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Review article

# Retinopathy of prematurity: controversies in the use of intraocular anti-angiogenics

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## 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-

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ment of malformations that may cause blindness.[1] 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),[4] 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 criteria[9] 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.[12,13] 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.[14] Mintz-Hittner et al. published the first randomized clinical trial where they compared the standard treatment with laser and the intravitreal injections of bevacizumab.[15] 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.[16-19] 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.[20,21]

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.[22,23] 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).[24,25]

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.[26]

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).[27] 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.[28] 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.[29]

## 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).[30-38] We must keep in mind that VEGF is

**Table 1.** Concerns in regard to treatment with intraocular bevacizumab in premature infants with severe retinopathy



- Dose
- Collateral effect
  - Abnormal organ development dependent on angiogenesis
  - Increase of neonatal mortality
- Prolonged ophthalmological follow-up
- Abuse in developing countries
- Legal implications

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.[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.[40]

Persistence of serum bevacizumab levels has been shown for >15 days.[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.[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.[42] In these patients it has been observed that severe ROP can be reactivated up to 5 months after application of IVAA 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.[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.[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. Good functional and structural results of these treatments in the long term have been extensively studied in clinical trials such as CRYO-ROP[45] and ETROP[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 devel-

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

| | Collateral effects | | | |
|---|---|---|---|---|
| | Local | | Systemic | |
| Agent | Premature infants | Adults | Premature infants | Adults |
| Bevacizumab | Fibrosis-retinal traction[30]<br>Permanent delay of vascular development[43]<br>Choroidal rupture[33]<br>Reactivation of disease up to 5 months after treatment[43] | Uveítis[34]<br>Endophthalmitis[35]<br>Vitreal hemorrhage[34]<br>Detached retina[34]<br>Central retina artery occlusion[34]<br>Retinal ischemia[34] | Higher mortality possibly due to pulmonary complications[15,31] | Thromboembolus[34]<br>Arterial hypertension[34]<br>Intestinal perforation[34]<br>Delayed wound healing<br>Pulmonary toxicity[31,38]<br>Renal toxicity37 |
| Ranibizumab | Scarce reports, its high cost limits its use | Uveitis[34]<br>Endophthalmitis[34]<br>Vitreous hemorrhage[34]<br>Retinal detachment[34] | Scarce reports, its high cost limits its use | Arterial thromboembolytic events[32]<br>AMI[32]<br>CVA[32] |



AMF, acute myocardial infarct; CVA, cerebrovascular accident.

opment 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.[47]

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

1. Secretaria de Salud. Reforma Artículo 61 de la Ley General de Salud. Diario Oficial de la Federación 25 de enero 2013;DCCXII (19, segunda sección):1.
2. Zepeda-Romero LC, Barrera-de-León JC, Camacho-Choza C, Gonzalez Bernal C, Camarena-García E, Díaz-Alatorre C, et al. Retinopathy of prematurity as a major cause of severe visual impairment and blindness in children in schools for the blind in Guadalajara city, Mexico. Br J Ophthalmol 2011;95:1502-1505.
3. Kong L, Fry M, Al-Samarraie M, Gilbert C, Steinkuller PG. An update on progress and the changing epidemiology of causes of childhood blindness worldwide. J AAPOS 2012;16: 501-507.
4. World Health Organization. Born too soon: the Global Action Report on preterm birth. The Partnership for Maternal, Newborn and Child Health. Available at: http://www.who.int/pmnch/media/news/2012/preterm_birth_report/en/index.html
5. Instituto Nacional de Estadística y Geografía. Estadísticas de Natalidad. Available at: http://www.inegi.org.mx/est/contenidos/proyectos/registros/vitales/natalidad/default.aspx
6. Zepeda Romero LC, Gutiérrez Padilla JA, De la Fuente-Torres-MA, Angulo Castellanos E, Ramos Padilla E, Quinn GE. Detection and treatment for retinopathy of prematurity in Mexico: need for effective programs. J AAPOS 2008;12:225-226.
7. Bradley MH, Motley WW 3rd. Pediatric ophthalmology fellowship training in laser ablation for retinopathy of prematurity. J AAPOS 2012;16:539-542.
8. Wong RK, Ventura CV, Espiritu MJ, Yonekawa Y, Henchoz L, Chiang MF, et al. Training fellows for retinopathy of prematurity care: a Web-based survey. J AAPOS 2012;16:177-181.
9. Darlow BA, Ells AL, Gilbert CE, Gole GA, Quinn GE. Are we there yet? Bevacizumab therapy for retinopathy of prematurity. Arch Dis Child Fetal Neonatal Ed 2013;98:F170-F174.
10. US Food and Drug Administration. News and Events. FDA Commissioner announces Avastin decision. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm280536.htm
11. Harnett ME, Penn JS. Mechanisms and management of retinopathy of prematurity. N Engl J Med 2012;367:2515-2526.
12. Chung EJ, Kim JH, Ahn HS, Koh HJ. Combination of laser photocoagulation and intravitreal bevacizumab (Avastin) for aggressive zone I retinopathy of prematurity. Graefes Arch Clin Exp Ophthalmol. 2007;245:1727-1730.
13. Travassos A, Teixeira S, Ferreira P, Regadas I, Travassos AS, Esperancinha FE, et al. Intravitreal bevacizumab in aggressive posterior retinopathy of prematurity. Ophthalmic Surg Lasers Imaging 2007;38:233-237.
14. Micieli JA, Surkont M, Smith AF. A systematic analysis of the off-label use of bevacizumab for severe retinopathy of prematurity. Am J Ophthalmol 2009;148:536-543.e2.
15. Mintz-Hittner HA, Kennedy KA, Chuang AZ; BEAT-ROP Cooperative Group. Efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity. N Engl J Med 2011;364:603-615.
16. Good WV, Palmer EA. Bevacizumab for retinopathy of prematurity. N Engl J Med 2011;364:2359; author reply 2361-2362.

17. Gilbert CE, Zin A, Darlow B. Bevacizumab for retinopathy of prematurity. N Engl J Med 2011;364:2359-2360; author reply 2361-2362.
18. Lim LS, Mitchell P, Wong TY. Bevacizumab for retinopathy of prematurity. N Engl J Med 2011;364:2360; author reply 2361-2362.
19. Gole GA, Camuglia JE, Ells AL. Bevacizumab for retinopathy of prematurity. N Engl J Med. 2011;364:2360-2361; author reply 2362.
20. Quiroz-Mercado H, Martinez-Castellanos MA, Hernandez-Rojas ML, Salazar-Teran N, Chan RV. Antiangiogenic therapy with intravitreal bevacizumab for retinopathy of prematurity. Retina 2008;28(3 suppl):S19-S25.
21. Azad R, Dave V, Jalali S. Use of intravitreal anti-VEGF: retinopathy of prematurity surgeons' in Hamlet's dilemma? Indian J Ophthalmol 2011;59:421-422.
22. Rosenfeld PJ, Brown DM, Heier JS, Boyer DS, Kaiser PK, Chung CY, et al. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med 2006;355:1419-1431.
23. Brown DM, Kaiser PK, Michels M, Soubrane G, Heier JS, Kim RY, et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. N Engl J Med 2006;355:1432-1444.
24. Hård AL, Hellström A. On the use of antiangiogenetic medications for retinopathy of prematurity. Acta Paediatr 2011;100:1063-1065.
25. Raizada S, Kandari JA, Sabti KA. Will the BEAT-ROP study results really beat ROP? Invest Ophthalmol Vis Sci 2011;52:9288-9289.
26. Bakri SJ, Snyder MR, Reid JM, Pulido JS, Ezza MK, Singh RJ. Pharmakokinetics of intravitreal ranibizumab (Lucentis). Ophthalmology 2007;114:2179-2182.
27. Sato T, Wada K, Arahori H, Kuno N, Imoto K, Iwahashi-Shima C, et al. Serum concentrations of bevacizumab (Avastin) and vascular endothelial grow factor in infants with retinopathy of prematurity. Am J Ophthalmol 2012;153:327-333.
28. Orozco-Gómez LP, Hernández-Salazar L, Moguel-Ancheita S, Ramírez-Moreno MA, Morales-Cruz MV. Láser-ranibizumab para tratar retinopatía del prematuro en estadio umbral-preumbral. Tres años de experiencia. Cir Cir 2011;79:225-232.
29. Avery RL. Bevacizumab (Avastin) for retinopathy of prematurity: wrong dose, wrong drug, or both? J AAPOS 2012;16:2-4.
30. Zepeda-Romero LC, Liera-Garcia JA, Gutiérrez-Padilla JA, Valtierra-Santiago CI, Avila-Gómez CD. Paradoxical vascular-fibrotic reaction after intravitreal bevacizumab for retinopathy of prematurity. Eye 2010;24:931-933.
31. Jalali S, Balakrishnan D, Zeynalova Z, Padhi TR, Rani PK. Serious adverse events and visual outcomes of rescue therapy using adjunct bevacizumab to laser and surgery for retinopathy of prematurity. The Indian Twin Cities Retinopathy of Prematurity Screening database Report number 5. Arch Dis Child Fetal Neonatal Ed 2013;98:F327-F333.
32. Sharma S, Johnson D, Abouammoh M, Hollands S, Brissette A. Rate of serious adverse effects in a series of bevacizumab and ranibizumab injections. Can J Ophthalmol 2012;47:275-279.
33. Atchaneeyasakul LO, Trinavarat A. Choroidal ruptures after adjuvant intravitreal injection of bevacizumab for aggressive posterior retinopathy of prematurity. J Perinatol 2010;30:497-499.
34. Day S, Acquah K, Mruthyunjaya P, Grossman DS, Lee PP, Sloan FA. Ocular complications after anti-vascular endothelial growth factor therapy in Medicare patients with age-related macular degeneration. Am J Ophthalmol 2011;152:266-272.
35. Goldberg RA, Flynn HW Jr, Isom RF, Miller D, Gonzalez S. An outbreak of streptococcus endophthalmitis after intravitreal injection of bevacizumab. Am J Ophthalmol 2012;153:204-208.e1.
36. Erinieri JP, Fong AJ, Kemeny NE, Brown KT, Getrajdman GI, Solomon SB. Timing of administration of bevacizumab chemotherapy affects wound healing after chest wall port placement. Cancer 2011;117:1296-1301.
37. Zhao J, Li H, Zhang L, Zhong W, Li LY, Wen YB, et al. Clinical and pathological analyses of bevacizumab-induced renal impairment in four patients. Zhongguo Yi Xue Ke Xue Yuan Xue Bao 2012;34:153-158.
38. Barber NA, Ganti AK. Pulmonary toxicities from targeted therapies: a review. Target Oncol 2011;6:235-243.
39. Gschwind A, Fischer OM, Ullrich A. The discovery of receptor tyrosine kinases: targets for cancer therapy. Nat Rev Cancer 2004;4:361-370.
40. Gruenewald F, Prota A, Giese A, Ballmer-Hofer K. Structure-function analysis of VEGF receptor activation and the role of coreceptors in angiogenic signaling. Biochim Biophys Acta 2010;1804:567-580.
41. Machado FG, Kuriki PS, Fujihara CK, Fanelli C, Arias SC; Malheiros DM, et al. Chronic VEFG blockade worsens glomerular injury in the remnant kidney model. PloS One 2012;7:e39580.
42. Hu J, Blair MP, Shapiro MJ, Lichtenstein SJ, Galasso JM, Kapur R. Reactivation of retinopathy of prematurity after bevacizumab injection. Arch Ophthalmol 2012;130:1000-1006.
43. Kaiser PK, Cruess AF, Bogaert P, Khunti K, Kelly SP. Balancing risk in ophthalmic prescribing: assessing the safety of anti-VEGF therapies and the risks associated with unlicensed medicines. Graefes Arch Clin Exp Ophthalmol 2012;250:1563-1571.
44. Ophthalmic Mutual Insurance Company: A Risk Retention Group. Anti-VEGF intravitreal injections for ROP: risk management analysis and recommendations. Available at: http://www.omic.com/rop-intravitreal-anti-vegf-injections-ris-management-recommendations/
45. Dobson V, Quinn GE, Summers CG, Hardy RJ, Tung B; Cryotherapy for Retinopathy of Prematurity Cooperative Group. Visual acuity at 10 years in Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) study eyes: effect of retinal residua of retinopathy of prematurity. Arch Ophthalmol 2006;124:199-202.
46. Phelps DL; ETROP Cooperative Group. The Early Treatment for Retinopathy of Prematurity study: better outcomes, changing strategy. Pediatrics 2004;114:490-491.
47. Wiles JR, Vinks AA, Akinbi H. Federal legislation and the advancement of neonatal drug studies. J Pediatr 2013;162:12-15.