Published in final edited form as:

Expert Opin Biol Ther. 2014 December ; 14(12): 1719–1722. doi:10.1517/14712598.2014.963049.

Immunopharmacotherapy of non-infectious uveitis: where do we stand?

Rupesh Agrawal, FRCS^{1,2,3}, Cecilia Lee, MD⁴, Sumita Phatak, DNB¹, and Carlos Pavesio, FRCOphth^{1,2}

Rupesh Agrawal: Rupesh_agrawal@ttsh.com.sg

¹Moorfields Eye Hospital, NHS Foundation Trust, London, UK

²UCL Institute of Ophthalmology, Biomedical Research Centre, London, UK

³National Healthcare Group Eye Institute, Tan Tock Seng Hospital, Singapore

⁴University of Washington, Seattle, WA, USA

Abstract

With ever-evolving concept of personalised medicine backed up with specific biomarkers for ocular inflammatory disease, there is a sudden surge of using biologics in non-infectious recalcitrant posterior uveitis. Have we understood these biologic agents enough to embark on this long enduring journey with the patient to optimise control of intraocular inflammation? On the other hand, there is still a strong inhibition of using these novel agents in management of uveitis even at tertiary referral centres. Immunopharmacotherapy of non-infectious uveitis poses a significant conundrum for both physicians and patients as it is like a two-edged sword effective to control inflammation but at the same time potentially toxic, suspected of causing long-term adverse effects. Systemic immunosuppressive therapy is used in a substantial number of most vision-threatening ocular inflammatory diseases. There is lack of randomised control trials establishing the safety of this therapy and our current practice pattern is based on retrospective studies and personal experience in using this treatment modality. This overview will highlight on the current dilemma faced by the clinicians in opting for steroid-sparing immunosuppressive therapy.

Keywords

biologics; corticosteroids; immunopharmacotherapy; immunosuppressives

We are sitting on the crossroads of personalised medicine where leveraging on the discovery of novel cytokines and biologics we are getting closer to the ultimate objective of taming visually threatening recalcitrant, non-infectious posterior uveitis. However, as it stands today, most physicians embark on corticosteroids as the first line of therapy. Steroids given

Correspondence to: Rupesh Agrawal, Rupesh_agrawal@ttsh.com.sg.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organisation or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents, received or pending, or royalties.

either by topical, intraocular or parenteral route still remain the gold standard therapy for a large proportion of cases of uveitis and further immunosuppression is usually reserved for selective cases.

The use of local therapy has also been pursued and with the advent of newer intravitreal agents and sustained release devices, a rather attractive dimension has been added to the management of selected cases of non-infectious posterior uveitis [1]. In addition to steroids, anti-VEGF, methotrexate, anti-TNF- α , antibodies and sirolimus [2] are the different local options available to physicians [1,2]. There is lack of current data to support the use of intravitreal TNF- α and there has been a call for a moratorium on the intravitreal use of this group of agents outside a well-designed clinical trial. Although the local adjuvant therapy has added another potential weapon to the armamentarium of the uveitis specialist, in most cases it still needs to be supplemented by systemic immunosuppressive therapy for optimal long-term control of inflammation; the effect of most local agents is short-lived and repeated procedures, with increased risk of complications, are needed to maintain the effect.

We have made remarkable progress in moving from corticosteroids as one final answer to all inflammatory eye diseases to this aeon of immunosuppressives and biologics. Over the past decade or so, there has been significant surge in the use of biologics for intraocular inflammation. Numerous reviews and studies have been published on the experience with these relatively novel agents in ophthalmology, with large number of publications in the past 2 years [3–11].

One concern addressed in all the reviews and articles advocating biologics therapy in uveitis is the potential risk associated with the prolonged use of corticosteroids and imminent serious hazards with non-selective immunosuppressive agents. However, it is questionable whether we have really established the safety and efficacy of biologic agents to promote the widespread use of these contemporary molecules among the nonspecialists and even the specialists in developing countries. Even in the USA, Nguyen *et al.* found the corticosteroids to be the preferred drug among most ophthalmologists in visually treating non-infectious uveitis and reported that the majority of physicians were not found to be following standard guidelines for use of steroid-sparing immunosuppressive therapy [3].

With the advent of biologics and efforts towards patient-tailored treatment approach, uveitis specialists face the challenge of choosing the best available option in managing intraocular inflammation. There is a significant dilemma among the physicians in deciding on a particular immunosuppressive or biologic agent for refractory, non-infectious posterior uveitis. Unfortunately, as of date we do not have any established algorithm to resolve these. A conventional approach adopted by most of the physicians who manage uveitis is to initiate oral corticosteroids as first line and then to escalate to other immunosuppressants or biologics as needed, which is dependent on clinical response and also on patient's systemic profile or onset of side effects with corticosteroids. Standard guidelines recommend introduction of second-line steroid-sparing agent when there is the failure to control inflammation with 10 mg/day of oral corticosteroids within 3 months of therapy. Nevertheless, the standard guidelines do not apply to all diseases. For example, Infliximab and adalimumab are recommended as first-line immunomodulatory agents in Behçet's

disease and as second line in patients with juvenile arthritis associated uveitis and other forms of severe ocular inflammation, including posterior, panuveitis and scleritis [12]. There is also good evidence of durable remissions of uveitis that can be achieved leading to drug-free remission with IFN- α therapy [13]. Also, there is ever-growing literature on use of B-cell mAb and anti-CD20 mAb (rituximab) for treatment of severe recalcitrant ocular inflammatory diseases and intraocular lymphoma [14]. This, hence, potentially leads to conflict of choosing one agent over other with lack of current evidence of beneficial effects of any particular agent in comparison to other existing or emerging agents.

One of the potential menaces of widespread non-regulated use of the biologic agents in uveitis is the risk of systemic malignancy or reactivation of latent infections and especially the potential risk of reactivation of latent tuberculosis in developing countries. In cases with non-responsive, recalcitrant uveitis, physicians may feel inclined to initiate biologics without a complete work up. Kempen *et al.* published long-term effects of immunosuppression on the risk of mortality and fatal malignancy in systemic immunosuppressive therapy for eye disease cohort study and compared the safety of these medications in ocular inflammatory disease in 9250 patients at five tertiary centres over up to 30 years [15].

However, conditions like presumed ocular tuberculosis and carcinoma-associated retinopathy can masquerade as non-infectious uveitis and become a diagnostic challenge. It is hence obligatory for the physician to be extra-vigilant before commencing on any biologics. It will likely require patience and time commitment for both patients and physicians to achieve prolonged remission and eventually improve patients' quality of life.

Besides potential side effects, one of the inherent limitations with biologic therapy is the prohibitive cost (Figure 1) that prevents its widespread use [16]. As evident in the scatter plot matrix (Figure 1), biologics cause a significant financial burden on healthcare costs.

Chu *et al.* recently published the socioeconomic burden among inpatients with non-infectious posterior uveitis in the USA [17]. Their findings indicated that the financial burden of non-infectious uveitis is quite comparable to other medical diseases and is almost equal or higher than that for cancer patients. The patients on biologics therapy were associated with highest per month per member (PMPM) cost as compared to corticosteroid or immunosuppressive treatment group ($p < 0.001$) at the beginning of therapy. Interestingly, as patients were placed on prolonged oral corticosteroid, immunosuppressives or biologics, the inpatient admission rate increased dramatically in the corticosteroid and immunosuppressive groups but not in the biologics group. This led to an increase in PMPM ($p < 0.001$) for the corticosteroids group, implying that the use of healthcare facilities and infrastructure by admission is significant among the corticosteroids treatment group [17]. This data also showed disproportionately larger number of inpatients being treated with corticosteroids without steroid-sparing agents, questioning the way biologic therapy is advancing in developed nations.

Over a decade since the advent of biologic therapy, there has been no significant change in trend for preferred treatment among physicians. In addition to the financial constraints, the

reluctance to switch to alternate therapy can be largely accounted by scepticism of physicians towards the efficacy of these novel drugs largely due to the lack of randomised controlled trials and limited knowledge about the mechanism of action or current guidelines. Ironically, we are able to embrace newer technology like femtosecond laser in the field of cataract surgery, but we are not able to eliminate our old doctrine of blind use of oral corticosteroids in treating uveitis, a potentially blinding condition with significant socioeconomic burden.

There had been inherent limitations with widespread use of novel therapies in a group of disorders characterised by poorly defined phenotypes with significant heterogeneity, small target population and subjective outcome measures. In sync with the development of novel biological agents, there has been a concurrent advancement in investigative tools for the monitoring patients with intraocular inflammation. Keane *et al.* published an objective way to grade vitreous inflammation using optical coherence tomography [18]. Development of novel biomarkers to monitor the disease activity and also to customise the biologic therapy has also complimented the management strategy in complex uveitic entities. Development of better outcome measures such as this will promote better collaboration between FDA, researchers and industry partners, which has been difficult due to lack of objective outcome measures to monitor drug efficacy in patients with intraocular inflammation and vitritis.

There is definitely a need for more evidence on the safety profile of biologics with the help of randomised controlled trials especially in developing nations. Vigilant treatment with steroid-sparing immunosuppressives can still be the treatment of choice in chronic non-infectious uveitis for long-term control of inflammation. With hundreds of articles on the application of biologics in uveitis in 2013, newer biologics are appearing on the market and many more are in the pipeline. Now, small-molecular-weight inhibitors are becoming available to uveitis specialists. With ever-growing network between the clinicians, researchers, public, industry, regulatory and funding bodies, it is imperative to foster multicentre collaboration and embark on more randomised controlled trials using the novel biologic agents. Hopefully there will be enough data generated to allow us to propose needed guidelines for better management of patients with non-infectious posterior uveitis.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Hazirolan D, Pleyer U. Think global–act local: intravitreal drug delivery systems in chronic noninfectious uveitis. *Ophthalm Res.* 2013; 49(2):59–65.
2. Sen HN, Larson TA, Meleth AD, et al. Subconjunctival sirolimus for the treatment of chronic active anterior uveitis: results of a pilot trial. *Am J Ophthalmol.* 2012; 153(6):1038–42. [PubMed: 22465364]
- 3••. Nguyen QD, Hatef E, Kayen B, et al. A cross-sectional study of the current treatment patterns in noninfectious uveitis among specialists in the United States. *Ophthalmology.* 2011; 118(1):184–90. Majority of physicians do not adhere to standard recommended line of management of uveitis. [PubMed: 20678806]
- 4•. Pasadhika S, Rosenbaum JT. Update on the use of systemic biologic agents in the treatment of noninfectious uveitis. *Biologics.* 2014; 8:67–81. Elaborated on biologics in uveitis. [PubMed: 24600203]

- 5•. Leung TG, Thorne JE. Emerging drugs for the treatment of uveitis. *Expert Opin Emerg Drugs*. 2013; 18(4):513–21. Highlighted some of the newer drugs in store on uveitis. [PubMed: 24274613]
6. Kruh J, Foster CS. The philosophy of treatment of uveitis: past, present and future. *Dev Ophthalmol*. 2012; 51:1–6. [PubMed: 22517200]
7. Heo J, Sepah YJ, Yohannan J, et al. The role of biologic agents in the management of non-infectious uveitis. *Expert Opin Biol Ther*. 2012; 12(8):995–1008. [PubMed: 22780091]
8. Gomes Bittencourt M, Sepah YJ, Do DV, et al. New treatment options for noninfectious uveitis. *Dev Ophthalmol*. 2012; 51:134–61. [PubMed: 22517211]
9. Agrawal R, Iyer J, Connolly J, et al. Cytokines and Biologics in non-infectious autoimmune uveitis: bench to bedside. *Indian J Ophthalmol*. 2014; 62(1):74–81. [PubMed: 24492505]
- 10•. Denniston AK, Dick AD. Systemic therapies for inflammatory eye disease: past, present and future. *BMC Ophthalmol*. 2013; 13:18. Compared past, present and future of systemic therapies in inflammatory eye disease. [PubMed: 23617902]
11. Gallego-Pinazo R, Dolz-Marco R, Martinez-Castillo S, et al. Update on the principles and novel local and systemic therapies for the treatment of non-infectious uveitis. *Inflamm Allergy Drug Targets*. 2013; 12(1):38–45. [PubMed: 23441991]
12. Levy-Clarke G, Jabs DA, Read RW, et al. Expert panel recommendations for the use of anti-tumor necrosis factor biologic agents in patients with ocular inflammatory disorders. *Ophthalmology*. 2014; 121(3):785–96. e3. [PubMed: 24359625]
13. Mesquida M, Molins B, Llorenç V, et al. Current and future treatments for Behcet's uveitis: road to remission. *Int Ophthalmol*. 2014; 34(2):365–81. [PubMed: 23729309]
14. Miserocchi E, Pontikaki I, Modorati G, et al. Anti-CD 20 monoclonal antibody (rituximab) treatment for inflammatory ocular diseases. *Autoimmun Rev*. 2011; 11(1):35–9. [PubMed: 21763790]
15. Kempen JH, Daniel E, Gangaputra S, et al. Methods for identifying long-term adverse effects of treatment in patients with eye diseases: the Systemic Immunosuppressive Therapy for Eye Diseases (SITE) Cohort Study. *Ophthalmic Epidemiol*. 2008; 15(1):47–55. [PubMed: 18300089]
16. Imrie FR, Dick AD. Biologics in the treatment of uveitis. *Curr Opin Ophthalmol*. 2007; 18(6):481–6. [PubMed: 18163000]
- 17•. Chu DS, Johnson SJ, Mallya UG, et al. Healthcare costs and utilization for privately insured patients treated for non-infectious uveitis in the USA. *J Ophthalm Inflamm Infect*. 2013; 3(1):64. Assessed healthcare cost and financial impact of biologics and steroids in the community.
- 18••. Keane PA, Karampelas M, Sim DA, et al. Objective Measurement of Vitreous Inflammation Using Optical Coherence Tomography. *Ophthalmology*. 2014; 121(9):1706–14. Proposed an objective, quantitative marker of inflammatory activity. [PubMed: 24835759]

Figure 1. Scatter plot matrix: cost of immunosuppressive therapy versus biologic therapy [16]
GBP: Great British Pound.