Treating the First Portuguese Patient with Luxturna: A Small Step for World Science, a Giant Leap for Portuguese Ophthalmology

O Primeiro Tratamento com Luxturna em Portugal: Um Pequeno Passo para a Ciência Mundial, um Salto Gigante para a Oftalmologia Portuguesa

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After a bumpy start with decades of disputed results and treatment failures, the first ever gene therapy drug (Gendicine®, a recombinant adenovirus engineered to express wild-type-p53) was approved by the China Food and Drug Administration in 2003 to treat head and neck cancer.[1] However, it was not until 2015 that the U.S. Food and Drug Administration (FDA) approved one of these medicines – talimogene laherparepvec (T-VEC, or Imlygic®), the first oncolytic virus therapy for patients with metastatic melanoma that cannot be surgically removed. In 2017, tisagenlecleucel (Kymriah®) was granted FDA approval for the treatment of B-cell lymphoblastic leukemia. Later that year, voretigene neparvovec (Luxturna®) became the first gene therapy for inherited blindness to receive FDA approval. This was a significant milestone for ophthalmology in particular and modern medicine in general, as Luxturna was also the first *in vivo* gene therapy ever approved. Treatment is directed at *RPE65*-associated retinal degeneration, a severe form of inherited retinal blindness. Gene augmentation therapy delivers a normal copy of the native human *RPE65* cDNA to the diseased retinal pigment epithelium (RPE) cells after subretinal injection of a recombinant adeno-associated virus (AAV).[2] Improved light sensitivity, visual field, and navigational ability under dim lighting conditions were reported, with preservation of the clinically meaningful effect for at least 4 years.[3] In November 2018, the European Medicines Agency (EMA) granted Novartis AG marketing authorization for the use of Luxturna in Europe, but the high cost and country-specific regulations hampered its widespread use. After cost-effectiveness for the national healthcare systems was reviewed,[4-7] several countries around the world started treating patients.

The *RPE65* gene is expressed in the RPE and plays a key role in the retinoid cycle as it encodes retinoid isomerohydrolase, an enzyme that regenerates *11-cis* retinal.[8] Biallelic loss-of-function mutations in the *RPE65* gene result in either a lack of RPE65 protein or protein that is non-functional. Without this important protein, phototransduction in photoreceptor cells is impaired, resulting in severe photoreceptor degeneration and ultimately death.[2] Like many inherited retinal dystrophies/degenerations (IRDs), *RPE65* mutation-associated retinal degeneration can be heterogenous, with a phenotypic continuum modulated by disease severity. Severe visual impairment or blindness is usually present from birth or in early childhood,

a clinical presentation that falls within the Leber congenital amaurosis (LCA)/early-onset retinal degeneration (EORD) spectrum. Although the true prevalence of *RPE65*-associated disease in unknown, estimates point towards an overall prevalence of 1 per 300 000 individuals.[9-11] *RPE65* is believed to account for 5%-6% of LCA cases and 2%-5% of autosomal recessive retinitis pigmentosa cases. In Portugal, for a population of approximately 10 million, estimates anticipate an overall number of between 33 and 67 *RPE65* mutation-associated IRD patients, which is considerably higher than what was reported in a recent multinational survey by the European Vision Institute Clinical Research Network (EVICR.net).[9] Two possible explanations are 1) patients who are currently followed at centers that are not members of the EVICR.net consortium and/or 2) patients that remain unidentified because genetic testing is not routinely performed (or available) in all Portuguese centers. Nevertheless, since most patients are blind by the end of the third or fourth decade,[12,13] the number of individuals who might benefit from gene therapy with voretigene neparvovec in Portugal is probably much lower. Given the degenerative nature of *RPE65*-associated disease, a window of opportunity for gene therapy exists and gene therapy candidates must be identified as early as possible. Early diagnosis and rapid referral of these patients to specialized centers cannot be overemphasized as *time is vision*.

May 2021 will be forever remembered as the date of the first gene therapy treatment of a Portuguese patient with inherited retinal blindness. In a small country like Portugal, being able to treat patients with this innovative therapy is a milestone that should make all ophthalmologists proud. Currently, Centro Hospitalar e Universitário de Coimbra (CHUC) is the only Portuguese Luxturna treatment center. Patient referral pathways are in place so that no patient is left behind.

Despite remarkable advances witnessed in the field, complex challenges remain. IRDs are still largely unknown among decision-makers, policy-makers, the general public, clinicians and other healthcare workers.[14] Even among ophthalmologists, it is crucial to raise awareness and fight the dis- and/or misinformation that exists towards IRDs so that patients can be granted full clinical, familial and socioeconomic support. Furthermore, obtaining a genetic diagnosis for every IRD patient is a vital step in moving the field forward and the single most important factor for gaining access to an approved treatment or gene therapy-based clinical trial.[15] To improve care for IRD patients in Portugal, we need to urgently address four pivotal unmet needs14: 1) improve disease awareness and education; 2) provide equitable access to genetic testing and genetic counselling; 3) establish referral pathways and minimize time to diagnosis; and 4) join forces to have all patients included in the IRD-PT registry.[16]

In conclusion, inherited retinal blindness was deemed incurable for a long time. Luxturna has changed the lives of individuals previously destined to live a life of blindness, but most importantly, it has fueled interest in developing additional gene therapy reagents targeting other genetic forms of inherited retinal disease. The field is currently in an exciting phase of expanding possibilities and the future has never looked brighter.

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Protection of Human and Animal Subjects: The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the 2013 Helsinki Declaration of the World Medical Association.

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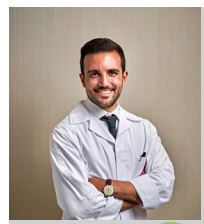

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