Current practice in the diagnosis and management of IBD-associated anaemia and iron deficiency in Germany: The German AnaemIBD Study☆

Irina Blumenstein a, Axel Dignass b,c, Stephan Vollmer d, Wolfgang Klemm e, Susanne Weber-Mangal f, Juergen Stein b,g,*

a Medical Dpt. 1, Frankfurt University Hospital, Frankfurt am Main, Germany
b Crohn Colitis Centre Rhein-Main, Frankfurt am Main, Germany
c Agaplesion Markus Hospital, Frankfurt am Main, Germany
d Gastroenterological Practice, Goeppingen, Germany
e Gastroenterological Practice, Cottbus, Germany
f Vifor Pharma Germany GmbH, Munich, Germany
g Hospital Sachsenhausen, Frankfurt am Main, Germany

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Inflammatory bowel disease;
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Abstract

Background/aim: Anaemia is a common complication in inflammatory bowel disease (IBD), frequently resulting from iron deficiency. IBD guidelines advocate intravenous iron administration although some patients respond to oral supplementation. This non-interventional study investigates the current status of anaemia management in German IBD patients.

Methods: Baseline data on pre-study treatment for anaemia were retrospectively analysed in IBD patients with anaemia participating in a prospective trial of the efficacy and safety of ferric carboxymaltose. Data were collected from 55 German gastroenterological centres up to August 2010. Subjects had received care at their centre for at least 12 months prior to baseline.

Abbreviations: IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn’s disease; IC, indeterminate colitis; NIS, non-interventional study; ID, iron deficiency; IDA, iron deficiency anaemia; GPC, German Physician’s Circular; CDAI, Crohn’s Disease Activity Index; CAI, Clinical Colitis Activity Index; ACD, anaemia of chronic disease; ICH, International Conference on Harmonisation; TSAT, transferrin saturation.

☆ The poster publishing data from this study was presented for the first time at the ECCO Congress in February 2013 in Vienna.

* Corresponding author at: Crohn Colitis Centre Rhein-Main, Schifferstrasse 59, 60594 Frankfurt am Main, Germany. Tel.: +49 69 9055978 10; fax: +49 69 9055978 29.
E-mail address: J.Stein@em.uni-frankfurt.de (J. Stein).

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1. Introduction

Anaemia represents the most common systemic complication in inflammatory bowel disease (IBD), affecting 16–68% of patients. Although the cause of anaemia in IBD is multifactorial, iron deficiency (ID) is one of the most prevalent underlying factors and has been shown to be present in 36–90% of patients. Anaemia in IBD has a strong influence on quality of life. Notably, an increase in haemoglobin (Hb) improves quality of life in anaemic IBD patients independent of changes in disease activity.

However, in contrast to patients with chronic kidney disease, anaemic IBD patients are still treated with iron substitution relatively infrequently. For example, in the study of Stein et al. examining anaemia management in IBD patients in seven European countries, only 20–28% of patients received iron supplementation. Voegtlin et al., who acquired data from 125 Swiss patients, reported that biological parameters of iron metabolism were not generally measured before iron supplementation, which was performed in only 40% of patients with iron deficiency anaemia (IDA) in private practices and 43% in university hospitals. Therefore, iron supplementation remains unsatisfactory in IBD patients despite the fact that numerous studies have convincingly demonstrated sufficient iron supplementation to have a positive effect on quality of life by increasing Hb levels and improving non-haematological symptoms of iron deficiency (e.g. hair loss, fatigue, cognitive functions) in both IBD and non-IBD patients.

Recent IBD guidelines recommend that IBD patients should undergo regular assessment for anaemia due to its high prevalence and considerable impact on quality of life and morbidity. The guidelines recommend that iron supplementation should preferably be administered intravenously, even though some patients may respond to orally administered iron. Since these guidelines recommend the regular monitoring of iron stores and limited use of oral iron substitution, we were interested to discover their potential impact on anaemia management in German IBD patients. Here, we present the results of a non-interventional study evaluating current routine practice in the diagnosis and treatment of IBD-associated anaemia and the use of iron therapy in non-hospitalised IBD patients.

2. Patients and methods

2.1. Study design

This report presents a retrospective analysis of baseline data from a single-arm, multicentric, prospective, observational study conducted in 55 German gastroenterological centres, investigating the efficacy and safety of ferric carboxymaltose (ferinject®, Vifor Pharma). The centres were selected on the basis of significant activity in the treatment of patients with inflammatory bowel disease (IBD).

The study started in November 2008 (first patient, first visit) and was terminated in August 2010 (last patient, last visit). Due to the non-interventional character of the study, subjects were treated based on the medical needs of their underlying disease in accordance with therapy requirements published in the German Physician’s Circular (GPC). The initial examination was performed in the respective study centre, obtaining demographic data, clinical characteristics, laboratory data, and status of anti-anaemic treatment during the last 6 months prior to study inclusion. Patients included in the observational study suffered from IBD, either Crohn’s disease (CD) or ulcerative colitis (UC), were at least 18 years of age, had anaemia, defined as Hb <12 g/dl in women and <13 g/dl in men, and had given consent to participate in this study. Furthermore, the patients had received care in their respective centre for at least 12 months prior to inclusion.

The study proposal had been submitted to the respective ethics commission as well as the German Federal Institute for Drugs and Medical Devices (BfArM). The participating investigators were reported to the National Association of Statutory Health Insurance Physicians. The study has been registered and published according to the VFA agreement: http://www.vfa.de/de/arnimittel-forschung/datenbanken-zu-arnimitteln/nisdb/nis-details/_232.

2.2. Assessment of disease activity

Disease activity was assessed using the Crohn’s Disease Activity Index (CDAI) and the Clinical Colitis Activity Index (CAI). Active disease was defined as CDAI ≥ 150 for CD patients and CAI ≥ 5 for UC patients.
2.3. Definition and classification of anaemia

Anaemia was defined, according to World Health Organization (WHO) criteria, as a haemoglobin concentration below 13.0 g/dl for men and 12.0 g/dl for women. In line with the WHO criteria, mild anaemia corresponded to a haemoglobin level ≥10.0 g/dl, moderate anaemia to a haemoglobin level of 8.0–9.9 g/dl, and severe anaemia to a haemoglobin level <8.0 g/dl. Anaemia was classified as iron deficiency anaemia (IDA), anaemia of chronic disease (ACD), or a combination of both (IDA/ACD), according to recently described algorithms. ACD was characterised by low transferrin saturation (TSAT) (<16%) with normal or increased serum ferritin concentration (>100 μg/ml), while IDA required the presence of anaemia associated with low serum ferritin (<30 μg/ml) or a transferrin saturation <16% combined with serum ferritin levels <30 μg/ml. The combination of IDA and ACD was characterised by TSAT <16% and serum ferritin >30 and ≤100 μg/ml. Patients not classifiable according to these definitions were categorised as having "other anaemia".

2.4. Data analysis

Descriptive statistics or frequencies were computed for all data as appropriate. Due to the nature of this non-interventional study, data were not available for all assessments, and thus the sample size was not equal for all parameters for each visit. All statistical methods were based on the International Conference on Harmonization (ICH E9): Guidance for Industry on Statistical Principles for Clinical Trials. Collected data were analysed and reported by SAS software (version 9.2). The analysis was performed in an exploratory manner, using descriptive statistical methods. For the evaluation of differences, a two-sided Student’s t-test with α = 0.05 was applied. In contrast to randomised clinical trials, data collected in a non-interventional, observational study are not controlled, so that a number of data are missing. No statistical measures were taken to compensate for missing data, and missing data representing protocol violations were eliminated from the data set.

3. Results

3.1. Baseline patient characteristics

Of the 55 study centres, 42 provided complete data sets describing 193 cases (safety population) of IBD-associated anaemia, with a median of 5 patients (range 1–13) included per centre. Baseline demographic and disease characteristics are presented in Table 1. In accordance with the average age, most patients were employed (53.4% full-time, 10.9% part-time), 14% of patients were retired and some younger patients were still attending educational institutions (13.0%). In the 12 months previous to the study, the patients had visited their respective centre an average of 10.6 ± 8.7 times.

3.2. Assessment of anaemia and iron status in patients with IBD

Anaemia and iron status were mainly assessed by the measurement of Hb (100% of patients), C-reactive protein (CRP) (97.4%) and serum ferritin (97%). TSAT was tested in 82% of patients (Table 2). Due to the retrospective and observational nature of the analysis, however, data on iron status were not always complete.

According to the respective WHO definitions, anaemia was mild in 147 patients (76.2%), moderate in 29 (15%) and severe in 17 (8.8%), with no difference in severity between patients with Crohn’s disease and those with ulcerative colitis. Age, gender and concurrent therapy with azathioprine had no influence on the prevalence of anaemia, although mean haemoglobin levels were lower in females than in males (9.9 ± 1.5 g/dl versus 10.4 ± 1.4 g/dl, P < 0.016). While patients with Crohn’s disease had Hb, TSAT and CRP values comparable to those of patients with ulcerative colitis, their serum ferritin values were higher (60.8 ± 143.4 versus 36.2 ± 78.8). However, this difference was not significant and most anaemic patients had IDA, followed by IDA/ACD and ACD, respectively (Table 3). ACD was associated with higher CRP values than IDA, although no differences were observed in disease activity scores between patients with ACD and IDA (data not shown). Patients with the combination of IDA and ACD had intermediate CRP values (data not shown).

Since ferritin is recognised to be an acute-phase protein, we further assessed the correlation of ferritin with CRP as well as disease activity. 67% of patients presented with elevated disease activity. However, clinical disease activity showed no correlation to the grade of inflammation as measured by CRP: In patients with elevated disease activity, average CRP values were no different to those observed in patients with normal disease activity (mean: 6.1 mg/dl).

3.3. Treatment during 6 months prior to inclusion

All patients included in the study suffered from anaemia. However, during the 6 months prior to initial examination, over half (56.5%) of the patients had received no anti-anaemic treatment. Of those who had received iron substitution, the most prevalent therapy (56%) was oral iron alone, followed by parenteral iron (15.5% i.v. iron alone, 19.0% i.v. iron in addition to oral iron and 3.6% i.v. iron in addition to transfusions), and 8 patients had been transfused, of whom 4 had also received iron supplementation (1 oral, 3 i.v.). Erythropoiesis stimulating agents had not been given.

A comparison of those patients classified as having severe IDA (subgroup with Hb <8 g/dl) with those found to have moderate/mild IDA (subgroup with Hb 11–12 g/dl in women or 11–13 g/dl in men), revealed the percentage of treated patients to be considerably higher in the severely anaemic (76.5%) than in those with moderate/mild IDA (31%). In all patient subgroups with Hb values of at least 8 g/dl, "no treatment" was the most common option. If treated, patients in all subgroups received oral iron as the preferred route (Table 4). UC patients were more often supplemented than CD patients (UC 51.4%, CD 48.3%), although the difference was not significant. Interestingly, however, we observed a gender
difference: While the frequency of supplementation of female IBD patients did not differ between CD and UC (59.7 vs. 65.1%), male patients with UC were substituted more often than those with CD (58.3 vs. 43.9%). Table 5 summarises anti-anaemic pre-treatment according to anti-inflammatory treatment.

4. Discussion

The present study provides the most comprehensive available record of management reality of IDA in IBD patients in Germany. It reveals two crucial findings which we consider to be of clinical importance. Firstly, the high prevalence of absolute iron deficiency (76%) and moderate to severe anaemia (56%) in patients with IBD suggests insufficient monitoring of iron status or inadequate implementation of effective iron replacement therapy. Secondly, although i.v. administration of iron is the recommended treatment of IBD-associated iron deficiency anaemia, most patients with IBD and anaemia, if treated, receive oral iron in current practice.

Anaemia and iron status were most commonly assessed using Hb (98% [81–99%]). Current guidelines recommend anaemia workup (including serum ferritin, TSAT and CRP) if Hb is below 12 g/dl (female, non-pregnant) or 13 mg/dl (male). However, while serum ferritin was determined in 95% [94–96%], TSAT values were measured only in 61% [35–86%] of patients, a rate which is, however, higher than those reported in recent studies of a Swiss IBD cohort and of current practice in other European countries. TSAT is a marker of iron availability for erythropoiesis, and although limited acute-phase reactivity is known to be present, it is nonetheless probably a more accurate iron status parameter in the presence of chronic inflammatory disease than the acute-phase protein serum ferritin. Absolute and functional iron deficiencies are associated with TSAT values <16%. In light of its superior sensitivity as an iron status marker, TSAT therefore appears to be underdeployed in this context.

In most cases anaemia was mild or moderate (haemoglobin ≥ 10.0 g/dl), concuring with the recent European study in which 56% [33–76%] of IBD patients presented with Hb levels ≥ 10 g/dl. However, since both study populations included only outpatients, cases of more severe anaemia requiring hospitalisation were probably missed. Severe or life-threatening anaemia (Hb < 8 g/dl) was diagnosed in 15% of all patients.

The high prevalence of IDA in both CD and UC may be related to the longer disease course at the time point of anaemia diagnosis, and is in contrast to the situation at disease diagnosis, when anaemia is usually due to isolated ACD. As demonstrated by the study data, IDA was treated only in 34.9% of female and 40.3% of male IBD patients. Bearing in mind that the analysis included only patients attending gastroenterological centres with considerable experience in IBD patient care, and that patients had attended regular consultations (mean: 10.6 visits, ± 8.7) during the year prior to data collection, the rates of treatment initiation for anaemia are strikingly low. In a recently published cross-sectional study from Switzerland, Voegtlin et al. reported 40% and 43% of patients being treated with iron supplements in private practice and university hospitals, respectively. Similar results have most recently been reported in a population-based study from southern Germany, demonstrating a treatment rate of 34.4% at diagnosis. This is somewhat astonishing, considering that anaemia is known to represent the most common systemic complication of IBD. Two factors may explain this finding: Firstly, many physicians apparently still accept the concept of “asymptomatic anaemia”, believing that, since IDA typically develops slowly in IBD, patients can adapt to low haemoglobin levels. They may therefore assume the impact of anaemia on the quality of life of IBD patients to be negligible or non-existent.

Table 1 Baseline patient characteristics.

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Crohn’s disease</th>
<th>Ulcerative colitis</th>
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<tbody>
<tr>
<td><strong>Patients</strong></td>
<td>193 (100%)</td>
<td>115 (59.6%)</td>
<td>77 (39.9%)</td>
</tr>
<tr>
<td>Age (years), mean (min–max)</td>
<td>39 (18–83)</td>
<td>38 (18–81)</td>
<td>41 (19–83)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>79 (41%)</td>
<td>43 (37%)</td>
<td>36 (47%)</td>
</tr>
<tr>
<td>Female</td>
<td>114 (59%)</td>
<td>72 (63%)</td>
<td>41 (53%)</td>
</tr>
<tr>
<td>CDAI (mean, min. and max. values)</td>
<td>202 (42–503)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP (mg/dl) (mean, min. and max. values)</td>
<td>5.9 (0–108)</td>
<td>7.1 (0–108)</td>
<td>4.6 (0–57)</td>
</tr>
<tr>
<td>CRP &lt; 5</td>
<td>144 (76.6%)</td>
<td>87 (78%)</td>
<td>56 (75%)</td>
</tr>
<tr>
<td>CRP ≥ 5</td>
<td>44 (23.4%)</td>
<td>25 (22%)</td>
<td>19 (25%)</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aminosalicylates</td>
<td>89 (46.1%)</td>
<td>55 (47.8%)</td>
<td>34 (44.2%)</td>
</tr>
<tr>
<td>Steroids</td>
<td>84 (43.5%)</td>
<td>55 (47.8%)</td>
<td>29 (37.7%)</td>
</tr>
<tr>
<td>Immunosuppressants</td>
<td>36 (18.7%)</td>
<td>18 (15.7%)</td>
<td>18 (23.4%)</td>
</tr>
<tr>
<td>Biologicals</td>
<td>36 (18.7%)</td>
<td>18 (15.7%)</td>
<td>18 (23.4%)</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>8 (4.1%)</td>
<td>3 (2.6%)</td>
<td>5 (6.5%)</td>
</tr>
<tr>
<td>Antidiarrhoeics</td>
<td>11 (5.7%)</td>
<td>3 (2.6%)</td>
<td>8 (10.4%)</td>
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</table>
However, a number of studies have in fact demonstrated that even "asymptomatic anaemia" has a substantial impact on quality of life, both in patients in general and in IBD patients.5,9,20

Secondly, as mild anaemia is frequently found in IBD patients, treating physicians may regard anaemia as an inevitable concomitant symptom of IBD, and therefore withhold iron supplementation unless anaemia is clinically manifest.21,22

A further surprising finding is that, of those patients treated, the majority had been given oral iron, with only a minority receiving i.v. iron (29% of treated patients). Even in patients with Hb <8 g/dl, oral supplementation was the preferred route (6/13). This is in clear discordance with current international guidelines which, on the basis of clinical comparative trials,23–25 recommend the use of i.v. preparations as first-line therapy in IBD patients, since oral iron is frequently poorly tolerated and can lead to the exacerbation of disease symptoms.10,26,27 Our finding concurs with the results of a recently-published study of current practice in other European countries showing that, except in Sweden (72%) and in Switzerland (52%), only a minority of iron-treated patients received an i.v. iron preparation (16–46%).6 Data for 2009 from a Swiss health insurance company revealed that some 40% of IBD patients treated with iron were substituted with i.v. preparations (10.1% of all patients).28 Data from the same cohort three years later showed a shift from oral to intravenous iron supplementation over time.28

Results of the current study showed that blood transfusions (RBC) were administered to a small minority of patients (<5%), reflecting current guidelines which recommend the use of transfusion only as an emergency option, favouring instead early detection and appropriate timely therapy of anaemia. While transfusions can effect a short-term improvement in Hb concentration, they do not tackle the underlying aetiologies of anaemia. Furthermore, blood transfusions are associated with considerable risks.29,30 None of the patients were treated with erythropoiesis-stimulating agents.

As a new finding, our study data demonstrate a correlation between anti-inflammatory and anti-anaemic treatment. However, of those patients for whom iron therapy was prescribed, the majority received oral iron supplementation, even those undergoing treatment with biologicals. This is not in line with current international guidelines which recommend i.v. replacement as the preferred route of iron administration in case of inflammation.10

5. Conclusions

On the basis of these data, we conclude that the high prevalence of absolute iron deficiency and moderate to severe anaemia in patients with IBD suggests insufficient monitoring of iron status or inadequate implementation of effective iron replacement therapy. Although i.v. administration of iron is the recommended treatment of IBD-associated iron deficiency

<table>
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<th>Table 2</th>
<th>Laboratory data.</th>
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<td></td>
<td>Hb [g/dl]</td>
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<tr>
<td>All patients</td>
<td>Mean ± SD</td>
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<tr>
<td>Crohn’s disease</td>
<td>Mean ± SD</td>
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<tr>
<td>Ulcerative colitis</td>
<td>Mean ± SD</td>
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<tr>
<th>Table 3</th>
<th>Frequencies of IDA, ACD and IDA/ACD according to the setting of care.</th>
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<tr>
<td>Item</td>
<td>IDA n (%)</td>
</tr>
<tr>
<td>UC (79)</td>
<td>49 (62.0)</td>
</tr>
<tr>
<td>CD (115)</td>
<td>89 (76.1)</td>
</tr>
</tbody>
</table>

IDA, ferritin <30 μg/l; ACD, ferritin ≥100 μg/l and CRP ≥5 mg/dl and TSAT <16%; IDA/ACD, ferritin 30–100 μg/l and CRP ≥5 mg/dl and TSAT <16%. Patients not falling into any of these categories are classified as having "other anaemia".

<table>
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<tr>
<th>Table 4</th>
<th>Anti-anaemic pre-treatment during 6 months prior to inclusion, stratified according to haemoglobin subgroups.</th>
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</thead>
<tbody>
<tr>
<td>Haemoglobin</td>
<td>Oral iron alone n (%)</td>
</tr>
<tr>
<td>&lt;8 g/dl</td>
<td>6 (60.0)</td>
</tr>
<tr>
<td>8–9.9 g/dl</td>
<td>14 (51.9)</td>
</tr>
<tr>
<td>≥10 g/dl</td>
<td>27 (62.8)</td>
</tr>
<tr>
<td>∑</td>
<td>47 (56.0)</td>
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</tbody>
</table>
anaemia, most patients with IBD and anaemia receive oral iron in current routine practice. Therefore, awareness of evidence-based recommendations for the management of iron deficiency in patients with IBD needs to be increased.

**Conflict of interest statement**

No conflicts of interest were disclosed to study participants in the informed consent form.

Irina Blumenstein: No conflicts of interest exist.

Axel Dignass: Speaker's honoraria from Vifor International and Vifor Germany.

Stephan Vollmer: No conflicts of interest exist.

Wolfgang Klemm: No conflicts of interest exist.

Susanne Weber-Mangal: Employee Vifor Pharma, Germany.

Jürgen Stein: Consultancy and speaker's honoraria from Vifor International and Vifor Germany.

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**Author contributions**

Irina Blumenstein: contributed to acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content.

Axel Dignass: contributed to acquisition of data; analysis and interpretation of data; critical revision of the manuscript for important intellectual content.

Stephan Vollmer: contributed to acquisition of data; analysis and interpretation of data; critical revision of the manuscript for important intellectual content.

Wolfgang Klemm: acquisition of data; analysis and interpretation of data; critical revision of the manuscript for important intellectual content.

Susanne Weber-Mangal: contributed to analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content, statistical analysis and study supervision.

Jürgen Stein: contributed to acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content and statistical analysis.

All authors read and approved the final manuscript.

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