Do not allow protocols to obliterate your art of treating

Não deixe que os protocolos apaguem a sua arte de tratar

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At the beginning of this century, there was a great revolution in the treatment of retinal diseases with the rise of intraviteal antiangiogenic agents. Initially, pegaptanib (Macugen) proved to be effective in inactivating VEGF 165, one of the isoforms of vascular endothelial growth factor (VEGF), which had been discovered as the great villain of wet age-related macular degeneration (wARMD) – and of several other retinal diseases.(1)

Between 2004 and 2007, two other drugs, bevacizumab (avastin) and ranibizumab (lucentis) appeared in the market.

Due to the high cost of pegaptanib and to the fact it is specially designed to act only on VEGF 165, its use had become obsolete, which opened the market to the two more recent drugs, which were shown to be able of inactivating antivegf A and to have lower cost.(2,3)

The years after their launch in the market witnessed great euphoria and expectations, with promises of curing wARMD, or rather, of stopping its progression, thus stabilizing the visual condition. Initially, that is what actually happened... Later, another drug appeared, aflibercept (Eylia), as an option for a more prolonged treatment effect, as bevacizumab and ranibizumab had a lower half life, with the need for reapplications on a monthly basis. Aflibercept had a different mechanism of action from the other two drugs, thus promising higher efficacy. We then had three anti-vegf drugs in the market, which were similar in their response to wARMD treatment after they were submitted to countless clinical trials, with similar side effects, as well, but with small differences in action time and some differences in cost.(4)

Euphoria with initial results was replaced by frustration. We started seeing patients who were responsive to anti-vegf at the beginning of the treatment having worse visual acuity after approximately two years of treatment, reaching the "baseline" vision level or worse, or even patients with poor or no response to the treatment. We started seeing active neovascular membranes rapidly becoming disciform membranes; we started to see an increase in geographical atrophy; and we were powerless. A chink was open to several protocols that varied, from the type of medication used to the frequency of applications. We discovered tachyphylaxis and started to change medications with some degree of success.(4-14) We started to have three different protocols guiding us as to the frequency of applications: 1) Pro re nata (PRN); 2) Treat and extend; 3) Monthly treatment. Which one is the best? Recent papers have suggested better results with "Treat and extend."(9,10,15)

Public Hospitals, Healthcare Plans, and Their Protocols

The world crisis in public healthcare, mainly in Brazil, has suppressed the offer of specialized treatments, adjusting need to cost. Although it is considered an off-label medication, bevacizumab (Avastin) started to be adopted in some countries due to its low cost. And for these reasons, it began to be vilified by competing laboratories. A strict criterion was created, determined by ANVISA for this medication to be used in medical practice,(16) thus restricting its use: its vial must be used in up to 48 hours, stored in a refrigerated environment, with aspiration and application of the required doses, and after this period, it must be disregarded. In order to comply with this criterion, several patients need to receive their application on the same day, and if that does not happen, the cost of the medication increases to the level of the competitors' drugs that are not off label. The provision of bevacizumab by public services generally takes place in hospitals with oncological service, where it is used for the treatment of colorectal metastasis. The price of these medication has caused healthcare plans to be more stringent in authorizing the treatment, thus delaying applications and collaborating with a worse disease prognosis. They started to require sophisticated supplementary exams, such as fluorescein angiography and optical coherence tomography (OCT), which are by no means less important, and detailed reports with analyses that aren't always rapidly provided. Worse still, these exams are provided in stages: OCT exam is only authorized after the fluorescein angiography result is received. Thus, it hampers both the implementation of a suitable protocol and access of patients to the treatment.

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Patients and Protocols

The most important studies which protocols are based on do not consider the "real world". In the real world, the patient is in the midst of scripts stipulated by medication prices and healthcare plans. It is unfeasible for patients to pay for their own access to treatment, as is maintaining a treatment within the stipulated protocols, since a very small part of the population would have conditions to pay for the treatment, considering the current socio-economic situation of the Brazilian population. The National Health System (SUS - Sistema Único de Saúde) started to offer treatment with bevacizumab; however, few people have access due to bureaucracies and to the continuation of applications.

The logistics to maintain a correct treatment is also complex. wARMD affects elderly patients with several comorbidities, who need companions available to escort them to doctors' appointments and to receive applications, as they frequently live far from reference hospitals and have precarious means of transportation.

There is also a great individual variation in responses to the treatment, which thus denotes lack of knowledge on disease ethiopathogeny: some patients remain stable for a long time with few doses while others continue to get worse despite successive applications even in the absence of geographical atrophy.

It is therefore worth rethinking: do we follow protocols? Or do we adjust them to the reality of our patients?

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