BEVACIZUMAB OR RANIBIZUMAB, OR THE TALE OF ROBIN HOOD AND KING RICHARD LION HEART

BEVACIZUMAB O RANIBIZUMAB, O LA LEYENDA DE ROBIN HOOD Y EL REY RICARDO

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Fortunately for our patients, their relatives and for those of us who have specialized in the treatment of choroidal neovascularization, more efficient treatments have emerged in recent times. However, no one could predict, not even the most imaginative of us, the way things happened.

Not too long ago, we lived comfortably with the idea that, in order to «loose less», photodynamic therapy was the best option to address wet age-related macular degeneration and other forms of choroidal neovascularization. And this by itself meant great progress when compared to the past helplessness. Back then, expectations ran high to know whether the advent of the first antioangiogenic drug would change substantially the visual prognosis of our patients. Unfortunately, even though the new treatment, pegaptanib sodium, was a more causal treatment and posed lesser threats to those cases of rebound aggressive neovascularization, the visual outcome was very similar to that obtained by means of photodynamic therapy. In the meantime, other heroic attempts were made with several associations to try and harness some benefit from the results obtained at the time, such as, for instance, the association with intravitreous triancinolone.

At the same time, the results obtained with another drug under clinical research, ranibizumab, remained unpublished. Nobody thought either at the time that things were going to change far too much. Apparently, the other antioangiogenic drug would be the same old story. But some good and surprising news emerged during the presentation of the Marina study’s findings at the gathering of the American Society of Retina Specialists (ASRS) held in July 2005 in Montreal. For the first time, the average visual acuity curbs of patients broke through the horizontal line, improved and maintained its improved condition. It was unprecedented and unexpected. It was the third revolution in the battle against AMD, while photodynamic therapy had been the first and the second was the discovery of pegaptanib sodium.

From that moment on, and for the first time in the history of treatments of all exudative or neovascular forms of age-related macular degeneration, the average vision of the patients treated increased. The goal from that point in time would not be loosing less, but rather not loosing at all, and in a great number of cases even recover some vision. In the past, 60 to 70 percent of mild visual loss were acceptable levels, whereas this percentage had gone up to 95 percent, and now in 70 percent of cases vision was actually preserved. By the end of the study, vision was kept above 20/40 in 40 percent of patients, and in some cases vision improved by 3 lines or more in similar proportions, an unthinkable outcome not too long ago. Thus, these results took the efficacy paradigm to another dimension, that of not loosing but rather gaining vision. Additionally, it was not necessary to maintain the old distinction between those subtypes for which treatment was more efficient: ranibizumab proved to be equally useful in the different forms of the disease.

At the same time, another unexpected event took place, something never seen before. And here comes the Robin Hood in our story. A drug designed for purposes different than intraocular use, bevacizumab —manufactured by the same pharmaceutical company— began to replace ranibizumab, since the latter was not available. While the «good» King Richard Lion Heart was fighting in the crusades far away from his homeland, the «humble, outlaw»

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Robin Hood acted as King in his absence, fighting against the «injustice» of the established powers of the time. We are referring to the fourth revolution.

Our colleague Phil Rosenfeld, from the Bascom Palmer Institute in Miami, observed that the systemic endovenous use bevacizumab in patients suffering from cancer and at the same time age-related macular degeneration improved the ocular condition. This fact encouraged this researcher and his colleagues to use this medication to treat AMD in spite of the significant risks in terms of systemic side effects. The treatment proved to be efficient, but the price to pay was high due to the risk of severe cardiovascular complications in elder patients. These reasons led researchers to use this drug directly inside the eye, just as pegaptanib or ranibizumab, even though it had not been originally designed for this use. It was first used with great caution, though rapidly extended throughout the world when noticing its apparent benefits, similar to ranibizumab’s, and exceeding the results obtained with the available drugs, even though this one was destined for off-label use or for a use different than its original purpose. The evidence in hundreds of users and the drug’s short-term benefits in patients determined, out of necessity, an early standardization of its use. And this is how Robin Hood charmed sweet Lady Marian, which in our history is the macula.

Nevertheless, after ranibizumab’s approval, things changed and the situation was far from simple. Since then, there is a drug with very high efficiency based on the evidence provided by several clinical trials in stage III (Marina, Anchor, Pier). Once this highly efficient drug had been approved for intraocular use, the use of bevacizumab became more complex, due to both scientific and legal issues. The legend has it that, upon King Richard Lion Heart’s return, Robin Hood had to kowtow to the King. Subsequently, the King handed over sweet Lady Marian to Robin Hood and ended his days as an outlaw. Similarly, the use of bevacizumab, justified in the absence of ranibizumab, ceased to make sense as it had in the past.

Undeniably, bevacizumab entailed benefits for thousands of patients. It is hard to believe that from one day to the next bevacizumab became an outlawed drug, taking into account the abundant evidence available. We would like to believe that, without questioning King Richard, Robin will be by his side, and go to those places where the King does not dare going. In this sense, we like to think that the use of bevacizumab may be subordinated to the greater use of ranibizumab but should not imply its disappearance. The experience during the past two years do not make it feasible. A certain coexistence would be desirable, at least until we obtain the results of the comparative clinical trial starting this summer under the coordination of doctor Daniel Martin and sponsored by the U.S. National Eye Institute.

This journey has made great progress, although much remains to be done. The next step will be to obtain drugs with similar efficacy but safer administration formats (for example, intravitreous injections every six months and not once a month as is the case today), or else obtaining drugs designed for transcleral release, and thus avoid the use of intravitreous injections and its associated risks. Some of these drugs are currently under study, and in short will undergo stage III clinical trials, as is the case of VEGF trap and bevasiranib. Supposedly, these are more powerful inhibitors than VEGF, but only the results yielded by clinical trials will confirm this apparent benefit. Furthermore, this is just the beginning. VEGF’s inhibition path is only but the first line of research. Today, other paths involved in the triggering of neovascularization are under study.

In any case and for the time being, we should harness the significant progress recently attained in this field of medicine, which has brought about drugs of much greater efficacy and benefits for our patients in the treatment of exudative age-related macular degeneration and, subsequently, in other forms associated to diseases such as pathologic myopia, angioid streaks, multifocal choroiditis, etc.