Clinical evaluation of novel markers in the diagnosis of anemia.

Published: 21-10-2014
Last updated: 22-04-2024

The objective of this study is to evaluate the additional value of novel anemia markers (RET-HE, RPI, sTfR, sTfR/log(ferritin), transferrin/log(ferritin)) in a prospective, randomized study design. Our hypothesis is that the novel anemia markers can...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Anaemias nonhaemolytic and marrow depression
Study type	Observational invasive

Summary

ID

NL-OMON41145

Source
ToetsingOnline

Brief title
Clinical evaluation of novel markers in the diagnosis of anemia.

Condition

- Anaemias nonhaemolytic and marrow depression

Synonym
anemia, iron-deficiency

Research involving
Human

Sponsors and support

Primary sponsor: Catharina-ziekenhuis
Source(s) of monetary or material Support: Initiatief voor het onderzoek ligt bij kliniek/laboratorium;soluble transferrine receptor reagens wordt gratis verstrekt door Roche Diagnostics. Personele kosten van de onderzoekers (K. Coene en N. Wlazlo) gaan uit opleidingsbudget;gezien onderzoek een regulier onderdeel uitmaakt van de opleiding tot

specialist. Eventuele andere kosten zullen gedekt worden door de betreffende afdelingsbudgetten.,Roche Diagnostics

Intervention

Keyword: anemia, iron-deficiency, RET-HE, soluble transferrin receptor

Outcome measures

Primary outcome

- Time from baseline until first classification of anemia (iron-deficiency,

anemia of chronic disease, other)

- Time from baseline until definitive diagnosis (stomach ulcer, colon

carcinoma, kidney failure, hematologic malignancy etc.)

- Time from baseline until start of therapy if applicable (f.e. iron suppletion)

- Therapy response: absolute Hb-increase 8 and 16 weeks from baseline

- Therapy response: percentage of required Hb-increase compared to baseline

- Therapy response: Delta values of anemia markers (MCV, ferritine, RET-HE,

sTfR, sTfR/log(ferritin), Reticulocytes, RPI, transferrin/log(ferritin)) at 16

weeks from baseline.

- Percentage of patients with normalization of Hb-lever at 16 weeks from

baseline (Hb>7.5 and >8.5 mmol/L for women and men respectively)

- Shifts in the Thomas plat subsequent to therapy

Secondary outcome

not applicable

Study description

Background summary

In current Dutch guidelines regarding diagnostic strategies for anemia (Duth Society for General Practitioners, Dutch Primary Care Collaboration Agreements) it is advised to make a first classification in anemia diagnosis based on MCV and ferritin level. Recent studies show that especially the MCV is not optimally suited to classifiy different causes of anemia (Leers et al. Int. Jnl. Lab. Hem 2010; 32, 572-581). Also, the interpretation of ferritin levels can be problematic when an underlying acute phase respons or inflammation is present, as this can cause an increase in the ferritin level that is not related to iron-stores. Because of these draw-backs, it can be difficult to diagnose iron-deficiency anemia from anemie of chronic disease. Recently, several novel markers have become available that can possibly aid in making this distinction. However, the additional clinical value of these markers has not been evaluated in a randomised prospective fashion. The goal of this study is to determine whether these novel anemia markers indeed have additional clinical value in the diagnosis of anemia.

Novel anemia markers comprise both cel-related markers as well as serum-based markers. The cel-related markers are already reported by the current generation hemocytometry analyzers. At the Catharina Hospital Eindhoven, Sysmex hemocytometry analyzers are used. Sysmex analyzers automatically report the reticulocyte hemoglobin equivalent (RET-HE) and the reticulocyte production index (RPI) when a reticulocyte count is performed. The RET-HE is an estimation of the hemoglobin concentration in reticulocytes. As reticulocytes are only present for 1 to 2 days in circulation, the RET-HE gives insight in the availability of iron for erythropoiesis in the previous 2 days. When a decreased RET-HE value is found, this means that iron-supply for erythropoieses was insufficient for adequate hemoglobinization of reticulocytes in the bone marrow. This is also referred to as functional iron deficiency. An underlying inflammation or acute phase response can disrupt the availability of iron for erythropoiesis. The RET-HE can then give insight in whether this decrease in iron availability has (already) led to functional iron deficiency. The RPI is a calculated index that indicates whether the reticulocyte repons on anemia is adequate or not. When a lower reticulocyte respons is found than expected for the severity of the anemia, this can also indicate an underlying problem of the bone marrow.

The novel plasma-related anemia markers include the ratio between ferritin and transferrin (Transferrin/log(ferritin) ratio, Castel et al. CCLM 50:8 2012). This ratio is suggested to aid in the diagnosis of iron deficiency anemie when a low-normal ferritin is found. Both transferrin and ferritin are part of our routine diagnostic process, and the ratio can be automatically calculated in the laboratory system when both a transferrin and a ferritin level are ordered.

An additional plasma-marker is the soluble transferrin receptor (sTfR). The sTfR is correlated to the expression of transferrin receptors on celmembranes; erytropoietic cells of the bone marrow have the highest expression of these receptors. When iron-requirements increase, this is accompanied by an increase in the expression of the transferrrin receptor. The sTfR therefore reflects the functional iron demand of the bone marrow, while ferritin is a marker for the total iron reserves of the body. In contrast to ferritin, sTfR is not

influenced by an underlying infection/inflammation. The sTfR/log(ferritin) ration kan also be used to better distinguish between iron-deficiency anemie and anemia of chronic disease. By plotting this ratio against the RET-HE, the so-called 'Thomas plot' is obtained (Thomas en Thomas, Clin Chem 2012 48(7); 1066-1076). This plot devides a patient population in three quarters with different diagnoses (anemia of chronic disease (ACD), latent iron-deficiency, iron-deficiency or a combination of ACD and iron-deficiency).
Another novel plasma marker in anemia diagnostics is hepcidin. Hepcidin is the central regulatory protein in iron homeostasis. It can bind to the iron-exporter ferroportin on duodenal cells and macrofages. By hepcidin binding, ferroportin is internalized and degraded, resulting in a decrease in dietary iron uptake and a decrease of iron availability for erythropoiesis. Inflammation leads to a increase in hepcidin expression, which can result in functional iron deficiency. On the contrary, absolute iron deficiency, meaning the depletion of total iron stores of the body, results in a decrease in hepcidin, so more iron can be obtained from the dietary intake. Because of these characteristics, hepcidin is also a marker that could aid in the diagnosis of ACD versus iron-deficiency anemie. In the current situation, no routine tests are available for measurement of hepcidin in plasma. The development of novel methods is ongoing and will hopefully lead to a more affordable method during the course of this study so hepcidin levels can be measured.

Study objective

The objective of this study is to evaluate the additional value of novel anemia markers (RET-HE, RPI, sTfR, sTfR/log(ferritin), transferrin/log(ferritin)) in a prospective, randomized study design. Our hypothesis is that the novel anemia markers can aid in an earlier classification of the anemie, so time before diagnosis and adequate treatment will be significantly shorter.

Study design

This study will start in Octobre 2014 and will end approximately in July 2015, if sufficient patients are included at that time. The doctor in internal medicine (Dr. W. Peters) who is responsible for referred patients from general practitioners or other specialists, selects patient older than 18 years who are referred because of anemia (or exhaustion). All study patient will be seen by researcher Dr. N. Wlazlo, who will select eligible patients previous to the first appointment. Dr. N. Wlazlo will make sure all patients eligible for the study will recieve an information letter regarding the study at least a week before their appointment. During the first appointment, additional questions can be discussed, and the patient can then decide to participate in the study and sign the informed consent form. The researcher will add the relevant clinical data of the patient to a SPSS-based case record form. Patients who participate in the study will be randomly devided, with a 50% chance, over a

'classical' and 'modern' branche of the study. In both branches, both the regular anemie markers as well as the novel anemia markers will be tested. However, in the 'classical' branche, the results from the novel anemia markers will not be available for the doctor and the researcher. In the 'modern' branche, these results are shown in the electronical patientfile together with a comment from the laboratory specialist (Dr. K. Coene or Dr. V. Scharnhorst).

Study burden and risks

We consider patient burden to be very low. Most novel anemia markers can be analyzed from materials that are already available from the 'classical' diagnostic approach to anemia. During each of the three blood samplings performed in this study, one extra tube of 3.5 ml is drawn for possible analysis of EPO, and/or hepcidin in the future.
We consider patient risk in this study to be very low. Patients in the 'classical' branche recieve diagnostic tests and treatment according to the current practice at the Catharina Ziekenhuis Eindhoven. Patients in the 'modern' branche have a risk of being treated earlier for iron-deficiency anemia based on the novel anemia markers. The treatment the patient will then recieve is equal to the standard treatment for iron-deficiency anemia, possible side-effects of these drugs are known and accepted in daily practice.

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

referral by general practitioner (or other specialist) for analysis of anemia
referral by general practitioner (or other specialist) for analysis of exhaustion
age 18 or above

Exclusion criteria

Age below 18

Study design

Design

Study type:	Observational invasive
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Single blinded (masking used)
Control:	Active
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	10-11-2014
Enrollment:	300
Type:	Actual

Ethics review

Approved WMO Date:	21-10-2014
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	NL50082.060.14