Oral versus intravenous iron in IBD patients with anti-inflammatory therapy

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Regarding the current recommended once daily dosing of oral iron (with probably less side effects than with a 3 times daily dose), and the decrease of hepcidin in patients on immunosuppressive medication, we hypothesize that patients with mild to...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Anaemias nonhaemolytic and marrow depression
Study type	Interventional

Summary

ID

NL-OMON56145

Source
ToetsingOnline

Brief title
OVI-IBD

Condition

- Anaemias nonhaemolytic and marrow depression
- Gastrointestinal inflammatory conditions

Synonym
crohn's disease, ulcerative colitis

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: ZonMW subsidie

Intervention

Keyword: IBD, iron suppletion

Outcome measures

Primary outcome

Normalization of Hb concentration (> 7.3 mmol/L (females) or > 8.0 mmol/L (males)) from baseline to week 12 in both oral and iv iron supplementation group.

Secondary outcome

- Change in Hb from baseline at week 4, 12 and 16 weeks

- Ferritine > 100 microg/l at week 4, 12 and 16

- Preference of patient for oral versus iv iron at baseline and at week 16

- Disease-specific Quality of life (IBDQ) and overall/generic Quality of life (EQ-5D-5L) at week 16 in comparison with baseline

- Healthcare use (using the iMCQ questionnaire19), at baseline and week 16

- Work productivity (Work Productivity Activity Index, WPAI20) at baseline and week 16

- Therapy adherence with the modified MMAS for patients in the oral iron group at week 4, 8 en 12 and at week 16 if patients still use iron according to the protocol.

- Side effects according to MedDRA criteria

- Hepcidin - and soluble Transferrin Receptor (sTfR) - fecal calprotectin / CRP ratio

For this outcome, blood will be stored at baseline and at week 12 to determine Hepcidine en soluble Transferin Receptor (sTfR) to can analyze potential

differences in retrospect (together with the results of ferritine, CRP and

fecal calprotectin).

- Does response to iron therapy correlate with disease activity?

- How often do patients experience hypophosphatemia as a side effect of

iron therapy?

Study description

Background summary

Inflammatory bowel disease (IBD) is a chronic inflammatory disease of the gut comprising Crohn*s disease (CD) and ulcerative colitis (UC). Of the 17*million inhabitants in the Netherlands, about 90.000 individuals have been diagnosed with CD (mean age of 37.7 (SD 15.9) years) and UC (mean age 46.2 (SD 16.8) years). The incidence rate (39 new individuals per 100*000 every year) continues to rise, posing an increasing burden on society. The natural history of the disease is characterized by shorter or longer periods of inflammation interspersed with periods of remission. In UC the majority of patients have a mild-moderate course, which is most active at diagnosis and then in varying periods of remission or mild activity; about 10%-15% of patients experience an aggressive course, and the cumulative relapse rate in CD is reported as 53%, 85%, and 90% at 1, 5, and 10 years, respectively.
Anemia is the most common systemic complication in patients with IBD, exceeding by far the frequencies of other extra-intestinal manifestations (e.g., rheumatic, dermatologic and ophthalmologic) commonly associated with IBD. Anemia in IBD is of multifactorial origin; it results from chronic intestinal blood loss, nutritional deficiencies, medication-induced myelosuppression, and iron malabsorption due to underlying inflammatory processes. The two most common types of anemia in IBD are iron-deficiency anemia (IDA), occurring in 45% in all patients with IBD, and anemia of chronic disease (ACD). Multiple recent studies have shown that iron deficiency anemia (IDA) has a significant impact on QoL and that iron supplementation can improve QoL, irrespective of disease activity.

Iron metabolism, including enteral absorption, has been clarified with the discovery of the master regulator*hepcidin.6 Hepcidin is a peptide hormone; that is synthesized and produced primarily by the liver. The effect of hepcidin on iron availability is negative: it reduces iron absorption in the duodenum by reducing the availability of the iron transporter ferroportin. Reducing the expression of ferroportin on macrophages and hepatocytes both also reduce the

amount of iron available for production of hemoglobin. In addition, hepcidin reduces iron release from the reticuloendothelial system (RES).

In a state of iron deficiency, hepcidin is low and ferritin, a marker of bodily iron stores, is also low and in this state the low hepcidin concentration facilitates iron absorption. During a state of inflammation, hepcidin can increase, thereby reducing iron absorption and availability. In ACD the hepcidin levels are also high, thereby resulting in a low serum iron and high ferritin levels. The high hepcidin levels that may be present in inflammation are the reason that iv iron is considered superior to oral iron in patients with active intestinal inflammation and IDA.

In IBD, successful treatment with either oral or intravenous iron is reflected by an increase of hemoglobin levels. The European Crohn*s and Colitis Organization (ECCO) guidelines recommend intravenous iron as a first-line treatment in patients with active IBD. Oral iron could constitute a valid alternative for anemia treatment. Side effects of oral iron supplementation (like nausea, abdominal pain) is the main reason for doctors and patients to prefer iv iron, especially in patients with active IBD. A 2015 meta-analysis did not show a dose-dependent effect of GI side effects of oral iron, but on the other hand, this is not studied properly for patients on daily 100mg iron (current recommended dose instead of 3 daily 200 mg till recently). A study in 2011 shows long term and low-dose oral iron with no more than 100 mg of total elemental iron to be equally effective compared with iv iron with a preferable tolerability and is therefore recommended in the current ECCO guidelines for patients with inactive disease. In patients with active disease, there are currently no studies comparing the effects of oral vs iv iron supplementation.

Oral iron supplementation in active disease states is controversial. Hepcidin levels can be considered as the sum effect of all regulatory processes. Studies suggested that iron stores and hypoxia reduce hepcidin levels even in an inflammatory state. This is also reflected by a study which demonstrated low levels of hepcidin in patients with ferritin levels under 30µg/ml, regardless of disease activity or type. Furthermore, studies show that immunosuppressive medication decrease the level of hepcidin. This raises the question: is oral iron a viable alternative for patients under immunosuppressive treatment for active IBD?

Study objective

Regarding the current recommended once daily dosing of oral iron (with probably less side effects than with a 3 times daily dose), and the decrease of hepcidin in patients on immunosuppressive medication, we hypothesize that patients with mild to moderate IBD activity on immunosuppressive medication, show the same level of Hb increase after 12 weeks after either oral or iv iron supplementation, while the price of oral iron supplementation is significantly

lower.

Study design

The proposed study is a multicenter prospective non-inferiority study. Patients with inflammatory bowel disease on immunosuppressive medication with iron deficiency anemia, with increased inflammation parameters, but without an elevated ferritin (<100 µg/L), will be randomized to a treatment group with either low dose oral iron or iv iron supplementation. This is the starting point (baseline) of the study.

Hb analysis will be repeated 4 weeks after start iron supplementation, according to the Dutch guideline regarding follow-up after iron supplementation (both iv and oral formulation). In case of iv supplementation, the iv infusion will be repeated in case of insufficient increase of the Hb.
In case of oral iron supplementation and if the Hb is normal at week 4, the recommendation is to continue ferrofumaraat during another 8-12 weeks at reduced doses (every other day). In the current study protocol we advise an additional 12 weeks of a doses regime of 100 mg every day.
In case of oral supplementation and if the Hb is still too low at week 4, 200 mg every day will be continued until week 12. When a normal Hb is present at week 12, supplementation at a dose of 100 mg every day will be continued until week 16. In case there is no increase in Hb at week 12, the patient is a treatment failure and the treatment decision will be made by the treating physician.

In conclusion, the total treatment duration is 16 weeks. If a patient develops IDA again, the treatment protocol starts again. In the current study protocol, each patient will be followed for these 16 weeks and after these 16 weeks regular care is resumed.

Visits will be planned in order to perform lab measurements (Hb, ferritine, transferrin saturation, CRP and fecal calprotectin at baseline, week 4, 12 and 16 weeks). Also patients will be asked for side effects every visit and to fill in questionnaires at baseline, week 12 and week 16 regarding quality of life, healthcare use, work productivity and patient preference.
The study coordinator works at the Leiden University Medical Center and in total 7 collaborating regional and academic hospitals in the Netherlands will participate in this study. All these centers are member of the ICC Consortium. The national ICC study coordinator will support the study coordinator with logistics during the course of the study (0.1 FTE).

Intervention

Study patients will be treated either with intravenous iron or oral iron. The brandname of the iv iron is dependent on the hospital policy and the doses will

be according to recommended guidelines (weight of patient, see below). Iv iron is intramural medication without add-on status and needs infusion at daycare. Patients randomized in the oral group, will all be prescribed ferrofumaraat 200 mg 1 dd. Both the iv as the oral formulations concerns care that is reimbursed (iv indirectly via DBC).

Study burden and risks

The risk for study subjects is negligible because patients do not run additional risk compared to Standard care. Even outside the context of the study, patients would have to get their biood samples tested as part of their IBD-care; in addition, they would need iron therapy for iron deficiency. Because patients need iron therapy, there is a risk of side effects or allergic reactions. These side effects are generally mild and reversible (e.g., constipation, tarry stool, or abdominal pain). Blood tests for study measurements will be done at the same time as tests for the Standard care; hence, patients wiii not have an increased risk related to venipuncture.
During 16 weeks, patients have to get tested four times, which yields an additional 40mi of blood for each blood withdrawal; however, the total amount of withdrawn blood volume is negligible and it will not increase patient's risk. Last but not least, patients will have to fill out several questionnaires over the course of the study. The questionnaires are short and not intrusive, it will take about 60 minutes to fill out all study questionnaires.
It is known that iron deficiency and anemia are frequent and recurrent problems in patients with IBD. Given that this is a study with a negligible risk, we think it is justified to perform this study. The results may lead to personalized iron therapy in patients with IBD.

Since proton-pump inhibitors increase the pH in the stomach and duodenum it can lead to lower oral iron absorption, given that an acidic environment is necessary for iron dissociation and absorption. Therefore, patients randomized to oral ferrous fumarate will be advised to stop using proton-pump inhibitors during iron therapy or will be advised to switch to other type of antacid (e.g., H2-antagonists that have been shown to have a smaller effect on iron absorption and association with iron deficiency compared with proton-pump inhibitors) during iron therapy. Patients randomized to intravenous iron group can continue using proton-pump inhibitors.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Established IBD diagnosis (Crohn's disease, ulcerative colitis, IBD-unclassified)
- Adults (>=18 years of age)
- Any single Hb level between 6,2 - 7,3 mmol/L (females) 6,2 - 8,0 mmol/L (males)
- Any single ferritin <100 µg/L and transferrin saturation <20% within 4 weeks of study inclusion
- CRP > 5 mg/L and / or fecal calprotectin > 150 within 4 weeks of randomization
- Patients on immunosuppressive medication (thiopurine, methotrexate, biologicals, JAK inhibitor) for at least 8 weeks or if prednisone, for at least 2 weeks
- Mild to moderate disease according to the treating physician; e/g/ a Physician Global Assessment (PGA) score of 1 or 2
- Documented informed consent

Exclusion criteria

- Anemia due to reasons other than iron deficiency or chronic disease (e.g. hemoglobinopathy).
- Severe disease with a PGA of 3
- IBD patients with a location of IBD at other places than ileum and / or colon (according to treating physician)
- Earlier significant side effect of oral iron
- Earlier significant side effects, including allergic reaction of iv iron (if another trade name of iv iron is given than in history, and the pharmacist also agrees, inclusion is allowed)
- Blood transfusion or therapy with oral and/or intravenous iron in the past eight weeks
- Folic acid deficiency (<2.5 µg/ml)
- Vitamin B12 deficiency (<150 mg/l)
- Documented history of bariatric surgery or gastric/duodenal resections due to benign or
malignant pathologies
- Documented history of liver cirrhosis, heart failure, hemoglobinopathies, autoimmune
hemolytic anemia, myelodysplastic syndrome, or chronic obstructive pulmonary disease
(COPD)
- Documented history of recent treatment for a malignancy (excluding dermatological
malignancies such as basal cell carcinoma or squamous cell carcinoma). Patients can
be included if the treatment for malignancy has been finalized >=6 months before the
inclusion date.
- End-stage renal disease (impaired renal function, defined as eGFR <30 ml/min/1.73m2)
- Documented pregnancy or breastfeeding at the time of inclusion
- Documented major operation (e.g., laparotomy) less than six weeks before inclusion
- Unable to give informed consent due to inability to onderstand Dutch language or incapacitation (e.g., due to cognitive/psychological conditions or hospitalization in Intensive Care)

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Health services research

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	02-06-2022
Enrollment:	152
Type:	Actual

Ethics review

Approved WMO

Date:	21-03-2022
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	30-03-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	08-12-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	18-03-2024
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL79363.058.21