American Journal of Ophthalmology Case Reports 18 (2020) 100633

Contents lists available at ScienceDirect

American Journal of Ophthalmology Case Reports

journal homepage: www.elsevier.com/locate/ajoc

Case report

Certolizumab pegol – Tumor necrosis factor inhibitor for refractory uveitis

Yael Sharon[a,*], David S. Chu[a,b]

[a] Metropolitan Eye Research and Surgery Institute, Palisades Park, NJ, USA
[b] Institute of Ophthalmology and Visual Science, New Jersey Medical School, Rutgers University, Newark, NJ, USA

ARTICLE INFO

Keywords:
Certolizumab pegol
Tumor necrosis factor inhibitor
Non-infectious
Refractory
Uveitis

ABSTRACT

Purpose: The purpose of our study is to report our experience with the use of certolizumab pegol in patients with refractory non-infectious uveitis.

Observations: We present a case series of three patients with non-infectious uveitis, treated with twice-monthly subcutaneous certolizumab pegol. All of our patients had different types of uveitis and different underlying etiologies. All of our patients had previously failed various immunomodulatory therapies and/or were intolerant to at least one tumor necrosis factor (TNF) inhibitor agent. Following initiation of therapy with certolizumab pegol, all three patients showed significant clinical improvement of their ocular inflammation. No adverse events from treatment with certolizumab pegol were observed.

Conclusions and Importance and Importance: We observed positive outcomes using the TNF inhibitor certolizumab pegol for the treatment of patients with refractory, non-infectious uveitis, in whom therapy with other TNF inhibitors was inadequate or in which there were tolerance issues. Patients who have failed other TNF inhibitors may benefit from treatment with certolizumab pegol.

1. Introduction

The primary goal in uveitis management is early and vigorous control of inflammation while avoiding the potential side effects of therapy. Corticosteroids have been the mainstay of uveitis treatment; however, due to numerous local and systemic side effects of long-term therapy with steroids, their use is limited.[1] Hence, the focus of research for therapeutic agents is centered on finding other agents with the ability to achieve long-term disease quiescence with minimal risk and good compliance. Therapies with good prospects include immunomodulatory agents which have become a preferable long-term treatment option for chronic inflammatory diseases due to their efficacy and overall good safety profile.

Within the category of immunomodulatory agents, tumor necrosis factor (TNF) inhibitors are used to treat various inflammatory and rheumatologic conditions such as rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis, Crohn's disease and ankylosing spondylitis,[2] as well as non-infectious uveitis.[3] TNF inhibitors selectively target and neutralize human TNF-α with a rapid onset of action. All TNF inhibitors competitively block the binding of TNF to its receptors. However, each TNF inhibitor has distinct pharmacokinetic and pharmacodynamic properties, leading to significant differences in their clinical efficacy.

Certolizumab pegol (Cimzia®, UCB Pharma Inc., Smyrna, GA, USA) is a recombinant humanized monoclonal antibody. It is approved by the US Food and Drug Administration (FDA) for the treatment of Crohn's disease, rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis.[4] To date, there are limited data available on the efficacy and safety of certolizumab pegol in the treatment of ocular inflammatory diseases.[5–8]

We present our experience with certolizumab pegol therapy in three patients with non-infectious uveitis who were refractory and/or intolerant to other immunomodulatory agents.

2. Findings

2.1. Case 1

Our first patient is a 21-year-old male, previously diagnosed with bilateral idiopathic pars planitis. The patient had a history of cataract surgery in his left eye, but there was no history of systemic illnesses and the patient's serology was unremarkable. Treatment with methotrexate (MTX), adalimumab, and leflunomide previously failed to control the ocular inflammation.

At the time of the referral, the patient was being treated with cyclosporine (100 mg twice daily) and infliximab (10 mg/kg every 8

* Corresponding author. Palisades Park, New Jersey.
E-mail address: yael@mersieye.com (Y. Sharon).

https://doi.org/10.1016/j.ajoc.2020.100633
Received 25 May 2018; Received in revised form 21 February 2020; Accepted 24 February 2020
Available online 27 February 2020

Table 1
Patient demographics and clinical characteristics.

Patient No.	Gender, Age (yrs)	Type of Uveitis	Etiology	Age at Start of Certolizumab Therapy (yrs)	Medications Intolerant to/or Failed	Ocular Complications
1	M, 21	IU	Idiopathic	17	MTX, CSA, infliximab adalimumab, leflunomide	cataract
2	F, 20	AU	Juvenile idiopathic arthritis	19	MTX, CSA, MMF infliximab, adalimumab etanercept, abatacept anakinra, tocilizumab rituximab, IVIG	cataract PS glaucoma papillitis CME
3	M, 17	AU	Crohn's disease	13	MTX, MMF, adalimumab, abatacept, rituximab	cataract glaucoma

M, male; F, female; Yrs, years; IU, intermediate uveitis; AU, anterior uveitis; MTX, methotrexate; CSA, cyclosporine; MMF, mycophenolate mofetil; IVIG, intravenous immunoglobulin; PS, posterior synechiae; CME, cystoid macular edema.

weeks). He reported increased floaters and blurred vision in both eyes for the past month. On ocular examination, the best corrected visual acuity (BCVA) was 20/30 in both eyes, there were 0.5 + vitreous cells and haze and the presence of snowballs in both eyes. Intraocular pressure (IOP) was within normal limits. The patient was intolerant to increasing the frequency of infliximab infusions (developed severe hives, headaches, fatigue and shortness of breath) and had persistently active uveitis.

Due to the patient's disease activity, therapy with certolizumab pegol (200 mg administered subcutaneously twice monthly) was initiated. Three months following initiation of treatment, the inflammation had subsided. On ocular examination, BCVA was 20/20 in the right eye and 20/25 in the left eye and no signs of active inflammation were noted, except for peripheral retinal scarring in both eyes. During his follow-up, the disease remained under control with certolizumab treatment and cyclosporine was discontinued after one year.

At the last follow-up, after 42 months of treatment with certolizumab, the BCVA was preserved with 20/20 in the right eye and 20/25 in the left eye. IOP was within normal limits and no active pars planitis was noted. There were no side effects from therapy.

2.2. Case 2

In our second case, the patient is a 20-year-old female diagnosed with bilateral non-infectious anterior uveitis and a history of juvenile idiopathic arthritis (JIA). The patient was treated with MTX (25 mg/ml injection once weekly), etanercept (20 mg/ml injection twice weekly) and topical steroids (loteprednol 0.5% 4 times daily) when she was first introduced to our clinic at age 5. Her arthritis was well controlled; however, her uveitis was active.

On initial ocular examination, BCVA was 20/30 bilaterally, there were 2 + cells in the anterior chamber and early posterior sub-capsular cataract in both eyes. On funduscopic examination there were signs of papillitis in her left eye, and elevated intraocular pressure requiring IOP lowering therapy. Initial treatment with mycophenolate mofetil (250 mg twice daily) and etanercept was ineffective. The patient was switched to infliximab (5 mg/kg every 4 weeks) and MTX, which achieved good control of her uveitis and arthritis.

After 18 months of treatment, the patient developed Hodgkin's lymphoma and underwent chemotherapy and radiation therapy. MTX and infliximab were discontinued and the patient experienced recurrent flares. Her parents were reluctant to re-initiate infliximab due to their concerns that it had precipitated the patient's cancer. Therefore, she was started on pulse intravenous (IV) steroid treatment, followed by oral prednisone and topical steroids, as well as MTX (25 mg once weekly). Multiple attempts to taper the topical and systemic corticosteroids, with the administration of different immunomodulatory agents, resulted in recurrent flares (including abatacept, anakinra, tocilizumab, rituximab, adalimumab and intravenous immunoglobulin (IVIG) infusions).

On ocular examination, the BCVA was 20/60 in the right eye and 20/50 in the left eye, there were 2 + cells in the anterior chamber, posterior synechiae and posterior subcapsular cataract, as well cystoid macular edema bilaterally. Treatment with certolizumab pegol (200 mg administered subcutaneously twice monthly) was initiated and subsequently topical and systemic steroids were tapered off. After initiation of the new combination of medications, the ocular inflammation subsided and the visual acuity improved; IOP was normal and no signs of adverse events were noted.

The patient was maintained on certolizumab pegol, MTX (25 mg once weekly) and topical steroids (difluprednate 0.05% once daily in both eyes). Although no significant flares were noted, low-grade inflammation after seven months of certolizumab therapy (0.5 + cells) and the need for maintenance dose of topical steroids led to the decision to restart treatment with infliximab. She responded to infliximab (10 mg/kg every 4 weeks) and remained in a good control of her uveitis and arthritis.

2.3. Case 3

Our third case is of a 17-year-old male who had a history of bilateral non-infectious anterior uveitis and Crohn's disease. He was referred to our clinic at the age of 12 due to active inflammation in his left eye. At the time of referral, he had been treated with mycophenolate mofetil (500 mg 3 times daily), adalimumab (40 mg injection every other week), and topical steroids (prednisolone acetate 1% once daily). On ocular examination, BCVA was 20/30 in the right eye and 20/25 in the left eye, there were 0.5 + cells in the anterior chamber and the IOP was normal bilaterally. Funduscopic examination was unremarkable.

In order to control his uveitis and wean him off topical steroids, adalimumab was increased to 40 mg weekly, followed by an increase in mycophenolate mofetil dose to 2000 mg daily. However, the patient experienced recurrent flares and required topical steroids chronically. Following consultation with the treating rheumatologist, the decision was made to change his systemic therapy to abatacept (125 mg/ml once weekly), followed by rituximab infusions which were both found to be ineffective.

We initiated treatment with certolizumab pegol (200 mg administered subcutaneously twice monthly). Topical steroids were successfully tapered to a maintenance dose (difluprednate 0.05% every other day). No signs of intraocular inflammation were observed and IOP was well controlled with topical IOP lowering agents. During follow up, the patient's course was complicated with posterior subcapsular cataract, for which he underwent cataract surgery in his left eye. The patient had steroid response glaucoma following cataract surgery that required glaucoma shunt surgery in his left eye.

He was eventually maintained on treatment with certolizumab for four years with two mild uveitis flares that were successfully managed with topical steroids. No adverse events were noted. At last follow up, the BCVA was 20/20 in each eye, IOP was within normal limits and no

Table 2
Clinical response of ocular inflammation to certolizumab pegol treatment.

Patient No.	Ocular Findings at Start of Certolizumab Treatment			Ocular Findings at Last Follow-Up with Certolizumab Treatment			Concomitant Medications at Last Follow-Up	Treatment Duration (months)
	BCVA (OD; OS)	Anterior Segment Inflammation[a]	Posterior Segment Inflammation[b]	BCVA (OD; OS)	Anterior Segment Inflammation[a]	Posterior Segment Inflammation[b]		
1	20/25; 20/25	0.5+ OU	1+ OD; 0.5+ OS	20/20; 20/25	0 OU	0 OU	none	42
2	20/60; 20/50	2+ OU	0 OU	20/40; 20/50	0.5+ OU	0 OU	diflupredнate 0.05%, MTX	7
3	20/20; 20/30	2+ OS	0 OU	20/20; 20/20	0 OU	0 OU	diflupredнate 0.05%	48

BCVA, best corrected visual acuity; OD, right eye; OS, left eye; OU, both eyes; MTX, methotrexate.
[a] Anterior chamber inflammation was graded according to the standardization of uveitis nomenclature (SUN) grading system.[18]
[b] Posterior segment inflammation was graded according to standardization of vitreal inflammatory activity grading scale.[19]

intraocular inflammation was observed. Although his uveitis remained well controlled, treatment with certolizumab was subsequently changed to infliximab due to his Crohn's disease activity.

3. Discussion

In this case series, we report our experience of uveitis management with a relatively new TNF inhibitor, certolizumab pegol. All three patients had chronic ocular inflammation resulting in various complications. Table 1 summarizes the patients' demographic data and clinical characteristics.

The patients had different types of uveitis and underlying etiologies; however, all were refractory to and/or intolerant to various treatments. In all patients, therapy with certolizumab was initiated due to the failure of previous agents, including at least one TNF inhibitor. Reasons for the cessation of other treatments included intolerance to therapy, allergic reaction to drug infusion, development of adverse events (such as skin rash, nausea, headache, fatigue and shortness of breath), inadequate inflammatory control, and reactivation of the patients' systemic disease. All cases were refractory to adalimumab treatment, the only TNF inhibitor that is FDA-approved for the treatment of non-infectious uveitis.

Certolizumab therapy allowed the tapering of systemic corticosteroids in all patients, while two patients remained on a low maintenance dose of topical steroids. Two patients who received other immunomodulatory agents were able to discontinue them. Certolizumab was well tolerated and no systemic or ocular adverse events were observed. Individual ocular examination findings, prior to and following initiation of certolizumab therapy, are summarized in Table 2.

Demonstration of elevated levels of TNF-α in serum and aqueous humor of patients with uveitis,[9] and the efficacy of TNF-α inhibitors shown in clinical data, suggest that TNF-α plays a pivotal role in the pathogenesis of ocular inflammation. A diverse range of pathways and mechanisms is involved, as opposed to a single mechanism.[10] This observation partially explains the variable clinical response of patients to different TNF inhibitors. Other factors include structural differences of each TNF-α inhibitors, variable drug half-life, dosing and drug concentration, as well as different degrees of induced immunogenicity among the TNF inhibitors. These biological differences allow for potential variability in therapeutic properties and drug efficacy, as well as different side effects profile for each TNF inhibitor. The current case series shows that the lack of clinical response to one TNF inhibitor does not preclude the potential efficacy of another.

The first group of TNF inhibitors employed in the US for the treatment of non-infectious uveitis were infliximab, adalimumab and etanercept. Adalimumab and infliximab have been extensively studied for their efficacy and safety in ocular inflammatory diseases.[11,12] Infliximab has been reported to be effective in refractory ocular inflammation.[11] Etanercept has been found to be ineffective and in some cases actually induces uveitis.[13,14] Other TNF inhibitors, including certolizumab pegol and golimumab are newer and less extensively studied in the treatment of ocular inflammatory conditions and their long-term safety and efficacy need to be determined.[5–8,15] The reported experience of certolizumab use in non-infectious uveitis is summarized in Table 3.

Certolizumab has several features that differentiate it from other TNF-α inhibitors; it is devoid of the Fc portion and does not induce complement activation, antibody-dependent cellular cytotoxicity, apoptosis, or granulocyte degranulation.[10] Certolizumab has a Fab fragment conjugated to polyethylene glycol (PEG) to enhance plasma half-life. Adverse events of certolizumab pegol have been documented in patients with Crohn's disease and rheumatoid arthritis; they are uncommon and include serious fungal, bacterial and viral infections, malignancy, injection site reaction and the formation of autoantibodies.[16,17]

The limitations of the study are its retrospective nature and the

Table 3
Demographics and clinical features of uveitis patients treated with certolizumab pegol in previous reports.

Author (year)	# of Cases	Gender	Age (yrs)	Type of Uveitis	Etiology	Treatment Duration (months)	Response to Therapy
Llorenc et al.[5]	7	4 males 3 females	42.4 ± 8.8	AU PU AU + SCL PAN	idiopathic BD AS PsA CD RP	10.4 ± 4.8	5 Yes 2 No
Tlucek et al.[6]	1	female	47	SCL	RA	6	Yes
Maiz Alonso et al.[7]	1	male	33	AU	AS + CD	25	Yes
Hernández M et al.[8]	13	10 males 3 females	49.5 ± 11.7	AU IU PAN	AS PsA IBD	17.8 ± 9.9	10 Yes 3 No
Current case series	3	2 males 1 female	19.3 ± 2	AU IU	idiopathic JIA CD	32.3 ± 18.1	3 Yes

AU, anterior uveitis; Yrs, years; PU, posterior uveitis; IU, intermediate uveitis; PAN, panuveitis; SCL, scleritis; BD, Behçet's disease; AS, ankylosing spondylitis; PsA, psoriatic arthritis; CD, Crohn's disease; JIA, juvenile idiopathic arthritis; RA, Rheumatoid arthritis; RP, relapsing polychondritis; IBD, inflammatory bowel disease.

small number of patients studied. However, due to the scarcity of reported cases, this study may encourage randomized prospective studies in larger numbers of patients to better evaluate the efficacy, dosing regimen, and safety of certolizumab therapy in non-infectious uveitis.

4. Conclusions

As presented in this case series, certolizumab may be effective in patients with chronic and refractory non-infectious uveitis, who have failed therapy with other TNF inhibitors. Nevertheless, this case series is not sufficient to establish the efficacy of certolizumab treatment in uveitis, and further studies are needed in order to investigate certolizumab role in uveitis management.

Patient consent

Written consent to publish this case has not been obtained. This report does not contain any personal identifying information. The study and data accumulation were carried out with approval from the appropriate Institutional Review Board (IRB).

Funding

None.

Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

The following authors have no financial disclosures: Dr. Yael Sharon.

Dr. David S. Chu serves as a consultant for Mallinckrodt Pharmaceuticals, AbbVie, Aldeyra Therapeutics, Allakos Inc., and Santen Pharmaceuticals.

Acknowledgements

None.

References

1. 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):184–190. https://doi.org/10.1016/j.ophtha.2010.03.029.
2. Cessak G, Kuzawińska O, Burda A, et al. TNF inhibitors - mechanisms of action, approved and off-label indications. *Pharmacol Rep.* 2014;66(5):836–844. https://doi.org/10.1016/j.pharep.2014.05.004.
3. Cordero-Coma M, Sobrin L. Anti–tumor necrosis factor-α therapy in uveitis. *Surv Ophthalmol.* 2015;60(6):575–589. https://doi.org/10.1016/j.survophthal.2015.06.004.
4. *CIMZIA® [prescribing Information]*. Smyrna, GA: UCB, Inc.; 2017https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125160s270lbl.pdf.
5. Llorenç V, Mesquida M, Sainz de la Maza M, et al. Certolizumab pegol, a new anti-TNF-α in the armamentarium against ocular inflammation. *Ocul Immunol Inflamm.* October 2014:1–6. https://doi.org/10.3109/09273948.2014.967779.
6. Tlucek PS, Stone DU. Certolizumab pegol therapy for rheumatoid arthritis–associated scleritis. *Cornea.* 2012;31(1):90–91. https://doi.org/10.1097/ICO.0b013e318211400a.
7. Maiz Alonso O, Blanco Esteban AC, Egües Dubuc CA, Martinez Zabalegui D. Effectiveness of certolizumab pegol in chronic anterior uveitis associated to Crohn's disease and ankylosing spondylitis. *Reumatol Clín (Engl Ed).* 2015;11(3):189–190. https://doi.org/10.1016/j.reumae.2015.01.005.
8. Hernández M, Mesquida M, Llorens V, et al. THU0381 Certolizumab pegol is effective in uveitis associated to spondyloarthritis refractory to other tumour necrosis factor inhibitors. *Poster Presentations.* vol. 76. BMJ Publishing Group Ltd and European League Against Rheumatism; 2017https://doi.org/10.1136/annrheumdis-2017-eular.4425 350.2-350.
9. Santos Lacomba M, Marcos Martín C, Gallardo Galera JM, et al. Aqueous humor and serum tumor necrosis factor-α in clinical uveitis. *Ophthalmic Res.* 2001;33(5):251–255. https://doi.org/10.1159/000055677.
10. Nesbitt A, Fossati G, Bergin M, et al. Mechanism of action of certolizumab pegol (CDP870): in vitro comparison with other anti-tumor necrosis factor α agents. *Inflamm Bowel Dis.* 2007;13(11):1323–1332. https://doi.org/10.1002/ibd.20225.
11. Rajaraman RT, Kimura Y, Li S, Haines K, Chu DS. Retrospective case review of pediatric patients with uveitis treated with infliximab. *Ophthalmology.* 2006;113(2):308–314. https://doi.org/10.1016/j.ophtha.2005.09.037.
12. Jaffe GJ, Dick AD, Brézin AP, et al. Adalimumab in patients with active noninfectious uveitis. *N Engl J Med.* 2016;375(10):932–943. https://doi.org/10.1056/NEJMoa1509852.
13. Galor A, Perez VL, Hammel JP, Lowder CY. Differential effectiveness of etanercept and infliximab in the treatment of ocular inflammation. *Ophthalmology.* 2006;113(12):2317–2323. https://doi.org/10.1016/j.ophtha.2006.04.038.
14. Foster CS, Tufail F, Waheed NK, et al. Efficacy of etanercept in preventing relapse of uveitis controlled by methotrexate. *Arch Ophthalmol.* 2003;121(4):437. https://doi.org/10.1001/archopht.121.4.437.
15. Cordero-Coma M, Salom D, Díaz-Llopis M, López-Prats MJ, Calleja S. Golimumab for uveitis. *Ophthalmology.* 2011;118(9):1892.e3–1892.e4. https://doi.org/10.1016/j.ophtha.2011.05.019.
16. Weinblatt ME, Fleischmann R, Huizinga TWJ, et al. Efficacy and safety of certolizumab pegol in a broad population of patients with active rheumatoid arthritis: results from the REALISTIC phase IIIb study. *Rheumatology.* 2012;51(12):2204–2214. https://doi.org/10.1093/rheumatology/kes150.
17. Sandborn WJ, Feagan BG, Stoinov S, et al. Certolizumab pegol for the treatment of Crohn's disease. *N Engl J Med.* 2007;357(3):228–238. https://doi.org/10.1056/NEJMoa067594.
18. Jabs DA, Nussenblatt RB, Rosenbaum JT. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. *Am J Ophthalmol.* 2005;140(3):509–516http://www.ncbi.nlm.nih.gov/pubmed/16196117.
19. Nussenblatt RB, Palestine AG, Chan CC, Roberge F. Standardization of vitreal inflammatory activity in intermediate and posterior uveitis. *Ophthalmology.* 1985;92(4):467–471http://www.ncbi.nlm.nih.gov/pubmed/4000641.