FROM THE ANALYST'S COUCH

Wet age-related macular degeneration

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Wet age-related macular degeneration (AMD) is the leading cause of blindness in the elderly. It results from the growth of abnormal leaky blood vessels beneath the macula that eventually damage the area of the eye responsible for central vision, which is essential for most fine-detail visual activities, including reading, driving and recognizing faces. In the US, an estimated 1.6 million adults over the age of 50 suffer from wet AMD and about 200,000 new cases are diagnosed annually. Worldwide, approximately 500,000 new cases of wet AMD are diagnosed each year. With only one drug indicated for the disease until just recently, the market for wet AMD therapeutics remains largely untapped. As a vision-threatening disease that affects a rapidly growing ageing population, AMD represents a considerable market opportunity for novel therapeutics[1].

Standard of care

Since its approval in 2000, verteporfin (Visudyne; QLT/Novartis) photodynamic (light-activated) therapy (PDT) has been considered the standard of care for the treatment of wet AMD. However, PDT with verteporfin represents only a palliative therapy. PDT temporarily stabilizes the existing leaky blood vessels in the eye, but does not prevent the formation of new abnormal blood vessels that will eventually leak and cause disease progression. Nevertheless, physicians consider PDT with verteporfin an important treatment choice that down the road could play a role as a combination therapy with newer agents.

Blocking blood vessel formation

Blocking abnormal blood vessel growth — the underlying cause of wet AMD — could serve as the basis for disease-modifying therapies, as such drugs could potentially slow down or even prevent disease progression. Vascular endothelial growth factor (VEGF) is a secreted protein that induces angiogenesis, and increases vascular permeability and inflammation, all of which are thought to contribute to the progression of wet AMD. Naturally, VEGF is a popular target for drugs in development for wet AMD.

In December 2004, the FDA approved pegaptanib (Macugen; Eyetech Pharmaceuticals/Pfizer), an aptamer that adopts a three-dimensional conformation that enables it to bind to extracellular VEGF. The initial uptake of pegaptanib by physicians has been encouraging — Eyetech has recently revised its sales estimates from US$135–150 million to $175–190 million for 2005. However, despite a great start, pegaptanib use could drop off significantly when the next anti-VEGF drug, ranibizumab (Lucentis; Genentech/Novartis), becomes available. Ranibizumab is an anti-VEGF antibody fragment in development for wet AMD both as a monotherapy and in combination with verteporfin PDT. Although pegaptanib clearly provides benefit over placebo, the vast majority of patients continue to lose vision while on this treatment. By contrast, recently presented data from Phase III trials of ranibizumab convincingly demonstrated improvement in the vision of treated patients. Depending on the dose of ranibizumab, 25–35% of patients showed meaningful improvement in visual acuity. Therefore, retinal specialists expect ranibizumab to rapidly become the first-line agent of choice for the treatment of wet AMD if and when it is approved and launched, which is anticipated in the second half of 2006. With a 95% efficacy rate and a very good safety profile, ranibizumab is setting a very high hurdle of efficacy.

Further down the pipeline

An intriguing and potentially more efficient way to target angiogenic pathways is to block the production of relevant protein factors in the first place. This approach is being pursued by a number of companies developing RNA interference (RNAi)-based therapeutics. RNAi can block the production of a specific protein within cells by activating an endogenous mechanism that leads to the degradation of the mRNA precursor of that protein[2]. Acuity Pharmaceuticals, Alnylam Pharmaceuticals, Sirna and Atugen AG (recently acquired by SR Pharma) are all in the race. Acuity's Cand5, which targets VEGF mRNA, became the first RNAi therapeutic ever to enter into human clinical trials in October 2004. Sirna followed closely thereafter, initiating Phase I studies of its lead candidate, targeting VEGF receptor mRNA, Sirna-027, in November 2004. So far, both drugs seem to be safe and well tolerated. Although it is too early to tell whether or not either drug is efficacious, interim Phase I data, released by Sirna, show a trend towards an improvement in visual acuity in patients treated with Sirna-027. These results are encouraging and potentially very exciting, as in addition to demonstrating benefit to AMD patients, they could serve as an initial basis for proving the concept that RNAi-based drugs could work in humans. Whether RNAi drugs can match or beat the efficacy of traditional therapeutics remains to be seen. However, RNAi developers hope that, at a minimum, their molecules would provide less frequent dosing regiments for wet AMD patients than the current treatments. Pegaptanib and ranibizumab, as well as RNAi-based drug candidates, are given by intravitreal injections — not the most pleasant procedure from a patient perspective. Reducing the frequency of dosing will clearly benefit the patients and could lead to greater compliance. If proven to be safe and effective, RNAi drugs are expected to appear on the market in 2008–2010.

Future outlook

The launch of novel agents for wet AMD is expected to lead to significant expansion of this market. However, increased competition in this field also poses significant challenges for the companies involved in the early stages of drug development for this indication. With the future availability of effective drugs, such as ranibizumab, it would be problematic to conduct placebo-controlled pivotal trials. Possible ethical solutions for this problem could include recruiting patients who have failed or have refused standard treatments into single-agent trials or developing combination therapies in pursuit of maximum efficacy. In either scenario, the size and complexity of trials will have to increase, resulting in longer and more expensive development — a daunting task for biotech start-ups, such as RNAi companies. Smaller players should consider gaining strong co-development/co-promotion partners for their AMD programmes, because competing in the market place against Pfizer/Eyetech and Genentech/Novartis will be challenging. ▶

WET AGE-RELATED MACULAR DEGENERATION | MARKET INDICATORS

Wet AMD is the most common cause of irreversible vision loss in patients over the age of 60 and as such continues to represent a true unmet medical need. The potential for disease-modifying wet AMD therapies (FIG. 1; TABLE 1) is immense. The market opportunity will be driven by increased incidence of the disease, demand for innovative treatments and premium pricing of novel drugs. Collective sales of newer agents are expected to drive the category growth from US$357 million in 2003 to in excess of US$1.6 billion by 2008 (FIG. 2). In addition to wet AMD, some of these drugs might find application in other eye diseases, such as diabetic retinopathy and central vein occlusion, thereby potentially expanding the market opportunity for these drugs.

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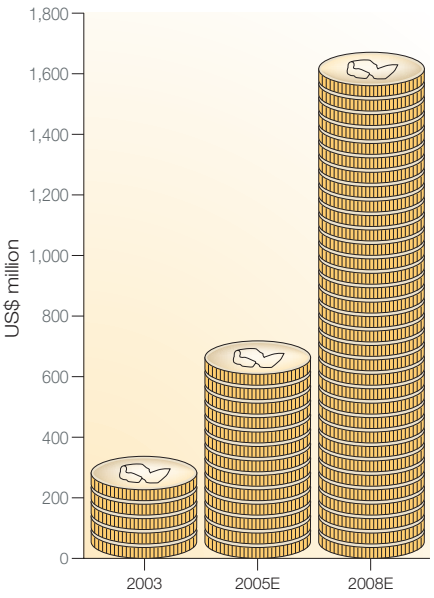

Figure 2 | **Projected growth of the wet age-related macular degeneration market.** Sources: Company filings, Leerink Swann/MEDACorp.

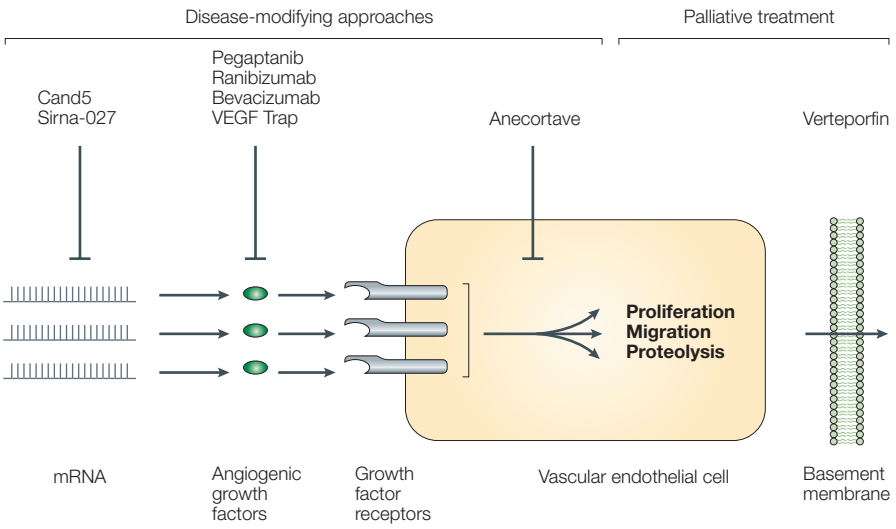

Figure 1 | **Modes of action of selected treatments for wet age-related macular degeneration in clinical development.** Sources: Company documents, MEDACorp. VEGF, vascular endothelial growth factor.

Table 1 | **Selected drugs in development for wet AMD**

Drug	Company	Development stage	Target/ mechanism	Technology	Administration route/ dosing
Pegaptanib (Macugen)	Eyetech/Pfizer	Marketed	VEGF protein	Aptamer	Intravitreal injection, 1x 6 weeks
Ranibizumab (Lucentis)	Genentech/ Novartis	Phase III	VEGF protein	Monoclonal antibody fragment	Intravitreal injection, 1x 4 weeks
Anecortave (Retaane)	Alcon	Filed NDA, Phase III	Anti-angiogenic	Small molecule	Extraocullar (juxtascleral) injection, 1x 6 months
Squalamine (Evizon)	Genaera	Phase III	Anti-angiogenic	Small molecule	Systemic, 1/week for a month, then 1x 4weeks
Bevacizumab (Avastin)	Genentech	Phase I	VEGF protein	Monoclonal antibody	Intravitreal, TBD
VEGF Trap	Regeneron	Phase I	VEGF protein	Recombinant protein, decoy receptor	Intravitreal, TBD
Cand5	Acuity	Phase I/II	VEGF mRNA	siRNA	Intravitreal, TBD
Sirna-027	Sirna	Phase I	VEGFR1 mRNA	siRNA	Intravitreal, TBD
ALN-VEG01	Alnylam/ Merck	Preclinical, IND 2H05	VEGF mRNA	siRNA	Intravitreal, TBD
RTP801i	Atugen AG acquired by SR Pharma/ Quark Biotech	Preclinical, IND 4Q05	HIF-1 mRNA	siRNA	Intravitreal, TBD

Sources: Pegaptanib (Macugen) prescription information, Company documents, MEDACorp Documents. AMD, age-related macular degeneration; HIF-1, hypoxia-inducible factor-1; IND, Investigational New Drug; NDA, New Drug Application; siRNA, small interfering RNA; TBD, to be determined; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor.

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