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The efficacy of adalimumab in treating patients with central multifocal choroiditis

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ABSTRACT

Purpose: To evaluate the efficacy of adalimumab in patients with central multifocal choroiditis (cMFC) refractory to conventional corticosteroid-sparing immunomodulatory agents (IMT).

Methods: Medical records were reviewed from all patients with cMFC and treated with adalimumab with follow-up of at least 12 months. The study focused on the 12 months prior to and after the start of adalimumab. The imaging results were independently evaluated by two ophthalmologists. The main outcomes were the number of patients without a relapse of disease activity in 12 months after the start of adalimumab and the ability to stop the systemic corticosteroids to evaluate the corticosteroid-sparing effect.

Results: Twelve patients (18 eyes) were included. In 8/12 (67%) patients no relapse of disease activity was observed in the 12 months after the start of adalimumab. In 9/12 patients the systemic corticosteroid treatment could be stopped and in an additional 2 patients tapered to ≤7,5mg daily. In the 12 months before the start of adalimumab, the patients experienced a median of 3 (range 2–4) relapses of disease activity. Nine patients experienced relapses while treated with a combination of systemic corticosteroids (mean dose 13,6 mg; range 5–25 mg) and IMT. Moreover, 3 patients treated with IMT, experienced relapses after tapering and stopping the systemic corticosteroids. In all eyes (n = 5) with CNV before the start of adalimumab, the intravitreal *anti*-VEGF injections could be stopped after the start of adalimumab.

Conclusions: AND IMPORTANCE: Adalimumab may be effective in patients with cMFC refractory to IMT and may be considered as a treatment option in patients with cMFC.

Introduction

Central multifocal choroiditis (cMFC), a rare idiopathic inflammatory condition, is part of the wider spectrum of the "white dot syndromes".[1] The term cMFC is introduced by the authors to cover all subtypes of idiopathic inflammation of the choroid in the posterior pole, including punctate inner choroidopathy (PIC), multifocal choroiditis (MFC) without panuveitis,[2] persistent placoid maculopathy (PPM) and serpiginous choroiditis (SC). The most frequent complication is the formation of secondary choroidal neovascularization (CNV) presumed to be triggered by a low-grade, often asymptomatic, level of inflammation.[3,4] The pathophysiology of cMFC is largely unknown but a dysregulation of the immune system is a proposed disease mechanism.[5,6] Moreover, this disease is predominantly observed in young Caucasian women with myopia without an association with a systemic disease.[7] During the active stage of disease, a short course of oral corticosteroids is often prescribed.[1,8] In severe or sight-threatening cases, preventive treatment with corticosteroid-sparing immunomodulatory therapy (IMT) is suggested to prevent retinal damage caused either by the relapsing choroiditis or by scarring due to the complication of secondary CNV.[8–11] Treatment with conventional IMT, such as mycophenolate mofetil and azathioprine, is generally accepted to be safe and effective for noninfectious ocular inflammatory diseases.[12–14] In cMFC, though evidence is scarce, these agents are suggested to decline the number of relapses of the choroiditis and reduce the number of relapses with active CNV.[9,11,15,16] In our experience, though conventional IMT is generally effective, few patients with cMFC have an insufficient response to these agents. Since adalimumab is increasingly prescribed and proven to be effective in treatment for noninfectious uveitis,[12,17–19] we aim to explore the efficacy of adalimumab in patients with cMFC with an insufficient response to conventional IMT.

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Materials and methods

A single center retrospective observational cohort study was performed at the University Medical Center (UMC) Utrecht, the Netherlands. This study was conducted with approval of the University Medical Center Utrecht institutional review board and in accordance with the tenets of the Declaration of Helsinki. Written informed consent was given by all participants.

Study population

All patients were diagnosed with cMFC and presented with choroidal scars in the posterior pole within the temporal arcades with no to minimum vitreous cells (grading score $\leq 1+$ following the National Institute of Health grading system for vitreous cells), and without papillitis, vasculitis or anterior uveitis (SUN criteria 0).[20,21] All patients had a diagnostic work-up to rule out tuberculosis and sarcoidosis (and when clinically indicated other less frequent causes for posterior uveitis, such as birdshot chorioretinopathy). Subtypes of central cMFC included punctate inner choroidopathy (PIC), idiopathic multifocal choroiditis, serpiginous-like choroiditis, and persistent placoid maculopathy. All patients were treated with adalimumab and followed for at least 12 months after the start of adalimumab.

Data collection

Clinical data between January 2014 and December 2019 was collected and focused on the 12 months before and after the start of adalimumab. Data of all affected eyes was obtained by reviewing the medical chart and by the evaluation of imaging results including optical coherence tomography (SD-OCT), fundus color pictures, fundus autofluorescence pictures and fluorescein and indocyanine green angiography (FA-ICG) (Spectralis HRA + OCT; Heidelberg Engineering, Heidelberg, Germany). The imaging results were presented anonymously and evaluated for disease activity of choroiditis and CNV by two ophthalmologists (JO-vN and LH) who were masked for all data from the medical records.

Outcome measures

The main outcome measure was the number of patients without a (sub)clinical relapse of disease activity in the 12 months after the start of adalimumab. A relapse of disease activity was assessed solely on imaging results and was defined as either 1. the development of new

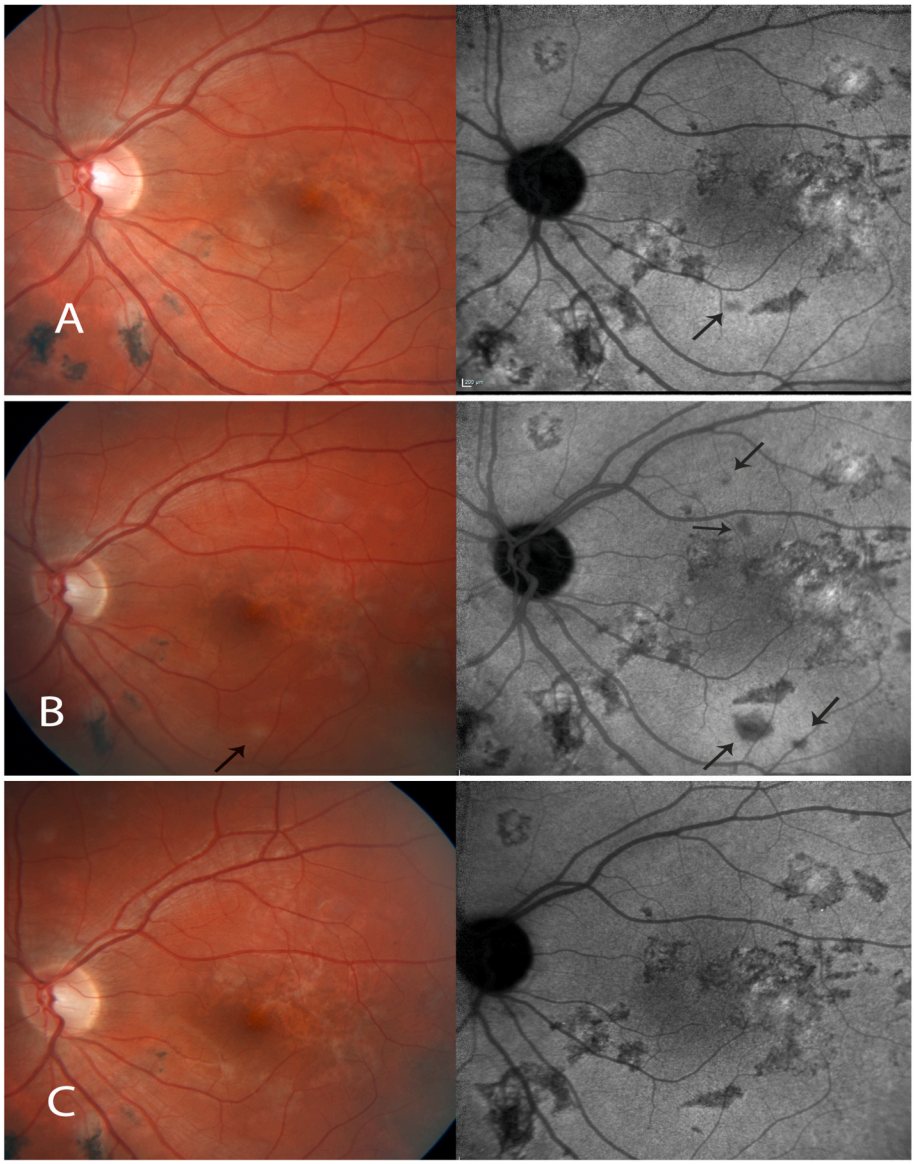

Fig. 1. Case 6 presenting with a relapse of disease activity Indocyanine green (ICG) pictures at 30 minutes and fundus pictures taken **A** + **B.** before the start of adalimumab whilst treated with ciclosporin A 200mg, mycophenolate mofetil 2000mg and prednisolone 10mg daily and **C.** during treatment with adalimumab 40mg/2 weeks, mycophenolate mofetil 2000mg and prednisolone 7.5mg daily **A.** 4 months before the start of adalimumab with almost complete quiescent disease except for one spot of choroiditis (black arrow). **B.** One month before the start of adalimumab, ICG angiography shows a relapse of disease activity with multiple spots of choroiditis (black arrows) and the fundus image shows one white-yellowish lesion (black arrow). **C.** Eight months after the start of adalimumab, imaging shows complete remission of disease activity. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

inflammatory lesions or CNV or 2. growth and/or reactivation of pre-existing inflammatory lesions or CNV (vague boundaries of the lesions on 20 minute ICG images/blurred boundaries or growth of subretinal lesions on OCT/leakage on FA images) after previous quiescent disease confirmed by imaging (Fig. 1). Moreover, the ability to taper and stop the prednisolone without disease reactivation was assessed in order to evaluate the corticosteroid-sparing effect.

Secondary outcomes included visual acuity (VA), adalimumab related side-effects, dose reduction of IMT after the start of adalimumab, the number of relapses of disease activity in the 12 months before the start of adalimumab including corresponding dose of prednisolone and finally the number of intravitreal *anti*-VEGF injections before and after the start of adalimumab. The presence of disease activity 12 months prior to the start of adalimumab was considered to be a relapse. Corticosteroid-sparing agents included methotrexate (MTX), azathioprine (AZA), mycophenolate mofetil (MMF)/mycophenolic acid (MPA), cyclosporine (CsA), and cyclophosphamide (CP). VA was converted to LogMAR (logarithm of the minimum angle of resolution) values for analysis and is presented as both LogMAR value and the Snellen equivalent. The Wilcoxon signed-rank test was conducted to analyze the change in VA.

Results

Baseline characteristics

Twelve patients (18 eyes) were included in this cohort study. The reason for starting adalimumab was treatment failure with conventional IMT in 10 patients and subjective side-effects experienced at sub-therapeutic doses of conventional IMT in 2 patients. All patients were treated with adalimumab (subcutaneously with a loading dose of 80mg, 40mg one week later and subsequently with 40mg every two weeks). The patient characteristics at the start of treatment with adalimumab are described in Table 1.

Visual acuity

The logMAR VA (Snellen equivalent) of the affected eyes did not change significantly during follow-up and was 0.17 (20/30) at the start of adalimumab and 0.18 (20/30) at 12 months follow-up.

Efficacy of adalimumab

In the 12 months before the start of adalimumab, all patients had at least two relapses of disease activity (median: 3 relapses, range 2–4). In the 12 months after the start of adalimumab, no subclinical or clinical relapse of disease activity was observed in 8/12 (67%) patients (Table 2, Fig. 2a). Two patients experienced a single minor subclinical relapse of disease activity after the start of adalimumab, resulting in a temporary dose escalation to adalimumab weekly for one month in case 3 and a single bevacizumab injection in case 4. In an additional 2 cases symptomatic relapses of disease activity were observed despite treatment with adalimumab (Table 2). Case 12, although less severe than prior to the start of adalimumab, still experienced 2 relapses of disease activity of the choroiditis. Case 10 presented with 3 relapses and adalimumab was considered ineffective and was stopped after 10 months. (Table 2). While treated with adalimumab, the systemic corticosteroids could be stopped in 9/12 (75%) patients. In 3 patients the systemic corticosteroids was not stopped 12 months after the start of adalimumab because of persistent disease activity (case 10 and 12) and on patient request despite disease inactivity (case 6). The mean daily dose of prednisolone was tapered from 17mg at the start of adalimumab to 2mg 12 months after the start of adalimumab (Fig. 2b). This is in contrast to before the start of adalimumab where 9/12 (75%) of the patients experienced a relapse of disease activity whilst treated with prednisolone (mean daily dose: 13 mg range 5–25 mg). The remaining 3 patients experienced a relapse of disease activity after tapering the prednisolone completely (Table 2).

Table 1
Patient characteristics at the start of treatment with adalimumab.

Patients (eyes)	12	(18)
Female gender, n (%)	10	(83%)
Age in years, mean (range)	44.3	(22–74)
VA, mean of all affected eyes (range)	20/30	(20/125–20/17)
Refractive error of all affected eyes		
High myopia[a], n (%)	2	(11%)
Mild to moderate myopia[b], n (%)	11	(61%)
Hypermetropia, n (%)	5	(28%)
CNV, n (%) of all affected eyes	5	(28%)
Bilateral disease, n (%) of all patients	6	(50%)

VA, visual acuity; D, dioptrics; CNV, choroidal neovascularization.
[a] High myopia: refractive error over -6D.
[b] Mild to moderate myopia: refractive error between 0 and -6D.

Imt

Patients were concomitant treated with IMT for the synergistic effect and to avoid the formation of antibodies against adalimumab. A dose reduction of ≥50% of the conventional IMT was achieved in 6/12 (50%) patients 12 months after the start of adalimumab.

Intravitreal anti-VEGF injections

In the 5 eyes with CNV, the treatment with intravitreal *anti*-VEGF injections could be extended and stopped after the start of adalimumab.

Side effects of adalimumab

In general, treatment with adalimumab was well tolerated. Case 9 and 12 were treated with monthly cyclophosphamide infusions for 6 months just before the start of adalimumab. Case 9 developed a pneumocystis jiroveci pneumonia and urosepsis within 2 months and case 12 a perforated diverticulitis within 3.5 months after the start of adalimumab. In both cases there was no direct relation between the adverse events and treatment with adalimumab.

Discussion

We report that in the majority of the patients with cMFC, no clinical relapse of disease activity occurred in the 12 months after the start of adalimumab. Moreover, in the majority of the patients, adalimumab had a steroid sparing effect. In particular, the younger patients with idiopathic MFC and PIC, frequently with pre-existent CNV, responded fast and well to adalimumab. On the contrary, the four patients diagnosed with persistent placoid maculopathy and serpiginous-like choroiditis without CNV, who were somewhat older, responded less well.

Treatment with conventional IMT is supported by a few studies and in our experience, it has shown to be effective in the majority of the patients.[9,15,16] Nevertheless, a minority of the patients continue to endure sight-threatening relapses of disease activity despite treatment with adequately dosed conventional immunosuppressive agents. These patients remain steroid-dependent often requiring a dose of corticosteroids above the safety dose of 7.5 mg prednisolone daily.[14] Due to the negative long-term effects of low-dose prednisolone, steroid dependency is considered to be an indication for additional immunomodulating treatment including biologicals such as adalimumab. The efficacy of adalimumab in patients with cMFC is not well described. A few case reports and small case series are available evaluating the safety and efficacy of adalimumab in serpiginous choroiditis,[22–24] persistent placoid chorioretinitis[25] and MFC in combination with acute zonal occult outer retinopathy.[26] None of these studies included patients with

Table 2
Overview of treatment with adalimumab, conventional IMT, systemic corticosteroids and *anti*-VEGF intravitreal injections.

Case/ age	Diagnosis	Eye	IMT[a]	12 months before start of adalimumab			12 months after start of adalimumab			
				Number of relapses	Prednisolone (mg)[b]	*anti*-VEGF IVI	IMT	Number of relapses	Prednisolone (mg)[c]	*anti*-VEGF IVI
1/23	Idiopathic MFC	OS	MMF	2[d]	5	0	MMF	0	0	0
2/44	Idiopathic MFC (CNV+)	OS	MPA, CsA	2	0	0	MTX	0	0	0
3/45	Idiopathic MFC (CNV+)	OD	MMF, CsA, MTX	3	0	1	AZA	1[e]	0	0
4/46	Idiopathic MFC (CNV+)	OD	MTX, AZA, MMF	3	0	5	MMF	1[f]	0	2[g]
5/22	Idiopathic MFC (CNV+)	OD	AZA + CsA, MMF + CsA	2	10	8	MPA	0	0	2[g]
6/23	Idiopathic MFC	ODS	AZA, MMF, MMF + CsA	3	10	0	MMF	0	7.5	0
7/54	Idiopathic MFC	ODS	MTX	3[d]	25	0	AZA	0	0	0
8/22	PIC (CNV+)	OS	AZA, MMF	3[d]	17.5	10	MMF	0	0	0
9/64	Serpiginous-like choroiditis	ODS	MMF, CP[h], AZA, MTX, MTX + CsA	4	20	1[i]	None[j]	0	0	0
10/74	Serpiginous-like choroiditis	ODS	MMF	2[d]	10	0	MMF	3	15	3[g]
11/66	Persistent placoid maculopathy	ODS	MTX, MPA, MPA + CsA MPA + MTX	2	10	0	MPA	0	0	0
12/48	Persistent placoid maculopathy	ODS	MMF, CP	3	15	0	MTX	2	7.5	0

IMT, corticosteroid-sparing immunomodulatory therapy; VEGF, vascular endothelial growth factor; IVI, intravitreal injection; MFC, multifocal choroiditis; MMF, mycophenolate mofetil; CNV, choroidal neovascularization; MPA; mycophenolic acid; CsA, ciclosporin A; MTX, methotrexate; AZA, azathioprine; PIC, punctate inner choroidopathy; CP, cyclophosphamide.

[a] All corticosteroid-sparing agents administered in the UMC Utrecht before the start of adalimumab.

[b] Dose of prednisolone in mg at the time a relapse of disease activity occurred. The highest dose is mentioned in case of multiple relapses.

[c] Dose of prednisolone in mg at 12 months after the start of adalimumab.

[d] Less than 12 months of follow-up were present prior to the start of adalimumab. For case 1 and 8, 11 months of follow-up was present, for case 10 this was 5 months and for case 7 this was 7 months.

[e] Due to a subclinical relapse of choroiditis 7 months after the start of adalimumab, the dose of adalimumab was temporarily increased to 40mg weekly for one month.

[f] Subclinical activity of CNV 2.5 months after the start of adalimumab, treated with a single intravitreal *anti*-VEGF injection.

[g] In case 4 and 5, two intravitreal *anti*-VEGF injections were administered within 3 months after the start of adalimumab as part of a treat and extend strategy. Case 10 was suspected for the development of CNV at 9 months after the start of adalimumab though in retrospect this was not confirmed.

[h] Intravenously administration of 750 mg/m2 per dose. A total of 6 doses were administered.

[i] A single prophylactic intravitreal *anti*-VEGF injection was administered without the development of CNV.

[j] Patient discontinued conventional immunosuppressive agent, on its own initiative, due to side-effects.

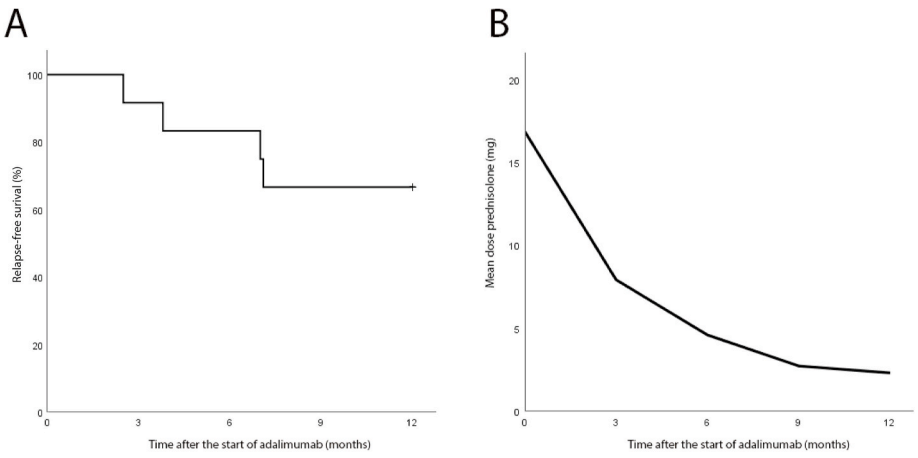

Fig. 2. Efficacy of adalimumab 2a. The relapse-free survival is presented as a percentage of the patients during the first 12 months of follow-up after the start of adalimumab. **2b.** The mean dose of prednisolone is presented at the start of adalimumab, and after 3, 6, 9 and 12 months of follow-up.

PIC or idiopathic multifocal choroiditis. In most cases, though not all, adalimumab was reported to be effective, which is in line with the results of our study. All patients were concomitantly treated with IMT for synergistic effect as well as prohibition of the formation of anti-drug antibodies to adalimumab, though literature is conflicting concerning the latter indication.[27]

In our study, intravitreal *anti*-VEGF injections were extended and discontinued after the initiation of treatment with adalimumab. We hypothesize that chronic or recurrent inflammatory activity in the choroid is a trigger for ongoing or new choroidal neovascular activity,

requiring intravitreal *anti*-VEGF injections.[3,4] Removing the inflammatory trigger is, in our opinion, a prerequisite to be able to permanently discontinue intravitreal *anti*-VEGF therapy in cMFC subtypes that are accompanied by CNVs.

Drawbacks of the current study were its retrospective nature and the low number of patients. We performed a within-patient study (i.e. longitudinal assessment) without the use of a control group to avoid the risk of a selection bias.

Strengths of our study are the homogeneous study population with standard treatment of 40mg adalimumab every two weeks with a standard follow-up of 12 months. Secondly, because of the lack of evidence in literature on the efficacy of adalimumab in cMFC, a relatively rare disease, the current series, though small, can be informative for ophthalmologist treating this potentially blinding disease in young patients. Thirdly, since relapses of choroiditis and CNV are often subtle and subject to subjective interpretation, imaging results were evaluated by two independent ophthalmologists. Eye-tracking technology in the OCT ensured an accurate assessment of changes in the outer retina, subretinal space and choroidal thickness.

In conclusion, adalimumab is potentially an effective treatment in patients with cMFC, in whom treatment with conventional IMT failed due to ineffectiveness or side effects.

Patient consent

All patients gave written consent the use medical data from their medical records for the purpose of medical research. All patients received a copy of their written consent. The original consent forms are stored within the University Medical Center Utrecht in a secured place. This study was conducted with approval of the University Medical Center Utrecht institutional review board and in accordance with the tenets of the Declaration of Helsinki.

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   a. Galvanistraat 1, 6716 AE Ede, the Netherlands

Authorship

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

Declaration of competing interest

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