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Ferric maltol Real-world Effectiveness Study in Hospital practice (FRESH): clinical characteristics and outcomes of patients with inflammatory bowel disease receiving ferric maltol for iron-deficiency anaemia in the UK

JR Fraser Cummings ,[1] Aileen Fraser,[2] Catherine Stansfield,[3] Ian Beales,[4] Shaji Sebastian,[5] Sami Hoque[6]

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For numbered affiliations see end of article.

Correspondence to
Dr JR Fraser Cummings; Fraser.Cummings@uhs.nhs.uk

ABSTRACT

Objective To assess outcomes in patients with iron-deficient inflammatory bowel disease (IBD) treated with ferric maltol in UK real-world practice.

Design/Method This observational, multicentre, retrospective cohort study included adults with IBD and iron-deficiency anaemia (IDA; haemoglobin ≥95 to <120 g/L (women) or ≥95 to <130 g/L (men) plus serum ferritin <30 µg/L or transferrin saturation <20%) who received ferric maltol. Data were extracted from patient records. The primary analysis was the proportion of patients with normalised haemoglobin (≥120 g/L (women); ≥130 g/L (men)) over 12 weeks. Iron indices and safety were assessed.

Results Thirty of 59 patients had data for the primary outcome, 19 of whom (63%) achieved haemoglobin normalisation at week 12. Mean±SD haemoglobin was 127±16 g/L at week 12 (increase of 14±17 g/L from baseline). Overall, 27 patients achieved haemoglobin normalisation by the end of the observation period; mean±SD time to normalisation was 49.5±25.6 days. Nine of 17 patients had normalised serum ferritin (30–300 µg/L) at week 12, and 16 patients had normalised ferritin at the end of the observation period; mean±SD time to normalisation was 71.3±27.6 days. Twenty-four adverse events occurred in 19 patients (32%); most frequent adverse events were abdominal pain or discomfort (n=9) and constipation (n=3).

Conclusion Ferric maltol increases haemoglobin and iron indices and is generally well tolerated in patients with IBD and IDA treated in clinical practice. These real-world data support findings from randomised controlled trials.

Summary box

What is already known about this subject?

- Ferric maltol, an orally available iron complex consisting of a single ferric ion (Fe^{3+}) chelated with high affinity to three maltol molecules, has high bioavailability and is designed to be better tolerated than the currently available oral ferrous (Fe^{2+}) products.
- Ferric maltol was effective at increasing haemoglobin and iron indices and was well tolerated in randomised controlled clinical trials in patients with iron deficiency in mildly to moderately active inflammatory bowel disease (IBD) who had poor tolerance of oral ferrous products (OFPs).

What are the new findings?

- Observational data from routine clinical practice in the UK support findings from these randomised controlled trials, demonstrating that ferric maltol increases haemoglobin and ferritin at 12 weeks in patients with IBD and iron-deficiency anaemia.
- Ferric maltol is well tolerated in routine clinical practice, with no new safety findings and fewer gastrointestinal adverse events than in published real-world data for OFPs.

How might it impact on clinical practice in the foreseeable future?

- The favourable benefit/risk balance of ferric maltol overcomes some of the major barriers to the management of iron-deficiency anaemia seen with other therapies, including the tolerability issues associated with OFPs and the inconvenience associated with intravenous iron therapy.
- Ferric maltol provides an alternative oral therapy for iron-deficiency anaemia in patients with IBD, even in cases of intolerance to OFPs.

INTRODUCTION

The most prevalent extraintestinal complication of inflammatory bowel disease (IBD) is anaemia,[1 2] which is defined by the WHO as haemoglobin <120 g/L in women (<110 g/L in pregnancy) or <130 g/L in men.[3] The physical effects of anaemia, including fatigue, reduced exercise tolerance, headache, dizziness, shortness of breath, tachycardia, reduced cognitive function and depression,

can have a significant impact on activities of daily living, work productivity and overall quality of life.[1 2 4]

One of the main causes of anaemia in IBD is iron deficiency, which results from a combination of impaired iron absorption due to an inflammatory state, reduced nutritional intake and chronic blood loss from the gastrointestinal tract.[1 2] In addition to impeding iron absorption, inflammatory cytokines impair the utilisation of stored iron.[1 2]

Iron replacement can be administered orally or intravenously. Some oral formulations of iron replacement—known as oral ferrous products (OFPs)—are poorly absorbed and are associated with gastrointestinal adverse events, which can limit efficacy and reduce compliance.[1 2] In addition, there is a risk that these formulations exacerbate the underlying disease and they may complicate assessment of IBD by adding to the symptoms.[5]

Intravenous iron can rapidly raise iron levels, particularly when absorption of iron is impaired by inflammation. However, it has resource implications compared with oral products, requires attendance at infusion clinics, which may be difficult or inconvenient for patients, and has the potential for anaphylaxis.[1 2]

Ferric maltol (Feraccru, Shield Therapeutics, London, UK, and Norgine, London, UK) is an iron complex consisting of a single ferric ion (Fe^{3+}) chelated with high affinity to three maltol molecules, which can be taken orally with high bioavailability. It is designed to be better tolerated than the currently available OFPs.[6 7] Randomised controlled clinical trials have demonstrated efficacy, tolerability and safety of ferric maltol in patients with iron deficiency in mildly to moderately active IBD who were documented as having poor tolerance of other OFPs,[4 8] supporting marketing authorisation in Europe in 2016.[9]

The objective of this observational study was to assess outcomes in patients with iron-deficient IBD treated with ferric maltol in real-world practice.

METHODS

FRESH (Ferric maltol Real-world Effectiveness Study in Hospital practice) was an observational, multicentre, retrospective cohort study conducted in seven UK secondary-care gastroenterology centres between 1 August 2017 and 6 June 2018.

The study population included adults with inactive Crohn's disease, ulcerative colitis or unspecified IBD plus iron-deficiency anaemia (IDA), which was defined as haemoglobin ≥95 g/L and <120 g/L for women or ≥95 g/L and <130 g/L for men plus serum ferritin <30 µg/L or transferrin saturation (TSAT) <20%. We included patients who received ferric maltol for IDA in IBD in routine practice, where initiation of ferric maltol was at the discretion of the treating clinician. Patients receiving ferric maltol in a clinical trial and patients requiring corticosteroids to treat IBD flare (determined by the clinician) at the time of ferric maltol initiation were not eligible for inclusion. All patients provided informed consent to participate.

Data were collected from patient records on demographic characteristics, medical history, IDA treatment history, clinical outcomes, haematology and biochemistry measures, adverse events and other tolerability issues relating to ferric maltol.

The primary analysis was the proportion of patients with haemoglobin within the normal range (≥120 g/L for women or ≥130 g/L for men) approximately 12 weeks after initiation of ferric maltol. A window from 10 to 16 weeks was permitted to allow for variation in timing of the routine '12-week' clinic visit. We assumed that the date of treatment initiation was the prescription date where no specific start date was available and that the date of treatment termination was the documented date of clinical decision. Changes in haemoglobin, ferritin and TSAT at weeks 4 and 12, time to normalisation of serum ferritin (defined as a value of 30–300 µg/L) and TSAT (defined as a value of 20%–50%), safety and tolerability of ferric maltol and characteristics of patients enrolled in the study were secondary analyses.

For quantitative variables, distributions and descriptive statistics of central tendency (arithmetic means and medians) and dispersion (SD and IQR) are provided. Nominal variables are described with frequencies, percentages and modes. Ordinal variables are described with medians and IQRs. Patients with missing data for individual variables were not included in the analyses of those variables.

RESULTS

Patient population

We had data on 59 patients (38 female, 21 male). The mean±SD age of patients was 42.9±17.7 years (range 18.5–83.5 years). Twenty-eight patients had Crohn's disease, 28 had ulcerative colitis and 3 had unclassified IBD. The median (IQR) time from diagnosis of IBD to enrolment was 6.7 (2.0–13.5) years and the median (IQR) time from diagnosis of IDA was 13.5 (0.0–46.8) days. Baseline laboratory values are summarised in table 1.

Previous iron therapy

Data on patients' previous experience of iron therapy were available for 25 patients (42%), who had received a total of 27 previous courses of OFPs, including ferrous sulfate (11 courses), ferrous fumarate (2 courses), other OFPs (6 courses), non-prescription oral iron supplements (3 courses) and unknown OFPs (5 courses). The most frequently quoted reasons for discontinuing ferrous sulfate were diarrhoea and nausea, whereas lack of efficacy was the most frequent reason for discontinuing other OFPs. Twenty-four patients (41%) were known to have previously received at least one course of intravenous iron.

Table 1 Baseline laboratory values

Laboratory value	Patients with data* (n)	Mean±SD
Haemoglobin (g/L)	57	111±0.9
Ferritin (µg/L)	46	13.4±14.1
Transferrin saturation (%)	6	7.8±6.8
Folate (µg/L)	24	8.6±5.9
Vitamin B_{12} (pmol/L)	23	354.6±266.7
Mean corpuscular volume (fL)	57	81.9±7.3
Mean corpuscular haemoglobin (pg/cell)	53	27.0±8.3
C reactive protein (mg/L)	41	11.9±18.0
Platelets (10^9/L)	56	370.7±131.4

*Data at the start of ferric maltol treatment were not available for all 59 patients; patients with missing data for individual variables at baseline are not included here.

Reasons for initiating ferric maltol

A range of reasons for initiating ferric maltol were reported in patient records, with multiple reasons recorded for some patients. The most frequently reported reason was intolerance of ferrous sulfate (n=22, 37%). Intolerance of ferrous fumarate (n=15, 25%) and ferrous gluconate (n=18, 31%) was also common. Other recorded reasons included intolerance of oral iron (compound not specified; n=7, 12%), clinician decision (n=6, 10%), ineffective previous treatment (n=5, 9%), anaemia/IDA diagnosis (n=2, 3%), 'intolerance to everything else' (n=1, 2%), and intolerance or refusal of IV treatment (n=1, 2%). For 13 patients (22%), no reason for ferric maltol initiation was recorded.

Efficacy

The primary analysis included 30 patients who had haemoglobin data available at both baseline and week 12. Of these patients, 19 (63%) met the primary outcome of normalised haemoglobin (≥120 g/L for women, ≥130 g/L for men). Mean±SD haemoglobin was 127±16 g/L at week 12, an increase of 14±17 g/L from baseline. As shown in table 2, increases in haemoglobin and ferritin were apparent at week 4 and week 12.

In addition to the 19 patients who met the primary outcome above, 8 further patients achieved haemoglobin normalisation during the study but did not have data available at both baseline and week 12. Among these total 27 patients, the mean±SD time to normalisation was 49.5±25.6 days after initiation of ferric maltol.

Of 17 patients who had a ferritin measurement recorded at week 12, 9 had ferritin in normal laboratory ranges (30–300 µg/L) at this timepoint. Overall, during the study observation period, 16 patients (27%) achieved serum ferritin within normal laboratory ranges, including 7 who did not meet the week 12 ferritin outcome. In these 16 patients, mean±SD time to normalisation of ferritin was 71.3±27.6 days.

Discontinuation of ferric maltol

At week 12, 30 patients (51%) remained on ferric maltol therapy. Four patients (7%) had discontinued treatment by week 4 and a further 10 patients (17%) had discontinued by week 12. In addition, 15 patients (25%) discontinued ferric maltol during the study observation period but the timing of discontinuation was not recorded.

A range of reasons for discontinuing ferric maltol were reported in patient records, with multiple reasons

Table 2 Change in haemoglobin and ferritin from initiation of ferric maltol to weeks 4 and 12

	Patients with data available (n)	Initiation	Endpoint	Change
Week 4				
Haemoglobin (g/L)	17			
Mean±SD		110±7	117±12	8±8
Median (IQR)		109 (104–116)	119 (112–124)	4 (2–15)
Range		98–118	90–137	–8 to 21
Ferritin (µg/L)	7			
Mean±SD		8.7±6.2	20.6±15.3	11.9±12.5
Median (IQR)		8.0 (5.0–8.5)	13.0 (9.5–31.0)	9.0 (3.0–16.0)
Range		4.0–22.0	5.0–45.0	0.0 to 36.0
Week 12				
Haemoglobin (g/dL)	30			
Mean±SD		113±8	127±16	14±17
Median (IQR)		114 (108–118)	125 (118–135)	12 (1–23)
Range		99–129	84–157	–30 to 50
Ferritin (µg/L)	17			
Mean±SD		12.9±6.2	31.9±36.5	19.1±36.0
Median (IQR)		10.5 (8.0–17.0)	15.0 (11.1–38.1)	5.2 (1.0–12.2)
Range		6.8–25.9	7.0–125.0	–8.0 to 111.2

Table 3 Adverse events

	Patients (n=59)
	N (%)
Abdominal pain or discomfort*	9 (15)
Constipation	3 (5)
Diarrhoea	2 (3)
Nausea	1 (2)
Lower abdominal abscess	1 (2)
Shoulder and back pain	1 (2)
Perianal sepsis (exacerbation of underlying disease)	1 (2)
Increased frequency of bowel movements, with some mucus	1 (2)
Flare in underlying condition	1 (2)
Clostridium difficile toxin and glutamate dehydrogenase causing exacerbation of ulcerative colitis flare	1 (2)
Right-sided buccal-space abscess requiring hospitalisation	1 (2)
'Feeling low'	1 (2)
Cellulitis	1 (2)

*Abdominal pain and discomfort' included the combined categories of abdominal pain, abdominal discomfort/distension, and abdominal pain and gastritis.

recorded for some patients. Reasons for discontinuation during the study period were abdominal pain (n=7), diarrhoea (n=2), constipation (n=2) and nausea (n=1). One patient discontinued because of lack of efficacy, and two patients discontinued because they had completed treatment within 12 weeks. A clinical decision or 'other' reasons (not specified) were recorded as the reason for discontinuation in three patients. For 10 patients, no reason for discontinuation was recorded.

Tolerability

Adverse events were recorded in 19 patients (32%), who had a total of 24 events (table 3). The most frequently reported adverse events were abdominal pain or discomfort (n=9, 15%) and constipation (n=3, 5%). The investigators judged that one event (constipation) was definitely related to ferric maltol and seven events (all gastrointestinal) were probably related.

Four serious adverse events were recorded: right-sided buccal-space abscess requiring hospitalisation (n=1), lower abdominal abscess secondary to Crohn's disease (n=1), gastritis and abdominal pain requiring hospitalisation (n=1) and haemoglobin 72 g/L at initiation of study drug (n=1). None of these serious adverse events was judged by investigators to be related to ferric maltol.

DISCUSSION

This study was designed to provide information about the real-world experience of patients who received ferric maltol as part of routine clinical practice at seven UK centres. The study population was broadly similar to that of the Phase III Safety and Efficacy Study of oral Ferric Iron to Treat Iron Deficiency Anaemia in Quiescent Ulcerative Colitis and Crohn's Disease (AEGIS 1 and 2 studies[4])as well as other real-world patient populations.[10]

In our sample of 59 patients, 30 had haemoglobin measurements at both baseline and week 12; approximately two-thirds of these patients (63%) achieved normalisation of haemoglobin by week 12, similar to the proportion who achieved normalisation in the AEGIS trial (66%)[4] and a higher proportion than that achieved with OFPs (29%) in another UK real-world study published in 2014.[10] The median time to normalisation of haemoglobin was similar in our study (46 days) to that reported in the AEGIS trial (57 days).[4] However, the mean increase in haemoglobin at week 12 (14 g/L) was somewhat lower than that reported in AEGIS (25.2 g/L in patients with ulcerative colitis and 19.3 g/L in patients with Crohn's disease).[4] The reason for this difference is unclear but could reflect the smaller sample size or higher rate of treatment discontinuation before 12 weeks in our study (49%) than in AEGIS (14%).[4] It is possible that more active management of adverse events under trial conditions, such as more time spent explaining the treatment and possible adverse events to participants, resulted in higher continuation rates in AEGIS than in our study. Despite this smaller increase in haemoglobin seen in the real-world setting with ferric maltol, it was still higher than that reported for OFPs (7 g/L for patients with Crohn's disease and 4 g/dL for patients with ulcerative colitis) in another real-world study.[10]

In our study, mean ferritin increased from baseline to week 12 (19 µg/L) to a similar extent to that seen in the AEGIS study (17 µg/L).[4] Unfortunately, in our study, only two patients had TSAT measurements at both baseline and week 4, and no patients had measurements at both baseline and week 12; therefore, we could not perform a meaningful analysis of change in TSAT over time. In the AEGIS study, mean TSAT increased by 18%.[4]

In the current study, approximately one-third of patients experienced adverse events, the most common of which were abdominal pain or discomfort (15%) and constipation (5%). The overall frequency of adverse events was lower in our study than in the AEGIS trial, where 58% of ferric maltol recipients reported a treatment-emergent adverse event; however, the rates of abdominal pain (13% in AEGIS) and constipation (8%in AEGIS) were similar in the two studies.[4] The adverse event rate in our study is also lower than that reported for patients on OFPs in a real-world study, where 51% of patients experienced an adverse event and 18%–20% experienced a gastrointestinal adverse event (constipation, abdominal pain, nausea and diarrhoea).[10]

As with any retrospective and observational study, the quality of our dataset was limited by the accuracy and completeness of the medical records of patients. Many patients did not have haemoglobin and other measurements at the 4-week assessment timepoints, and several also did not have measurements at the 12-week assessment,

limiting the analyses that could be performed. It could be that patients had tests performed at timepoints outside our specified windows (3–5 weeks for the 4-week analysis and 10–16 weeks for the 12-week analysis) as a result of differences in follow-up times in real-world practice or missed appointments. However, our dataset implies that there could be a need for clinicians in the UK to improve monitoring of patient response to ferric maltol.

An expanded, prospective real-world study would provide a deeper understanding of the effectiveness of ferric maltol in routine clinical practice. Such a study might also help to clarify the increase in haemoglobin that could be expected with routine 12-week ferric maltol therapy and could explore factors associated with treatment continuation.

CONCLUSIONS

Optimal management of IDA in IBD presents an opportunity for significant improvement in the care and outcomes of people with IBD. This observational study indicates that ferric maltol works effectively to increase haemoglobin and iron indices and is generally well tolerated in patients with IBD and IDA treated in routine clinical practice, supporting the findings of randomised controlled trials. With this favourable benefit/risk balance, ferric maltol overcomes some of the major barriers to IDA management observed with other therapies, including the tolerability issues associated with OFPs and the inconvenience associated with intravenous iron therapy.

Author affiliations
[1]Department of Gastroenterology, University Hospital Southampton NHS Foundation Trust, Southampton, UK
[2]Gastroenterology, University Hospitals Bristol NHS Foundation Trust, Bristol, UK
[3]Department of Gastroenterology, Salford Royal NHS Foundation Trust, Salford, UK
[4]Department of Gastroenterology, Norfolk and Norwich University Hospitals NHS Foundation Trust, Norwich, UK
[5]IBD Unit, Hull University Teaching Hospitals NHS Trust, Hull, UK
[6]Department of Gastroenterology, Barts Health NHS Trust, London, UK

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Competing interests JFC has served as consultant, advisory board member or speaker for AbbVie, Amgen, Celltrion, Falk, Ferring, Janssen, MSD, Napp Pharmaceuticals, Pfizer, Pharmacosmos, Sandoz, Biogen, Samsung, Shield therapeutics, Vifor and Takeda. He has received research funding from Biogen, Amgen, Hospira/Pfizer, Janssen, GSK and AZ. AF has received fees for speaker services from Takeda UK, Dr Falk Pharma, Tillotts, AbbVie, Shield, Ferring, Pharmacosmos, Allergan, Actavis and Janssen and has acted on advisory boards for Takeda, Dr Falk, AbbVie, Ferring, Pharmacosmos, Allergan and Janssen. CS has received fees for speaker services from Shield Therapeutics. IB has acted on advisory boards for AbbVie, Gilead, Pharmacosmos and Vifor; has received educational grants from AbbVie, Allergan, Amgen, Genentech, Gilead, Janssen, Pfizer, Pharmacosmos, Shield, Takeda, Torax and Vifor; and has received research funding from AbbVie, Allergan, Amgen, Genentech, Gilead, Pfizer, Shield, Shire, Takeda and Vifor. SS has received grants from Takeda, Tillots Pharma and Amgen; personal fees from Takeda, Janssen, Tillots Pharma, AbbVie and Amgen; and non-financial support from Takeda, Janssen, Tillots Pharma and Abbvie.

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ORCID iD
JR Fraser Cummings http://orcid.org/0000-0002-9659-3247

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