FROM THE ANALYST'S COUCH

Wet AMD market

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Munro 3 seater sofa, Donna Wilson, image from www.scp.co.uk

Age-related macular degeneration (AMD) is the leading cause of vision loss in patients over 60 years of age in the developed world, and it remains an area of unmet medical need. There are two forms of AMD, dry (non-neovascular) and wet (neovascular), which affect over 16 million people in the United States and Europe. The annual incidence is expected to increase with an ageing population, and prevalence in Western countries is anticipated to reach 25 million by 2020 (REF. 1). The wet form of AMD is characterized by abnormal neovascularization (angiogenesis) into the central region of the retina. The process results in severe vision loss due to retinal damage caused by ensuing leakage and scar formation. Around 10% of patients exhibit wet AMD; however, it accounts for over 90% of the serious loss of vision. Although there are currently no US Food and Drug Administration (FDA)-approved drug therapies for the more common dry form, moderately effective treatments are available on the market for wet AMD.

Visudyne photodynamic therapy

Until the 1990s, laser-based therapies were the mainstay of treatment for wet AMD. Verteporfin (Visudyne; QLT/Novartis), used with photodynamic therapy, became the first FDA-approved drug in 2000. The treatment is palliative and only suitable for patients with retinal neovascularization in a well-defined 'predominantly classic' pattern, a subtype that accounts for around 25% of wet AMD cases. These treatments as monotherapies had limited success in improving visual outcome; however, they may have a role in the future as combination therapies.

VEGF blockers

Macromolecular drugs have revolutionized the management of wet AMD by directly inhibiting vascular endothelial growth factor (VEGF). Until this year, three anti-VEGF therapies were widely used to treat wet AMD: pegaptanib (Macugen; Eyetech/Pfizer), ranibizumab (Lucentis; Genentech/Roche) and bevacizumab (Avastin; Genentech/Roche). Pegaptanib, an aptamer antagonist, was the first anti-VEGF treatment and approved by the FDA in December 2004. However, many patients continued to lose vision while on the therapy. The drug ceded way to ranibizumab, a monoclonal antibody fragment that inhibits VEGFA. Approved by the FDA in 2006, it remains the current standard of treatment for wet AMD. Prior to the commercial availability of ranibizumab, bevacizumab (a colon cancer therapy) was attempted as an off-label VEGF inhibitor to control exudative AMD. Off-label bevacizumab is estimated to hold ~60% of the US wet AMD market by volume. The drug costs around US$50 per dose compared to $1,950 for ranibizumab and therefore has not gained, by value of sales, a significant share of the retinal disease market. Ranibizumab is currently the bestselling ophthalmic agent on the market (FIG. 1).

Aflibercept (Eylea)

In November 2011, the FDA approved aflibercept (Eylea; Regeneron) for wet AMD. It is a protein composed of key portions of the extracellular domains of human VEGF receptor 1 (VEGFR1) and VEGFR2 fused with the Fc portion of human immunoglobulin G1, and acts as a 'VEGF trap'. It blocks all VEGFA isoforms and placental growth factor, and shows enhanced VEGF binding compared to ranibizumab (100-fold) and bevacizumab (1,000-fold). Clinical data from two Phase III trials established comparable results to the current standard of treatment, ranibizumab. Possible other indications for aflibercept include central retinal vein occlusion and diabetic macular oedema; as Zaltrap, it is being co-developed with Sanofi for colorectal and prostate cancer.

Genentech and Regeneron both own VEGF trap-related patents. In early 2012, the two companies settled their patent dispute over infringement of Genentech's Davis–Smyth patents. Genentech has, however, filed a separate suit against Regeneron and Sanofi alleging that Zaltrap, approved by the FDA in August 2012, also infringes its Davis–Smyth patents[2]. Genentech and Regeneron are likely to face competition in the near future as various other companies have pipeline wet AMD products in development (TABLE 1).

Emerging therapies

Although anti-VEGF treatments have become clinically and commercially established, trials continue to investigate ways of increasing their efficacy and adherence. Another option is to block the effects of VEGF by targeting components of the signalling cascade downstream of VEGFR. The protein tyrosine kinase inhibitors AL-39324 (Alcon) ▸

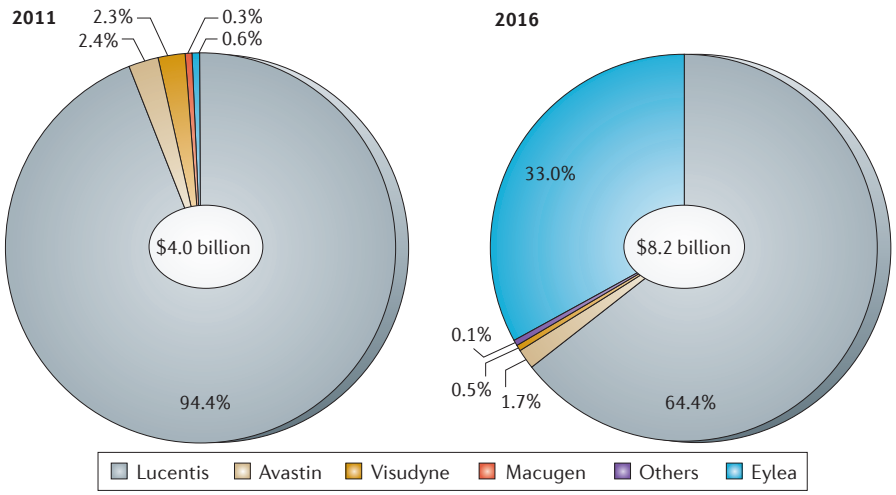

Figure 1 | **Leading products in the wet age-related macular degeneration market.** Source: company reports; Visiongain.

Table 1 | **Selected treatments in clinical development for wet AMD***

Products	Company	Target or mechanism of action	Development stage
Posurdex/SK-0503 and Lucentis	Allergan	Corticosteroid and VEGF inhibitor	Phase III
KH902	Chengdu Kanghong Biotech	VEGF receptor decoy	Phase III
Sirolimus (DE-109)	Santen/Othera	mTOR inhibitor	Phase III
Sirolimus	MacuSight/Santen	mTOR inhibitor	Phase II
DARPin	Allergan	VEGF inhibitor	Phase II
E10030 and Lucentis	Ophthotech	Anti-PDGF aptamer	Phase II
Vatalanib (PTK787 or PTK/ZK)	Bayer/Novartis	Tyrosine kinase inhibitor	Phase II
AL-39324	Alcon (Novartis)	Tyrosine kinase inhibitor	Phase II
Pazopanib	GlaxoSmithKline	Tyrosine kinase inhibitor	Phase II
TG100801	TargeGen	Tyrosine kinase inhibitor	Phase II
Zybrestat (fosbretabulin)	OXiGENE/ Symphony ViDA	VDA and cadherin 5 inhibitor	Phase II
Ocriplasmin	ThromboGenics	Truncated form of HSPP	Phase II
Iluvien (fluocinolone acetonide)	pSivida/Alimera	Corticosteroid (intravitreal insert)	Phase II
ATG3 (mecamylamine)	CoMentis	nAChR antagonist	Phase II

AMD, age-related macular degeneration; DARPin, designed ankyrin repeat protein; HSPP, human serine protease plasmin; mTOR, mammalian target of rapamycin; nAChR, nicotinic acetylcholine receptor; PDGF, platelet-derived growth factor; VDA, vascular disrupting agent; VEGF, vascular endothelial growth factor. *Source: ClinicalTrials.gov website, company reports.

and pazopanib (Votrient; GlaxoSmithKline) are in Phase II trials. DARPin (designed ankyrin repeat protein; Allergan), a binding ligand developed as an alternative to immunoglobulin, targets VEGF directly and is in Phase II trials; KH902 (Chengdu Kanghong Biotech), a VEGFR–Fc fusion protein, is entering Phase III trials.

There is also scope for anti-VEGF therapies to be augmented by combination regimens that can target multiple pathways at once. Possible targets include platelet-derived growth factor B (PDGFB), which supplies pericyte populations to support neovascularization. E10030 (Ophthotech), an aptamer targeting PDGFB, is in Phase II trials in combination with ranibizumab. The combination of anti-VEGF treatment with radiotherapy is being explored by Oraya Therapeutics (Phase II) and NeoVista (Phase III). Alongside combination therapies, the potential game-changer is the use of anti-VEGF agents as a preventive treatment for wet AMD. The development of a sustained-delivery anti-VEGF agent, together with better disease markers (derived from the study of drusen, the pigmentary epithelium, retinal changes and possibly genotyping) will make earlier intervention effective.

A range of innovative biological approaches to treat wet AMD have fallen by the wayside, including the once-promising small interfering RNAs (siRNAs); PF-04523655 (Quark), in Phase II trials, is the last siRNA in development for AMD and is likely to be discontinued. However, Phase II trials continue for ocriplasmin (ThromboGenics), an anti-fibronectin, laminin and type IV collagen fibre biologic; in addition, the gene therapy candidate AVA-101 (Avalanche Biotechnologies) is in Phase I/II trials. In the longer term, stem cells may yield a potential cure, with Pfizer and the UCL Institute of Ophthalmology using human embryonic stem cells to derive retinal pigment epithelium cells to repair damage caused by wet AMD. Clinical trials are scheduled to begin in 2012.

Future outlook

The wet AMD market is estimated to be worth approximately $4 billion a year and expected to reach $8.2 billion by 2016 (compound annual growth rate: 15.9%, 2011–2016), making it an attractive niche ophthalmic segment[1]. The market is dominated by ranibizumab, which accounted for 94.4% of wet AMD sales. The drug has generated $11.95 billion in revenues since it was first launched. If aflibercept lives up to the promise it showed in trials then the drug could replace ranibizumab as the high-cost option. With its lower price ($1,850 per injection) and less frequent injection schedule (dosing every 2 months compared to monthly for ranibizumab), the drug could realize 20–30% market share in 2012. Regeneron's latest sales forecasts for the drug were revised from $500–550 million to $700–750 million in the United States in 2012, indicating rapid uptake of the drug since its launch at the beginning of the year. Off-label bevacizumab will remain as a low-cost option for physicians.

Currently, anti-VEGF therapy is the treatment of choice for wet AMD but it is constrained by the frequent need for intravitreal re-injections and their associated risks, treatment burden and financial costs. Also, a substantial number of patients with wet AMD do not respond to anti-VEGF treatment. For example, intervention with ranibizumab only improves vision in one-third of patients and around 10% do not respond to the therapy. With over 70% of wet AMD patients showing no significant vision improvement with anti-VEGF agents, high potential exists for alternative cost-effective therapies, if they can be clinically proven. However, to compete with current treatments, new therapies will need to improve on the criteria that influence physicians' prescribing decisions: convenience, increased efficacy as well as improved safety and tolerability.

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doi:10.1038/nrd3790
Published online 19 October 2012

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Competing interests statement
The authors declare no competing financial interests.