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Short Communication Open Access

Complications of Intravitreal Anti-VEGF Drugs: A Report on Our Personal Experience

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Intravitreal anti-vascular endothelial growth factor (VEGF) agents usage is widely spread as primary treatment of many vitreo-retinal disease such as neovascular age-related macular degeneration, diabetic macular edema, macular edema secondary to retinal vein occlusion and other conditions. Recently we conducted a five year retrospective chart analysis of patients that arrived at the Macular Disease Center of our institute in order to assess the frequency of local and systemic complication in patients undergoing intravitreal bevacizumab, ranibizumab and/or pegaptanib for the treatment of different ocular diseases [1].

Information about the safety of ranibizumab and pegaptanib comes from several large-scale randomized clinical trials evaluating their utilization in patients with choroidal neovascularization secondary to age-related macular degeneration (AMD) [2-4]. These studies concluded that complications from these injections are extremely rare, if the procedure is conducted with proper precautions. Moreover, additional assessments about adverse effects (ocular or systemic) are reported in recent retrorospective case-series [5,6].

With respect to bevacizumab, major ocular complications associated with treatment are severe uveitis [7], tractional retinal detachment [8], intraocular pression (IOP) elevation [9-11] and ocular hemorrhage [12]. Detailed safety data reports for ranibizumab injection in the treatment of neovascular AMD (ANCHOR and MARINA) showed important association with ocular inflammation (prevalence range 1-2%). Other reports referred episodes of ocular hemorrhage following ranibizumab [13,14]. In trials evaluating continuous injection of pegaptanib, no ocular safety problems have been found (most complications were attributed to injection procedure) [15].

Also, rare systemic adverse reactions have been associated with intravitreal injection of anti-VEGF. The overall incidence of systemic adverse events in the ranibizumab trials was low, but the apparent increase in nonocular hemorrhages and thromboembolic events suggested potential increased risks with ranibizumab treatment. During the 3 years of experience with pegaptanib in the VISION trials no systemic safety concerns have emerged in subjects receiving pegaptanib. The most common nonocular adverse events were infections (18%), respiratory (15%) and gastrointestinal disorders (14%). An increase in blood pressure was the most common systemic side effect associated with bevacizumab injections, followed by cerebrovascular accidents (0.21%) and myocardial infarction. Rate of cardiovascular events was low and not always attributable to the drug itself [16,17].

Given the growing importance of anti-VEGF factors in the management of various ocular diseases, a closer look at their potential side-effects is advisable. Furthermore the majority of clinical trials assessing the handling of these medications are focused on their utilization in the treatment of AMD; therefore detailed information about their usage in other ocular pathologies is still incomplete.

In our study we observed that 9.02% of the 732 eyes treated with bevacizumab presented side-effects, while ratings in the ranibizumab and pegaptanib groups were respectively 9.83% (out of 365 eyes) and 20% (out of 29 eyes treated). A total of 117 complications were detected. Ocular side effects registered were sustained IOP elevation (10 after bevacizumab, 9 after ranibizumab and 1 after pegaptanib), infectious uveitis, tractional retinal detachment and a case of sub-retinal hemorrhage after bevacizumab injection; mostly occurred in patients affected by Age-related Macular Degeneration (AMD). Other cases were related to transient IOP elevation immediately after injection.

Systemic complication registered were one case of nausea and uneasiness plus one episode of chest pain with acute vision loss in both eyes after bevacizumab injection; and one episode of acute blood hypertension after pegaptanib.

Significant adverse effects were infrequent, with transient post-operatory IOP elevation as most detected ocular complication. However it was difficult to assess if such complication was actually related to anti-VEGF therapy, since the majority of events occurred in eyes who received less than six injection with a large portion detected at the time of the first injection. Clinical chart analysis indicates that additional injections did not seemed to be strongly related to the incidence of such adverse effect. Moreover ocular hypertension was transient and returned to baseline values after instillation of anti-glaucoma drops immediately after IOP measurement, and remained mostly stable during follow-up. Therefore post-operative IOP elevation may be related to injection procedure itself rather than use of anti-VEGF and so may interfere with the effective. On the contrary, we observed a significant correlation between anti-VEGFs and developing of sustainable IOP elevation, especially after multiple bevacizumab and ranibizumab injections.

The majority of ocular and systemic adverse effects registered in the study population seemed to involve patients affected with AMD that received bevacizumab. This can be explained with the larger indication dedicated to the disease. However eyes with diabetic macular edema, central retinal vein occlusion, branch retinal vein occlusion and macular myopic disease were often related to ocular adverse manifestations after injections with bevacizumab, too. Moreover side-effects were detected mostly in eyes who underwent 3 or more total injections (especially at the time of second injection) reflecting

increasing rates with the length of treatment. Finally, pegaptanib injections were related to less complications compared with other anti-VEGF and no systemic events were identified after ranibizumab treatment.

These 5-year findings suggest that bevacizumab treatment leads to side-effects with greater frequency than other anti-VEGF agents; however results may be affected by this greater utilization, with its consolidated efficacy and lower costs if compared with ranibizumab with no difference in efficacy [18]. For this reasons, this anti-VEGF remains widely used in the treatment of coroidal neovascularization related conditions. Similar conclusions can be applied to adverse events related to pegaptanib, because of its currently limited use that may possibly alter the effective incidence of adverse effects.

Even though complications are rare, they should not be overlooked, given the importance of anti-VEGF in the treatment of neovascular ocular diseases. In contrast to ranibizumab and pegaptanib, randomized controlled trials evaluating the intravitreal use of bevacizumab have not yet been conducted, resulting in lack of valid and reliable safety data. In addition, most patients (especially those affected by AMD) may require long-term maintenance therapy.

Even newer intravitreal medications currently underutilization for the treatment of AMD or diabetic macular edema, such as VEGF-trap molecules (for example aflibercept) may require further evaluation in order to assess their efficacy and safety, also in comparison with the classical anti-VEGF drugs. For this reason it is advisable to improve the current findings with further evaluations and data colletion through long lasting clinical trials, in order to better delineate the safety profile of these drugs.

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