European Journal of Pharmaceutics and Biopharmaceutics 95 (2015) 158–172

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

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

Research Paper

Antibody therapies and their challenges in the treatment of age-related macular degeneration

Cornelia Volz, Diana Pauly *

Department of Ophthalmology, University Hospital Regensburg, Regensburg, Germany

ARTICLE INFO

Article history:
Received 6 November 2014
Revised 16 February 2015
Accepted in revised form 20 February 2015
Available online 26 February 2015

Keywords:
Age-related macular degeneration
Therapeutic antibody
Intravitreal
Anti-angiogenic
Anti-complement system
Anti-inflammatory
Anti-amyloid β
Clinical studies

ABSTRACT

Age-related macular degeneration (AMD) is the leading cause of vision loss in the western world. This multifactorial disease results from the combined contributions of age, environment and genetic predisposition. Antibody-based treatment of late-stage neovascular AMD with inhibitors of vascular endothelial growth factor has had great success, which is now the goal for currently untreatable AMD manifestations. The existence of an immune-privileged environment in the eye supports the feasibility of localized antibody therapy. Many different antibodies against various targets are being developed for the treatment of AMD, which reflects the etiological complexity of the disease. This review provides an overview of 19 potential therapeutic antibodies targeting angiogenesis, the complement system, inflammation or amyloid beta deposition in the eye. It summarizes the immunoglobulin structure, the specific target and study outcomes for each approach. The latter include beneficial results or adverse effects in AMD models and patients. Finally, this article discusses the challenges in the development of antibody-based drugs to treat degenerative processes in the posterior eye. In spite of these difficulties, to date, the following four antibodies have overcome the technical and preclinical hurdles and are being tested in active clinical studies: Lampalizumab, Sonepcizumab, GSK933776 and LFG316. We conclude that, while there are some antibody-based drugs that have made it into clinical practice, a successful transfer from bench to beside is still pending for many promising approaches.

1. Introduction

1.1. Ocular immune privilege and therapeutics

The eye is a small, highly specialized sensory organ that is protected by a homeostatic mechanism limiting local immune and inflammatory responses in order to preserve normal function [1]. This phenomenon, known as immune privilege, is maintained by passive and active factors to ensure immunological ignorance, peripheral tolerance of eye-derived antigens and development of an intraocular immunosuppressive microenvironment. Several anatomical features, i.e., the blood–retinal barrier and lack of lymphatic drainage, pose a barrier to the diffusion of macromolecules [2]. Proteins smaller than 76.5 kDa can freely diffuse across the human retina [3]. Antibodies or molecules larger than 150 kDa are arrested at the inner limiting membrane of the retina or can only cross the barriers through receptor-mediated transcytosis [4,5]. This restricted environment has both advantages and disadvantages for drug delivery and pharmacokinetics in the eye. On one hand, high local bioavailabilities lead to better treatment efficacy, reduce systemic drug exposure and require lower antibody dosing [6]. On the other hand, one of the greatest challenges is overcoming the blood–retinal barrier for drug administration. Due to poor penetration across the barrier, antibody therapeutics are typically not given systemically for ocular targets. Intravenous applications would involve large drug doses to achieve an effective bioavailability in the retina, and such doses are often associated with systemic side effects [7]. Topical instillation of eye drops or ocular ointments can be applied by patients without help from medical professionals but are washed away within minutes; such

Abbreviations: AMD, age-related macular degeneration; RPE, retinal pigmented epithelium; CNV, choroidal neovascularization; VEGF, vascular endothelial growth factor; IgG, immunoglobulin γ; Fab, antigen binding fragment; FDA, Food and Drug Administration; EDTRS, early treatment for diabetic retinopathy study; VEGFR-2, VEGF receptor 2; TF, tissue factor; CFH, complement factor H; CFI, complement factor I; CFD, complement factor D; mAb, monoclonal antibody; MASP-2, mannan-binding lectin-associated serine protease; CFB, complement factor B; TNF, tumor necrosis factor; IL-2R, interleukin-2 receptor; Aβ, amyloid beta; iv, intravenously; ivt, intravitreally.

* Corresponding author. Department of Ophthalmology, University Hospital Regensburg, Franz-Josef-Strauss-Allee 11, 93042 Regensburg, Germany. Tel.: +49 941 944 9228.

E-mail address: diana.pauly@klinik.uni-regensburg.de (D. Pauly).

http://dx.doi.org/10.1016/j.ejpb.2015.02.020
0939-6411/

treatments are generally used to address problems within the anterior eye. Intraocular applications of antibodies or other macromolecules are the most common method for treatment of the posterior segment of the eye. Volumes of 20–100 μL can generally be injected into the eye without affecting vision [8]. Inside the vitreous humor, large molecular weight therapeutics have half-lives of days and weeks [9]. After a single injection of 1.25 mg of a full-length antibody (Bevacizumab), the maximum drug concentration reached 93 μg/mL in the choroid/retina and maintained its effective concentration for up to 7 weeks in the rabbit eye [10]. For chronic diseases, repeated intravitreal injections are needed and may result in adverse effects such as retinal detachment, retinal hemorrhage or endophthalmitis [8]. Therefore, the established intravitreal antibody treatment of patients with neovascular age-related macular degeneration (AMD) exposed to more than 30 injections is an unexpected success that motivates further development of intra-ocular antibody therapeutics to treat AMD despite the potential side effects.

1.2. Antibodies as therapeutics

In the late nineteenth century, Emil von Behring (1854–1917) and Paul Ehrlich (1854–1915) pioneered the therapeutic application of antibodies with their groundbreaking work on serum therapy [11,12]. Since then, with both setbacks and successes, enormous progress has been made in methods of antibody generation and their use for the treatment of disorders. After almost all murine-derived monoclonal therapeutics (–o–, Fig. 1) failed in clinical evaluation in the late 1970s, recombinant technologies were employed to develop antibodies with a reduced level of murine-derived sequences. Chimerization technologies (–xi–, Fig. 1) resulted in antibody hybrid molecules containing a variable rodent region fused to a constant human antibody framework [13,14], but human anti-chimeric antibodies were still generated against the variable regions. The next step was to replace only the antigen-binding site from the human antibody with that of the specific mouse region [15]. These humanized antibodies (–zu–, Fig. 1) reduced immunogenicity, limited safety issues and increased efficiency. Early in the 1990s, phage display technology [16–18] and transgenic mice [19,20] revolutionized the generation of therapeutic antibodies as the preparation of fully human antibodies (–u–, Fig. 1) raised the hope that the human immune system would not recognize these antibodies as foreign proteins. It was soon realized, however, that the Fc glycosylation pattern or antigen-binding regions from phage display libraries may differ from those of human immunoglobulins. Nevertheless, these problems were negligible compared to those previously encountered with animal antibodies. Currently, antibodies are produced as monospecific, human or nearly human molecules (Fig. 1) and are modified using affinity maturation, Fc engineering and manipulating glycoforms to provide high-affinity target binding and long serum half-life.

1.3. Age-related macular degeneration

As the leading cause of blindness among the elderly in developed countries [21], AMD is estimated to affect 14 million people worldwide. AMD is a degenerative disease that damages the retinal pigment epithelium (RPE) and photoreceptors. It has high variability in clinical symptoms and representation. In early disease stages, extracellular debris accumulates in the sub-RPE space and forms drusen (Fig. 2). The disease progresses to one of two late-stage AMD forms, dry or wet AMD (Fig. 2A and B) [22]. Dry AMD is characterized by areolar photoreceptor and RPE loss in the macula, leading to geographic atrophy and subsequent vision loss (Fig. 2A). Currently, no therapy exists for dry AMD, and only a healthy lifestyle might prevent or slow down disease progression.

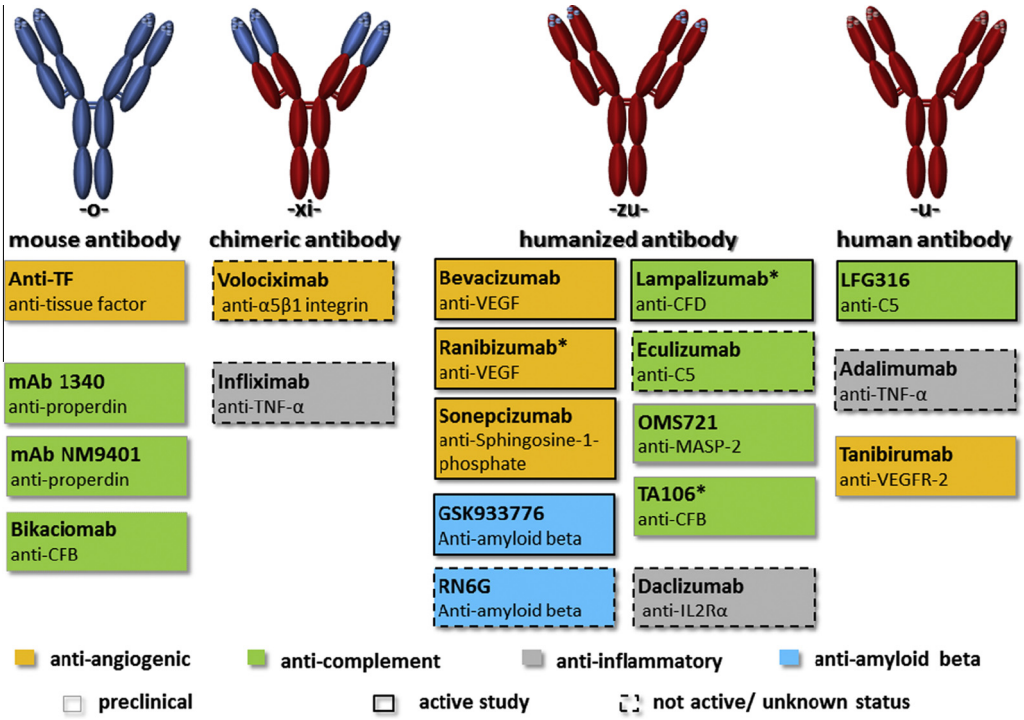

Fig. 1. Structures of therapeutic antibodies for AMD therapy. The ratio of murine (blue) and human (red) amino acids in an antibody molecule is one parameter affecting immunogenicity. Murine antibodies (–o–) are in preclinical studies (gray frame). The structure of immunoglobulins in active (bold frame) or inactive (dashed frame) clinical studies is independent of the target pathways of angiogenesis (yellow), complement pathway (green), inflammation (gray) or amyloid β deposition (blue). Immunogenicity declines from chimeric (–xi–) to humanized (–zu–) and human (–u–) therapeutic antibodies. Antibodies are either full-length molecules or include only the variable Fab region (*). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)