Journal of Autoimmunity 74 (2016) 139–160

Contents lists available at ScienceDirect

Journal of Autoimmunity

journal homepage: www.elsevier.com/locate/jautimm

Review article

The diagnosis and management of the haematologic manifestations of lupus

Alba Velo-García [b, 1], Sara Guerreiro Castro [c, 1], David A. Isenberg [a, *]

[a] Department of Rheumatology, University College London, UK
[b] Internal Medicine Department, University Hospital Complex of Pontevedra, Pontevedra, Spain
[c] Autoimmune Diseases Unit, Internal Medicine 7.2 Department, Hospital Curry Cabral, Centro Hospitalar Lisboa Central, Lisbon, Portugal

ARTICLE INFO

Article history:
Received 29 June 2016
Accepted 1 July 2016
Available online 25 July 2016

Keywords:
Systemic lupus erythematosus
Anaemia
Leukopaenia
Thrombocytopaenia

ABSTRACT

Haematological manifestations in systemic lupus erythematosus (SLE) are frequently observed. They are diverse and range from mild to severe. Therefore, different treatment approaches are needed from simply keeping vigilant to significant immunosuppression. Most treatment evidence is based on case-reports or small retrospective studies, as few randomized controlled trials have been performed. The development of biological therapy has opened new possible ways to treat the most severe cases but further clinical trials are necessary.

In this review we consider the most common and characteristic haematological manifestations of SLE patients, focusing on their pathogenesis and management.

Contents

* Corresponding author. Rayne Institute, UK.
E-mail addresses: alba.velo@gmail.com (A. Velo-García), saragcastro@gmail.com (S.G. Castro), d.isenberg@ucl.ac.uk (D.A. Isenberg).

[1] Alba Velo-García and Sara Guerreiro Castro contributed equally to this review.

http://dx.doi.org/10.1016/j.jaut.2016.07.001
0896-8411/

1. Introduction

Haematological manifestations in systemic lupus erythematosus (SLE) are common and diverse. Their frequency varies in different populations [1]. These manifestations can be due to the disease itself, another concomitant disease or iatrogenic. Haemolytic anaemia, leukopaenia, lymphopaenia and thrombocytopaenia are incorporated into both the 1997 update of the 1982 American College of Rheumatology (ACR) [2] and the 2012 Systemic Lupus International Collaborating Clinics (SLICC) [3] classification criteria for SLE.

Most of these manifestations are caused by increased peripheral destruction of blood cells associated with circulating autoantibodies. The major haematological manifestations of SLE are anaemia, leukopaenia, thrombocytopaenia, and the antiphospholipid syndrome (APS). The bone marrow (BM) may also be a target in SLE and features such as myelofibrosis, aplastic anaemia and pure red cell aplasia can also occur. In this review we will consider the pathogenesis and management of these specific manifestations.

2. Red blood cell associated pathologies

A summary of red blood cell associated pathologies in SLE patients is shown in Table 1.

2.1. Anaemia

Anaemia is frequent, affecting more than 50% of patients throughout the course of the disease [4,5].

Anaemia is defined as haemoglobin of less than 12 g/dl in women and 13.5 g/dl in men [6]. It can be both immune and non-immune mediated in SLE patients.

2.1.1. Anaemia of chronic disease

2.1.1.1. Introduction. Anaemia of chronic disease (ACD) is the most common type of anaemia in SLE patients, responsible for about one third of the cases [7].

It usually presents as normocytic and normochromic anaemia, with normal or elevated serum ferritin levels and a normal BM.

2.1.1.2. Pathogenesis. The aetiology of ACD in SLE is still not fully understood but it seems to be related to changes in iron homeostasis, inadequate erythropoietin (EPO) response or activity and impaired erythropoiesis. A schematic explanation is presented in Fig. 1.

2.1.1.2.1. Iron homeostasis. During inflammation, iron homeostasis is significantly affected, as hepcidin production is regulated by iron. Hepcidin is a hormone produced in the liver that prevents iron from entering into the plasma compartment, by inhibiting iron absorption in the duodenum and its release from hepatocytes and macrophages. It is tightly regulated by the levels of serum iron and its production increases when iron is abundant, preventing further absorption and release from stores. Its production diminishes or ceases when iron is deficient [8]. It prevents iron efflux by interacting with ferroportin 1 at the cell surface, leading to internalization and degradation of ferroportin 1 protein [9].

Hepcidin production also seems to be regulated by inflammatory cytokines. IL-6 induces the production of hepcidin and a consequent hypoferraemic state [10]. Similarly adding IL-6-neutralizing antibodies to hepatocyte cultures ablated hepcidin production. IL-6 levels were significantly higher in SLE patients with active haematological disease and in those patients with anaemia the mean levels of IL-6 were significantly higher than in those patients without it [11]. The Signal Transducer and Activator of Transcription 3 (STAT3) binding site at position −64/-72 of the hepcidin promoter controls IL-6-dependent transcriptional activation and knockdown of STAT3 by RNAi reduces hepcidin mRNA expression, implying that stimuli which activate hepatic STAT3 may also enhance hepcidin expression [12]. Inflammatory immune regulators such as IFN-γ and lipopolysaccharides seem to increase monocytes iron acquisition, by stimulating divalent metal transporter 1 (DMT-1) expression and to retain the metal within the cells by inhibiting ferroportin synthesis [13]. In contrast, pro-hepcidin levels do not seem to correlate with disease activity, cytokine levels or serum iron levels in SLE patients [14].

Other cytokines, including TNF-α, IFN-γ and IL-1, are part of iron homeostasis by reducing the concentration of transferrin receptor on cell surface and increasing ferritin synthesis [9].

2.1.1.2.2. Erythropoietin. The pathogenesis of ACD in different autoimmune diseases is related to reduced EPO activity, due to reduced production and erythroid cells resistance. EPO is