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OPINION ARTICLE

Past, Present, and Future of Propranolol for Hemangiomas of Infancy[☆]

Hemangiomas de la infancia: pasado, presente y futuro del tratamiento con propranolol

E. Baselga

Servicio de Dermatología, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

Hemangiomas of infancy are the most common vascular tumors of childhood, affecting 10% of newborns, especially females. Hemangiomas are biologically unique, and unlike other proliferative lesions, they tend to regress and resolve spontaneously through mechanisms involving intracellular events or signals that are still only partially understood. In many cases, a wait-and-see approach is therefore all that is required. About 10% of hemangiomas are treated, however, because they may compromise vital functions, because ulceration develops, or because they potentially leave the skin disfigured. While it is true that these tumors resolve, treatment can be justified by the fact that they will not necessarily disappear without a trace.¹ Furthermore, full resolution can take years and the psychological impact the birthmark may have during the early years of a child's socialization is unpredictable. In this issue of *Actas Derma-Sifiliográficas*, Bernabeu and coworkers² report on a relatively large series of infantile hemangiomas treated with propranolol, one of the most recently introduced therapeutic alternatives. In this article I review what is known about these vascular tumors, reflect on past and present approaches to management, and outline my view of what the future will bring.

Hemangiomas of Infancy: The Past

Perhaps as a result of their high frequency, hemangiomas have generally been understood to be benign. Nevertheless, medicine has still searched persistently for a way to treat them. New treatment modalities have been greeted with enthusiasm, although some were then abandoned in spite of their efficacy because the side effects could not be justified for the treatment of what remains a benign lesion. Others, such as oral corticosteroids, have prevailed over the years as we have waited for better or safer treatments to appear. Some options, such as surgical removal, were taken up once again after periods of disuse, as occurred when radiotherapy, which was popular in the 1950s, was later proscribed after follow-up brought to light complications such as radio-dermatitis and skin cancer in the irradiated zone.³

When hemangiomas were reported to respond to systemic corticosteroids at the end of the 1960s,⁴ this therapy became perhaps the first major advance in the medical management of these tumors and over time we gained a better understanding of the optimal dosage as well as the risks. One of the main disadvantages of systemic corticosteroid treatment is that these drugs only act on the proliferative phase, leaving a very small window of opportunity to initiate therapy with assurance of success given that hemangiomas reach 80% of their size within the first 3 months. Oral corticosteroids halt growth in nearly 80% of patients, but rapid reduction in volume occurs in only a third. Moreover, the use of these drugs to treat hemangiomas requires much higher dosages (nearly 3 mg/kg/d) than those used for other indications. High dosages can lead

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E-mail address: dra.baselga@gmail.com

to delayed growth and suppression of the hypothalamic-pituitary-adrenal axis, although the effect is reversed on suspension of treatment. The greatest concern, however, is immunosuppression, which can increase the risk of serious opportunistic infections, such as *Pneumocystis jiroveci* pneumonia, in children who are in fact being treated for a birthmark that is not life-threatening.⁵ Another unresolved problem is interference with the child's vaccination schedule: at present we do not know if it is appropriate to vaccinate patients under such treatment or if vaccination should be delayed until after treatment or repeated once treatment is complete.⁶

In the 1990s, a group led by Folkman, who pioneered research on the mechanisms of angiogenesis, described the efficacy of interferon in hemangiomas of infancy even in cases that were unresponsive to corticosteroids.⁷ However, the description of spastic diplegia in up to 10% of treated patients relegated this approach to use only in tumors that were resistant and life-threatening.⁸

In the search for safer antiangiogenic drugs for cases refractory to oral corticosteroids, Enjolras and coworkers⁹ tested vincristine. This drug, while slow to act, proved highly effective and had few adverse effects. The only route of administration, however, is a central venous line, which presents evident problems when treating an infant for a nonmalignant growth.

Hemangiomas of Infancy: The Current Situation

The discovery that propranolol was effective in this setting was a casual observation by alert French dermatologists,¹⁰ whose report once again changed our therapeutic approach to these tumors radically. Response to propranolol is so good and rapid that nearly 100 articles have been published on this use since the first study appeared in 2008. This drug is not new: it has been on the market since 1964, and its pharmacokinetics and side effects are well known. Propranolol has been shown to be effective on hemangiomas of all types and locations, including lesions affecting the throat and liver and those that have become ulcerated. Moreover, this drug acts well beyond the proliferative phase, even benefiting patients as old as 2.5 years.¹¹ Response is so rapid that color changes can be seen within 24 hours. Maximum response is usually evident at 10 weeks and a plateau occurs at around 20 weeks.¹² The dosage in most studies has been 2 mg/kg/d, divided into 2 or 3 doses. Assessment by a cardiologist is recommended prior to treatment, and blood pressure, heart rate, and blood sugar levels should be monitored, especially after the first few doses and after any increase in dosage.

Hemangiomas of Infancy: The Future

Given the excellent results seen with propranolol, it is my opinion that this drug will replace systemic corticosteroids as the first-line therapy for hemangiomas of infancy.

Many questions remain, however.¹³ The dose-response curve has not yet been established, for example. Although most studies have prescribed 2 mg/kg/d, many have used lower or higher dosages with good results. That there is a

dose-effect relationship is known, as a better outcome has been observed at higher doses. However, we do not know if using higher doses will allow us to prescribe shorter regimens or if, on the other hand, lower doses taken over a longer period might give the same results with less risk. The optimal duration of treatment has also not yet been established. Although there is a notion that the hemangioma is likely to grow back if treatment is interrupted before the age of 6 to 9 months, no clinical trials have yet compared treatment regimens with different durations. In fact, we have sometimes seen hemangiomas grow back after interrupting treatment at 18 months of age, well past the tumor's proliferative phase. We have also yet to see trials comparing propranolol to oral corticosteroids, or trials assessing combination therapy. The mechanism that might explain propranolol's effect on hemangiomas of infancy is also poorly understood at this time, although it has been suggested that it may be related to control of hypoxia, the induction of apoptosis, the reduction of vascular endothelial growth factor or fibroblast growth factor, or even attenuation of renin-angiotensin system activity in the endothelium of the hemangioma itself.¹³⁻¹⁵

When large facial hemangiomas are treated with propranolol, we still know little of the possible risks or the best way to monitor for the main adverse events (principally hypotension, bradycardia, bronchospasm, hypoglycemia, and hyperkalemia). For this reason, individual hospitals have established their own protocols in keeping with available resources; practices range from hospital admission for the first days of treatment to observation in a day hospital, outpatient monitoring by health care staff, or parent monitoring of blood pressure at home.¹⁶ The risk of treating large facial hemangiomas accompanied by agenesis, hypoplasia, and tortuosity of large cerebral vessels (PHACE syndrome) is another area where knowledge is lacking.

It is very important to remember that propranolol has not been approved for use in treating infantile hemangioma. Its prescription therefore necessarily falls into the category of compassionate use. This should be of particular concern to us, as these tumors are not usually life-threatening and as most patients are in the age range when the incidence of sudden infant death is highest. Written informed consent must therefore be obtained before treatment can start. Even when parents have consented, however, the prescribing physician's burden of responsibility is great, particularly since it is not usually difficult to obtain permission from parents who trust their doctor. The answer to our questions about the use of this drug in hemangiomas of infancy, and the approval of this indication, will depend on the completion of randomized clinical trials. Unfortunately, trials of drugs that have been on the market for so long are always difficult and costly because the pharmaceutical industry usually lacks interest in funding them.

Analysis of the 36 hemangiomas in the series reported by Bernabeu and coworkers,² in spite of the limitations of its retrospective study design, supports the view of this drug's prospects as I have explained them: its clinical efficacy is more than promising and its safety profile is good, as shown by the adoption of this therapeutic alternative by important centers in Spain and its inclusion in international guidelines.

Various randomized placebo-controlled trials are underway to compare different doses of the drug over different

periods, and there are also trials comparing propranolol to oral corticosteroids and other β -blockers such as nadolol. A list of such studies can be consulted at <http://clinicaltrials.gov/>. At this time I would like to encourage pediatric and other dermatologists who treat infants with hemangiomas to explain this option to families. If the infant's lesion might be treatable with propranolol, the physician can propose enrollment in a worldwide multicenter study in which Spain is participating. The inclusion criteria can be read at <http://clinicaltrials.gov/ct2/show/study/NCT01056341>. Participating hospitals include Hospital de la Santa Creu i Sant Pau in Barcelona and Hospital San Juan de Dios in Barcelona; Hospital La Paz and Hospital del Niño Jesús in Madrid; Hospital Virgen del Rocío in Seville; Hospital Universitario de La Coruña in La Coruña; and Hospital Universitario de Valencia in Valencia.

In conclusion, hemangiomas of infancy constitute a fast-moving field in which treatment options are constantly being reconsidered, as reflected in the changes that have taken place over the past 4 decades. The recent addition of propranolol to the therapeutic arsenal for hemangioma has improved the clinical response we can expect. As we learn more about this drug's mechanisms of action in this clinical setting, we can also expect to extend our understanding of the pathogenesis of these benign endothelial tumors.

Conflict of Interest

Dr Baselga is a principal investigator and coordinator of the HEMANGIOL study in Spain.

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