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Anaemia and iron deficiency in patients with rheumatoid arthritis and other chronic diseases*

Niedokrwistość i niedobór żelaza u chorych na reumatoidalne zapalenie stawów i inne choroby przewlekłe

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Summary

Anaemia is one of the most common symptoms accompanying many chronic diseases, e.g. collagenases, neoplasms, and chronic inflammations (inflammatory bowel disease, chronic kidney disease and heart failure). Iron deficiency anaemia is the most common type of anaemia (80%). It affects 1% to 2% of the population. Iron deficiency (ID) – absolute or functional – is characterised by reduced ferritin levels and transferrin saturation (TSAT) of less than 20%. Iron deficiency is the most common dietary deficiency. However, iron deficiency might be one of the common causes of anaemia of chronic disease (ACD). Anaemia affects 33% to 60% of patients with RA. Rheumatoid arthritis (RA) is a chronic immune-mediated systemic connective tissue disease, in which chronic inflammation of the synovial tissue of the joints damages articular cartilages, bones and other joint structures. The prevalence of RA is approximately 0.3% to 2%. Low haemoglobin levels in RA patients are significantly correlated with disability, activity and duration of the disease as well as damage to joints and joint pain. Treatment of anaemia in RA patients includes iron supplementation, blood transfusions, the use of erythropoiesis-stimulating agents, and treatment of the underlying condition. Biological treatments used in RA patients, such as e.g. infliximab, tocilizumab and anakinra, not only slow the progression of joint involvement but also prevent anaemia.

Keywords: **iron management, rheumatoid arthritis, iron deficiency anaemia, biological agents**

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Abbreviations: **anti-CCP** – anti-cyclic citrullinated peptide antibodies; **ACD** – anaemia of chronic disease; **ACR** – American College of Rheumatology; **CBC** – complete blood count; **DIP** – distal interphalangeal joints; **DMT1** – divalent metal transporter 1; **EULAR** – European League Against Rheumatism; **ID** – iron deficiency; **IDA** – iron deficiency anaemia; **IRIDA** – iron-refractory iron deficiency anaemia; **MCH** – mean corpuscular haemoglobin/mean cell haemoglobin; **MCHC** – mean corpuscular haemoglobin concentration; **MHC** – major histocompatibility complex; **MCP** – metacarpophalangeal joints; **PIP** – proximal interphalangeal joints; **RF** – rheumatoid factor, **sTfR** – soluble transferrin receptor, **TSAT** – transferrin saturation, **TIBC** – total iron blood capacity, **UIBC** – unsaturated iron binding capacity.

RHEUMATOID ARTHRITIS (RA): DEFINITION AND CRITERIA

Rheumatoid arthritis (RA) is a chronic immune-mediated systemic connective tissue disease, in which chronic inflammation of the synovial tissue of the joints damages articular cartilages, bones and other joint structures. Joint involvement in RA is usually symmetrical. The systemic manifestations of the disease include involvement of extra-articular organs, including the heart, kidneys, eyes as well as the respiratory, nervous and haematopoietic systems. Untreated, or inadequately treated, systemic complications and changes in the locomotor system lead to disability, invalidity and premature death.

Depending on the presence or absence of serum immune markers, such as the rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibodies, RA may be either seropositive or seronegative. The classification criteria by the American College of Rheumatology (ACR) of 1987 are commonly used for the diagnosis of RA [6] (Table 1).

Table 1. 1987 ACR classification criteria for RA [1]

RA is diagnosed when at least 4 criteria are met. Criteria 1–4 must have been present for at least 6 weeks
1. Morning joint stiffness lasting at least 1 hour
2. Arthritis of at least 3 joints, except for DIP, shoulder and temporomandibular joints
3. Arthritis of at least 1 hand joint (at least one joint area swollen in the wrist, MCP or proximal interphalangeal – PIP joints)
4. Symmetric arthritis
5. Rheumatoid nodules
6. Positive RF
7. Radiographic changes (erosions) in hand or wrist joints in AP view

DIP – distal interphalangeal joints; PIP – proximal interphalangeal joints; MCP –metacarpophalangeal joints of a total score of 6 or greater in four categories.

The ACR criteria mainly pertain to the diagnosis of more advanced RA. Therefore, classification criteria relating mainly to early RA diagnosis, developed by both EULAR (European League Against Rheumatism) and the ACR, were published in 2010 [45] (Table 2). According to those criteria, classification of RA as definite RA is based on the confirmed presence of synovitis in at least one joint, absence of an alternative diagnosis and achievement of a total score of 6 or greater in four categories.

Epidemiology of rheumatoid arthritis

The prevalence of RA in the general population is estimated at between 0.3% and 2%. The disease affects approximately three times as many women as men. The mean onset age of RA is approximately 40; the onset of the disease occurs earlier in women than in men. The prevalence of RA varies depending on the geographical latitude and the research methodology used. In Europe, the prevalence is between 0.5% and 1% and is lower in the southern part of the continent (3.3/10 thousand in the south; 5.9/10 thousand in the north) [2, 68].

Pathophysiology of rheumatoid arthritis

The etiopathogenesis of RA is not completely understood. A number of factors play a role in the development of RA, including genetic factors, e.g. the presence of major histocompatibility complex (MHC) class II antigens, including in particular DRB antigens, environmental factors (e.g. exposure to viral and bacterial infections) and immune disorders [13, 56].

One of the environmental factors linked to a higher risk of developing RA is smoking, which probably increases the citrullination of peptides [22].

The literature also includes studies which indicate that obesity plays a role in the development of seronegative RA and suggest that adipose tissue has an impact on immune response. Most likely, Porphyromonas gingivalis, a bacterium which is implicated in the development of periodontal diseases and which is capable of producing specific antibodies against citrullinated enolase, which react with human citrullinated antibodies through molecular mimicry, is involved in the pathogenesis of RA [40].

Apart from histocompatibility antigens (DRB*0401, DRB*0404, DRB*0101, DRB*1402), the genetic factors which

Table 2. 2010 EULAR/ACR classification criteria for RA [2]

RA may be suspected in patients who: have at least one joint with definite clinical synovitis with the synovitis not better explained by another disease	
a score of 6/10 is needed for classification of a patient as having definite RA	
JOINT INVOLVEMENT (swollen or tender joints on examination, with synovitis confirmed by imaging, e.g. MRI or ultrasound scans; distal interphalangeal joints and first metatarsophalangeal joints are excluded from assessment)	
1 large joint (shoulder, elbow, hip, ankle)	0
2–10 large joints	1
1–3 small joints (with or without involvement of large joints)	2
4–10 small joints (with or without involvement of large joints)	3
> 10 joints (at least 1 small joint)	5
SEROLOGY (at least one test result is needed for classification)	
Negative RF and anti-CCP	0
Positive RF or anti-CCP ≤ 3 x ULN	2
Positive RF or anti-CCP > 3 x ULN	3
INFLAMMATION PARAMETERS (at least one test result is needed for classification)	
normal CRP or ESR	0
increased CRP or ESR	1
DURATION OF SYMPTOMS	
< 6 weeks	0
≥ 6 weeks	1

CRP – C-reactive protein; ESR – erythrocyte sedimentation rate; anti-CCP – anti-cyclic citrullinated peptide autoantibodies; ULN – upper limit of normal.

play a role in the development of RA include the polymorphism of the protein tyrosine phosphatase non-receptor type 22 gene, polymorphisms of the TNF-α promoter gene, interleukin-1 gene, interleukin-1 receptor antagonist and chemokine receptor CCR5 as well as the polymorphism of the gene coding for peptidylarginine deiminase (PAD14), which is mainly prevalent in the Asian population [18, 27, 47, 68].

The initiation and persistence of inflammation is most likely linked to the response of memory cells (TCD45RO+) to an antigen in genetically predisposed individuals. Stimulation of T cells occurs through the formation of the antigen-MHC complex. The costimulatory proteins in this reaction include CD4 and CD28 molecules on the surface of T cells [53].

Early changes in the synovial tissue of joints show a Th1 response linked to the production of cytokines such as: IL-2, IFN-γ, TNF-α and GM-CSF. Activated (macrophage-like) synoviocytes start to produce IL-1β, TNF-α and IL-6, which contribute to joint destruction through the activation of osteoclasts and matrix metalloproteinases. In addition, IL-6 is responsible for the differentiation of B cells and the production of antibodies. In turn, TNF-α activates surface adhesion molecules, which are involved in the migration of inflammatory cells. TNF-α also stimulates the release of other proinflammatory cytokines, such as IL-1, IL-6 and IL-8, as well as matrix metalloproteinases, which contribute to cartilage damage. TNF-α has an impact, both direct and indirect (through the RANKL/RANK system), on osteoclasts [9, 46, 57, 64].

On the one hand, all the aforementioned factors constitute a mechanism for the formation of inflammatory pannus, which is involved in cartilage damage and bone erosions in joints. On the other hand, some cytokines are the targets of certain drugs used in the treatment of RA (e.g. tocilizumab – an IL-6 pathway inhibitor) [59].

ANAEMIA AND IRON DEFICIENCY

Anaemia is a pathological condition in which the amount of red blood cells and circulating haemoglobin is insufficient to ensure adequate oxygenation of peripheral tissues [10].

Anaemia is defined as a reduction of more than two standard deviations below the mean of either the haemoglobin or haematocrit concentration, or the red blood cell count. Anaemia can be classified by severity as mild (haemoglobin – 10–12 g/dl in women and 10–13.5 g/dl in men), moderate (haemoglobin – 8–9.9 g/dl), severe (haemoglobin – 6.5–7.9 g/dl)or life-threatening (haemoglobin <6.5 g/dl) [30].

Anaemia of chronic disease (ACD) is a multifactorial anaemia in which the activation of cell-mediated immunity and the increased production of proinflammatory cytokines and hepcidin play an important role. One characteristic feature of this type of anaemia is decreased production of erythrocytes [11, 34].

The most common causes of ACD include infections (bacterial, parasitic and fungal), malignancies, autoimmune diseases (rheumatoid arthritis) and chronic urinary tract infections.

In laboratory tests, the following is found: normocytic, normochromic anaemia or, more rarely, microcytic and hypochromic anaemia, small number of reticulocytes, increased ESR, increased cytokine (Il-6) and acute-phase protein (CRP) levels, low iron (Fe) levels, reduced or normal transferrin levels, reduced transferrin saturation, normal or increased serum ferritin levels, normal serum soluble transferrin receptor (sTfR) levels, reduced ratio of sTfR to the logarithm of ferritin, increased hepcidin level, normal or reduced erythropoietin levels [58].

Iron deficiency anaemia (IDA) is characterised by impaired haem synthesis and the production of erythrocytes, which are smaller than normal and contain less haemoglobin as a result of iron deficiency. It is the most common type of anaemia (80%). It affects 1% to 2% of the general population. In Europe, iron deficiency affects approximately 10% of women and 4% of men. The main causes of iron deficiency (ID) include the following:

1. blood loss through the genital tract, gastrointestinal tract, kidneys or respiratory tract,

2. blood loss as a result of injuries and through the gastrointestinal tract caused by the use of nonsteroidal anti-inflammatory drugs,

3. frequent blood donation,

4. prematurity, non-breastfed infants,

5. adolescence,

6. pregnancy and lactation,

7. increased erythropoiesis during B12 supplementation,

8. impaired gastrointestinal absorption (also in the course of H. pylori infection or coeliac disease and in patients with a history of intestinal resection),

9. vegetarian diet, low-protein diet, diet rich in phosphates, oxalates, phytates and tea.

CBC tests show the following:

– hypochromic anaemia (reduced MCH – mean corpuscular haemoglobin/mean cell haemoglobin and MCHC – mean corpuscular haemoglobin concentration), microcytic anaemia (MCV of approximately 75 fl);

– leucopoenia in patients with high iron deficiency;

– normal or increased platelet count;

– hypochromic and microcytic erythrocytes with anisocytosis, poikilocytosis, elliptocytosis and cigar cells in the erythrogram.

Additional tests show reduced serum ferritin levels (<12 ng/ml), reduced serum iron levels, reduced transferrin saturation, increased TIBC, increased transferrin receptor levels and reduced serum hepcidin levels [4, 17, 51]. Rarely, iron deficiency may also be caused by the autosomal recessive mutation of the matriptase-2 gene (a protein involved in hepcidin regulation), which leads to iron-refractory iron deficiency anaemia (IRIDA) [21].

Iron deficiency

Iron deficiency (ID) is defined as a reduction in ferritin levels and transferrin saturation (TSAT) of less than 20%. ID may lead to anaemia, defined as a reduction of more than two standard deviations below the mean of the haemoglobin and haematocrit concentrations, and the red blood cell count. As a result of this process, the ability of red blood cells to carry oxygen is reduced.

Iron deficiency is the most common dietary deficiency. It is estimated that it affects over 2 billion people around the world [74]. The prevalence of ID varies depending on such factors as age, sex as well as physiological, pathophysiological, environmental and socioeconomic factors [16, 41]. Iron deficiency is a major problem in both developing and well-developed countries. For instance, in the USA, ID affects 2% of men and 9% of women [31]. Iron deficiency is commonly associated with low haemoglobin levels. In addition to anaemia, ID leads to poor pregnancy outcomes, impaired school performance and lower productivity [74].

The major causes of anaemia include the loss of erythrocytes as a result of bleeding or haemolysis as well as reduced or impaired erythropoiesis in bone marrow.

The following tests are used to assess iron deficiency and determine its type: ferritin, hepcidin, TIBC (total iron binding capacity) and UIBC (unsaturated iron binding capacity).

Ferritin is both an acute-phase protein and the main protein which stores iron in the body. A total of 1 µg/l of ferritin is equivalent to 8 mg of stored Fe. As ferritin is an acute-phase protein, its concentration is increased in patients with infectious disease, inflammation (rheumatic diseases), malignancy, liver disease or chronic kidney disease. Particularly high ferritin levels, exceeding even 10.000 µg/l, are observed in patients with Still's disease or haemophagocytic syndrome [54, 55].

Hepcidin, a peptide hormone, or more precisely its 25-amino acid form (hepcidin-25), is involved in iron metabolism [19]. As a ferroportin antagonist, it reduces serum iron levels. Its concentration is lower in iron deficiency anaemias [54].

Total iron-binding capacity (TIBC) is a measure of the total amount of iron that can bind to transferrin. One gram of transferrin binds 1.41 mg of Fe. TIBC is increased in both latent and overt anaemia [7].

Unsaturated iron-binding capacity (UIBC) represents the portion of iron binding sites on transferrin that are not occupied by iron. UIBC values are increased in patients with iron deficiency and are reduced in patients with anaemia of chronic disease [7].

ID may be absolute or functional, depending on its pathophysiology [73]. Absolute ID occurs when body iron stores are depleted. Therefore, in such a case, iron measurement is based on the measurement of peripheral blood ferritin levels, which correspond to stored iron, mainly in hepatocytes and reticuloendothelial cells. In functional ID, there are iron stores in the body, but the iron is stored in compartments where it is not available for metabolic processes; it is mainly trapped inside the reticuloendothelial system [29, 48].

It is believed that this is due to excessive inflammatory activation and the resulting increased production of proinflammatory cytokines (mainly interleukin-6) and

hepcidin [8, 25]. Hepcidin is the main protein which regulates systemic iron metabolism. As a result of its excessive expression, iron becomes "trapped" in reticuloendothelial cells and the absorption of iron by enterocytes in the gastrointestinal tract is inhibited. As a consequence, tissues do not receive the amount of iron they need for metabolic processes [28, 29, 48].

Clinical symptoms of iron deficiency include:

– general: weakness, fatigability, impaired concentration and focus, headache, dizziness, pale skin and mucous membranes and, in severe iron deficiency, tachycardia and shortness of breath;

– symptoms not related to anaemia: selective and distorted appetite (e.g. craving for starch), which sometimes precedes anaemia; pain, burning and smoothing of the tongue, dry mouth, dry skin, painful cracking of lip corners, changes in nails (pale, brittle, with vertical ridges), fine and brittle hair with split ends, hair loss [42].

IRON DEFICIENCY IN SERIOUS CHRONIC DISEASES: FREQUENCY, PROGNOSTIC AND CLINICAL CONSEQUENCES

Iron deficiency occurs relatively frequently in patients with different chronic conditions. The majority of randomised clinical trials relating to the treatment of iron deficiency have concerned patients with chronic kidney disease [65]. Recently, studies on iron deficiency in patients with heart failure have also been conducted [5, 33, 51].

Heart failure

In heart failure, iron prevents anaemia and is essential for the functioning of cells that have a high mitotic rate and metabolic turnover (including haematopoietic cells) and high-energy demands due to the intensive mechanical work performed (cardiomyocytes, skeletal muscle cells). It was shown that in patients with heart failure, iron deficiency correlates with impaired exercise tolerance, aggravation of depression symptoms, lower quality of life and increased risk of hospitalisation and death (including cardiovascular death) [32, 33, 48].

According to Okonko et al., the risk of death in patients with iron deficiency is twice as high as that observed in patients with anaemia without iron deficiency [49].

The results of the multicentre FAIR-HF trial confirm the effectiveness of treatment with iron supplementation in patients with heart failure with or without anaemia [5].

Chronic kidney disease

Iron deficiency – both absolute and functional – is one of the two leading causes of anaemia in patients with chronic kidney disease. A reduction in iron stores is secondary to blood loss relating to frequent blood draws or occult gastrointestinal bleeding as well as blood loss during haemodialysis, which may be between ten and twenty times higher compared to that of healthy individuals [24, 50]. Iron deficiency affects 48% to 98% of pre-dialysis patients with chronic kidney disease [62].

Other causes of iron deficiency include impaired iron absorption from the gastrointestinal tract caused by uremic gastropathy, the use of drugs that suppress the secretion of hydrochloric acid or bind phosphates in the gastrointestinal tract, chronic inflammation and vitamin B and C deficiency [15].

Functional iron deficiency is linked to the unavailability of iron for erythropoiesis despite normal iron stores in the body. This occurs during inflammation, which results in iron being bound in ferritin and hemosiderin complexes in the reticuloendothelial system [38].

In the early stages of chronic kidney disease, oral supplementation is used, whereas intravenous supplementation is recommended where oral supplementation proves ineffective. In patients with stage 4 or stage 5 chronic kidney disease, intravenous iron supplementation is used [57].

Both oral and intravenous iron supplementation improves red blood cell parameters and complements treatment with erythropoietin in patients with chronic kidney disease [39].

However, some researchers claim that iron supplementation in patients with chronic kidney disease has adverse effects, i.e. a higher risk of serious cardiovascular incidents and infectious complications [1].

Inflammatory bowel disease

Inflammatory bowel disease is often accompanied by iron deficiency, which is caused by insufficient supply or supplementation of iron or its impaired absorption or excessive loss. Iron deficiency anaemia affects 49% to 74% of patients with inflammatory bowel disease, and over half of patients with inflammatory bowel disease suffer from chronic inflammation [63].

Iron deficiency and the resulting anaemia are associated with a lower quality of life, fatigue, impaired exercise tolerance, higher risk of cardiovascular incidents, lower work capacity (76%, 63% and 60% of patients) as well as an increased risk of hospitalisation and blood transfusions [66]. It was found that oral iron supplementation is an effective treatment method. However, 21% of patients discontinue the treatment due to its side effects [36].

In the active stage of inflammatory bowel disease, oral supplementation is ineffective due to increased hepcidin and TNF-alpha levels [67].

In patients with inflammatory bowel disease, indications for intravenous iron supplementation include: intolerance or ineffectiveness of oral supplementation, severe anaemia

and high bowel inflammatory activity. It has been found that this form of treatment is successful [3].

ANAEMIA AND IRON DEFICIENCY IN PATIENTS WITH RHEUMATOID ARTHRITIS

Prevalence of anaemia and iron deficiency in patients with rheumatoid arthritis

Anaemia is one of the most common complications in patients with rheumatoid arthritis. Its prevalence is 33% to 60%, depending on the research methodology used [26, 72]. The causes of anaemia in RA patients include the following: iron deficiency caused by blood loss, e.g. as a result of long-term treatment with non-steroidal anti-inflammatory drugs, bone marrow hypoplasia resulting from the use of drugs, e.g. cyclophosphamide, vitamin B12 deficiency or folic acid deficiency, e.g. during treatment with methotrexate. Approximately 60% of anaemia in patients with RA is anaemia of chronic disease (ACD). There is no clear data in the literature with regard to iron deficiency in RA patients.

Pathophysiology of anaemia and iron deficiency in patients with rheumatoid arthritis

The pathomechanism of anaemia in patients with RA is complex and multifactorial. On the one hand, in RA, immunecompetent cells become activated and the production of cytokines increases. The latter, i.e. TNF alpha, interferon gamma (most potent inhibitor), and interleukin-1, have direct suppressive effects on the red blood cell system in bone marrow, which results in decreased erythropoiesis. In addition, the production of erythropoietin and iron management become impaired. TNF alpha and interferon gamma inhibit the production of erythropoietin in the kidney. Moreover, the half-life of erythrocytes is decreased as a result of increased erythrophagocytosis, which is of lesser importance [43]. A lower sensitivity of bone marrow to erythropoietin has been observed in patients with ACD, which most likely results from the reduced number of erythropoietin receptors and increased apoptosis of precursor cells in bone marrow [26, 70]. The cytokines such as IL-1, IL-6, IL-10, interferon gamma and TNF-alpha are secreted in RA. This, in turn, leads to the activation of macrophages and the deposition of iron in macrophages [26, 69]. Interferon gamma increases the expression of divalent metal transporter 1 (DMT1) on macrophages, which stimulates the uptake of ferrous iron. The interleukin-10 increases transferrin receptor expression and uptake of transferrin bound iron. TNF alpha induces macrophages to phagocytose erythrocytes for the recycling of iron. Interferon gamma decreases the expression of the iron transporter ferroportin 1, which inhibits iron export from macrophages. This process is also induced by hepcidin. TNF alpha, interleukin-1, interleukin-6, and interleukin-10 induce ferritin expression, which stimulate the retention of iron in macrophages [70]. The aforementioned processes result in reduced serum iron levels and anaemia.

On the other hand, during inflammation, the release of hepcidin, which binds to ferroportin and initiates its destruction, is increased. As a result, hepcidin inhibits the absorption of iron in the gastrointestinal tract and the release of iron from the reticuloendothelial system. IL-6 through STAT3 induces the transcription of the hepcidin-coding gene [26, 44]. As a result of both the processes which take place in RA, iron is not sufficiently available for erythroblasts, despite normal iron storage in the body. Therefore, in patients with RA, increased anaemia severity correlates with excessive production of IL-6 [20, 52].

It was observed that both anaemia and iron deficiency (without anaemia) in inflammatory diseases other than RA, e.g. heart failure, may be associated with reduced exercise tolerance, a worse prognosis and thus reduced work capacity [23, 33].

Clinical consequences of anaemia in patients with rheumatoid arthritis

There is evidence that low haemoglobin levels in RA patients are significantly correlated with disability, activity and duration of the disease as well as damage to joints and joint pain [60]. Treatment of anaemia in RA patients includes iron supplementation, blood transfusions and the use of erythropoiesis-stimulating agents. Importantly, the treatment of the underlying condition itself may lead to an increase in haemoglobin levels [14].

In chronic inflammatory diseases, iron deficiency, even without anaemia, may cause fatigue as well as the aggravation of a given chronic condition, which leads to increased morbidity and mortality. Iron deficiency is very common. However, it is often disregarded, especially in patients with chronic conditions, even though it has an impact of the wellbeing of patients. In the literature, there are reports concerning iron deficiency in patients with heart failure, renal failure and chronic bowel diseases. There are no such reports or treatment recommendations for patients with RA [32].

Anaemia and iron deficiency in patients with rheumatoid arthritis treated with biological agents

Biological treatments used in patients with RA, e.g. infliximab (anti-TNF-α monoclonal antibody), tocilizumab (anti-IL-6 receptor antibody) and anakinra (anti-IL-1 antibody), not only effectively inhibit the progression of joint involvement, but may also prevent anaemia [61].

Tocilizumab is a humanised monoclonal antibody targeted at both membranous and soluble (Mil-6R, Sil-6R) IL-6 receptors. The drug was initially used in the treatment of Castelman disease. In 2009, it was registered in the European Union for the treatment of moderate and severe RA in combination with methotrexate (MTX) or in monotherapy. It is administered by intravenous infusion every 4 weeks at a dose of 8 mg/kg of bodyweight [35]. Blockade of IL-6, a key inflammatory cytokine produced mainly by monocytes and macrophages, which is mediated mainly by IL-1, makes it possible, among other things, to block the activation of antigen-recognising T cells and stimulate

differentiation of B cells into plasma cells that synthesize antibodies and to block the synthesis of acute-phase proteins in the liver [37]. However, despite the pathophysiological relationship between ID with anaemia and inflammation, data on iron management in RA patients is quite enigmatic. There are only a few studies which analyse anaemia in RA patients with iron deficiency [12]. It is also not clear whether anti-inflammatory treatment (e.g. blocking the IL-6 pathway) may have an impact on iron management in RA patients.

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