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Therapeutic monoclonal antibodies in ophthalmology

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A B S T R A C T

Monoclonal antibodies (mAbs) can be used therapeutically by binding to molecular targets with high specificity. Therefore, they have excellent therapeutic applications in ophthalmology. This manuscript presents four aspects of the therapeutic use of mAbs in ophthalmology: the scientific rationale, the unique characteristics of selected mAbs, the current state-of-the-art application, and relevant therapeutic mAbs for future applications in ophthalmology. We identified in the literature various single-agent therapies that inhibit the following targets: tumor necrosis factor (TNF), epithelial growth factor receptor, vascular endothelial growth factor (VEGF) receptor, basic fibroblast growth factor receptor, platelet-derived growth factor, and cluster of differentiation antigens. The roles of all biochemical targets in ocular diseases were evaluated. Current and future mAbs against various cytokines were assessed for the treatment of ocular diseases. The medical literature showed the clinical benefits of mAbs for treating angiogenic and inflammatory ocular diseases. Two anti-VEGF mAbs, bevacizumab and ranibizumab, and three anti-TNF agents, infliximab, etanercept, and adalimumab, control ocular neovascularization and intraocular inflammation. Other mAbs such as rituximab, daclizumab, efalizumab, and alemtuzumab showed positive results in animal and early clinical studies and may represent useful adjuvant therapies for ocular lymphoma or ocular inflammation. Ranibizumab is the only FDA-approved therapy; for other mAbs the so-called off-label application remains the standard. Intravenous administration of mAbs has demonstrated acceptable toxicity profiles, while intraocular injection may decrease the chances of systemic complications and increase the amount of drug available to the retina and choroid. In conclusion, effective clinical use of mAbs in ophthalmology is more commonly seen in the field of angiogenic vitreoretinal and autoimmune inflammatory diseases. The challenge for the future is combining biologic therapies to improve the quality and duration of responses while diminishing side effects. The role of mAbs within ophthalmic treatments will be defined according to future clinical experience and the results of randomized clinical trials.

Contents

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1. Introduction

Monoclonal antibodies (mAbs) are a class of antibody molecules comprised of one type of immunoglobulin produced from one B-cell clone that recognizes a specific antigenic target (Teillaud et al., 2002). mAb production was introduced as a research tool in 1975 with the advent of hybridoma technology in animals, followed by the development in 1986 of the murine anti-CD3 mAb for therapies (Kohler and Milstein, 1975; Goldstein et al., 1986). Rejection of these murine mAbs by the human immune system was a barrier to human use, but advances in biotechnology reduced this problem with the production of high-quality chimeric, humanized, or completely human mAbs (Fig. 1) (Jones et al., 1986; Lonberg, 2005; Vitetta and Ghetie, 2006). These advances led to the development of excellent therapeutic agents for neoplastic, rheumatologic, and infectious diseases, with a substantial impact on improvement in human health (Reichert, 2001; Waldmann, 1991).

In ophthalmology, therapeutic mAbs have been introduced recently to treat inflammatory and angiogenic diseases (Fig. 2) (Avery et al., 2006; Bashshur et al., 2006; Hale and Lightman, 2006; Joseph et al., 2003; Lindstedt et al., 2005). The rationale for mAb application in ophthalmology also is based on a recent understanding of the molecular biology of various ocular diseases. In inflammatory ocular conditions, cytokine tumor necrosis factor alpha (TNF-α, or TNF-A) participates in the pathogenesis of autoimmune ocular inflammatory diseases, e.g., uveitis, and chimeric anti-TNF-α mAb infliximab and the newer adalimumab control uveitis and other inflammatory eye diseases (Dick et al., 2004; Singh and Rai, 2001). Regarding ocular angiogenesis, cytokine vascular endothelial growth factor (VEGF) participates actively in new vessel formation in various neovascular conditions including diabetic retinopathy (DR) and age-related macular degeneration (AMD) (Duh and Aiello, 1999; Miller, 1997). Recently, full-length mAb anti-VEGF bevacizumab (Avastin, Genentech, South San Francisco, CA) and VEGF-fragment ranibizumab (rhuFabV2, Lucentis, Genentech, South San Francisco, CA) have been reported to promote marked regression of intraocular neovascularization in experimental and clinical studies (Kaiser, 2006; Campochiaro, 2004). In the current manuscript, we review the advantages, limitations, efficacy, and risks of mAb application in ophthalmology with emphasis on ocular angiogenesis and inflammation. A list of mAbs used in ophthalmology is summarized in Table 1. Although the role of cytokines may overlap with the pathophysiology of human ocular disease, this manuscript focused on each cytokine involved in ocular diseases to provide better comprehension.

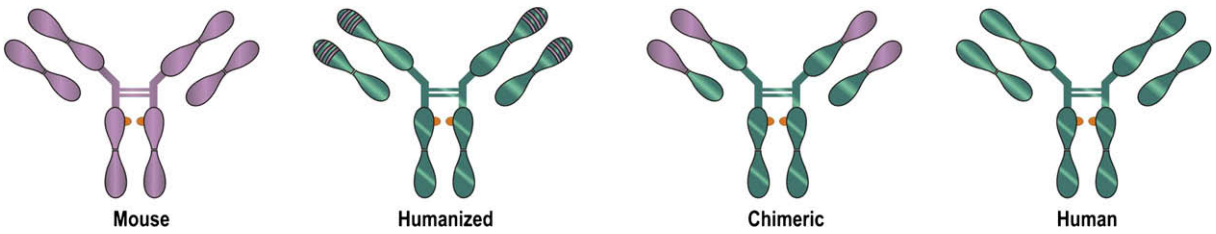

Fig. 1. Schematic description of the four main types of mAbs composition for therapeutics. Purple: mouse sequences; green: human sequences; orange circle: areas of glycosilation.