The Role of Interleukin-6 in Castleman Disease

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KEYWORDS

• Interleukin-6 • Humanized anti-IL-6 receptor antibody • Tocilizumab
• Chimeric anti-IL-6 antibody • Siltuximab • Multicentric Castleman disease
• IL-6 blocking therapy

KEY POINTS

- Since its discovery in 1956, Castleman disease has been the target of ongoing research, which has led to safe and effective treatment.
- Interleukin-6 (IL-6) has been implicated in Castleman disease. Most systemic symptoms of plasma cell variant of Castleman disease were linked to the hyperfunction of IL-6, which is continuously produced in the affected lymph node in 1989.
- A humanized anti-IL-6 receptor antibody (myeloma receptor antibody [MRA], tocilizumab, actemra) was generated in 1993 and used in the treatment of multicentric Castleman disease (MCD).
- Most MCD symptoms and abnormal laboratory findings were reported to be improved by tocilizumab and siltuximab therapy, respectively, in 2000 and 2009.
- Although other treatment agents for MCD are being refined, such as JAK inhibitors and rapamycin, current research is now focused on discovering the mechanisms that render tocilizumab effective in treating MCD.

INTRODUCTION

Castleman disease is a lymphoproliferative disease with benign hyperplastic lymph nodes and is classified pathologically in 2 forms: hyaline vascular and plasma cell. Multicentric Castleman disease (MCD) has the characteristics of plasma cell infiltration in the

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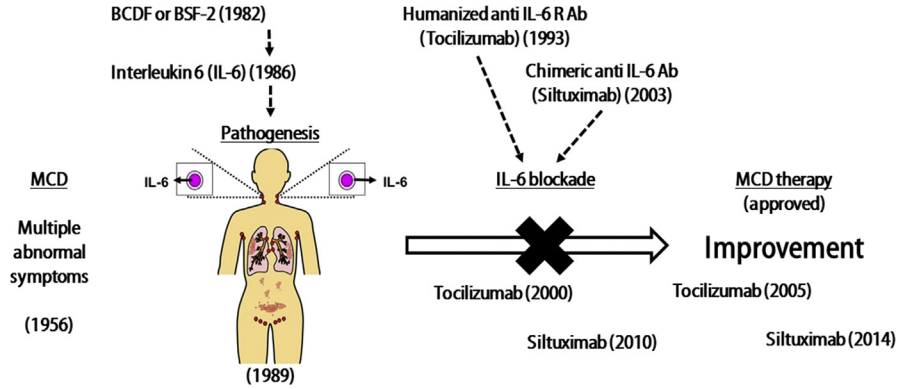

Fig. 1. Development of IL-6 blocking therapy on MCD. Ab, antibody.

affected lymph nodes with systemic manifestations, such as fever, fatigue, anemia, hypergammaglobulinemia, hypoalbuminemia, and an increase in acute phase proteins, such as C-reactive protein (CRP), serum amyloid A (SAA), fibrinogen, and hepcidin. Interleukin-6 (IL-6) is a pleiotropic cytokine that regulates immune responses, induces acute phase proteins, and supports hematopoiesis. IL-6 has been implicated in Castleman disease, and over the years, there has been an increasing body of research that aims to uncover the role IL-6 as well as its mechanism of action in Castleman disease.

This article is a review of IL-6 and IL-6 blocking therapy for MCD (Fig. 1). The authors describe how IL-6 was first identified and how anti-IL-6 treatments have progressed over the years, and discuss discoveries that have been made about the mechanism whereby IL-6 blocking agents alleviate MCD. This report discusses the case of 2 patients with plasma cell variant Castleman disease that allowed the first confirmation of IL-6 production in their affected lymph nodes. These 2 cases highlighted the correlation between IL-6 serum levels and clinical features, indicating that dysregulated production of IL-6 in enlarged lymph nodes might be responsible for the systemic manifestations of MCD. In later studies, attempts have been made to treat MCD using IL-6 blocking therapy with a humanized anti-IL-6 receptor antibody (tocilizumab) or a chimeric anti-IL-6 antibody (siltuximab). Results from these studies have demonstrated that both forms of IL-6 blocking therapy are safe and have delivered remarkable results in treating MCD patients.

DISCOVERY, PRODUCTION, AND FUNCTION OF INTERLEUKIN-6

IL-6 was first isolated from lymphocyte culture supernatants and was originally characterized and cloned as a B-cell differentiation factor (BCDF or BSF-2) that induces the final maturation of B cells into immunoglobulin-producing cells.[1,2] IL-6 is a glycoprotein secreted by T cells, B cells, and macrophages and has an apparent molecular weight of 22 to 27 kDa. It is composed of 212 amino-acid residues, including 28 amino-acids signal peptides (Fig. 2A).[3] IL-6 is produced by various cells, including immunocompetent cells (T cell, B cell, macrophage, dendritic cells), hematopoietic cells, endothelial cells, epithelial cells, fibroblasts, synovial cells, and osteoblasts. IL-6 production is induced through innate and acquired immune responses and is augmented in response to various antigenic stimulations, including bacteria, virus, several biomolecules, cytokines, and chemokines. IL-6 has pleiotropic functions, as shown in Fig. 3. IL-6 induces cell growth and differentiation, cytokines, immunoglobulins, and acute phase proteins[4–6] as well as the activation of sympathetic nerve, including the central nervous system. Therefore, when IL-6 production increases or