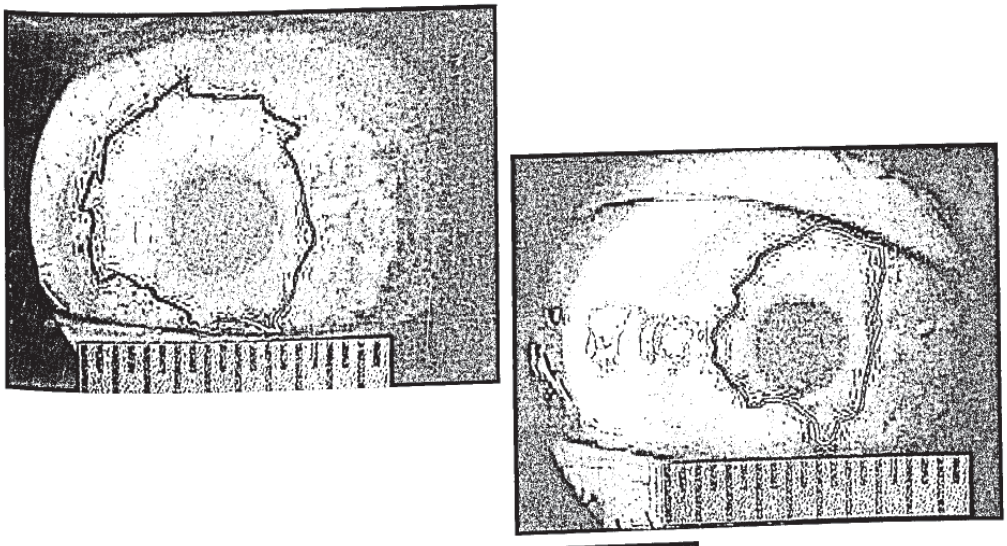
print
ISSN 0030–3755
Ophthalmologica
223(6) 351–422 (2009)
223 | 6 | 09
online
ISSN 1423–0267
www.karger.com/oph

Ophthalmologica



Medical
Basel · Freiburg
London · New York ·
Bangalore · Bangkok · Shanghai ·
Sydney

Ophthalmologica

ISSN Print Edition: 0030–3755
ISSN Online Edition: 1423–0267

Journal Homepage: www.karger.com/oph

Publication Data: 'Ophthalmologica' is published 6 times a year. Volume 223 with 6 issues appears in 2009.

Subscription Rates: Subscriptions run for a full calendar year. Prices are given per year.

Personal subscription:

Print or Online	Print+Online combined
CHF 787.50	CHF 832.50
EUR 562.50	EUR 594.50
USD 750.00	USD 793.00

postage and handling (added to print and print+online)
CHF 37.80 Europe, CHF 56.70 Overseas
EUR 27.–
USD 53.70

Institutional subscription:

Print or Online	Print+Online combined
CHF 1575.–	CHF 1733.–
EUR 1125.–	EUR 1238.–
USD 1500.00	USD 1650.00

postage and handling (added to print and print+online)
CHF 47.40 Europe, CHF 70.80 Overseas
EUR 33.60
USD 67.20

Airmail surcharge: CHF 48.– / USD 45.60

Discount subscription prices:

- Association for Research and Vision in Ophthalmology (ARVO)
- Dutch Ophthalmological Society
- EVER
- Schweizerische Ophthalmologische Gesellschaft
- and other related societies

Back Volumes and Single Issues: Information on availability and prices of single print issues and print or electronic back volumes can be obtained from Customer Service at *service@karger.ch.*

Bibliographic Indices: This journal is regularly listed in bibliographic services, including *Current Contents®* and PubMed/MEDLINE.

Subscription Orders:
Orders can be placed at agencies, bookstores, directly with the Publisher

S. Karger AG
Medical and Scientific Publishers
P.O. Box
CH–4009 Basel
Switzerland
(for courier services only:
Allschwilerstrasse 10
CH–4055 Basel)
Tel. +41 61 306 11 11
Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

Change of Address:
Both old and new address should be sent to the subscription source.

or further Karger offices or representatives:

France:
Librairie Medi-Sciences Sarl
36, bd de Latour-Maubourg
75007 Paris
France
Tél. +33 (0) 1 45 51 42 58
Fax +33 (0) 1 45 56 07 80
E-Mail librairie@medi-sciences.fr
www.medi-sciences.fr

Germany:
S. Karger GmbH
Postfach
79095 Freiburg
Deutschland
(Hausadresse: Lörracher Strasse 16A
79115 Freiburg)
Tel. +49 761 45 20 70
Fax +49 761 45 20 714
E-Post information@karger.de
www.karger.de

India, Bangladesh, Sri Lanka:
Panther Publishers Private Ltd.
33, First Main
Koramangala First Block
Bangalore 560 034
India
Tel. +91 80 25505 836
Tel. +91 80 25505 837
Fax +91 80 25505 981
E-Mail panther_publishers@vsnl.com
www.pantherpublishers.com

Japan:
Karger Japan, Inc.
Yushima S Bld. 3F
4-2-3, Yushima, Bunkyo-ku
Tokyo 113-0034
Japan
Tel. +81 3 3815 1800
Fax +81 3 3815 1802
E-Mail publisher@karger.jp

China, Taiwan and Malaysia:
Karger China
Suite 409, Apollo Building
1440 Central Yan An Road
Shanghai 200040
China
Tel. +86-21-6133 1861
Fax +86-21-6133 1862
E-Mail karger.ray@gmail.com

South America and Central America:
Cranbury International LLC
7 Clarendon Ave., Suite 2
Montpelier, VT 05602
USA
Tel. +1 802 223 6565
Fax +1 802 223 6824
E-Mail
eatkin@cranburyinternational.com
www.cranburyinternational.com

United Kingdom, Ireland:
S. Karger AG
c/o London Liaison Office
4 Rickett Street
London SW6 1RU
United Kingdom
Tel. +44 (0) 20 7386 0500
Fax +44 (0) 20 7610 3337
E-Mail uk@karger.ch

USA:
S. Karger Publishers, Inc.
26 West Avon Road
P.O. Box 529
Unionville, CT 06085
USA
Toll free: +1 800 828 5479
Tel. +1 860 675-7834
Fax +1 860 675-7302
E-Mail karger@snet.net

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

The Journal Home Page is available at:
www.karger.com/oph

Review

Ophthalmologica

Ophthalmologica 2009;223:401–410
DOI: 10.1159/000228926

Received: December 11, 2008
Accepted after revision: January 29, 2009
Published online: July 20, 2009

Emerging Pharmacologic Therapies for Wet Age-Related Macular Degeneration

Zhang Ni[a–c] Peng Hui[a–c]

[a]Department of Ophthalmology, First Affiliated Hospital of Chongqing Medical University, [b]Chongqing Key Laboratory of Ophthalmology, [c]Chongqing Eye Institute, Chongqing, PR China

Key Words
Age-related macular degeneration · Vascular epithelial growth factor · Choroidal neovascularization · Antiangiogenesis · Anti-inflammatory · Target therapy

Abstract
As researchers and clinicians are beginning to understand that wet age-related macular degeneration (AMD) is more than simply a vascular disease that includes angiogenic, vascular and inflammatory components, they are exploring new agents with different mechanisms of action addressing multiple targets in this complex pathophysiology. Some of them are already available in human trials or even approved vascular epithelial growth factor (VEGF) blockers such as Macugen, Lucentis, Avastin, VEGF Trap-Eye and Cand5; VEGF receptor blockers such as TG100801, vatalanib, pazopanib, Sirna-027 and a vaccine approach; inflammation inhibitors and immunosuppressants such as Retaane, Kenalog, ARC1905, POT-4, OT-551. The last group is mixed, containing agents such as Zybrestat, AdPEGF, Sirolimus, JSM6427, ATG003, E10030. This article reviews these currently emerging agents and briefly discusses the next step for the treatment of wet AMD.

Introduction

One of the most common and poorly treated back-of-the-eye diseases is age-related macular degeneration (AMD). It is the leading cause of blindness in the developed countries for people over 50 years [1]. The most severe form, wet AMD, accounts for 10% of cases, but 90% of the severe vision loss is associated with all AMD [2]. It is complicated by choroidal neovascularization (CNV), during which the choroidal new vessels invade the subretinal space through Bruch's membrane to form fibrovascular proliferative tissue containing vascular endothelial cells, fibroblasts, retinal pigment epithelial cells, and various inflammatory cells [3]. Retinal neurons are irreversibly damaged by lipid leakage and bleeding from the immature new vessels in the CNV tissue. Although molecular and cellular mechanisms are not fully elucidated, various efficacious target therapies are emerging and successful in human trials.

Against VEGF

Out of a panel of recently discovered and promising therapeutic targets, the most efficacious CNV treatment has relied on the vascular endothelial growth factor (VEGF). It is a subfamily of growth factors including members of VEGF-A, VEGF-B, VEGF-C, VEGF-D,

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

0030–3755/09/2236–0401$26.00/0

Accessible online at:
www.karger.com/oph

Peng Hui
Department of Ophthalmology
First Affiliated Hospital of Chongqing Medical University
Chongqing 400016 (PR China)
Tel. +86 23 8901 3056, E-Mail pengh9@yahoo.com.cn

VEGF-E and placenta growth factor [4]. They are important signalling proteins involved in vasculogenesis, angiogenesis and vascular permeability. VEGF-A is the most important member which is up-regulated by hypoxia. It has been shown to stimulate endothelial cell mitogenesis and cell migration. It is also a vasodilator that increases microvascular permeability. There are multiple isoforms of VEGF-A including VEGF-A_{121}, VEGF-A_{145}, VEGF-A_{148}, VEGF-A_{162}, VEGF-A_{165}, VEGF-A_{183}, VEGF-A_{189} and VEGF-A_{206} (classified by amino acid number) [5], of which VEGF-A_{121} and VEGF-A_{165} are the most abundantly expressed isoforms in the retina [6].

Macugen (Pegaptanib Sodium 0.3 mg; Eyetech/Pfizer)

Pegaptanib [7] is a 28-base ribonucleic acid aptamer, covalently linked to two branched 20-kDa polyethylene glycol moieties to increase residency time within the eye following intravitreal injection (IVT). It selectively binds to the VEGF-A_{165}, which is the most potent and prevalent isoform expressed during pathologic neovascularization [8]. Macugen was approved by the Food and Drug Administration (FDA) in December 2004 for the treatment of wet AMD [9], becoming the first pharmacological agent approved for ocular angiogenesis.

Its efficacy and safety were confirmed by a pivotal phase III trial VISION [7], in which 1,208 patients with all CNV subtypes secondary to AMD received Macugen IVT or sham injections every 6 weeks for 48 weeks. The results demonstrated that 70% of Macugen-treated patients lost fewer than 15 letters compared with 55% of sham-treated patients at 12 months ($p < 0.001$). Among the adverse events that occurred, endophthalmitis (1.3%), traumatic injury to the lens (0.7%), and retinal detachment (0.6%) were the most serious that have been reported and required vigilance.

Lucentis (Ranibizumab 0.5 mg; Genentech/Novartis Ophthalmics)

Ranibizumab is a 48-kDa humanized monoclonal antibody fragment that neutralizes and inhibits all known forms of VEGF-A, including their protein degradation products [10]. It was approved by FDA in June 2006 for the treatment of wet AMD [11].

In a pivotal clinical trial, MARINA [10], 716 patients with minimal classic or occult CNV secondary to AMD were treated with a 0.3- or 0.5-mg dose of Lucentis IVT or sham injections monthly. The results demonstrated that 94.5 and 94.6% of Lucentis-treated patients lost fewer than 15 letters (0.3 and 0.5 mg, respectively), compared with 62% of sham-treated patients after 12 months. What is more, the Lucentis-treated patients gained an average of 6.5 and 7.2 letters of visual acuity (VA), whereas the sham-treated patients lost an average of 10.4 letters ($p < 0.001$ for each comparison).

The results of another pivotal clinical trial, ANCHOR [12], were very similar; 423 patients with predominantly classic CNV secondary to AMD were treated with a 0.3- or 0.5-mg dose of Lucentis IVT monthly and sham photodynamic therapy (PDT) or sham injection and PDT every 3 months. 94.3 and 96.4% of Lucentis-treated patients lost fewer than 15 letters compared with 64.3% of PDT-treated patients. Mean VA increased by 8.5 letters and 11.3 letters in the Lucentis-treated patients compared with a decrease of 9.5 letters in the PDT-treated patients ($p < 0.001$ for each comparison).

These two trials, as well as the other key trials, PIER [13], FOCUS [14] and SAILOR [15], suggested that the treatment of Lucentis IVT is well tolerated and efficacious. More recently, the study HORIZON [16] supported the long-term safety of Lucentis. It is a phase III extension study allowing patients completing the trials MARINA, ANCHOR and FOCUS to continue to receive Lucentis less frequent 'as needed', but patients on average had a 5.3-letter decline in VA with 3–4 injections over the entire year, suggesting that monthly dosing may be better in some patients.

Avastin (Bevacizumab, 1.25 mg; Genentech/Novartis Ophthalmics)

Avastin [17] is a 149-kDa humanized full-length monoclonal antibody which is approximately 3 times larger than Lucentis and is capable of inhibiting all isoforms of VEGF-A. It was FDA approved in February 2004 for the treatment of metastatic colon cancer, but was not yet originally approved for ocular disease [18]. In spite of this, as there were several uncontrolled studies [19, 20] on wet AMD showing that Avastin IVT may be efficacious and safe, also at much lower cost than Lucentis, it is used as off-label drug to treat patients with wet AMD and macular edema.

Recently, the result of a small study [21] comparing Lucentis and Avastin monotherapy in 46 patients for the treatment of wet AMD has shown that Lucentis has a slight advantage over Avastin. But due to the small number of patients and the retrospective nature of this analysis, conclusions should be made with caution.

What is desperately needed is a larger head-to-head comparison of the efficacy and adverse consequences between Avastin and Lucentis or Macugen. A randomized phase II trial, MAAM [22], comparing Avastin and Ma-

cugen IVT in 60 patients with wet AMD is under way and will soon be finished. Another ongoing clinical trial is CATT [23]. It is a phase III trial comparing Avastin and Lucentis IVT in 1,209 patient with wet AMD. If the trials demonstrate equivalence between these two drugs this would allow more affordable and widespread use of anti-VEGF therapy.

VEGF Trap-Eye (Regeneron)

VEGF Trap-Eye [24] is a 110-kDa recombinant protein with the binding portions of VEGF receptors (VEGFR) VEGFR-1 and VEGFR-2 fused to the Fc region of human IgG that binds all forms of VEGF-A, placenta growth factor and VEGF-B with a very high affinity (about 140 times that of Lucentis).

In a phase I trial (CLEAR) AMD-1 was administered intravenously for the treatment of CNV. The investigators found a dose-dependent decrease in the central retinal thickness, as well as a dose-dependent increase in systemic blood pressure with a maximum tolerated dose of 1 mg/kg. Since then, systemic VEGF Trap-Eye was halted, only IVT is being evaluated for ocular disease [25].

Recently, the result of CLEAR IT-2 [26] was released. In this phase II trial, patients were initially treated with either fixed monthly or quarterly doses for 12 weeks and then continued to receive treatment for another 40 weeks on a PRN (as needed) dosing schedule. It demonstrated up to 9 mean letters gained in VA and up to 161 μm reduction in central retinal thickness at 52 weeks ($p < 0.0001$). The patients received on average only two additional injections over 40 weeks after a 12-week fixed dosing period. It was generally well tolerated, and there were no drug-related serious adverse events.

After these positive initial results, it is reasonable to take VEGF Trap-Eye into phase III clinical trials VIEW1 [27] and VIEW2 [28], which are ongoing to compare with Lucentis in 2,400 patients with wet AMD in the US, Europe, Asia, Japan, Australia and South America. These global clinical programs will provide additional data to further evaluate the efficacy and safety of VEGF Trap-Eye.

Cand5 (Bevasiranib; OPKO Health)

Cand5 [29] is a small interfering mRNA working by shutting down the mRNA specific to the genes that encode for the production of VEGF-A; it therefore inhibits CNV, but has no effect on residual VEGF in the eye.

In a phase I dose-escalation study [30] in 15 patients with wet AMD, Cand5 was found to be safe and well tolerated at doses up to 3.0 mg over a 6-week period, and the investigators concluded that Cand5 did not escape the eye to the systemic circulation.

During a phase II randomized study of trial CARE [29], 129 patients with classic or active minimally classic AMD, including those patients who had failed previous treatments, received multiple Cand5 IVT of 3 doses over 6 months. The results showed that the average time to rescue (need for another injection) in patients given the lowest dose (0.2 mg) was 153 days [31]. Patients who received higher doses (1.5 and 3 mg) had an average time to rescue that was much longer.

Due to its different mechanisms of action, compared to the other anti-VEGF agents, researchers considered that combining Cand5 with a VEGF-binding agent might offer a better response. Therefore, a phase III clinical trial, CARBON [32], is under way that will compare the efficacy of Cand5 administered every 8 weeks or 12 weeks after an initial pretreatment with 3 injections of Lucentis versus Lucentis monotherapy every 4 weeks in patients with wet AMD.

Against VEGFR and PDGFR

VEGFR mediate the biological functions of the VEGF family. They consist of three protein-tyrosine kinases (VEGFR-1, VEGFR-2, and VEGFR-3) and two non-protein kinase coreceptors (neuropilin-1 and neuropilin-2) [33]. VEGFR-2 appears to mediate almost all of the known cellular responses to VEGF; the role of VEGFR-1 has been characterized as a decoy receptor evolved to trap free VEGF-A, that prevents continuous VEGFR-2 activation [34]. Platelet-derived growth factor is a growth factor which has been demonstrated to stimulate angiogenesis and pericyte recruitment [35]. Loss of pericytes in retinal vessels is thought to be associated with abnormalities and instability of vasculature, including the formation of microaneurysms and vascular permeability, and it was also thought to be associated with regression of maturing neovascularization [36, 37]. Therefore, inhibition of VEGFR and platelet-derived growth factor receptor (PDGFR) seems to be another approach to prevent CNV.

TG100801 (TareGen)

TG100801 is a potent tyrosine kinase inhibitor and a prodrug administration of TG100572, which binds VEGFR and PDGFR and inhibits their activity [38]. Data have suggested that the delivery of the agent occurs by local penetration through the sclera rather than by system-

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.