Final Study Report

Study Title: *Effect of intravenous replenishment of iron in the preoperative management of anemia in patients with colon cancer: RIPAC-trial*
EU reference number: *2018-004213-41*

Study protocol/CIP code: *RIPAC trial*

ClinicalTrials.gov identifier: NA

Sponsor: *Ghent University Hospital*

Contact details sponsor: *C. Heymanslaan 10, 9000 Gent*

National Coordinator/ Coordinating Investigator: *prof. dr. Karen Geboes*

Funder: *Vifor pharma*

Author: *Prof. Dr. Karen Geboes*

Date of report: *09/May/2024*

By signing this final study report, I acknowledge that the information is accurate and complete.

Name and signature Coordinating Investigator: .....

Date signature Coordinating Investigator: 10/06/2024 .....

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1. Introduction

Up to 50% of patients with a colorectal carcinoma (CRC) who undergo surgery, are anemic (Hb < 12g/dl in men and < 13g/dl in women) preoperatively. Severe to moderate anemia (Hb < 11g/dl in men and < 10g/dl in women) was found in 20% of the patients. Anemia is most prevalent in patients with cancer of the proximal colon and gradually diminishes as tumors are located more distally towards the rectum. Patients older than 65 year are most at risk for developing anemia [1]. In CRC, preoperative anemia can be attributed to gastro-intestinal blood loss, neoadjuvant chemotherapy or radiotherapy and nutritional deficiencies. These may be exacerbated by activation of the immune system with release of inflammatory cytokines, which results in a functional iron deficiency, formerly also called anemia of chronic disease. This is characterized by low serum iron and decreased transferrin saturation, in the face of adequate body iron stores with a serum ferritin value within or above normal limits [2]. Although it is proven that anemia implicates an increased risk for perioperative blood transfusion and increased perioperative mortality and morbidity, correcting anemia preoperatively in patients with CRC is still no standard of care [3,4].
Currently there are three options in the treatment of anemia: allogenic blood transfusion (ABT), erythropoietin stimulating agents (ESAs) and iron supplementation. Blood transfusion and ESAs are effective modalities in increasing Hb levels. However, several studies have shown a detrimental effect of these two treatments in patients with CRC or cancer in general. In a meta-analysis, there was a higher rate of tumor recurrence after ABT compared to those not transfused with a clustered OR of 1.42 [3]. In a more recent meta-analysis, ABT has been shown to increase all-cause mortality (OR= 1.72), cancer-related mortality (OR = 1.71) and morbidity, such as wound infection (OR = 3.27) after CRC resection [4]. One study showed an increased risk of perioperative thrombosis after CRC resection [5]. Subsequently, a restrictive approach for perioperative ABT is recommended. Also, the use of ESAs is not recommended in anemic CRC patients, as these are associated with a greater incidence of thrombosis and a 17% increase in overall mortality [6] .

There are three randomized controlled trials (RCT) and three cohort studies that investigated the effect of iron supplementation on several outcome parameters in the perioperative setting in patients with CRC.

The first RCT of Keeler et al. compared oral iron with intravenous (IV) iron. There was a significantly higher increase in hemoglobin (Hb) with IV compared to oral iron, which resulted in fewer anemic patients at the time of surgery. Despite this finding, there was no difference in use of blood transfusion between the two groups. IV iron substitution did not reduce 90-day mortality, complication severity or risk of infective complications compared to oral iron supplementation. [7]. The RCT of Edwards et al showed that the administration of IV iron in patients with CRC at least 2 weeks before surgery had no benefit in treating preoperative anemia, reducing the rate of ABT or reducing length of hospital stay in comparison with placebo [8]. In the third RCT of Lidder et al, there was a higher increase in Hb in the oral iron-

supplemented group compared to the placebo group. The patients in the iron-supplemented group were less likely to require blood transfusion during surgery than the placebo group [9].

The cohort study of Laso-morales et al. compared IV iron to standard care (oral iron or no iron). In this study, IV iron was more effective in terms of increasing preoperative Hb levels in CRC patients with anemia and appeared to reduce infection rate, although it did not reduce the rate of postoperative ABT [10]. In the cohort study of Okuyama et al. oral iron supplementation for at least 2 weeks before surgery significantly increased Hb and reduced the need for intraoperative transfusion compared to no iron substitution [11]. In the third observational cohort study of Calleja et al. preoperative administration of IV iron compared to oral iron significantly increased Hb levels and significantly reduced ABT requirements and hospital length of stay [12].

In conclusion, based on the available studies, we can say that IV iron is more effective in treating preoperative anemia in CRC compared with oral iron (Grade A, level 1b). Despite this finding, IV iron therapy in the treatment of anemia preoperatively in CRC patients is still no standard of care in Belgian hospitals.

Until now, there is not enough evidence that IV iron is more effective in reducing the need for ABT and postoperative morbidity and mortality in patients with CRC.

This is due to limitations in design of the studies: small study populations, heterogeneity in the administered iron substitution, lack of postoperative morbidity and mortality outcomes and some of the studies include both anemic and non-anemic patients. All of the above underlines the need for a new trial on the effect of IV iron therapy in the treatment of anemia in CRC patients and its effect on outcomes after surgery compared with no therapy.

In this multicenter randomized controlled trial our aim is to assess whether IV iron is more effective in the treatment of anemia in patients with colon cancer that are eligible for curative surgery compared to no iron and whether IV iron is more effective in decreasing the need for perioperative blood transfusion and the postoperative morbidity and mortality.

2. Objectives of the study

2.1 Primary objective is

1. To investigate the increase in preoperative Hb after intravenous iron substitution compared with no iron substitution in patients with colon cancer and iron deficiency anemia who are eligible for surgery.

2.2 Secondary objectives

2. To investigate the need for perioperative ABT after intravenous iron substitution compared with no iron substitution in patients with colon cancer and iron deficiency anemia who are eligible for surgery.

3. To investigate the rate of postoperative morbidity after intravenous iron substitution compared with no iron substitution in patients with colon cancer and iron deficiency anemia who are eligible for surgery.

4. To investigate the quality of life 30 days after surgery after intravenous iron substitution compared with no iron substitution in patients with colon cancer and iron deficiency anemia who are eligible for surgery.

3. Investigational Medicinal Product

3.1 Composition and dosing

Patients who were randomized for the no iron group will not receive iron substitution

Patients who were randomized in the IV iron group received a ferric carboxymaltose (injectafer®). Injectafer 1 gram was administered at least two weeks before surgery. Depending on the Hb level and the weight of the patient, another infusion (500 or 1000mg) was administered one week later.

Hb (g/dl)	**Patients with a body weight between 35kg and 70 kg**	**Patients with a body weight of ≥70 kg**
< 10	1.500 mg	2.000 mg
≥ 10	1.000 mg	1.500 mg

Table 1: calculation of the dose of Injectafer

1 ml solution contains 50 mg iron as ferric(III)carboxymaltose (ferric carboxymaltose). 1 ml solution contains a maximum of 5,5 mg (0.24 mmol) sodium.

3.2 Producer / Distributor

Injectafer:

Vifor Pharma België NV
Uitbreidingstraat 84
2600 Antwerpen
België

3.3 Packaging

Injectafer: 500 mg iron / 10 mL single-use vial

3.4 Administration way

Injectafer: Administer Injectafer intravenously, either as an undiluted slow intravenous push or by infusion. When administering as a slow intravenous push, give at the rate of approximately 100 mg (2 mL) per minute. When administered via infusion, dilute up to 750 mg of iron in no more than 250 mL of sterile 0.9% sodium chloride injection, such that the concentration of the infusion is not less than 2 mg of iron per mL and administer over at least 15 minutes. When added to an infusion bag containing 0.9% Sodium Chloride Injection, at concentrations ranging from 2 mg to 4 mg of iron per mL, Injectafer solution is physically and chemically stable for 72 hours when stored at room temperature. To maintain stability, do not dilute to concentrations less than 2 mg iron/mL.

3.5 Labelling

Commercially available medication; medication will be labeled with a "type 2 label" according to the Eudralex volume 4, Annex 13 guidelines. The following will be mentioned on the label: EudraCT number, trial subject ID number, initials, date of visit, for clinical trial use only, investigator name, contact details investigator.

3.6 Storage conditions

Injectafer:

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Do not freeze.

The medication will be stored at the pharmacy of the participating sites.

3.7 Known side effects of the medication

Injectafer:

nausea, high blood pressure (hypertension), flushing or hot flashes, dizziness, vomiting, injection site reactions or skin discoloration, headache, changes in the sense of taste, low blood pressure (hypotension), constipation, or a decrease in blood phosphorus levels

4. Study Protocol Summary

4.1 Study design

The study is designed as a multicenter, open, randomized controlled trial comparing ferric(III)carboxymaltose (Injectafer®) infusion with no iron substitution in the treatment of preoperative anemia in colon cancer patients. Patients with a proven iron deficiency anemia who undergo segmental colonic resection because of M0-stage colon carcinoma and meet the inclusion criteria, are eligible. Iron deficiency anemia is defined by a Hb lower than 13g/dl in men and 12g/dl in women with a transferrin saturation lower than 20%. Patients will be computer randomized for either intravenous iron or no substitution. Randomization will be stratified for age, left or right sided carcinoma and baseline Hb. The ratio of randomization will be 1:1. The patients will be followed intensively until 30 days after surgery. The study will be finished after 30 days. The patient will be followed up further after the study according to the standard guidelines by his or her gastroenterologist.

The centers that will participate in this study are the UZ Gent, AZ Delta Roeselare/ Menen and Sint-Andriesziekenhuis Tielt.

4.2 Inclusion criteria

- Patients with a M0-stage colon carcinoma who are scheduled for segmental colonic resection
- Patients with a Hb higher than 6.5 g/dl or 7.5 g/dl in patients with cardiac disease at moment of diagnosis
- Patients with a proven iron deficiency anemia at diagnosis defined by a Hb lower than 13g/dl in men and 12g/dl in women with a transferrin saturation lower than 20%.
- Obtained informed consent
- ≥18 years; female or male

4.3 Exclusion criteria

- The period between diagnosis and surgery is less than two weeks
- Hemochromatosis, iron overload, defined as TSAT > 45%
- Known hypersensitivity to Injectafer®
- Metastatic colon disease

- Patients not suitable for surgery due to age or comorbidities
- Pregnancy, lactation or woman of childbearing potential who don't use an effective method of contraception
- Administration of IV iron/oral iron/ESA in the past three months before inclusion
- Administration of blood transfusion in the past month before inclusion
- Chronic kidney disease with a eGFR < 30 ml/min
- Hematological disorders as a cause of anemia (myelodysplastic syndrome, leukemia, chronic hemolysis)
- Vitamin B12 and/or serum folate deficiency
- Patients undergoing endoscopic excision of a (rectal) carcinoma (EMR/ESD)

4.4 Primary endpoint

Mean Hb increase at moment of surgery

(Time point of evaluation: day of surgery/1 or 2 days before surgery)

4.5 Secondary endpoints

1. Number of patients that need perioperative (interval: day of surgery until 7 days postoperative) blood transfusion

(time point of evaluation: 1 week after surgery)

2. Postoperative morbidity measured by the The Clavien-Dindo classification (table 3)

(time point of evaluation: 1 week and 1 month after surgery)

3. Postoperative morbidity measured by length of hospital stay

(time point of evaluation: 1 week and 1 month after surgery)

4. Postoperative quality of life 30 days after surgery measured by the EORTC QLQ-C30

(time point of evaluation: 1 month after surgery)

Table 3: The Clavien-Dindo classification for surgical complications

Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions. Allowed therapeutic regimens are: drugs such as antiemetics, antipyretics, analgetics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II	Requiring pharmacological treatment with drugs other than allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
Grade IIIa	Surgical, endoscopic, or radiological intervention that is not under general anesthesia
Grade IIIb	Surgical, endoscopic, or radiological intervention that is under general anesthesia
Grade IVa	Life-threatening complication requiring intermediate care or intensive care unit management, single organ dysfunction (including dialysis, brain hemorrhage, ischemic stroke, and subarrachnoidal bleeding)
Grade IVb	Life-threatening complication requiring intermediate care or intensive care unit management, multi-organ dysfunction (including dialysis)
Grade V	Death of a patient
Suffix "d"	If the patient suffers from a complication at the time of discharge, the suffix "d" (for "disability") is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication

4.6 Procedures

- Patients in the IV iron group: Injectafer 1 gram will be administered at least two weeks before surgery. Depending on the Hb level and the weight of the patient, another infusion (500 or 1000mg) will be administered one week later.

- Clinical evaluations: 2 weeks before surgery, day of or 1 day or 2 days before surgery, 1 week after surgery, 1 month after surgery

- Blood collection: 2 weeks before surgery, day of or 1 day before surgery, 1 week after surgery, 1 month after surgery

On the first blood analysis, a pregnancy test will be done for women of childbearing potential not using an effective method of contraception

- Questionnaire about postoperative quality of life: 30 days after surgery.

4.6.1 Flowchart

1. Start of the study (at least two weeks before surgery):

   ➢ Blood sampling + clinical evaluation

   ➢ Randomisation

   ➢ A pregnancy test will be performed on women of childbearing potential.

2. At least two weeks before surgery:

➢ IV iron group: Injectafer 1 gram will be administered. Depending on the Hb level and the weight of the patient, another infusion (500 or 1000mg) will be administered one week later.

3. 2 or 1 day (s) before surgery or day of surgery

➢ Blood sampling + clinical evaluation

4. 5-10 days after surgery

➢ Blood sampling + clinical evaluation

5. 25-35 days after surgery

➢ Blood sampling + clinical evaluation

➢ Questionnaire about postoperative quality of life

The expected total duration of the trial is 6 to 8 weeks.

The blood samples will always be destroyed a few days after collection.

4.7 Randomisation and blinding

Patients will be computer randomized for either intravenous iron or no substitution. Randomization will be stratified for age, left or right sided carcinoma and baseline Hb. The ratio of randomization will be 1:1

4.8 Monitoring and quality measures

Monitoring of this study will be organized by Hiruz CTU from the Ghent University Hospital. The nature and extent of the monitoring will be discussed in the monitoring plan.

5. Study analysis

The study was closed in January 2023 – last action that had been undertaken was mentioned 21 june 2021. Seven patients had been included. The study had been prolonged up to 25 dec 2022, thinking that poor accrual was because of the covid-pandemic, but actually certain procedures had changed in the study centres in the meantime and eventually it was concluded that it would not be possible to achieve the recruitment objective.

The number of subjects was too low to perform a(n interim) statistical analysis.

6. Independent Ethics Committee and Competent Authority

OVERVIEW APPROVED DOCUMENTS		
Initial submission: - Protocol v1 dd 31-Mar-2019 - Protocol summary v1 dd. 31-Mar-2019 - "Patient card v2 dd. 20-Dec-2016	**Approval date Central EC: 12-Jun-2019**	**Approval date FAMPH:06-May-2019**

- ICF v1 dd. 31-Mar-2019 (revised version based on comments EC 24-May-2019) - Label Injectafer v1 dd. 31-Mar-2019 - SmPC Injectafer v1 dd. Dec-2018 - Questionnaire EORTC QLQ-C30 v3		
Amendment 1: - Prolongation study until 25-Dec-2021	**Approval date Central EC: 02-feb-2021**	**Approval date FAMPH: N.A.**
Amendment 1: - Prolongation study until 25-Dec-2022	**Approval date Central EC: 17-Nov-2021**	**Approval date FAMPH: N.A.**

7. Results

7.1 Subject enrollment and demographics

In total 7 patients were included. Due to poor inclusion rate, the target of 60 included patients was not reached. Patient 001 and 002, both included in UZ Gent, did not meet the study criteria: Patient 001 was included and randomized, but eventually did not undergo surgery. Patient 002 had surgery too early. Baseline characteristics are shown in table 2.

Table 1: overview inclusion of patients:

Site	Number of Subjects included?	Date of first inclusion?	date of site closure (LPLV)
AZ Delta Roeselare/Menen	3	20/08/2020	22-Jan-2021
Sint-Andries Tielt	0	NA	NA
UZ Gent	4	02/06/2020	21-Jun-2021

Table 2: Baseline characteristics

Characteristics	**Group with iron substitution N= 2**	**Group without iron substitution N= 5**	**Total**
Sex (female)	0 (0%)	3 (60%)	3 (42,9%)
Age	85.0 ± 9.9	77.6 ± 9.2	79.1 ± 9.3
Baseline Hb level ≤ 10	2 (100%)	2 (40%)	4 (57.1%)

Number of subjects prematurely discontinued	1 (50%)	1 (20%)	2 (28.5%)

Values are mean ± SD or n (%).

7.2 Study specific results

Subject ID			randomisation	surgery	D25-35
1	IV iron 2x	No surgery			
2	No iron	Early surgery			
3	No iron	Hb	9.1		9.1
		Iron	16		31
		Ferritine	107		32
		Transferrine	6		8
4	No iron	Hb	10.2	10	10.7
		Iron	38	18	37
		Ferritine	41	13	43
		Transferrine	11	5	9
5	iron	Hb	9.4	12.6	13.1
		Iron	26	51	92
		Ferritine	28	277	234
		Transferrine	7	15	29
6	No iron	Hb	9.7	10.2	10.9
		Iron	18	25	91
		Ferritine	17	18	278
		Transferrine	4	5	2.8
7	No iron	Hb	10.1	10.9	10.6
		Iron	32	64	41
		Ferritine	54	43	31
		Transferrine	10	17	9

These are the main results for blood analyses of the patients in study – only one patient actually got IV iron: an analysis of the intervention is not possible. Reasons for the poor recruitment are mentioned above.

8. Safety

There has been 1 serious adverse events during the study period.

SAE Overview				
Subject ID	Study Arm (if applicable)	SUSAR (Y/N)	SAE Description	Outcome (ongoing, resolved, death, ...)
6	No Iron group	N	Post-operative Ileus/ gout	Resolved 05JAN2021

The SAE was not reported within the timelines mentioned in the latest protocol: within 2 working days after becoming aware of the SAE. Site staff was aware of the SAE on 29-Dec-2020 and reported the SAE on 22-Jan-2021.

9. Protocol deviations

Centre	Patient number	deviation
UZ Gent	3	no blood at surgery
UZ Gent	7	no blood d5-10 after surgery

10. Discussion and overall conclusions

The study was closed for poor acrcrual in january 2023 – last action that had been undertaken was mentioned 21 june 2021.

Seven patients had been included. The study had been prolonged up to 25 dec 2022, thinking that poor accrual was because of the covid-pandemic, but actually certain procedures had changed in the study centres in the meantime and eventually it was concluded that it would not be possible to achieve the recruitment objective.

The number of subjects was too low to perform a(n interim) statistical analysis. Only one patient actually got IV iron and surgery.

11. References

References:

[1] Edna TH, Karlsen V, Jullumstro E, Lydersen S. Prevalence of Anaemia at Diagnosis of Colorectal Cancer: Assessment of Associated Risk Factors. Hepato-Gastroenterol. 2012;59(115):713-6.

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Appendix 1: Summary of results for lay persons

1. Clinical trial identification

Study Title: Effect of intravenous replenishment of iron in the preoperative management of anemia in patients with colon cancer: RIPAC-trial

EU reference number: 2018-004213-41

Study protocol/CIP code: RIPAC trial.

2. Name and contact details of the sponsor

Sponsor: Ghent University Hospital

Contact details sponsor:

National Coordinator/ Coordinating Investigator: prof. dr. Karen Geboes

Funder: Vifor Pharma

3. General information

Primary objective is To investigate the increase in preoperative Hb after intravenous iron substitution compared with no iron substitution in patients with colon cancer and iron deficiency anemia who are eligible for surgery.

Study was open from June 2020 until June 2021.

4. Population of subjects

The study is designed as a multicenter, open, randomized controlled trial comparing ferric(III)carboxymaltose (Injectafer®) infusion with no iron substitution in the treatment of preoperative anemia in colon cancer patients. Patients with a proven iron deficiency anemia who undergo segmental colonic resection because of M0-stage colon carcinoma and meet the inclusion criteria, are eligible. Iron deficiency anemia is defined by a Hb lower than 13g/dl in men and 12g/dl in women with a transferrin saturation lower than 20%. Patients will be computer randomized for either intravenous iron or no substitution. Randomization will be stratified for age, left or right sided carcinoma and baseline Hb. The ratio of randomization will be 1:1. The patients will be followed intensively until 30 days after surgery. The study will be finished after 30 days. The patient will be followed up further after the study according to the standard guidelines by his or her gastroenterologist.

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Number of subjects prematurely discontinued	1 (50%)	1 (20%)	2 (28.5%)

5. Investigational medicinal products used

Injectafer:

Vifor Pharma België NV
Uitbreidingstraat 84
2600 Antwerpen
België

6. Description and frequency of adverse reactions

Patient 6, who was randomized to the NO-Iron group suffered from post-operative ileus.

7. Overall results and comments on the outcome of the clinical trial

The study was closed in January 2023 – last action that had been undertaken was mentioned 21 june 2021. Seven patients had been included. The study had been prolonged up to 25 dec 2022, thinking that poor accrual was because of the covid-pandemic, but actually certain procedures had changed in the study centres in the meantime and eventually it was concluded that it would not be possible to achieve the recruitment objective.

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