

Sights set on the eye

The destruction of cells in the retina often results in severe visual impairment and a significant loss of quality of life. Underlining Bayer's presence in ophthalmology, researchers from Bayer HealthCare are now testing a new eye drop formulation which is under investigational use for the potential treatment of wet age-related macular degeneration.

Blood vessels play a vital role for our organs; not only do they supply each cell with the nutrients and oxygen it needs, but they also rid the body of the waste products of metabolism. The responsibility for maintaining these transport pathways and growing new vessels lies mainly with a protein molecule known as Vascular Endothelial Growth Factor (VEGF). It is transported in the blood and promotes the formation of new blood vessels by binding to what are termed VEGF receptors, which are located in the vessel walls. "This is the signal for the cells there to start growing," explains Dr. Jürgen Klar, a biologist in Bayer HealthCare's Ophthalmology Research Department in Wuppertal, Germany. The resultant protrusion of the vessel wall eventually leads to the formation of a new blood vessel.

Advanced macular degeneration makes reading impossible

In the context of wet age-related macular degeneration (wet AMD for short), however, this mechanism can cause severe visual impairment and serious damage to the eye. The setting for this disease is a yellow area in the middle of the retina, known as the macula. Although only a few millimeters in diameter, it has amazing capabilities: it has a particularly high density of the light-sensing cells which are responsible for high-resolution vision. It also helps us to see detail and distinguish between thousands of different shades of color. Wet AMD is characterized by abnormal blood vessel proliferation in the vicinity of the retina. Unfor-



Focus on the retina: Dr. Jürgen Klar and Dr. Michael Böttger (left to right) from Bayer HealthCare in Wuppertal evaluate images showing the condition of the blood vessels at the back of the eye.

tunately, the walls of the new, abnormal blood vessels are leaky, enabling blood to enter the retina and causing edema, or swelling. This causes the light-sensing cells of the macula to gradually degenerate. Sufferers generally notice a loss of vision within a short period of time, and the visual impairment worsens as the disease progresses. "Patients usually end up losing the ability to read or drive," explains Dr. Brigitte Stemper, a physician who works in Clinical Development at Bayer HealthCare. Straight lines appear wavy, road signs are blurry and colors look faded. There is a rapid loss of visual acuity. By later stages, the central field of vision may have deteriorated to such an extent that it is just a gray patch.

"Although patients may be able to see a clock, they are no longer able to make out its hands. Or they can no longer recognize the face of the person in front of them," says Stemper.

The condition mainly affects people over 65 years of age. "The number of patients with wet AMD is increasing as life expectancy rises," comments Dr. Gesa Deeg, Global Program Head at Bayer HealthCare. Left untreated, the condition leads to blindness in most cases. But although wet AMD can still not be cured today, current treatments involving an injection into the patient's eye several times a year are now able to delay or even stop progression of the disease. The Bayer research team headed up by Deeg is now looking for new approaches that could open up additional therapeutic options for wet AMD for doctors and patients, for example in the form of eye drops containing the active ingredient regorafenib.

Active substance inhibits abnormal growth of blood vessels

Regorafenib is a multikinase inhibitor which blocks the function of VEGF receptors that play a part in the formation of new blood vessels by inhibiting specific kinases (enzymes). The mechanism and active ingredient are familiar from cancer medicine. For the treatment of eye diseases like wet AMD, however, the oral tablet formulation used to treat cancer patients is not suitable. In eye indications, regorafenib must only be effective in the eye and must reach the retina in sufficient quantities. The researchers therefore



Enhanced vision: a new eye drop formulation may help patients with wet age-related macular degeneration.

Clarity for the retina

Patients suffering from wet age-related macular degeneration (AMD) face a rapid loss of visual acuity, affecting above all the central visual field. The active ingredient regorafenib – administered as eye drops – targets the cause of the disease: the uncontrolled growth of new blood vessels.

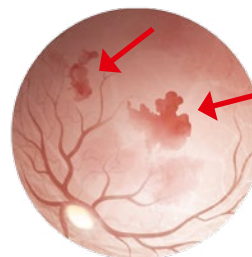
Before

What a wet AMD patient sees



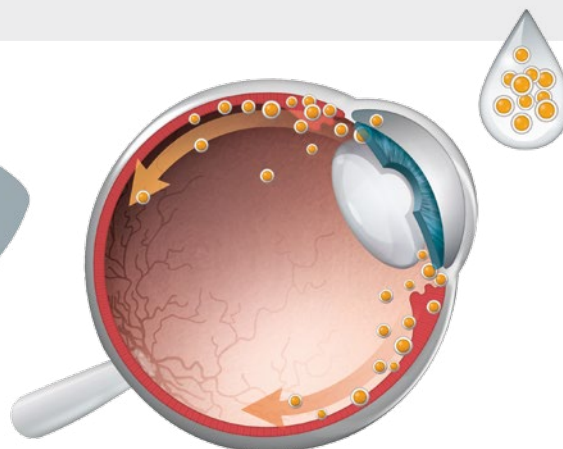
What is happening in the retina

Uncontrolled growth of blood vessels leads to leaks and the accumulation of fluid. These edemas destroy the visual cells.



Therapy

Applied as eye drops, the active ingredient regorafenib makes its way into the retina. Here the substance intervenes in signal transmission and inhibits the uncontrolled growth of new blood vessels.



After

What a patient treated with regorafenib sees



What is happening in the retina

The active ingredient regorafenib suppresses the formation of new blood vessels, leading to improved vision.



When the retina drowns

The macula is a site of high metabolic activity. Any waste products which arise are disposed of via a pigment layer under the retina. But as aging progresses, the eye loses its natural ability to remove these substances. Instead, they accumulate in the area of the macula, disrupting the supply of oxygen and nutrients to the retinal cells. This causes the cells to gradually die off, and the patient's central visual acuity deteriorates. When the body now tries to compensate for the damage to the retina by forming new blood vessels, the disease may progress in a rather aggressive way. The new vessels are leaky and abnormal: blood and fluid escape, causing edemas which destroy the light-sensing cells. Wet age-related macular degeneration (AMD), as this condition is termed, affects approximately 10 to 15 percent of all patients. If left untreated it can lead to irreparable visual damage within a few months.

had to enter completely new territory and overcome numerous hurdles to develop their own ophthalmological formulation that would make the active ingredient usable for the treatment of eye diseases. "A brand new development was needed," explains Dr. Annett Richter, a pharmacist in Formulation Development at Bayer HealthCare. "Our objective was to develop a formulation of the active ingredient which we could administer in the form of eye drops."

Eye drops deliver the active ingredient to the retina

This is a major challenge, since the new formulation needs to be not only effective, but also stable and well tolerated, while at the same time capable of ensuring that the active ingredient will find its way to the back of the eye. In the early research phase, Richter worked closely with her research colleagues, testing different types of formulation. An oily suspension formulation emerged as the most suitable delivery form. The team then had to develop a suitable manufacturing and sterilization process. The eye drops have since been tested successfully in animal models and the data give the researchers reason to hope that it will be possible to improve the symptoms of wet AMD in humans by treatment with regorafenib eye drops. "And this despite the fact that experts had previously been skeptical

about whether sufficient efficacy could be achieved to treat a condition such as wet AMD with eye drops," explains Richter, not without pride. "There is good evidence to show that the active ingredient is delivered from the cornea to its site of action in the retina," she says. Once administered into the eye, regorafenib inhibits the function of the VEGF receptors, thereby blocking transmission of the signal for new blood vessel formation in the retina. "Although VEGF is still able to dock onto the receptors in the vessel wall, the cells are now deaf to the growth signal," explains Klar.

The risk of unwanted new vessel formation and edema may then be reduced. "Interruption of the VEGF growth signal in the eye may suppress the pathologic vessels and improve vision in AMD patients," adds the biologist. It took around five years to get from the idea stage to initial testing in humans, which began with a Phase I trial in which healthy volunteers were tested to determine how well tolerated the new eye drops are. And the trial had a positive outcome. "Regorafenib is well tolerated in this formulation," states Dr. Michael Böttger, the physician at Bayer HealthCare responsible for the early clinical development of the project. "The active ingredient was hardly detectable in the systemic circulation, which is an advantage of local administration in eye disorders." Moreover, when asked, the trial participants indicated that they could well



Research for clear vision: Dr. Brigitte Stemper, Dr. Annett Richter and Dr. Gesa Deeg, Bayer HealthCare Berlin (left to right), have conducted ground-breaking work to find a suitable formulation for the active substance regorafenib.

envisage using the medication on a daily basis over an extended time.

Research team is delighted with the progress to date

"We're pleased that the preclinical development and Phase I trials have gone so well," says Böttger. The researchers entered Phase II of clinical development in October 2014 with great optimism. As Böttger explains, "In this study, we want to test whether regorafenib eye drops are effective in wet AMD patients." If the outcome is positive, investigations will follow on directly as part of the same study to determine the optimum dosage and frequency of administration. "The innovative two-phase study design and close cooperation between Research and Development could shorten the overall development time," adds Stemper. The oily formulation is a new approach. "These drops have the potential to become the first non-invasive treatment option for wet AMD," explains Project Head Deeg. "Patients can administer eye drops by themselves." This could potentially lead to a completely new form of treatment that differs from the currently available products, which have to be injected into the eye.



www.research.bayer.com/regorafenib
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