

Consistent with the high prevalence of ID, almost all patients (92%; range: 84–100%) received iron as current or last treatment (Fig. 3). A minority of patients (17%; range: 7–29%) had received RBC transfusions at some stage (wave 1) or during the last 12 months (wave 2). Erythropoiesis-stimulating agents were administered to 13% of patients, often in combination with iron therapy. Notably, national variations showed either low rates of erythropoiesis-stimulating agent administration (2–8% of patients in NL, UK, DE, SE, FR) or rates of ~25% (24–26% of patients in IT, SP, AT). Iron was administered more frequently by entirely or partially office-based gastroenterologists (98.0 vs. 91.6%; $P < 0.001$), whereas RBC transfusions were administered more frequently by

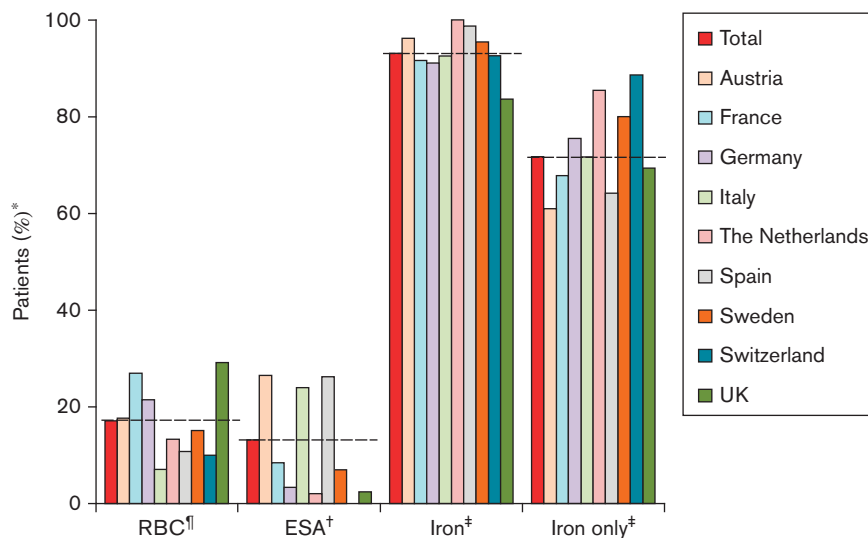
gastroenterologists who were entirely hospital based (18.7 vs. 11.7%; $P < 0.005$).

Whereas the majority of patients were treated with oral iron (67%; range: 24–83%), only a minority received i.v. iron supplementation (28%; range: 16–72%) (Fig. 4). In only two countries, SE and CH, the prescription of i.v. iron was found to be more common than prescription of oral iron (72 and 52%, respectively). In most cases, iron was provided as monotherapy (72%; range: 61–89%).

Wave 1 (FR, DE, SP, CH, UK) included analysis of additional details on iron therapy. For the majority of patients in wave 1, the first iron therapy prescribed was an oral formulation (82% of first prescriptions; range: 22–96%), the only exception being CH, where 78% of first prescriptions were for an i.v. iron formulation. At commencement of iron therapy, the average Hb, ferritin and TSAT levels were 9.5 g/dl (range: 9.2–10.2 g/dl), 31.4 ng/ml (range: 18.6–47.7 ng/ml) and 19.9% (range: 11.3–23.2%), respectively. A comparison of current versus previous iron treatment showed that iron supplementation was only rarely switched from one route to another. Only 23% switched iron therapy, most commonly from oral to i.v. iron (in 47% of cases).

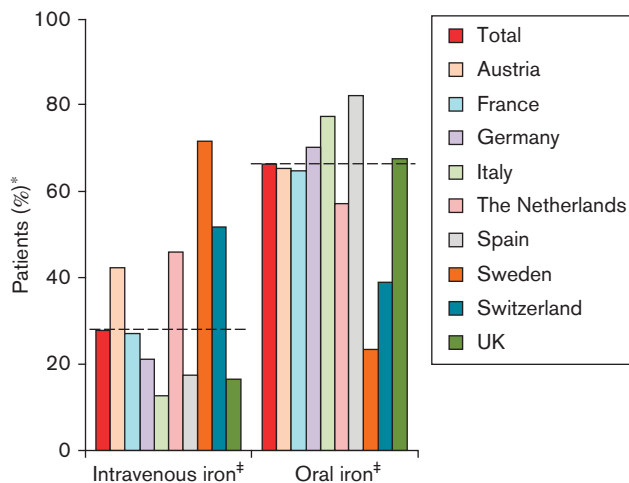
The reasons for treatment selection were surveyed during wave 1 and analysed in the extended patient sample. 'Rapid onset of action' was stated by 52% of the physicians as the main reason for choosing i.v. iron administration, whereas 'familiarity' and 'easy/convenient

Fig. 3



Treatments used for inflammatory bowel disease-associated anaemia. Almost all patients (92%) received iron supplementation as current or last treatment. Iron was mostly administered as the sole anaemia treatment (in 76% of patients). RBC transfusions and erythropoiesis-stimulating agents were included only in a minority of patients. *Patients without current treatment (only in wave 1) were censored from the analysis; [‡]current (wave 1) or last (wave 2) treatment received; [†]patients who received RBC transfusion at some stage (wave 1) or during the last 12 months (wave 2); [‡]current treatment (wave 1) or treatment received during the last 12 months (wave 2). RBC, red blood cells; ESA, erythropoiesis-stimulating agents. Dotted line indicates the total for all patients across countries.

Fig. 4



Administration routes used for iron therapy of anaemic inflammatory bowel disease patients. A large majority of patients received oral iron. An intravenous preparation was used in only 28% of iron-treated patients. Exceptions were Sweden and Switzerland, where 72 and 52% of iron-treated patients, respectively, received intravenous iron. *Patients without current treatment (only in wave 1) were censored from the analysis. [‡]Current (wave 1) or last (wave 2) treatment received. Dotted line indicates the total for all patients across countries.

administration' were the main reasons for selecting an oral iron preparation (52 and 48%, respectively). Iron treatment was most commonly initiated by gastroenterologists

(95% of i.v. and 96% of oral iron treatments) and only rarely by a general practitioner.

The criteria for anaemia diagnosis varied considerably, with participating gastroenterologists (surveyed in wave 1: FR, DE, SP, CH, UK) applying Hb cut-off levels of less than 12.2 g/dl (range: 11.8–13.0 g/dl) in male patients and less than 11.2 g/dl (range: 11.0–12.0 g/dl) in female patients. Self-reported Hb cut-off levels prompting treatment initiation were 11.0 g/dl (range: 10.5–12.4 g/dl) and 10.3 g/dl (range: 9.9–11.3 g/dl) for male and female patients, respectively. The mean target Hb levels were 12.3 g/dl (range: 11.8–13.7 g/dl) and 11.6 g/dl (range: 11.2–12.7 g/dl) for male and female patients, respectively. Gastroenterologists based in CH reported the highest values for all three Hb thresholds. For the large majority of gastroenterologists, correction of Hb/ferritin values and improvement in anaemia symptoms were the two primary treatment objectives. Notably, 76% of the gastroenterologists stated the correction of Hb levels as their primary goal of therapy, whereas only 23% prioritized the normalization of ferritin levels.

Analysis of treatment by Hb category indicated oral iron as most frequent first-line therapy in anaemic patients with higher Hb levels (91% of iron-treated patients with initial Hb levels > 10 g/dl received oral iron), whereas i.v. iron was increasingly preferred in patients with more markedly reduced Hb levels (48% of patients with initial Hb levels < 8 g/dl received i.v. iron).

Detailed questions on the use of RBC transfusion were asked during wave 2 (AT, IT, NL, SE). Among wave 2 countries, an average of 12% of patients (range: 7–18%) had received an RBC transfusion in the last 12 months before the survey. The majority (80%; range: 67–100%) of these patients received the transfusion as an emergency administration because of blood loss. Although in most cases (59%), emergency transfusions were triggered by blood loss directly related to IBD, 21% of transfusions were necessitated because of other conditions. Notably, in 20% of transfused patients, transfusion had been considered a regular treatment option (AT: 33%; IT: 0%; NL: 25%; SE: 15%).

Comparison of anaemia management in 2009 and 2011

A follow-up survey was conducted in wave 1 countries (FR, DE, SP, CH and UK) in 2011, in which 710 cases of IBD-associated anaemia were reported by 142 gastroenterologists. The patient population analysed in this follow-up survey was comparable with that included in the initial survey, with a similar sex and age distribution (47% men, mean age 40 years). The majority (68%) of the surveyed gastroenterologists were hospital based only, whereas 32% were at least partially office based.

As in the initial survey, the most frequently used parameters for the assessment of anaemia and iron status were Hb and serum ferritin (Table 2). The rate of Hb testing in anaemia diagnosis was almost identical to 2009 (94 vs. 95%), whereas serum ferritin was less frequently assessed (69 vs. 86%). TSAT was even less commonly used than in 2009 (23 vs. 30%). The mean values for Hb,

serum ferritin and TSAT at initial diagnosis were comparable in the two surveys, but the percentage of patients presenting with severe or life-threatening anaemia (Hb \leq 8 g/dl) was higher in 2011 compared with 2009 (19 vs. 14%). As in 2009, the large majority of patients were iron-deficient at the time of diagnosis, with serum ferritin levels 30 ng/ml or less and TSAT 20% or less (in 79 and 89% of tested patients, respectively).

At the time of the survey, 83% of patients (range: 61–94%) were treated for anaemia (vs. 2009: 71%; range: 59–79%) and almost all of these (96%; vs. 2009: 92%) received iron therapy, mainly as monotherapy (84%; vs. 2009: 78%). The majority (68%) of iron-treated patients received oral iron. Compared with 2009, the number of iron-treated patients receiving i.v. iron had slightly increased but the proportion remained low (32% vs. 2009: 26%).

Discussion

This study assessing routine management of IBD-associated anaemia and ID in Europe showed a high frequency of absolute ID (76%) and severe anaemia (15%), suggesting insufficient monitoring and repletion of iron status in IBD patients diagnosed with anaemia.

Guidelines recommend an anaemia workup including serum ferritin and TSAT assessment if Hb is below normal (12 g/dl in nonpregnant women, 13 g/dl in men) [4]. In practice, iron status assessment is mainly based on serum ferritin, whereas TSAT is underused as a diagnostic marker. However, in patients with chronic disease and a high risk of inflammatory reactions, TSAT may be a more reliable iron status marker than the acute-phase protein serum ferritin [19] and TSAT less than 20% is related to both absolute and functional ID.

The study also shows that management of IBD-associated anaemia in Europe continues to rely on oral iron preparations (except in SE and CH). Although oral iron may be used in patients with mild anaemia, national (UK) and international guidelines stress the associated risk that oral iron may be poorly tolerated and may exacerbate symptoms [4,10,20]. Accordingly, and on the basis of the results of clinical comparative trials [15–17], current international guidelines and European consensus recommend i.v. iron replacement therapy as the preferred route of iron administration in IBD patients, particularly in cases of severe anaemia (< 10 g/dl) and intolerance or lack of response to oral iron [4,10]. The results of a study in CH, showing that in 2009, ~40% of iron-treated IBD patients had received i.v. iron (i.e. 10.1% of all patients) [21], correlate well with the 52% reported here. In line with current guidelines, RBC transfusions were mainly used as an emergency option. However, in AT and NL, transfusions were considered a regular treatment option for 30% of RBC-treated patients despite the fact that RBC transfusions elevate Hb only transiently [22] and are associated with several risks [23,24]. Although the sample size for this

Table 2 Anaemia treatment practice over time

	2009 (N=829) ^a	2011 (N=710)
Used diagnostic tests (%) ^b		
Hb	95 (86–99)	94 (86–97)
Ferritin	86 (69–96)	69 (52–80)
TSAT	30 (19–43)	23 (8–33)
Hb and iron status at initial diagnosis of anaemia		
Mean Hb (g/dl)	9.4 (9.0–10.5)	9.3 (8.9–10.2)
Mean ferritin (ng/ml)	32 (18–45)	28 (17–43)
Mean TSAT (%)	19.0 (9.8–22.6)	13.1 (9.2–21.4)
% below cut-offs ^c		
Hb \leq 10 g/dl	55 (33–72)	64 (42–81)
Hb \leq 8 g/dl	14 (4–18)	19 (7–26)
Ferritin \leq 30 ng/ml	78 (65–87)	79 (73–90)
TSAT \leq 20%	62 (50–86)	89 (53–100)
Used treatment options (%) ^d		
Iron therapy	92 (84–99)	96 (87–100)
Iron monotherapy ^e	78 (66–97)	84 (78–91)
Intravenous iron	26 (18–56)	32 (16–79)
ESA	10 (0–26)	3 (0–13)
RBC	21 (10–29)	17 (11–22)

Data shown for all countries combined and range across countries.

ESA, erythropoiesis-stimulating agent; Hb, haemoglobin; RBC, red blood cell; TSAT, transferrin saturation.

^aPatients without current treatment (only in wave 1) were censored from the analysis.

^b% of all patients.

^c% of tested patients.

^d% of treated patients.

^e% of iron-treated patients.

analysis was rather small (59 patients), analysis of an additional 94 RBC-treated patients in the follow-up survey in 2011 confirmed this observation (data not shown).

The follow-up survey conducted in 2011 (i.e. 2 years after the initial survey in 2009) showed no significant changes in routine management of IBD-associated anaemia and ID. TSAT was still being underused and there was a decrease in the frequency of serum ferritin assessment. Notably, the percentage of patients presenting with severe or life-threatening anaemia at diagnosis was even higher in 2011 compared with the initial survey (19 vs. 11%) and more patients presented with TSAT below normal (89 vs. 61%). Most iron-treated patients still received oral iron, whereas the use of i.v. iron had increased only slightly compared with 2009. Despite publication of additional data on effective anaemia correction with i.v. iron [25], more time and an increase in awareness may be needed to establish guidelines in routine clinical practice. Thus, it would be of interest to repeat this survey with a longer time interval between analyses.

Some caution is required in generalizing these study results as only data of patients with diagnosed and treated anaemia were analysed and the study was designed as a brief assessment of routine anaemia diagnosis and treatment. Therefore, information on comorbidities, but not clinical history, disease specifics and activity, or other causes of anaemia (e.g. vitamin B12 or folate deficiency), was collected. Although the majority of anaemic IBD patients may benefit from i.v. iron supplementation, the decision to start iron replacement therapy should include consideration of individual factors in addition to Hb and iron status.

Notably, the use of diagnostic tests and anaemia treatment options was comparable for hospital-based and office-based gastroenterologists. Even statistically significant differences were of small magnitude, particularly in comparison with the differences between countries.

Conclusion

Despite considerable variations in medical practice in the management of IBD-associated anaemia across different European countries, consistent trends could be observed. On the one hand, there is still a widespread reliance on oral iron preparations despite the fact that these are known to be problematic in IBD patients, whereas on the other, i.v. iron is still markedly underused. In addition, the diagnosis of ID continues to rely largely on serum ferritin measurements, whereas TSAT, a more reliable diagnostic marker of iron status in IBD patients, is underused. Accordingly, there is a clear need to increase awareness and implementation of evidence-based recommendations on the management of anaemia and ID in patients with IBD.

Acknowledgements

Preparation and conduct of the study have been supported by Vifor Pharma (Glattbrugg, Switzerland).

All authors contributed to the interpretation of data, critical revision of the manuscript and important intellectual content independently and made the decision for submission independently. Daniell Mitchell contributed further to the study concept and design and analysis of data. Surveys of the first and second waves were conducted by A A Healthcare Market Research (UK) and the follow-up survey was conducted by EUMARA AG (Germany). Medical writing support in the preparation of the manuscript was provided by Bettina Dümmler, SFL Regulatory Affairs & Scientific Communication (Switzerland) and funded by Vifor Pharma. Janet Collins, Interdisciplinary Crohn Colitis Centre Rhein-Main, performed an interim language revision.

Conflicts of interest

The authors have served as advisory board members for Vifor Pharma Ltd (Glattbrugg, Switzerland). Jürgen Stein has received speaker honoraria and research funding from Vifor Pharma, Pharmacosmos A/S and Medici. Christoph Gasche has received research funding and speaker honoraria from Vifor Pharma, Pharmacosmos A/S, Fresenius Medical Care and Renapharma Sweden. Fermin Mearin has received speaker honoraria from Vifor Pharma. Bas Oldenburg has received research funding from Vifor Pharma. Maja Gudehus and Daniell Mitchell are employees of Vifor Pharma. For the remaining authors there are no conflicts of interest.

References

- Gisbert JP, Gomollon F. Common misconceptions in the diagnosis and management of anemia in inflammatory bowel disease. *Am J Gastroenterol* 2008; **103**:1299–1307.
- Graff LA, Vincent N, Walker JR, Clara I, Carr R, Ediger J, et al. A population-based study of fatigue and sleep difficulties in inflammatory bowel disease. *Inflamm Bowel Dis* 2011; **17**:1882–1889.
- Stein J, Hartmann F, Dignass AU. Diagnosis and management of iron deficiency anemia in patients with IBD. *Nat Rev Gastroenterol Hepatol* 2010; **7**:599–610.
- Gasche C, Berstad A, Befrits R, Beglinger C, Dignass A, Erichsen K, et al. Guidelines on the diagnosis and management of iron deficiency and anemia in inflammatory bowel diseases. *Inflamm Bowel Dis* 2007; **13**:1545–1553.
- Kulnigg S, Gasche C. Systematic review: managing anaemia in Crohn's disease. *Aliment Pharmacol Ther* 2006; **24**:1507–1523.
- Semrin G, Fishman DS, Bouvaros A, Zholudev A, Saunders AC, Correia CE, et al. Impaired intestinal iron absorption in Crohn's disease correlates with disease activity and markers of inflammation. *Inflamm Bowel Dis* 2006; **12**:1101–1106.
- Weiss G, Goodnough LT. Anemia of chronic disease. *N Engl J Med* 2005; **352**:1011–1023.
- Fillet G, Beguin Y, Baldelli L. Model of reticuloendothelial iron metabolism in humans: abnormal behavior in idiopathic hemochromatosis and in inflammation. *Blood* 1989; **74**:844–851.
- WHO. *Iron deficiency anaemia: assessment, prevention, and control. A guide for programme managers*. Geneva, Switzerland: WHO 2001; Available at: http://www.who.int/nutrition/publications/en/ida_assessment_prevention_control.pdf. [Accessed 11 September 2013].
- Van Assche G, Dignass A, Bokemeyer B, Danese S, Gionchetti P, Moser G, et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 3: special situations. *J Crohns Colitis* 2013; **7**:1–33.
- Beguin Y. Prediction of response and other improvements on the limitations of recombinant human erythropoietin therapy in anemic cancer patients. *Haematologica* 2002; **87**:1209–1221.

- 12 Alleyne M, Horne MK, Miller JL. Individualized treatment for iron-deficiency anemia in adults. *Am J Med* 2008; **121**:943–948.
- 13 Lyseng-Williamson KA, Keating GM. Ferric carboxymaltose: a review of its use in iron-deficiency anaemia. *Drugs* 2009; **69**:739–756.
- 14 De Silva AD, Tsironi E, Feakins RM, Rampton DS. Efficacy and tolerability of oral iron therapy in inflammatory bowel disease: a prospective, comparative trial. *Aliment Pharmacol Ther* 2005; **22**:1097–1105.
- 15 Kulnigg S, Stoinov S, Simanenkov V, Dudar LV, Karnafel W, Garcia LC, *et al.* A novel intravenous iron formulation for treatment of anemia in inflammatory bowel disease: the ferric carboxymaltose (FERINJECT) randomized controlled trial. *Am J Gastroenterol* 2008; **103**:1182–1192.
- 16 Lindgren S, Wikman O, Befrits R, Blom H, Eriksson A, Granno C, *et al.* Intravenous iron sucrose is superior to oral iron sulphate for correcting anaemia and restoring iron stores in IBD patients: a randomized, controlled, evaluator-blind, multicentre study. *Scand J Gastroenterol* 2009; **44**:838–845.
- 17 Schroder O, Mickisch O, Seidler U, de Weerth A, Dignass AU, Herfarth H, *et al.* Intravenous iron sucrose versus oral iron supplementation for the treatment of iron deficiency anemia in patients with inflammatory bowel disease – a randomized, controlled, open-label, multicenter study. *Am J Gastroenterol* 2005; **100**:2503–2509.
- 18 National Comprehensive Cancer Network Inc. *NCCN practice guidelines in oncology; cancer and chemotherapy-induced anemia – v.1.2013*. Fort Washington, PA, USA: National Comprehensive Cancer Network (NCCN); 2013.
- 19 Wish JB. Assessing iron status: beyond serum ferritin and transferrin saturation. *Clin J Am Soc Nephrol* 2006; **1** (Suppl 1):S4–S8.
- 20 Mowat C, Cole A, Windsor A, Ahmad T, Arnott I, Driscoll R, *et al.* Guidelines for the management of inflammatory bowel disease in adults. *Gut* 2011; **60**:571–607.
- 21 Vavricka SR, Schoepfer AM, Safroneeva E, Rogler G, Schwenkgenks M, Achermann R. A shift from oral to intravenous iron supplementation therapy is observed over time in a large swiss cohort of patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2013; **19**:840–846.
- 22 Osterborg A. Recombinant human erythropoietin (rHuEPO) therapy in patients with cancer-related anaemia: what have we learned? *Med Oncol* 1998; **15** (Suppl 1):S47–S49.
- 23 Spahn DR, Moch H, Hofmann A, Isbister JP. Patient blood management: the pragmatic solution for the problems with blood transfusions. *Anesthesiology* 2008; **109**:951–953.
- 24 Vamvakas EC, Blajchman MA. Transfusion-related mortality: the ongoing risks of allogeneic blood transfusion and the available strategies for their prevention. *Blood* 2009; **113**:3406–3417.
- 25 Evstatiev R, Marteau P, Iqbal T, Khalif IL, Stein J, Bokemeyer B, *et al.* FERGICor, a randomized controlled trial on ferric carboxymaltose for iron deficiency anemia in inflammatory bowel disease. *Gastroenterology* 2011; **141**:846–853.