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REVIEW

The investigation and treatment of secondary anaemia

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ABSTRACT

Secondary anaemia or the anaemia of chronic disease (ACD) is the commonest form of anaemia in hospitalised patients and the second most prevalent anaemia worldwide after iron deficiency. It is characterised by defective iron incorporation in erythropoiesis, an impaired response to erythropoietin, a decrease in erythropoietin production and cytokine induced shortening of red cell survival.

For many patients with ACD the cause is apparent but for many others the underlying disease needs to be determined and such patients are often referred to haematologists for investigation. The search for the cause can be a fascinating exercise in good history taking, examination skills and performing and interpreting appropriate investigations. This review covers the pathogenesis and causes of ACD and then discusses the clinical and laboratory investigation of a patient with suspected ACD. Finally, the management of a patient with ACD is discussed including erythropoiesis stimulating agents (ESAs), intravenous iron and future therapies.

1. Introduction

Secondary anaemia is the commonest form of anaemia in hospitalised patients and the second most prevalent worldwide after iron deficiency[1]. It occurs in patients with chronic illnesses such as chronic infections, cancer, autoimmune disorders and chronic kidney disease and is also known as 'anaemia of chronic disease' (ACD) or 'anaemia of inflammation'.

For many patients the underlying cause of the ACD is obvious. Others will present with the ACD and the search for the cause can be an interesting and rewarding piece of clinical medicine. The anaemia is often ignored and assumed not to contribute to the patients' symptoms. However, there is now strong evidence that it can independently worsen morbidity and mortality and negatively impact on a patient's quality of life[2,3]. Therefore, increasingly there is a drive to improve the management of this anaemia although it will need to be proven that improving the haemoglobin concentration will have a positive impact on either patients' quality of life, life expectancy or both.

This review will briefly cover the pathogenesis of ACD and then discuss the investigation and management in detail.

2. Pathogenesis

There are four known mechanisms that contribute to the development of anaemia in chronic disease; defective iron incorporation in developing red blood cells, a blunted erythropoietin response to anaemia, decreased sensitivity of erythroid precursors to erythropoietin and shortened red cell survival. These are all thought to be immunologically based, and therefore occur in patients with conditions that cause acute or chronic immune activation such as those listed in Table 1. In patients with chronic kidney disease the marked reduction in erythropoietin production is the most important factor in causing anaemia but these patients also have features of the ACD.

2.1. Defective iron incorporation in developing red blood cells

Approximately 10 years ago, the liver polypeptide, hepcidin[4,5] was discovered. It plays a pivotal role in iron homeostasis[6] and immunological driven changes in hepcidin levels are critical for the development of ACD.

Table 1
Conditions that can be associated with anaemia of chronic disease.

Autoimmune disease
Rheumatoid arthritis, polymyalgia rheumatica, systemic lupus erythematosus, inflammatory bowel disease
Malignancy
Solid tumours (especially metastatic), haematological cancers
Infections
AIDS, infective endocarditis, tuberculosis, osteomyelitis
Renal disease
Chronic kidney disease

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As outlined in Fig. 1, hepcidin is predominantly produced by hepatocytes and inhibits iron release from macrophages and iron uptake by intestinal epithelial cells. In macrophages it accelerates the degradation of the trans membrane iron exporter, ferroportin 1 mRNA. In intestinal epithelial cells it is believed to down-regulate divalent metal transporter 1 (DMT-1) which is involved in the transfer of iron across the intestinal wall[7]. Hepcidin expression is controlled by the bone morphogenetic protein (BMP) receptor, its signalling pathway and the accessory proteins; HFE, hemojuvelin and transferrin receptor 2 (TfR2). High saturation of TfR2 is conveyed to the BMP receptor complex via HFE and hemojuvelin and this then up-regulates transcription of hepcidin by Smad4[8]. Hepcidin then acts to down-regulate release of iron from macrophages and iron absorption. In normal conditions; the presence of hypoxia, iron deficiency and ineffective erythropoiesis reduces the

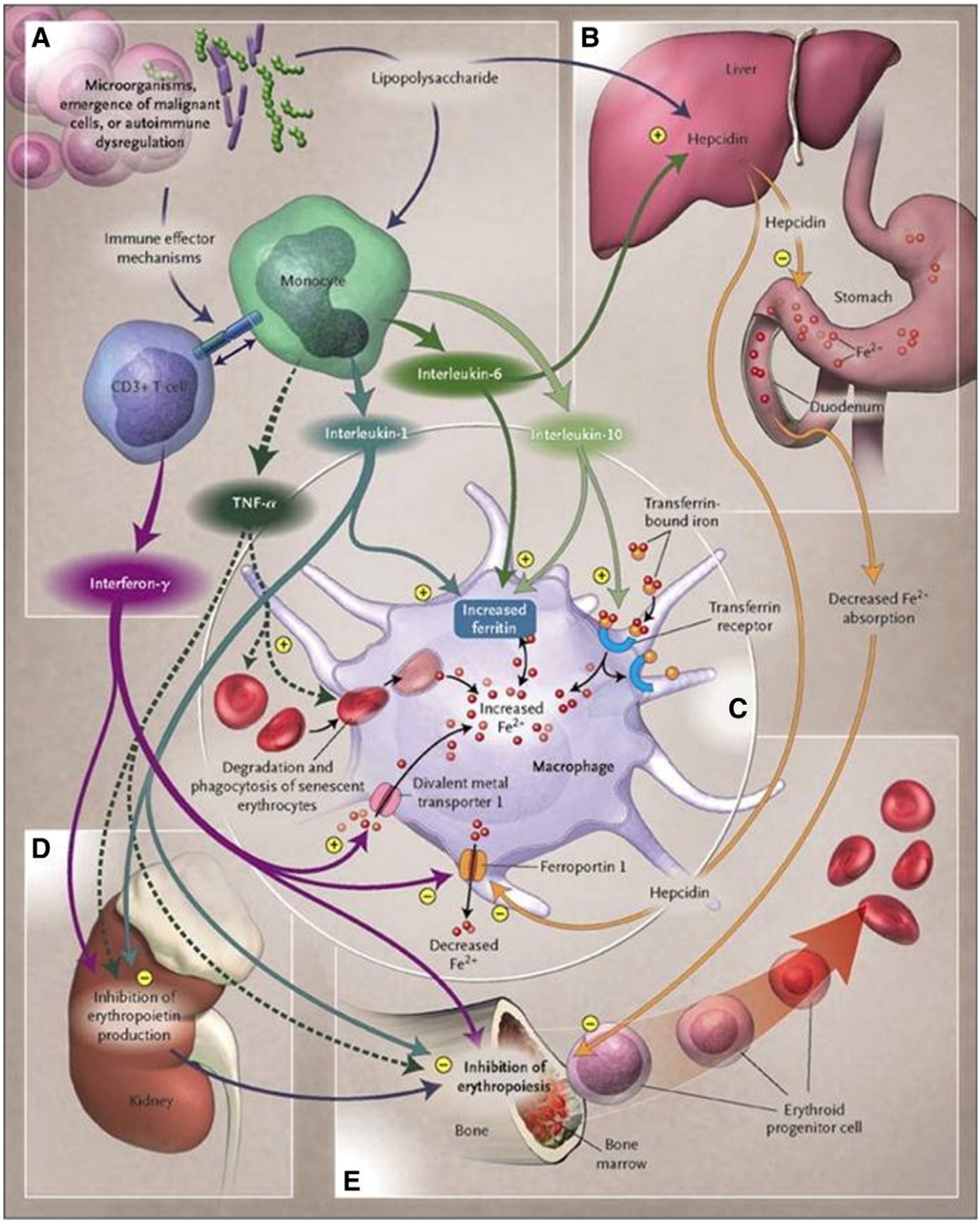

Fig. 1. The pathophysiology of the anaemia of chronic disease.
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