Institution: University College London

Unit of Assessment: 1 – Clinical Medicine

Title of case study: Development of new treatments for uveitis

1. Summary of the impact (indicative maximum 100 words)

Research at the UCL Institute of Ophthalmology over the last 15 years has developed new treatments for management of uveitis and its sight-threatening complications, which have subsequently become standard practice. Our work, in previously untreatable disease, has allowed restoration of vision in many patients and prevention of further visual loss in others. Many patients have been able to reduce systemic medication, limiting adverse effects of treatment.

2. Underpinning research (indicative maximum 500 words)

Uveitis is an uncommon eye condition, which affects two to five in every 10,000 people in the UK every year. Although rare, it is a leading cause of visual impairment in patients of working age. Chronic uveitis is associated with a high incidence of vision-threatening complications such as cataract, macular oedema, and, most importantly, glaucoma, which may cause irreversible visual loss. Research at UCL, over the last 15 years, has developed new treatments for uveitis and its complications.

In 1999 we assessed the usefulness of mycophenolate mofetil (MMF), an immunosuppressant used extensively in transplant medicine, but not previously used in uveitis. Our findings indicated that MMF was a useful immunosuppressive drug for controlling ocular inflammation **[1]**; it proved to be more effective with fewer adverse effects than other drugs used to treat uveitis (ciclosporin and methotrexate).

Further to this, in 2001 we undertook a pilot study in six patients with idiopathic uveitis complicated by visually significant cystoid macular oedema (CMO) that was resistant to periocular and/or systemic corticosteroid treatment. We demonstrated that one injection into the eye of the steroid triamcinolone (TA) was an effective short-term treatment for resistant CMO in uveitis **[2]**. This paper changed the way that refractory macular oedema was considered in uveitis. Previously it was thought that oedema was refractory because permanent blood-retinal barrier breakdown had occurred. By demonstrating that vision could be improved by injecting TA into the eye where previous systemic and periocular medication had failed, the research had shown that oedema was reversible using this method of steroid delivery. A larger study in 2005 confirmed these findings, showing that in patients with uveitic CMO, intravitreal TA can effectively reduce CMO and improve visual acuity. In some patients it allows the cessation and/or major reduction of systemic immunosuppressive therapy **[3]**. For the first time, previously incurable visual loss could now be treated, resulting in vision gain and subsequent improvement in the quality of life for patients. This led to a profusion of papers on TA and then to the licensing of longer acting intraocular steroids, now a NICE-approved therapy.

In 2009 we undertook a study to determine whether the use of topical prostaglandin (PG) analogues to treat raised intraocular pressure (IOP) in patients with uveitis resulted in an increase in uveitis reactivation or CMO. This was thought likely and these drops were then contraindicated in uveitis. We demonstrated that PG analogues are potent topical medications for lowering raised IOP in patients with uveitis and are not associated with an increased risk of CMO or uveitis reactivation **[4]**. The study allowed these very effective drops to be brought into the management of uveitic glaucoma and reduced the need for surgery to prevent visual loss.

In the same year we undertook a pilot study in 15 patients to evaluate the use of intravitreal methotrexate (MTX) for the treatment of uveitis and uveitic CMO as an alternative to intravital steroids. We showed that in these patients, intravitreal MTX can improve visual acuity and reduce CMO and, in some patients, allows the reduction of immunosuppressive therapy **[5]**. This study

introduced intraocular methotrexate as a successful treatment option for macular oedema in patients who cannot have intraocular steroids – this led to an international series and widespread use and for the first time offered a non-steroid intraocular treatment regime for those in whom periocular/intraocular steroids are contraindicated. Many of these patients were able to come off systemic therapy as a result with good vision maintained.

Most recently, we assessed the visual prognosis of patients with ocular Behçet disease, who have the worst visual prognosis of all patients with uveitis, to determine factors predictive of visual loss and severe visual loss. These patients are all young and both eyes are usually affected. We showed that the use of anti-TNF-α drugs was associated with a statistically significant reduction in the rate of severe visual loss, with a greatly reduced risk of visual loss at 5 and 10 years **[6]**. This has led to the early introduction of biologics for treatment in these patients.

3. References to the research (indicative maximum of six references)

[1] Larkin G, Lightman S. Mycophenolate mofetil. A useful immunosuppressive in inflammatory eye disease. Ophthalmology. 1999 Feb;106(2):370-4. http://dx.doi.org/10.1016/S0161-6420(99)90078-7

[2] Young S, Larkin G, Branley M, Lightman S. Safety and efficacy of intravitreal triamcinolone for cystoid macular oedema in uveitis. Clin Experiment Ophthalmol. 2001 Feb;29(1):2-6. http://dx.doi.org/10.1046/j.1442-9071.2001.00360.x

[3] Kok H, Lau C, Maycock N, McCluskey P, Lightman S. Outcome of intravitreal triamcinolone in uveitis. Ophthalmology. 2005 Nov;112(11):1916.e1-7. http://dx.doi.org/10.1016/j.ophtha.2005.06.009

[4] Chang JH, McCluskey P, Missotten T, Ferrante P, Jalaludin B, Lightman S. Use of ocular hypotensive prostaglandin analogues in patients with uveitis: does their use increase anterior uveitis and cystoid macular oedema? Br J Ophthalmol. 2008 Jul;92(7):916-21. http://dx.doi.org/10.1136/bjo.2007.131037

[5] Taylor SR, Habot-Wilner Z, Pacheco P, Lightman SL. Intraocular methotrexate in the treatment of uveitis and uveitic cystoid macular edema. Ophthalmology. 2009 Apr;116(4):797-801. http://dx.doi.org/10.1016/j.ophtha.2008.10.033

[6] Taylor SR, Singh J, Menezo V, Wakefield D, McCluskey P, Lightman S. Behçet disease: visual prognosis and factors influencing the development of visual loss. Am J Ophthalmol. 2011 Dec;152(6):1059-66. http://dx.doi.org/10.1016/j.ajo.2011.05.032

4. Details of the impact (indicative maximum 750 words)

Our research over the last 15 years has developed new local and systemic treatments for uveitis, and these have become standard practice. Our work has introduced new treatments where none existed, specifically patients with uveitis that is not responsive to steroid therapy or in which steroid therapy is contraindicated because of adverse effects. For these patients, treatment with mycophenolate or intraocular methotrexate may be sight-saving. In other patients, as a result of these treatments, vision has been restored and the dose of systemic steroids reduced or stopped completely. MMF is now the major second-line drug used in management of uveitis. Our demonstration of its effectiveness in 1999 was key in bringing the potential of this drug to the attention of the inflammatory eye disease community. Our study was also quoted in US guidelines in 2000 **[a]** and provided the impetus for several additional studies over the years (e.g. Teoh et al 2008 **[b]**). A recent review of the management of uveitis demonstrates that the use of MMF is established practice **[c]**.

A further recent article states: "*Antimetabolites now enjoy favor as a first choice of treatment with IMT [immunomodulatory therapy] in most cases of posterior uveitis*." Two of the key drugs used are MMF and MTX **[d]**. The importance of MMF and MTX as treatments for uveitis is further

emphasised by a recently commenced clinical trial that compares the two agents as first line therapy for steroid unresponsive uveitis **[e]**.

Robust data concerning the numbers of patients affected globally by uveitis where steroids are either ineffective or toxic are not available. However, from our own institution MMF is the major drug used with steroids in about 80% of these patients **[f]**.

Cystoid macular oedema is a particularly challenging complication of uveitis and is the most common cause of blindness and visual impairment in chronic uveitis patients occurring in up to one third. Our studies have contributed greatly to the present best practice in the management of this condition. We demonstrated that vision could be improved by injecting TA into the eye where systemic and periocular medication had failed. This led to a profusion of papers on TA and then to the longer acting intraocular steroids being developed. Our research also introduced intraocular methotrexate as a successful treatment option for macular oedema in patients who cannot have intraocular steroids. A recent review notes the use of both intraocular TA and methotrexate in the management of uveitic cystoid macular oedema. Regarding the former, it notes that "*intravitreal triamcinolone (various formulations) is commonly used for CME*" **[g]**. A number of studies are cited, of which ours was notably the first and largest. Our paper on intraocular methotrexate is also cited in both this review, and another from India in 2013 **[h]**.

A further complication of uveitis is glaucoma, which developes in up to 20% of patients. Prior to our research, ocular hypotensive **prostaglandin analogues** had been used successfully in primary open angle glaucoma but there was major concern about their use in uveitis patients. Our study allowed these very effective drops to be brought into the management of uveitic glaucoma and reduced the need for surgery **[i]**.

Our demonstration in 2011 that **anti-TNF drugs** can reduce the risk of visual loss in patients with Behcet's disease, who have the worst visual prognosis of all patients with uveitis, is now being quoted worldwide in support of this treatment **[j]**.

5. Sources to corroborate the impact (indicative maximum of 10 references)

[a] Jabs DA, Rosenbaum JT, Foster CS, Holland GN, Jaffe GJ, Louie JS, Nussenblatt RB, Stiehm ER, Tessler H, Van Gelder RN, Whitcup SM, Yocum D. Guidelines for the use of immunosuppressive drugs in patients with ocular inflammatory disorders: recommendations of an expert panel. Am J Ophthalmol. 2000 Oct;130(4):492-513. http://www.sciencedirect.com/science/article/pii/S0002939400006590

[b] Teoh SC, Hogan AC, Dick AD, Lee RW. Mycophenolate mofetil for the treatment of uveitis. Am J Ophthalmol. 2008 Nov;146(5):752-60, 760.e1-3. doi: 10.1016/j.ajo.2008.03.004. Epub 2008 May 2. http://dx.doi.org/10.1016/j.ajo.2008.03.004 *Cites two of our papers - see references 11 and 14*.

[c] Gallego-Pinazo R, Dolz-Marco R, Martínez-Castillo S, Arévalo JF, Díaz-Llopis M. Update on the principles and novel local and systemic therapies for the treatment of non-infectious uveitis. Inflamm Allergy Drug Targets. 2013 Feb;12(1):38-45. http://dx.doi.org/10.2174/1871528111312010006

[d] http://www.retinalphysician.com/articleviewer.aspx?articleID=107380

[e] http://clinicaltrials.gov/ct2/show/NCT01829295

[f] Moorfields pharmacy data provided by Chief Pharmacist. Copy available on request.

[g] http://www.jhasio.com/files/articlefiles/pdf/ASIO_7_2p60_67.pdf

[h] http://www.ijo.in/article.asp?issn=0301-

4738;year=2013;volume=61;issue=6;spage=277;epage=283;aulast=Babu

[i] Horsley MB, Chen TC. The use of prostaglandin analogs in the uveitic patient. Semin Ophthalmol. 2011 Jul-Sep;26(4-5):285-9. http://dx.doi.org/10.3109/08820538.2011.588650

[j] Pato E, Muñoz-Fernández S, Francisco F, Abad MA, Maese J, Ortiz A, Carmona L; Uveitis Working Group from Spanish Society of Rheumatology. Systematic review on the effectiveness of immunosuppressants and biological therapies in the treatment of autoimmune posterior uveitis. Semin Arthritis Rheum. 2011 Feb;40(4):314-23. http://dx.doi.org/10.1016/j.semarthrit.2010.05.008