Editorial

Recent Advancements in Management of Uveitis

Uveitis is a sort of "umbrella term" that encompasses many different diseases, with different etiologies, treatment and prognosis. However, there is a common denominator among them: the potential, more or less important, to produce severe and permanent deficit in visual acuity and/or visual function.[1] This concept should be kept in mind whenever we face a patient with uveitis and need to establish the treatment modality. This patient will be most of times young and in working age. Disease's impact on his life and his social circle should not be underestimated, nor the impact of uveitis as a cause of morbidity and socio-economic blindness within the society.[2]

In recent years, much emphasis has been put to define, specifically, each clinical entity. Results of this effort are the criteria for the diagnosis of Behcet's disease[3,4], sarcoidosis[5] or Vogt-Koyanagi-Harada syndrome.[6] The SUN criteria (Standardization of Uveitis Nomenclature), although wider, also help in defining a particular clinical picture, esential step before choosing diagnostic and therapeutic strategies and comparing results among different centers.[7] Speaking the same "language" shortens distances and facilitates experience exchanges.

Different uveal diseases appear in different geographic regions and genetic backgrounds; epidemiological knowdelge about uveitis in the part of the world we are working will render our task easier. Major emphasis should be put on epidemiologic research everywhere, but specially in countries of the so called developing world: appraisal of our patient population is key when taking decisions, mainly in a context where resources are far to be unlimited.

During the last years, we have been privileged witness of a breakthrough in ancillary tests for disease diagnosis. Just as an example, in 1948, Posner and Schlossman described for the first time the clinical picture of hypertensive cyclitis that bears their names.[8] Their original description of a benign and recurrent syndrome is far from the current understanding of this form of infectious, hypertensive and severe uveitis. Sixty years passed and thousands of molecular techniques were developed and applied to aqueous humor analysis. Our knowledge of uveitic entities moved steadily from the description of biomicroscopic findings to the molecular and imaging characterization of each syndrome. The arrival of Spectral Domain Optical Coherence Tomography (SD-OCT) shed light on various posterior uveitic diseases, mainly the group of the so called white dot syndromes: the almost histological resolution of images combined with the non-invasive acquisition mode render this tool esential in the diagnosis and monitoring of the disease.[9] The near future is the Enhanced Depth Imaging OCT (EDI-OCT), which will "remove the veil" from the choroid, a so frequent target within the spectrum of uveitis.[10]

How to define the active or quiescent nature of uveitis remains crucial and difficult to implement. How to predict which patients will have a more torpid evolution or will develop complications more often, how to know who will respond less to treatment.... The quantification of proteins in the anterior chamber using the laser flare meter (LFM) technology represents a great improvement for disease activity assesment, objectively measured in terms of blood-aqueous barrier rupture.[11] The method proved to be useful in the management of juvenile idiopathic arthritis (JIA) – associated uveitis and was a good predictor of progression to more severe forms of the disease.[12] Similarly, the indocyanine green (ICGA) angiography allowed us to "see" choroidal inflammation, to defined choroidal tissue as the primary site of inflammation in many entities and to monitor treatment response.[13] The concept of recurrence in VKH syndrome, for example, traditionally considered as an anterior uveitis requiring topical treatment, radically changed due to ICG angiography: we know now that disease reactivation involves also the primary site of the autoimmune insult and that treatment should be systemic.[14]

Perhaps the greatest progress (and also the next frontier) has to do with treatment. The development of biological drugs in the field of rheumatology and oncology allowed us to benefit our patients with a better treatment targetted to the molecular level. The shift from systemic to intraocular delivery, whenever

possible, is by far our great contribution. The family of tumor necrosis factor (TNF) alpha blockers proved to be important agents in the treatment of uveitis and showed interesting differences between uveal inflammation and inflammation affecting elsewhere in the body: *Etanercept*, for example, although very useful in cases of arthritis, spondylitis, or psoriasis, presents few advantages (if any) in the management of uveitis.[15] Is the intraocular approach really superior to systemic immunosuppression? Even though it seems its advantages are clear, this issue is still a matter of discussion. Surprisingly, the MUST (Multicenter Uveitis Steroid Treatment Trial) study did not find clear benefits from local therapy with the Retisert implant compared to systemic corticosteroid administration (with immunosuppressants if needed).[16] The goal of therapy is to achieve as many periods of remission as possible with the lowest doses and the least adverse effects (ocular or systemic). Keeping this in mind, we are still waiting for more results of the Ozurdex implant.[17]

In short time, uveitis has moved from being considered a purely infectious disease, mainly linked to tuberculosis or syphilis, to represent a wide and diverse group of diseases, infectious, autoimmune or autoimmune infectiously - triggered. From being considered a guarded prognosis disease, where the balance between the damage from disease itself and the one related to steroid therapy was difficult to establish, to be thought as a group of very different entities, each one with specific challenges and molecularly targeted treatments. The genetic pathway (and the differences in treatment response according to genetic polymorphisms in each different patient) is still waiting to be explored. And even more important, in the era of globalization of disease management, in a world where frontiers are difficult to establish and knowledge is global, resources are far away of being homogeneously distributed. How to bring the gold standard of care to every patient suffering from uveitis, regardless where he is, represents definitely our next big challenge.

REFERENCES

1. **Durrani OM, Meads CA, Murray PI.** Uveitis: a potentially blinding disease. Ophthalmologica. Journal international d'ophtalmologie. International journal of ophthalmology. Zeitschrift fur Augenheilkunde. 2004; 218 (4): 223-236.
2. **Durrani OM, Tehrani NN, Marr JE, Moradi P, Stavrou P, Murray PI.** Degree, duration, and causes of visual loss in uveitis. The British journal of ophthalmology. 2004; 88 (9): 1159-1162.
3. Criteria for diagnosis of Behcet's disease. International Study Group for Behcet's Disease. Lancet. 1990; 335 (8697): 1078-1080.
4. **Okada AA, Stanford M, Tabbara K.** Ancillary testing, diagnostic / classification criteria and severity grading in Behcet disease. Ocular immunology and inflammation. 2012; 20 (6): 387-393.
5. **Herbort CP, Rao NA, Mochizuki M.** Members of Scientific Committee of First International Workshop on Ocular S. International criteria for the diagnosis of ocular sarcoidosis: results of the first International Workshop On Ocular Sarcoidosis (IWOS). Ocular immunology and inflammation. 2009; 17 (3): 160-169.
6. **Read RW, Holland GN, Rao NA, et al.** Revised diagnostic criteria for Vogt-Koyanagi-Harada disease: report of an international committee on nomenclature. American journal of ophthalmology. 2001; 131 (5): 647-652.
7. **Khairallah M.** Are the Standardization of the Uveitis Nomenclature (SUN) Working Group criteria for codifying the site of inflammation appropriate for all uveitis problems? Limitations of the SUN Working Group classification. Ocular immunology and inflammation. 2010; 18 (1): 2-4.
8. **Posner A, Schlossman A.** Syndrome of unilateral recurrent attacks of glaucoma with cyclitic symptoms. Arch Ophthal. 1948; 39 (4): 517-535.
9. **Onal S, Tugal - Tutkun I, Neri P, C PH.** Optical coherence tomography imaging in uveitis. International ophthalmology. 9 2013.
10. **Fung AT, Kaliki S, Shields CL, Mashayekhi A, Shields JA.** Solitary idiopathic choroiditis: findings on enhanced depth imaging optical coherence tomography in 10 cases. Ophthalmology. 2013; 120 (4): 852-858.
11. **Herbort CP, Guex-Crosier Y, de Ancos E, Pittet N.** Use of laser flare photometry to assess and monitor inflammation in uveitis. Ophthalmology. 1997; 104 (1): 64-71; discussion 71-62.
12. **Davis JL, Dacanay LM, Holland GN, Berrocal AM, Giese MJ, Feuer WJ.** Laser flare photometry and complications of chronic uveitis in children. American journal of ophthalmology. 2003; 135 (6): 763-771.
13. **Herbort CP, Mantovani A, Papadia M.** Use of indocyanine green angiography in uveitis. International ophthalmology clinics. 2012; 52 (4): 13-31.
14. **Bouchenaki N, Herbort CP.** Indocyanine green angiography guided management of vogt-koyanagi-harada disease. Journal of ophthalmic & vision research. 2011; 6 (4): 241-248.
15. **Kakkassery V, Mergler S, Pleyer U.** Anti-TNF-alpha treatment: a possible promoter in endogenous uveitis? observational report on six patients: occurrence of uveitis following etanercept treatment. Current eye research. 2010; 35 (8): 751-756.
16. **Kempen JH, Altaweel MM, Holbrook JT, Jabs DA, Louis TA, Sugar EA, Thorne JE.** Randomized

comparison of systemic anti-inflammatory therapy versus fluocinolone acetonide implant for intermediate, posterior, and panuveitis: The multicenter uveitis steroid treatment trial. Ophthalmology. 2011; 118 (10): 1916-1926.

17. **Lowder C, Belfort R, Jr., Lightman S, et al.** Dexamethasone intravitreal implant for noninfectious intermediate or posterior uveitis. Archives of ophthalmology. 2011; 129 (5): 545-553.

Karina Julian, MD
Uveitis – Instituto de la Visión
Ophthalmology Department, Austral University Hospital
Austral University – School of Medicine
Buenos Aires – Argentina