Ranibizumab in Treating Age-Related Macular Degeneration

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Summary and Conclusions

SBU's appraisal of the evidence

- Monthly treatment with ranibizumab has a substantial inhibitory effect on the course of disease compared to photodynamic therapy or sham injection in patients with neovascular age-related macular degeneration – in followup ≤2 years (Evidence Grade 1)*.
- Monthly treatment improves vision to a substantially higher degree in patients treated with ranibizumab compared to those who received photodynamic therapy or sham injection – in followup ≤2 years (Evidence Grade 1)*.
- Scientific evidence is insufficient* regarding the effects of treatment when delivered less frequently than once per month, or for periods exceeding 2 years.
- It is unclear whether treatment can be discontinued, or if further treatments are necessary to maintain the effects (Insufficient Scientific Evidence)*.
- Scientific evidence is insufficient* to assess the cost-effectiveness of the method.

***Criteria for Evidence Grading SBU's Conclusions;**

Evidence Grade 1 – Strong Scientific Evidence. The conclusion is corroborated by at least two independent studies with high quality and internal validity, or a good systematic overview.

Evidence Grade 2 – Moderately Strong Scientific Evidence. The conclusion is corroborated by one study with high quality and internal validity, and at least two studies with medium quality and internal validity.

Evidence Grade 3 – Limited Scientific Evidence. The conclusion is corroborated by at least two studies with medium quality and internal validity.

Insufficient Scientific Evidence – No conclusions can be drawn when there are not any studies that meet the criteria for quality and internal validity.

Contradictory Scientific Evidence – No conclusions can be drawn when there are studies with the same quality and internal validity whose findings contradict each other.

TECHNOLOGY AND TARGET GROUP In Western nations, age-related macular degeneration (AMD) is the most common cause of visual impairment in people older than 60 years. AMD can lead to the loss of central visual acuity and reading vision in the affected eye, while peripheral vision usually remains intact. The disease appears in three different forms – one early and two late, atrophic (dry) and neovascular (wet) AMD. Most of the AMD that is diagnosed is of the early type where visual acuity remains completely or largely intact. Currently, no effective treatment is available for the early type or for atrophic AMD, which causes successive loss of vision.

In neovascular AMD, newly formed blood vessels grow from the choroid into and under the retina or the retinal pigment epithelium. These newly formed vessels are often fragile and can leak fluid, proteins, and blood. They eventually heal, but scars remain. The course can be rapid and can lead to severe vision loss within a short time. The disease usually affects both eyes, but often to different degrees and at different times.

Previously, photodynamic therapy (PDT) was the dominant method in treating certain types of neovascular AMD. This treatment method, like pegaptanib (Macugen) – the other drug approved for treating neovascular AMD, was found to reduce vision loss and eventually stabilize visual acuity, but offered very little improvement in visual acuity.

Ranibizumab (Lucentis) can potentially improve visual acuity in some patients and is the first antibody-based drug for treating neovascular AMD. The drug inhibits a growth factor important for the formation of new blood vessels. Treatment involves injecting the drug into the vitreous body of the eye on repeated occasions.

Around 30 000 people in Sweden have neovascular AMD. The disease is detected in approximately 3500 people annually. Since both eyes are often affected, the number of cases (eyes) diagnosed is much higher than the number of patients with the disease. Approximately 5000 cases (eyes) are diagnosed annually. Of these, it is estimated that 4000 meet the criteria for treatment.

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PRIMARY QUESTIONS

- What are the effects of ranibizumab treatment on visual acuity in patients with neovascular AMD?
- How does treatment affect visual function as experienced by the patient?
- What complications and side effects can be attributed to treatment?
- What does treatment cost? Is it cost-effective?

PATIENT BENEFIT Two large randomized controlled trials have shown that monthly, intravitreal injection of ranibizumab has a substantial inhibitory effect on the course of disease in neovascular AMD. Visual acuity was the primary outcome measure in both studies. After 1 year of treatment with ranibizumab, 90% to 95% of the patients (in both studies) had stable visual acuity, ie, the reduction in visual acuity was less than 3 lines measured on a standard eye chart. The corresponding figure for the control group, which in one study was comprised of patients receiving a sham injection, was 62%. In the other study, where the control group received PDT, 64% had stable visual acuity after 1 year. Results from followup after 2 years of ranibizumab treatment showed that the effects remained in approximately 90% of the patients. The corresponding figures in the control groups were 53% (sham injection) and 66% (PDT).

In both randomized trials, vision improved in 33% to 40% of the subjects treated with ranibizumab. Vision improved in 6% of the patients treated with PDT and in 4% of those receiving sham injections.

These trials also studied visual function as experienced by patients themselves and found that ranibizumab treatment had a positive effect compared to sham injection or PDT.

Serious side effects associated with ranibizumab treatment are uncommon and relate mainly to the injection itself. The frequency of endophthalmitis (vision-threatening eye infection) was reported to be less than 0.1%. Serious side effects related to the drug itself are also relatively rare, but include eye inflammation.

In a third randomized trial, patients were treated with ranibizumab or sham injections once per month for the first 3 months. Thereafter, treatment was administered every third month. After 2 years, visual acuity had stabilized in approximately 80% of the patients treated with ranibizumab compared to 41% of the control patients. However, no average improvement in visual acuity was noted.

ECONOMIC ASPECTS The estimated cost for each injection is somewhat over 13 000 Swedish kronor (SEK), of which the drug alone costs SEK 10 000. If the total target group were to be treated based on the same principle applied in the two large randomized trials, ie, injection once per month, the costs would total approximately SEK 160 000 per patient and year. Assuming that 2 years of monthly injections would be sufficient, the annual healthcare costs for treating all patients would be SEK 1.3 billion.

No evidence is currently available to show how often, and for how long, treatment must be administered to maintain its effects. If repeated treatments are needed during the remainder of a patient's life, the cost would exceed the figure reported above.

The estimate presented above does not include indirect costs, which reflect lost productivity in conjunction with treatment. Likewise, the estimate does not include the diagnostic costs required to select patients. Treatment could also generate some cost savings. For example, the need for health care and social services would probably decrease, and some fall-related injuries could be avoided in patients with improved eyesight. These, however, were not included in the calculation since there are no supporting data.

Although a few studies address the method's cost-effectiveness, their findings are uncertain since the duration of treatment and its long-term effects are not clear.

ETHICAL ASPECTS The fact that ranibizumab treatment for neovascular AMD is shown on one hand to be effective, but on the other hand requires substantial resources, creates an ethical dilemma. It raises the question of whether it is ethically defensible to deny patients an effective treatment. At the same time, one can question whether it is defensible to start a costly treatment if we do not know how long it must be continued and have insufficient knowledge about the long-term effects of treatment. Current resources in ophthalmology, in terms of equipment and trained staff, are insufficient to treat every patient who could benefit from treatment. Hence, it will be necessary to prioritize between this treatment and other urgent care needs within, or outside of, ophthalmology.

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