Clinical Immunology (2013) **148**, 335–343

available at www.sciencedirect.com

Clinical Immunology

www.elsevier.com/locate/yclim

REVIEW

Cytokine inhibition as a strategy for treating systemic lupus erythematosus

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Received 2 September 2012; accepted with revision 4 November 2012
Available online 12 November 2012

KEYWORDS
Cytokine Inhibitors;
Lupus

Abstract Cytokines regulate and control the immune system. In systemic lupus erythematosus, several of these cytokines are overexpressed and contribute to the pathogenesis of the disease. Cytokine inhibition has been successfully used to treat other rheumatic and autoimmune diseases, and several cytokines are currently being investigated to determine whether inhibition would be therapeutic in lupus. The cytokines discussed in this review have all undergone clinical trials, and include TNF-α, IL-1, IL-6, IL-10, IL-15, IL-17, IL-18 and IL-23. Inhibition of the majority of these targets was safe and showed some efficacy in treating lupus. Cytokine inhibition strategies have just started to realize their potential for the treatment of this difficult disease, and show great promise for the future.

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1521-6616/$ - see front matter
http://dx.doi.org/10.1016/j.clim.2012.11.001

1. Introduction

Systemic lupus erythematosus (SLE) is a highly complex and diverse disease. Despite substantial research, the etiology and pathogenesis of lupus are still not well understood. Additionally, the course of lupus, with its remission and flares, makes evaluation of therapies difficult. Due to these obstacles, treatment for lupus has lagged behind many other diseases, with only one new medication for lupus treatment approved by the United States Food and Drug Administration (FDA) in the last 50 years.

Infusion with monoclonal antibodies or other specific proteins, such as soluble receptors that specifically target and inhibit cytokines is revolutionizing the practice of rheumatology. These agents have been used with good effect in the treatment of rheumatoid arthritis and other autoimmune or inflammatory disorders such as Crohn's disease and psoriasis. Given the importance of inflammation and immune control in lupus, these agents hold great promise for treating lupus as well. Inhibition of several cytokines as therapeutics for lupus is under investigation, and one has met with success and FDA approval. However, given the complexity and course of lupus, the results of these trials have been somewhat mixed. This review will summarize the current approaches and strategies for inhibiting cytokines as a therapeutic mechanism in the treatment of lupus, and will include a discussion of cytokine inhibitors that have been tested in lupus as well as those which are applicable to lupus and have been tested in other diseases.

2. Current cytokine inhibitors undergoing trials as lupus treatments

Two of the most promising cytokines that have been inhibited as a treatment for lupus, BLyS and IFN-α, will be discussed in other articles in this special issue, therefore they will not be included here. Instead, the cytokines IL-6, TNF-α, IL-1 and IL-10, inhibitors of which have undergone clinical trials for lupus, will be discussed.

2.1. Interleukin 6

IL-6 is a cytokine produced by many cell types. It has multiple effects on many target cells, inducing CD4+ T cell differentiation, B cell development, and the production of acute phase proteins. It also drives production of IL-17-producing T cells [1]. IL-6 is found at increased levels in lupus patients compared to controls [1], and is also higher in lupus patients with nephritis compared to either controls or lupus patients without renal involvement [2]. B cell-produced IL-6 has been shown to contribute to autoantibody production [3]. Certain IL-6 promoter polymorphisms may contribute to genetic risk for lupus [4].

IL-6 deficient mice are resistant to lupus. IL-6-deficient MRL-Fas(lpr) mice have delayed onset nephritis and much higher survival than control mice, along with decreased cellular infiltration, complement deposition, and Ig deposition [5]. Other IL-6 deficient mice showed that anti-DNA antibody production was dependent on IL-6 in pristane-induced lupus, although the development of antibodies against RNA-binding proteins was not [6], suggesting different pathways for autoantibody production in lupus (Fig. 1).

An anti-IL-6 receptor antibody, Tocilizumab, is approved for use in rheumatoid arthritis, with seven phase three trials completed [7]. The safety profile and effectiveness of IL-6 blockade in rheumatoid arthritis is therefore well-established. There has been one successful open-label phase I dose-escalation trial of Tocilizumab in SLE [8]. The major side effect of treatment was neutropenia, with 56% of participants experiencing neutropenia at the highest dose (8 mg/kg). One participant was withdrawn because of neutropenia, however, no neutropenia-related infections were identified [8]. Neutropenia was also noted in the studies of Tocilizumab for rheumatoid arthritis, but in those studies was also not associated with infection or malignancy [7], although there is a higher risk of infection with Tocilizumab treatment (Table 1).

Tocilizumab showed promise in treating lupus, with effects that seemed directed at autoantibody production. The modified SELENA-SLEDAI scores decreased moderately but significantly from a mean of 9.5 to 5.5 [8], with most of the improvement in rash and arthritis. Anti-dsDNA levels decreased by a mean of 46.8%. This decrease in autoantibodies may be associated with decreased circulating plasma cells. Circulating plasma cells decreased by nearly 36% in the treated individuals, and remained at this low level during follow up [8]. It may be the case that the drop in plasma cells and therefore autoantibodies is responsible for the decreased rash and arthritis in treated volunteers, but these clinical responses may also be due to some other aspect of IL-6 blockade.

2.2. Tumor necrosis factor-α

TNF-α is a proinflammatory cytokine with pleiotropic effects on multiple cell types. TNF-α activates macrophages, induces the release of further proinflammatory cytokines, regulates apoptosis of lymphocytes and other cells, and aids in cell migration [9]. In lupus, TNF-α acts as a growth factor for B cells stimulating production of IL-6 and IL-1. NZB/W mice with low expression of TNF-α develop severe lupus-like disease, but addition of TNF-α later in disease also exacerbates lupus [10–12]. These results suggest that TNF-α aids in preventing the development of lupus, but once established, worsens the resulting inflammation and pathogenesis.

Inhibition of TNF-α has met with substantial success in treating rheumatoid arthritis, as well as other inflammation-mediated diseases such as Crohn's disease and spondyloarthritis. Lupus would seem at first glance to be a good candidate for TNF-α inhibition, since TNF-α is significantly increased in the