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Review article

Immunomodulators in SLE: Clinical evidence and immunologic actions

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ABSTRACT

Systemic lupus erythematosus (SLE) is a potentially fatal autoimmune disease. Current treatment strategies rely heavily on corticosteroids, which are in turn responsible for a significant burden of morbidity, and immunosuppressives which are limited by suboptimal efficacy, increased infections and malignancies. There are significant deficiencies in our immunosuppressive armamentarium, making immunomodulatory therapies crucial, offering the opportunity to prevent disease flare and the subsequent accrual of damage. Currently available immunomodulators include prasterone (synthetic dehydroeipandrosterone), vitamin D, hydroxychloroquine and belimumab. These therapies, acting via numerous cellular and cytokine pathways, have been shown to modify the aberrant immune responses associated with SLE without overt immunosuppression.

Vitamin D is important in SLE and supplementation appears to have a positive impact on disease activity particularly proteinuria. Belimumab has specific immunomodulatory properties and is an effective therapy in those with specific serological and clinical characteristics predictive of response. Hydroxychloroquine is a crucial background medication in SLE with actions in many molecular pathways. It has disease specific effects in reducing flare, treating cutaneous disease and inflammatory arthralgias in addition to other effects such as reduced thrombosis, increased longevity, improved lipids, better glycemic control and blood pressure. Dehydroeipandrosterone is also an immunomodulator in SLE which can have positive effects on disease activity and has bone protective properties.

This review outlines the immunologic actions of these drugs and the clinical evidence supporting their use.

Contents

1. Introduction

Systemic lupus erythematosus (SLE) is a chronic, multisystem,

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autoimmune condition characterized by the presence of autoantibodies to nuclear material and immune complex deposition in involved tissues. Whilst numerous advances have been made in unraveling the pathogenesis of this complex disease, it remains incompletely understood. A multitude of cell types and molecules, participating in many cellular mechanisms have been implicated in SLE. Abberancies in apoptotic pathways and in innate and adaptive immune mechanisms are found in patients with SLE, with genetic, epigenetic, environmental and hormonal factors known to contribute to the disease. There are a number of central events in the development of SLE, these include increased production of autoantibodies during apoptosis, decreased clearance of cellular debris with dysregulated handling and presentation. Subsequent disease activity and tissue damage is mediated by autoantibodies, immune complexes and complement activation with numerous cytokine and interferon pathways implicated. The complexity of these disease mechanisms have meant that there are a multitude of possible targets for immunomodulation in SLE. However, at present, there are few tools in our therapeutic armamentarium which can be considered immunomodulatory. For the most part, we rely on immunosuppressives, in particular for organ specific disease.

Improvements have been made in pharmacotherapy over the past 50 years which have positively impacted upon the prognosis of SLE although, disappointingly, poor renal outcomes [1,2], cardiovascular disease and the accumulation of organ damage often incited by high dose prednisone remain major challenges. Therapeutic advances include anti-malarials, corticosteroids, immunosuppressives, ace inhibitors, antibiotics, B-cell therapies, vitamin D supplementation and dehydroeipandrosterone (DHEA). Despite these therapies SLE continues to associate with premature mortality and morbidity. Current strategies rely heavily on the immunosuppressive properties of corticosteroids to control inflammation. Chronic and high dose corticosteroids associate with significant morbidity and are responsible for much of the long-term damage accrual in SLE. Other immunosuppressives, such as mycophenolate mofetil, methotrexate and azathioprine, are essential in the management of organ specific disease, however they are limited by efficacy, in particular in renal disease.

Immunomodulating therapies that are not immunosuppressive, are a more attractive therapeutic option, offering the opportunity to modify the aberrant immune responses in SLE and thus prevent inflammation and subsequent damage without the risks of infection and malignancy. Current strategies, considered to have immunomodulating properties, include hydroxychloroquine (and other antimalarials), vitamin D, dehydroeipandrosterone and certain B cell therapies. Stem cell transplantation is as of yet unproven in randomized controlled studies for SLE but offers a fascinating perspective on immunomodulation and may, in the future, be a therapeutic option for those with severe, life threatening disease. Here we review current immunomodulating strategies in SLE, their clinical efficacy and examine their mechanisms of action.

2. Dehydroeipandrosterone

Dehydroeipandrosterone is a weak androgenic steroid and with its metabolite, dehydroepiandrosterone sulphate (DHEAS), is the most abundant adrenal steroid hormone. Dehydroeipandrosterone is a precursor of both androgens and estrogens and is synthesized primarily by the adrenal cortex (zona reticularis) from 17 α-hydroxypregnenolone. It can then be sulphated, at the 3β'-hydroxyl group, into dehydroepiandrosterone sulphate in the adrenals and in peripheral tissues, dehydroeipandrosterone is also metabolized further into more active steroids including androstenedione, testosterone and estrogen [3]. In its drug form it is called prasterone.

Normal serum levels of dehydroeipandrosterone range from 1 to 50 nM. During fetal development, plasma dehydroepiandrosterone sulphate levels are 100– 200 μg/dL (3– 7 μM), falling rapidly after birth and remaining low until adrenarche. Levels then increase rapidly, followed by an age related decline [4]. This decline is possibly mediated by decrease in 17,20-lyase activity [5]. The rate of decline of blood levels is in the region of 2% per year, by the 8th-9th decade residual levels are 10–20% of their peak [6]. There are gender differences to consider with higher levels in males [7]. In addition to these considerations there are genetic variations. Genome-wide association studies (GWAS) indicate that serum levels of dehydroepiandrosterone sulphate are regulated at approximately 60% by genotypes near these genes: BCL2L11, ZKSCAN5, ARPC1A,TRIM4, HHEX, CYP2C9, BMF, and SULT2A1[8].

Dehydroeipandrosterone does not have a specific receptor. It can bind to steroid hormone receptors (reviewed by Triash et al. [9], and by Webb et al. [5]) pregnane X receptor/steroid and xenobiotic receptor (PXR/SXR, NR1I2) [5]; estrogen receptors α and β, androgen receptors [10]; peroxisome proliferator activated receptors [5]; and pregnane X receptor [11]. At most of these sites, dehydroeipandrosterone acts as a partial agonist with weak affinity due to competition for binding. Taking into account the fact that dehydroeipandrosterone is itself a precursor for many of the higher affinity molecules, it is difficult to estimate the degree to which dehydroeipandrosterone itself is effective.

The principal regulator of dehydroeipandrosterone production, is adrenocorticotropic hormone. This in turn depends on corticotropin releasing hormone of hypothalamic origin for regulation [3]. In adults, dehydroeipandrosterone levels peak in the morning, following the circadian pattern of ACTH secretion [12]. The biological effects of dehydroeipandrosterone can be considered both androgenic and estrogenic since it is a precursor of both. Labrie et al. suggest that more than 30% of total androgen in men and over 90% of estrogen in postmenopausal women are derived from peripheral conversion of dehydroeipandrosterone [13]. Elevated dehydroeipandrosterone contributes to disorders associated with hyperandrogenic states such as in polycystic ovarian disease and non-classical 21-hydroxylase deficient congenital adrenal hyperplasia [14]. Low levels have been associated with many age related disorders and with multiple autoimmune conditions, including SLE.

Women with SLE have been shown in numerous studies, reviewed by McMurray et al., to have significantly depressed concentrations of androgens and elevated levels of estradiol compared with both males with SLE and healthy controls [15]. In female patients with SLE, levels of both dehydroeipandrosterone and dehydroepiandrosterone sulphate are low [15–17]. Lahita et al. demonstrated low levels of all androgens in females with SLE with the lowest amount of both metabolites in those with active disease [16]. The fact that SLE is commonly treated with corticosteroids has been considered to be a confounding factor due to inhibitory feedback mechanisms. However, steroid naïve SLE patients have also been shown to have low levels of dehydroeipandrosterone [16].

Dehydroeipandrosterone exerts anti-proliferative and anti-inflammatory effects, and modulates immune function. Prasterone (synthetic dehydroeipandrosterone) therapy has been shown in small studies to be beneficial in depression [18] with promise in the management of the negative symptoms of schizophrenia [19,20]. There is little evidence to lend support to the theory that it may have anti-aging effects. As it is known to have some androgenic properties, supplementation has been associated with mild virilization, acne, voice changes and terminal hair growth.

There is evidence that dehydroeipandrosterone has activity on multiple cytokine and immunologic pathways. Numerous studies