Case Report

Adalimumab Monotherapy in the Treatment of Idiopathic Multifocal Choroiditis: A Case Report

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Keywords
Adalimumab · Azathioprine · Multifocal choroiditis · Primary inflammatory choriocapillaropathy

Abstract
In this study, we report a case of multifocal choroiditis that was successfully treated with adalimumab monotherapy. A 25-year-old male presented with a history of bilateral multifocal choroiditis which was resistant to a combination of azathioprine, valacyclovir, and prednisone. Dilated fundoscopy revealed small creamy-yellow lesions around the arcades in both eyes (OU). Indocyanine green angiography (ICGA) revealed active hypocyanescent lesions around the arcades and macula OU. Valacyclovir was stopped, adalimumab subcutaneous injections bi-weekly were added to the regimen, and prednisone was tapered after the second adalimumab loading dose. At 3-month follow-up, ocular examination and ICGA were unremarkable OU. After 30 months of remission, azathioprine was tapered and stopped. After 40 months of remission, adalimumab was tapered and stopped. Four months after stopping adalimumab injections, the patient returned with new floaters in his right eye (OD). ICGA and macular optical coherence tomography detected active lesions OU. The patient was restarted on adalimumab subcutaneous injections as monotherapy. At 3-month follow-up visit, his symptoms had resolved, and ICGA showed resolution of the lesions OD and improvement of the lesions in the left eye (OS). He has been in remission for 6 months at the time of writing since restarting adalimumab monotherapy. We conclude from this study that long-term adalimumab monotherapy can be employed effectively and safely in the re-treatment of patients with multifocal choroiditis resistant to other immunomodulatory therapy even after successful tapering and discontinuation of concurrent therapies.

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Published by S. Karger AG, Basel
Introduction

Idiopathic multifocal choroiditis (MFC), also known as primary inflammatory choriocapillaropathy (PICCP), is an inflammatory disorder characterized by unilateral or bilateral chorioretinal lesions. The lesions can eventually progress to chorioretinal scars and frequently cause chorioidal neovascularization (CNV) as a secondary complication. While MFC or PICCP can be associated with panuveitis, anterior chamber and vitreous inflammation are rare, and they are not considered to be disease-defining signs [1].

It has been demonstrated that MFC or PICCP can affect the choriocapillaris. This extension explains the aggressive course and frequent development of CNV as a complication [2]. The aggressive course of MFC or PICCP and its secondary sight-threatening complications justify early and aggressive treatment with immunomodulatory therapy (IMT).

The efficacy and safety of adalimumab subcutaneous injections in combination with a conventional IMT has been reported previously in very few studies. In this case report, we study the efficacy and safety of adalimumab monotherapy in the treatment of MFC or PICCP.

Case Report

A 25-year-old male was referred to our uveitis clinic for further evaluation and treatment of progressive choroidal lesions despite being treated with 200 mg of azathioprine daily, 1 g of valacyclovir twice daily, and 20 mg of prednisone daily for 5 months. The patient’s main complaints were floaters in both eyes (OU) and visual distortions in the left eye (OS), both of which started 9 months prior to presentation at our clinic. The patient’s past ocular, medical, and family history were unremarkable. Prior workup was unremarkable, with the following serologic markers negative or within normal limits: interferon-gamma release assay for tuberculosis; rapid plasma reagin and fluorescent treponemal antibody absorption tests for syphilis; Lyme disease IgM and IgG, angiotensin-converting enzyme, and lysozyme for sarcoidosis; antinuclear antibodies; antineutrophil cytoplasmic antibodies; double stranded deoxyribonucleic acid; complement factors 3 and 4; total hemolytic complement; human leukocyte antigens (HLA)-A, B, C, DR, DQ, and DS; beta-2-microglobulin; interleukin-6 (IL-6); IL-2 receptor; and a urinalysis. Fluorescein angiography was performed by the referring team and was reported negative; however, he developed a significant allergic reaction to the dye, including hives and shortness of breath. Therefore, fluorescein angiography was not performed throughout follow-up in our clinic.

On initial examination, best corrected visual acuity was 20/15 OU. Slit-lamp examination showed 0.5+ cells in the anterior chamber based on Standardization of Uveitis Nomenclature classification and 1+ cells in the anterior vitreous (OU) based on the International Uveitis Study Group (IUSG) classification [3] and was otherwise unremarkable. Dilated fundoscopy examination revealed small creamy-yellow lesions around the arcades OU. Fundus multicolor photos (Fig. 1a, b) and blue autofluorescence (Fig. 1c, d) confirmed these lesions. Widefield (55°) and ultra-widefield (102°) indocyanine green angiography (ICGA) on scanning laser angiography (Spectralis, Heidelberg Engineering Inc., MA, USA) revealed more active hypocyanescent lesions around the arcades and macula OU (Fig. 2a, b).

Given the history of disease progression on a combination of prednisone, azathioprine, and valacyclovir, we decided to add 40 mg of adalimumab subcutaneous injections every 2 weeks to the treatment regimen, with two weekly loading doses of 80 mg and 40 mg. He was instructed to stop the valacyclovir due to very low suspicion of viral involvement and to taper the prednisone by 5 mg per week after the second adalimumab loading dose. At the 3-month
follow-up visit, ICGA was unremarkable (Fig. 2c, d). After 6 months of follow-up, he developed leukopenia, so azathioprine was reduced to 150 mg daily, with no disease activity or progression. After 30 months of remission, we started to taper the azathioprine by 50 mg every 3 months. At 40 months of remission, adalimumab was tapered to 40 mg every 3 weeks for 3 months and then every 4 weeks for another 3 months; adalimumab was then stopped. We monitored the patient every 2 months thereafter.

Four months after stopping the adalimumab subcutaneous injections, the patient came back with new floaters OD. Best corrected visual acuity was 20/15 OD and 20/20 OS. Slit-lamp examination revealed 0.5+ cells in the anterior chamber and 1+ cells in the anterior vitreous OU. Neither dilated fundoscopic examination and fundus multicolor photography (Fig. 3a, b) nor fundus autofluorescence (Fig. 3c, d) revealed any new lesions. However, ICGA (Fig. 2e, f) and macular optical coherence tomography (OCTM) (Fig. 4a, b) detected active lesions in both eyes. The patient was restarted on biweekly 40 mg adalimumab subcutaneous injections as monotherapy without additional topical or systemic medications. At a follow-up visit 3 months later, his symptoms had completely resolved. Ocular examination was unremarkable OU, as was fundus multicolor photography (Fig. 3e, f) and fundus autofluorescence (Fig. 3g, h). ICGA (Fig. 2g, h) and OCTM (Fig. 4c, d) showed complete quiescence OD and a single resolving lesion OS. At the time of writing, the patient has been restarted on

Fig. 1. a, b Fundus multicolor photos of the right and left eye, respectively, before adding adalimumab subcutaneous injections to azathioprine and oral prednisone which showed faint small yellow-creamy lesions along the vascular arcades in both eyes. c, d Blue autofluorescence (BAF) of right and left eye, respectively, before adding adalimumab subcutaneous injections to azathioprine and oral prednisone which shows small hypo-fluorescent spots along the arcades in both eyes.
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adalimumab monotherapy for 6 months, has not developed any adverse effects, and has had no further disease activity.

**Discussion**

Reports on the treatment of MFC or PICCP are limited. The combination of systemic corticosteroids in addition to IMT has been suggested for the treatment of newly diagnosed active disease or disease reactivation. Conventional IMT has been successfully employed in the treatment of MFC or PICCP as both monotherapy or in combination with systemic corticosteroid therapy. de Groot et al. [4] demonstrated that both the frequency of disease recurrence and the number of anti-vascular endothelial growth factor (VEGF) injections required for CNV significantly decreased in patients treated with conventional IMT.

Very few studies have reported the role of adalimumab subcutaneous injections in the treatment of MFC or PICCP [4–6]. de Groot et al. [5] reported the efficacy of adalimumab in treating patients with central MFC over a 12-month period, achieving steroid-free remission in 75% of their patients during follow-up. These patients were concomitantly treated with at least one other IMT agent other than adalimumab, given the synergistic effect of other IMT agents with adalimumab therapy due to the reduced chance of developing anti-adalimumab antibodies [5].

Shmueli and Amer [6] also reported the efficacy of biweekly adalimumab therapy in 7 patients with punctate inner choroidopathy and MFC. All of the patients were treated, in addition to adalimumab, with another IMT agent and low-dose daily prednisone, which they defined as ≤7.5 mg. With all due respect to the study by Shmueli and Amer [6], our mission in the treatment of patients with uveitis is steroid-free remission, and we do not agree with the concept of ≤7.5 mg of daily prednisone as a safe practice in the long-term treatment of patients with uveitis due to epitope spreading and the side effects of chronic systemic corticosteroid use. The theory of epitope spreading postulates that the longer inflammation persists, the more resistant and stubborn it will become as cell destruction by the activated immune system exposes more cryptogenic self-antigens to the immune system, further stimulating autoimmune inflammation [7, 8]. This is believed to happen in patients with more resistant cases of uveitis, including MFC or PICCP [9, 10]. In addition, even a few milligrams of daily prednisone can lead to long-term side effects such as weight gain, bone density loss (especially in post-menopausal women), and sleep/mood disturbances. We believe that, while corticosteroids are the best option for controlling acute ocular inflammation, they are not potent enough to modulate the immune system as long-term therapy, therefore allowing inflammation to smolder and cause epitope spreading [11].

In our case, azathioprine and adalimumab combination therapy were able to be gradually tapered off after 30 and 40 months of remission, respectively. Adalimumab monotherapy was started when the patient’s disease recurred as they had failed azathioprine and oral

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**Fig. 2.** a, b Indocyanine green angiography (ICGA) of the right and left eye, respectively, before the addition of adalimumab to azathioprine and oral prednisone therapy. Hypocyanescent lesions are seen in both eyes. c, d ICGA of the right eye and left eye, respectively, 3 months after the addition of adalimumab subcutaneous injections. Resolution of hypocyanescent lesions is demonstrated in both eyes. e, f ICGA of the right and left eye, respectively, after relapsing and before restarting adalimumab monotherapy. Hypocyanescent lesions can be seen in both eyes. g, h ICGA of the right eye and left eye, respectively, 3 months after restarting adalimumab monotherapy. Complete resolution of the hypocyanescent lesions is seen in the right eye, while a resolving hypocyanescent lesion superior to the optic nerve head is seen in the left eye.

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Maleki et al.: Adalimumab for Multifocal Choroiditis

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prednisone therapy when they first presented to our clinic. Our patient achieved remission of disease activity, both subjectively and objectively via ICGA and OCTM findings, after 3 months of adalimumab monotherapy, which was compatible with the outcome of the study by Shmueli and Amer [6]. As such, we suggest that adalimumab monotherapy can be effectively employed in a patient with MFC or PICCP who fails other IMT. An exception to this may be in cases of MFC or PICCP with involvement close to the fovea, where any activation or complication of the disease can cause severe vision loss. However, this should be examined with larger and more rigorous studies.

We performed widefield and ultra-widefield ICGA for this patient to rule out involvement of the periphery or mid-periphery. Although the importance of ultra-widefield imaging has been recognized in the retina field for more than two decades, it has been more recently started to be employed in the diagnosis and treatment of patients with various uveitides and the associated complications [12]. Moreover, it was shown that both Optos (Optos Inc., Marlborough, MA, USA) and Spectralis systems allow visualization of peripheral retinal pathology beyond the traditional ETDRS standard fields. Interestingly, it was shown that the Optos visualizes a larger total retinal surface area compared to the Spectralis; however, the effect of the eyelids and lashes considerably limits high-quality view to the far superior and inferior periphery [13]. The Spectralis non-contact wide-field lens was able to image peripheral pathology located superiorly and inferiorly, which may be missed with an Optos ultra-widefield fluorescein angiography [13].

This case report is unique, in part, due to the long-term follow-up period of 6 years. Moreover, it is important to note that our patient was retreated successfully with adalimumab as it is well known that adalimumab may lose efficacy with re-treatment. Additionally, tapering IMT after 30 months of achieving steroid-free remission and eventually stretching adalimumab subcutaneous injections to every 3 and 4 weeks were other new concepts seen in our case. However, disease recurrence 3 months after tapering warrants slower tapering to find the minimum dose of adalimumab that can maintain remission. In conclusion, adalimumab monotherapy can be employed effectively and safely in the re-treatment of patients with MFC or PICCP resistant to other IMT even after successful tapering and discontinuation of adalimumab and other concurrent IMT agents.

Statement of Ethics

This study was approved by the New England Institutional Review Board (wcg IRB), which has issued a waiver of informed consent for the retrospective chart review analysis. The IRB tracking number is 120160012, and the expiration date is May 10, 2022. This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. Written informed consent was obtained from the patient for publication of the details of their medical case, data, and any accompanying images.

Fig. 3. a, b Fundus multicolor photos of the right and left eye, respectively, during disease recurrence but before resumption of adalimumab monotherapy. c, d Blue autofluorescence of the right and left eye, respectively, during disease recurrence but before resumption of adalimumab monotherapy. e, f Fundus multicolor photos of the right and left eye, respectively, 3 months after resumption of adalimumab monotherapy. g, h Blue autofluorescence of the of right and left eye, respectively, 3 months after resumption of adalimumab monotherapy. All images are unremarkable for new changes.
Conflict of Interest Statement

No conflicting relationship exists for any author. Dr. C. Stephen Foster declares the following: consultancies with Aldeyra Therapeutics (Lexington, MA, USA), Allakos (Redwood City, CA, USA), Bausch & Lomb Surgical, Inc. (Rancho Cucamonga, CA, USA), Eyegate Pharma (Waltham, MA, USA), Genentech (South San Francisco, CA, USA), Novartis (Cambridge, MA, USA), and pSivida (Watertown, MA, USA); grants or grants pending with Aciont (Salt Lake City, UT, USA), Alcon (Aliso Viejo, CA, USA), Aldeyra Therapeutics (Lexington, MA, USA), Bausch & Lomb (Rochester, NY, USA), Clearside Biomedical (Alpharetta, GA, USA), Dompé pharmaceutical (Milan, Italy), Eyegate Pharma (Waltham, MA, USA), Mallinckrodt pharmaceuticals (Staines-upon-Thames, UK), Novartis Pharmaceuticals (Cambridge, MA, USA), pSivida (Watertown, MA, USA), and Santen (Osaka, Japan); payment for lectures including service on speaking bureaus from Alcon (Aliso Viejo, CA, USA), Allergan (Dublin, Ireland), and Mallinckrodt pharmaceuticals (Staines-upon-Thames, UK); and stock or stock options from Eyegate Pharma (Waltham, MA, USA). The other authors have nothing to declare.

Funding Sources

No funding received.

Author Contributions

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published. Drs. Arash Maleki, Andrew Philip, and C. Stephen Foster had substantial and equal contributions to the conception, interpretation of results, drafting the work, final approval, and agreement to be accountable for all aspects of the work.
Data Availability Statement

All data generated or analyzed during this study are included in this article.

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