ABSTRACT

The increase in survival rates among preterm infants, characteristics of neonatal care for such infants and a lack of suitable programs for preventing, detecting and treating retinopathy of prematurity (ROP) are factors that have made this disease the main cause of preventable blindness among children in Mexico.

The advent of anti-angiogenic agents in cancer treatment and their off-label use with favorable results in the treatment of proliferative vessel disease of the retina among adult patients, as well as anecdotal reports in the literature and a series of cases showing serious methodological flaws, have prompted their use in the treatment of retinopathy of prematurity. Unfortunately, these agents used indiscriminately in our country have a systemic absorption and secondary effects on the preterm patient’s body. There are no long-term monitoring studies that guarantee their safe use in this segment of the population. This article describes the situation in our country and warns of the risks posed by the use of this type of drug on the preterm infant population.

Key words: retinopathy of prematurity, anti-angiogenics, intravitreal injections.

INTRODUCTION

During the first decade of the 21st century, the decrease in mortality of extremely premature newborns, for the most part in regions of Latin American and in Mexico, has represented an important achievement in pediatric medicine. This change in the prognosis of survival in neonatology is the result of a greater understanding of this condition, of better medical care by neonatologists and specialized nurses and of the availability of high-technology medical equipment that allows the efficient control of the diseases associated with these patients.

However, this decrease in neonatal mortality, especially in premature newborns, has brought with it another serious problem for which our health system is not prepared: the timely diagnosis and treatment of retinopathy of prematurity (ROP). The recent reform of article 61 of the General Health Law in the Congress establishes as compulsory the use of neonatal ophthalmological screening at the fourth week of birth for the early diagnosis and treat-
ment of malformations that may cause blindness. The current statistics on visual impairment in Mexico and other countries of high and medium urban development place ROP as the principal cause of preventable legal blindness in the pediatric population.2,3

National concern in the screening of retinopathy of prematurity
Although the rate of premature newborns in Mexico is one of the lowest in the continent (7.3/100 births), the trend is increasing.5 Only a fifth of the neonatal intensive care units (NICU) in Mexico have structured programs for ROP screening.6 On the other hand, there are few hospitals that include, within their programs of specialization in ophthalmology, training in evaluation of the fundus of the eye in premature infants that are still in incubators in the NICU. And much rarer is the training of the residents on the laser application through the indirect binocular ophthalmoscope. This problem in training in the treatment of ROP is not exclusive to our country. In the U.S. there is also a great lag in the training of ophthalmologists with skills for examining a premature infant at risk of irreversible blindness and how and according to what modality adequate treatment should be provided. The problem is of such magnitude that the creation of a special program of training in ROP has been suggested.7,8

Lack of training in ROP is not the only problem. The advent of new therapies used in Latin America with injectable monoclonal antibodies that block retinal angiogenesis is causing its use to be excessive in severe ROP, even in premature infants who do not meet the international treatment criteria9 and in locations where laser therapy is available.

Therapeutic use of anti-angiogenics in systemic diseases
Anti-angiogenics are medications that may inhibit the formation of new vessels, in almost any part of the body. For many years they have been used for different diseases. Perhaps the best known medication is thalidomide, whose indiscriminate use (in the middle of the last century in pregnant women) caused severe malformations in the development of lower and upper extremities of the fetus. Monoclonal antibodies developed for selectively blocking the molecular pathway of the angiogenesis were initially developed for the treatment of cancer, especially of the colon and ovary. The best known is bevacizumab (Avastin®, Roche, Genetech), which inhibits vascular endothelial growth factor A. In November 2011, this medication was suspended by the U.S. FDA for its use in metastatic breast cancer due to the lack of effectiveness and safety because there were severe adverse effects found such as arterial hypertension, hemorrhage and intestinal perforations, among others.10

Role of endothelial growth factor in the pathophysiology of ROP
The fetal retina develops before its vascular network. The blood vessels begin their growth from the optic nerve towards the periphery. The high demand for oxygen of the retinal tissue in development causes a wave of “physiological hypoxia,” which precedes growth of the vessels. In response to the hypoxia, the astrocytes stimulate growth of the blood vessels via the vascular endothelial growth factor (VEGF). The formation of these new retinal vessels decreases hypoxia and, in turn, decreases the expression of VEGF. In this manner, vascular growth is further reduced through a mechanism of local feedback mechanism. The supplemental oxygen interferes with the role of VEGF in the normal development of the vasculature. There are two phases recognized in ROP. Phase 1 (between 22 and 30 weeks postgestation) is characterized by relative hyperoxia (greater than the intrauterine environment) that suppresses the expression of VEGF with decrease in its levels, resulting in the loss of physiological wave necessary for VEGF to support vascular growth. Phase 2 (between 31 and 44 weeks postgestation) involves relative hypoxia and increase of the VEGF. This decrease in oxygen tension can lead to an increase in the wave of expression of VEGF and the abnormal growth of new vessels in the retina to the vitreous accompanied by fibrovascular tissue.

Understanding this relationship between oxygen and VEGF has allowed the improvement of ROP management strategies including prevention and early management in phase 1 and the delayed treatment in phase 2.11 Bevacizumab causes a transient blockage of VEGF —unlike the laser, which produces a progressive and sustained decrease of this factor— for which the ROP could be modified in an unpredictable way causing among others, failures in the interpretation and follow-up of these changes.
Use of anti-angiogenics in ocular diseases

In 2007 the first series of cases on the use of intravitreous use of anti-angiogenics (IVAA) in the treatment of severe ROP were published. After these reports, up to now >50 articles on IVAA have been published (most of them being case series with short follow-up). In 2009, Micieli et al. carried out a review on the use of off-label bevacizumab for severe ROP. Data available up to this time were considered to be of a very low level of clinical evidence given the randomness of the studies, especially the reports of cases and retrospective reviews. Mintz-Hittner et al. published the first randomized clinical trial where they compared the standard treatment with laser and the intravitreal injections of bevacizumab. The authors concluded that bevacizumab was superior to laser for the resolution of severe ROP. However, serious methodological errors and a great frequency of neonatal deaths in the intravitreal bevacizumab group (although not statistically significant) were noted in a variety of letters to the editor. The experience of the Mexican ophthalmologists reported in a small nonrandomized sample without a control group in this treatment has also been seriously questioned because bevacizumab was shown as a “miracle” drug for all stage 3+ of ROP without proving its safety. Also, medical indications for its use and patient follow-up were not clearly established.

This recent acquisition in the ophthalmological therapeutic arsenal seems to be a very tempting option for the treatment of severe ROP for several reasons. First, the experience in intraocular administration in adults with a retinal disease —also potentially fatal for vision and age-related macular degeneration— has been successful with this medication through a quick, seemingly simple procedure with rare side effects. Second, lack of training of the Mexican ophthalmologists in laser treatment using an indirect ophthalmoscope has made the previous therapeutic option gain supporters by being a faster and less complex procedure to perform. The application of IVAA in repeated injections and “prophylactically” in patients who have not developed severe ROP has been observed. The shortage of clinical trials with internal and external validity and with long-term follow-up demonstrating safety and superiority of this modality have been a concern among experts—neonatologists and ophthalmologists in industrialized countries (Table 1).

Ranibizumab is another anti-angiogenic that has been used in ophthalmological diseases. It is an aptamer of a monoclonal antibody that acts directly on all the isoforms of VEGF. Although it was approved by the FDA in June 2006 for the treatment of age-related macular degeneration in its moist variety, its use has not been approved in severe ROP. Multiple studies are being carried out in other ocular proliferative diseases such as diabetic retinopathy and venous occlusions with excellent anatomic and functional results.

The molecular characteristics of the different anti-angiogenics are decisive for use in preterm infants. The ranibizumab molecule is smaller than the bevacizumab (40 kD vs. 149 kD) and its pharmacological effect is shorter (2.88 days unlike bevacizumab whose half-life is 8.82 days). Unlike bevacizumab, the presence of antibody in the contralateral eye has not been found after intravitreal ranibizumab administration. In a non-comparative, nonrandomized prospective pilot study, Orozco-Gomez et al. used ranibizumab together with transpupillary laser in patients with prethreshold ROP with apparent good results at 3 years of follow-up. Ranibizumab may offer greater safety than bevacizumab in the premature patient; however, controlled clinical trials with long-term follow-up to test this theory is required.

Local and systemic side effects of intravitreal anti-angiogenics

It is not surprising that reports of ocular and systemic side effects with the use of anti-angiogenics are beginning to appear (Table 2). We must keep in mind that VEGF is...
a glycoprotein produced by various cell types in response to diverse stimuli. It acts on vascular endothelial cells through the specific tyrosine-kinase membrane receptors, thereby regulating cellular functions such as proliferation, differentiation, migration and cellular survival.\textsuperscript{39} It also has effects beyond vasculogenesis and angiogenesis. The eye is necessary for normal development of the neural retina independent of angiogenesis. In the brain it is neurotropic and neuroprotective. In the lungs it plays an important role in pulmonary alveologenesis as well as in surfactant synthesis. It is also essential for glomerulogenesis and skeletal growth.\textsuperscript{30}

Persistence of serum bevacizumab levels has been shown for \textgreater 15 days.\textsuperscript{27} Intravitreal anti-angiogenics could decrease systemic levels of VEGF and affect organ development, which itself is compromised in the premature patient such as in the renal and respiratory systems in which complications have been reported in experimental models and in adults during use of these medications.\textsuperscript{41}

Another concern about this treatment is the need for a prolonged ophthalmological follow-up of patients. Hu et al. showed that severe ROP can be reactivated in a late manner in patients treated with bevacizumab because it modifies the natural history of the disease.\textsuperscript{42} In these patients it has been observed that severe ROP can be reactivated up to 5 months after application of IV AA and will eventually require laser for its control.

### Legal implications for use of anti-angiogenics

The unapproved use of off-therapy for an ocular disease in seriously ill premature newborns may have legal implications.\textsuperscript{43} The most important company in the U.S. that insures ophthalmologists against malpractice (Ophthalmic Mutual Insurance Company, San Francisco, CA) issued a statement where it warns of the imprecise safety profile of this therapy. It emphasizes that the approved treatment for severe ROP is the laser and sponsors its affiliated physicians to take courses and attend lectures on ROP.\textsuperscript{44}

Primary prevention of ROP should be performed with appropriate neonatal care, avoiding the variability of oxygen saturation through the recommended levels and adequately treating the associated risk factors such as sepsis, intraventricular hemorrhage, bronchopulmonary dysplasia and all those diseases that could cause metabolic stress to the premature infant.

The medical treatment of severe ROP by IVAA injection should be restricted in the large majority of premature infants. Ablation of the avascular retina using transpupillary laser or cryotherapy with indirect binocular ophthalmoscope continues to be the treatment of choice. Functional and structural results of these treatments in the long term have been extensively studied in clinical trials such as CRYO-ROP\textsuperscript{45} and ETROP\textsuperscript{46} (Early Treatment of Retinopathy of Prematurity), which endorse its effectiveness.

IVAA injection should not be used as a substitute for laser treatment and much less as prophylaxis in the develop-

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### Table 2. Local and systemic collateral effects reported for bevacizumab and ranibizumab

<table>
<thead>
<tr>
<th>Agent</th>
<th>Local</th>
<th>Systemic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Premature infants</td>
<td>Adults</td>
</tr>
<tr>
<td>Bevacizum</td>
<td>Fibrosis-retinal traction\textsuperscript{30}</td>
<td>Uveitis\textsuperscript{34}</td>
</tr>
<tr>
<td></td>
<td>Permanent delay of vascular development\textsuperscript{43}</td>
<td>Endophthalmitis\textsuperscript{35}</td>
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<tr>
<td></td>
<td>Choroidal rupture\textsuperscript{39}</td>
<td>Vitreal hemorrhage\textsuperscript{34}</td>
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<tr>
<td></td>
<td>Reactivation of disease up to 5 months after treatment\textsuperscript{43}</td>
<td>Retinal ischemia\textsuperscript{34}</td>
</tr>
<tr>
<td>Ranibizum</td>
<td>Scarce reports, its high cost limits its use</td>
<td>Uveitis\textsuperscript{34}</td>
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<td></td>
<td></td>
<td>Endophthalmitis\textsuperscript{34}</td>
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<td></td>
<td></td>
<td>Vitreous hemorrhage\textsuperscript{34}</td>
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<td></td>
<td></td>
<td>Retinal detachment\textsuperscript{34}</td>
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AMF, acute myocardial infarct; CVA, cerebrovascular accident.
Development of severe ROP because, to date, the existing medical evidence about side effects—both ocular and systemic—is very limited. Studies that have been published in this regard have serious methodological errors and biases that may be wrongly interpreted.

The neonatologist should always participate actively in the final decision on the use of this therapy. The ophthalmologist who applies this treatment should commit to weekly examination of the fundus of the eye for at least 5 months. Also, parents should receive complete information about the short-, medium, and long-term risks associated with IVAA, about the need for frequent ophthalmological examinations for several months, even after the patient has been discharged, and about all therapeutic options for the treatment of severe ROP.

Those NICUs without adequate trained personnel and ophthalmologic equipment must seek, as a temporary measure, support from other units with those resources. At the same time they should promote the training of their ophthalmologists in the diagnosis and timely treatment of this disease and urgently request from the authorities of the Department of Health, IMSS or Institute of Social Security and Services for State Workers the necessary equipment to address this serious health problem. Sufficient scientific evidence that demonstrates the superiority or therapeutic equivalence of the IVAA compared with transpupillary laser is not far in the future. Much remains to be done in terms of regulation of therapeutic use of recently appearing drugs in infants because, as is well known, pharmacological therapeutic trials rarely include premature infants in their studies.

IVAA is likely to be a valuable therapeutic tool for certain cases of ROP. Although there is a lack of sufficient evidence, laser treatment should be sought as this therapy has proven its effectiveness and efficiency for >20 years with minimal systemic morbidity. Rigorous studies using existing ethical standards in research in neonatology will be welcome in order to provide sufficient evidence to identify new safe and effective therapies in the treatment of this terrible disease.

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REFERENCES