Visual and Clinical Outcome of Macular Edema Complicating Pediatric Noninfectious Uveitis

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• PURPOSE: To investigate the clinical course and visual outcome of macular edema (ME) in pediatric patients with chronic noninfectious uveitis.
• DESIGN: Retrospective case series.
• METHODS: The databases of the uveitis clinics of 4 tertiary medical centers in Israel and the UK were searched for all children treated for uveitic ME in the years 2005–2015. Data were collected from the medical records as follows: demographics, diagnosis, visual acuity, clinical and imaging findings, and treatment given specifically for ME. Findings at baseline and at 3, 6, 12, and 24 months were evaluated.
• RESULTS: The cohort included 25 children (33 eyes) of mean age 8.5 ± 3.4 years. The most common diagnosis was intermediate uveitis, in 14 children (7 idiopathic, 7 pars planitis). Uveitis was active at ME diagnosis in 28 eyes (84.8%). Median duration of follow-up was 48 months. Median time to resolution of ME was 6 months, with complete resolution in 25 eyes (75.8%) by 24 months. Baseline visual acuity was ≥20/40 in 8 eyes (24.2%), increased to 57.6% at 3 months ($P < .0001$), and remained stable thereafter. Treatment regimens included corticosteroids (systemically and/or locally), immunosuppression, and biologic therapies. No correlation was found between outcome and either structural characteristics of ME or specific treatment strategy.
• CONCLUSIONS: The prognosis of pediatric uveitic ME is favorable despite its chronic course. Larger randomized controlled trials are needed to define differences among treatment regimens. (Am J Ophthalmol 2019;202:72–78. © 2019 Elsevier Inc. All rights reserved.)

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CHILDREN ACCOUNT FOR 2%–14% OF ALL PATIENTS who present to tertiary uveitis clinics.[1] Pediatric uveitis poses a challenge owing to the often-delayed diagnosis, chronic course, difficulty of examining young children, side effects of medical treatment, and risk of amblyopia. Major sight-threatening complications of uveitis in this age group include cataract, ocular hypertension, glaucoma, and macular edema (ME).[2]

Most studies of ME associated with uveitis have focused on adults, in whom it is a major cause of visual loss.[3,4] The visual deterioration may persist even when the active inflammation subsides. It may be affected by such factors as advanced age, chronic inflammation, and the presence of specific uveitis-related conditions such as birdshot chorioretinopathy and acute retinal necrosis.[4] Data on visual outcome in children with ME are sparse. de Boer and associates[5] studied 26 children with uveitis and visual acuity (VA) ≤20/200 and found ME to be the third-leading cause of severe visual loss (2 children), after macular scars and secondary glaucoma. In the series of Jain and associates,[6] ME was the most common cause of visual loss, identified in 8 of 26 children with intermediate uveitis. As in adults, resolution of ME may not always be associated with improved VA owing to the presence of structural degenerative changes, amblyopia, glaucoma, and cataract.[7,8]

The aim of the present study was to assess the clinical course of uveitis-related ME in children, and specifically, the rate of ME resolution and visual outcome.

METHODS

THE DATABASES OF UVEITIS CLINICS OF 4 TERTIARY MEDICAL centers, 1 in the United Kingdom and 3 in Israel, were retrospectively searched for all patients younger than 18 years who were treated for noninfectious uveitis–related ME in the period 2005–2015. In all patients included in the study, uveitis was diagnosed on the basis of the classification of the Standardization of Uveitis Nomenclature (SUN). ME was defined as the presence of intraretinal fluid or cysts and/or subretinal fluid, with/without central macular thickening (>300 μm) and/or epiretinal membrane on optical coherence tomography (OCT). Patients with a follow-up period shorter than 3 months were excluded. The study followed the tenets

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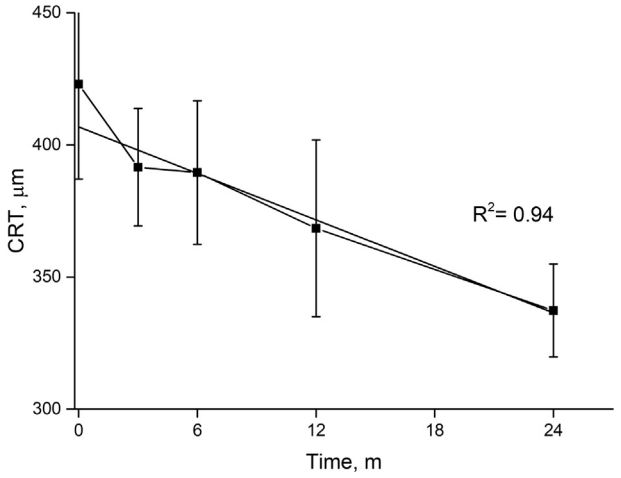

FIGURE 1. Change in average central retinal thickness (CRT) during follow-up. The decrease from 423.04 ± 35.94 µm at baseline to 337.33 ± 17.59 µm by 24 months was statistically significant ($R^2 = 0.94$, $P = .003$).

of the Declaration of Helsinki and was approved by the institutional review boards of all 4 medical centers.

The medical charts of the eligible patients were retrospectively reviewed for the following data: age and sex, best-corrected visual acuity (BCVA), intraocular pressure, anterior segment cells and flare, type of uveitis (SUN guidelines; accordingly, pars planitis was diagnosed only when snowballs and/or snowbanking was present), complications of uveitis, presence of cataract, presence of vitreous haze, and retinal findings. The clinical findings were analyzed at 5 time points: baseline (time of diagnosis of ME) and 3, 6, 12, and 24 months after diagnosis. Local and systemic treatments administered for ME at each time point were recorded as well, as were findings on OCT and fluorescein angiography when available, in order to characterize the diagnosis of ME and evaluate the response to treatment. An improvement in ME was clinically defined as a reduction of ≥20% in central retinal thickness on OCT, as demonstrated in the MUST trial.[9] ME resolution was defined as a normal foveal reflex with no perifoveal thickening and/or complete disappearance of intraretinal and subretinal fluid on OCT. The majority of imaging was performed using spectral-domain OCT (Spectralis, Heidelberg Engineering GmbH, Heidelberg, Germany). A few of the oldest imagings were performed using time-domain OCT; therefore we chose to calculate differences rather than absolute numbers.

Most of our clinical decisions regarding initiation, change, or termination of treatment were performed based on OCT examinations. Nevertheless, in some of the patients we did not have access to the central macular thickness values and these are therefore not included in the statistical analysis. In a small subset of patients, when a normal fovea was observed by clinical examination of the uveitis specialist who exclusively followed the patient, OCT reassurance was not obtained.

• **STATISTICAL ANALYSIS:** Continuous data are presented as mean ± standard error of the mean (SEM) and categorical data as proportions. Changes in BCVA over time were evaluated by linear regression analysis with application of a generalized estimating equation to account for correlations between the 2 eyes of the same patient. A Cox regression model was used for multivariate analysis and calculation of the probability of ME resolution (relative risk) in relation to clinical features and treatment regimens, with adjustment for correlations between the 2 eyes of the same patient. The Kaplan-Meier estimator was used to evaluate survival to ME resolution and log-rank test was applied to explore differences in resolution by anatomic features. Analyses were performed with SPSS statistical software (version 25; IBM Corp, Armonk, New York, USA). A P value of $<.05$ was considered significant.

RESULTS

THE STUDY COHORT INCLUDED 25 CHILDREN, 11 FEMALE and 14 male, of mean age 8.5 ± 3.4 years at baseline. The median follow-up time from baseline was 48 months (range, 6–194 months). Fourteen patients (56.0%) had intermediate uveitis (7 idiopathic and 7 pars planitis), 4 had panuveitis, 4 had chronic anterior uveitis related to juvenile idiopathic arthritis, and 3 had chronic idiopathic anterior uveitis. Six patients were diagnosed between 2005 and 2006 and therefore their documented findings were retrospectively defined according to the SUN classification.

Uveitis was associated with ME in 33 eyes. ME was diagnosed simultaneously with uveitis in 14 eyes (11 patients, 42.4%) and after uveitis in the remainder, with an interval of up to 6 months in 7 eyes (5 patients, 21.2%), 6–12 months in 3 eyes (3 patients, 9.1%), and >1 year in 8 eyes (6 patients, 24.2%); in 1 patient, the time of ME onset after uveitis was unknown. At the time of diagnosis of ME, the uveitis was active in 28 eyes of 22 patients (84.8%; including 13 with intermediate uveitis) and inactive in 3 eyes of 2 patients with juvenile idiopathic arthritis and 2 eyes of 1 patient with idiopathic intermediate uveitis.

The majority of patients were examined in close proximity to the assessed time points: 25 (100%) at baseline, 23 (92%) after 3 months, 25 (100%) after 6 months, 23 (92%) after 12 months, and 20 (80%) after 24 months. The follow-up included a clinical examination in all the patients. An OCT was performed in 18 (72%), 13 (52%), 12 (48%), 9 (36%), and 8 (32%) patients at baseline and after 3, 6, 12, and 24 months, respectively. Fluorescein angiography was performed in 7 (28%), 1 (4%), 2 (8%), and 1 (4%) patients at the abovementioned time points.

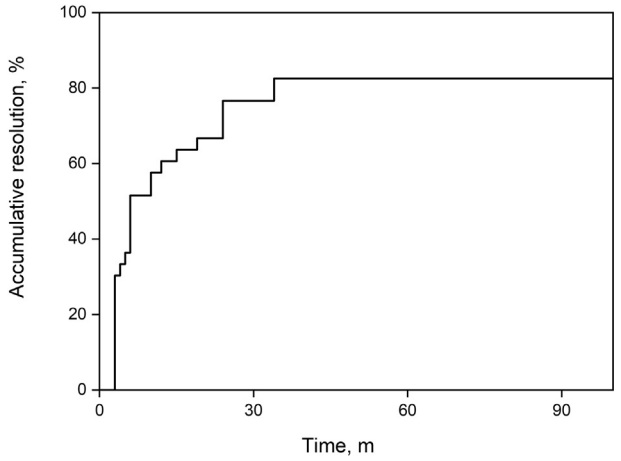

FIGURE 2. Kaplan-Meier survival plot for accumulative macular edema resolution during follow-up. Median time to resolution was 6 months. Complete resolution was achieved in 76% of eyes during the 24-month follow-up.

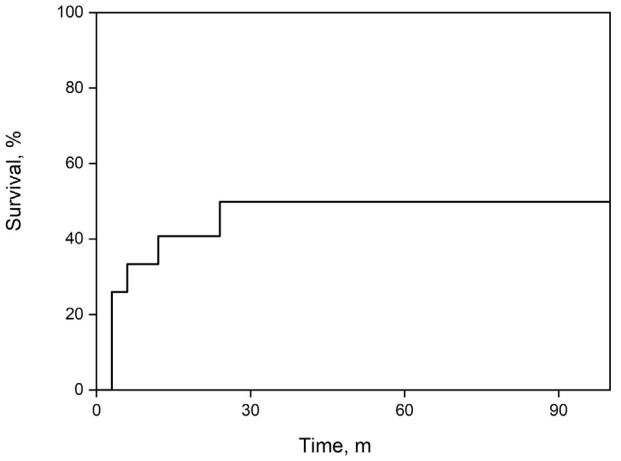

FIGURE 3. Kaplan-Meier survival plot for accumulative improvement of ≥20% in central retinal thickness during follow-up. An improvement of ≥20% was observed in 7 eyes (21.2%) at 3 months and 9 eyes (27.3%) at 6 months.

By 24 months, there was an average decrease in central retinal thickness from 442.27 ± 31.77 μm (interquartile range [IQR] 317.25–557.75) at baseline to 337.33 ± 17.59 μm (IQR 282–401.25, $R^2 = 0.94$, $P = .003$; Figure 1). Median time to resolution of ME was 6 months (95% confidence interval [CI] 0.5–19). Complete resolution of ME was achieved in 25 eyes (75.8%) at the 24-month follow-up (Figure 2). An improvement of ≥20% in central retinal thickness was observed in 7 eyes (21.2%) at 3 months and 9 eyes (27.3%) at 6 months (Figure 3). During the remainder of follow-up, in many patients, the macula looked clinically normal and therefore OCT was not performed.

At baseline, subretinal fluid was observed in 11 eyes (33.3%) and intraretinal cysts in 14 eyes (42.2%); 9 eyes had both (27.3%). Neither of these factors affected the rate of ME resolution or the final VA. Rates of ME resolution were 81.8% for eyes with subretinal fluid and 70.0% for eyes without subretinal fluid (odds ratio [OR] 2.11, 95% CI 0.77–5.79, $P = .15$); corresponding rates for eyes with and without intraretinal cysts were 78.6% and 62.5% (OR 1.43, 95% CI 5–4.14, $P = 0.51$).

Rates of VA ≥20/40 at 24 months were 72.7% in eyes with subretinal fluid and 80.0% in eyes without subretinal fluid (OR 0.49, 95% CI 0.1.8–1.34, $P = .16$); corresponding rates in eyes with and without intraretinal cysts were 64.3% and 100% (OR 0.86, 95% CI 0.33–2.27, $P = .77$).

There was a trend for a faster ME resolution in eyes with subretinal fluid (5 months, 95% CI 3–34 vs 24 months, 95% CI 10–24 in eyes without subretinal fluid, $P = .11$); however, no statistically significant difference was achieved. Resolution in eyes with intraretinal cysts was 6 months (95% CI 3–24) compared to 10 months in eyes without cysts (95% CI 5–15, $P = .48$) (Figure 4A and B).

The rate of ME resolution was also analyzed in relation to the anatomic location of the uveitis. The median time to resolution of ME was 6 months both in patients with (7 patients) and without (18 patients) anterior uveitis (95% CI 4–19 vs 95% CI 3–24; $P = .23$, log-rank test) (Figure 5). Of the 9 eyes in which ME failed to resolve by 24 months, 5 had an epiretinal membrane (55.5% of all eyes with epiretinal membrane) and 3 had vitreoretinal traction (60.0% of eyes with vitreoretinal traction); 1 eye had both (Figure 6A–D). Two eyes had no complications. Of the 24 eyes in which ME resolved, 5 had retinal vasculitis and 2 had retinal neovascularization; neither of these factors affected ME resolution.

BCVA improved significantly from baseline to 3 months (0.6 ± 0.07 logMAR vs 0.35 ± 0.08 logMAR, $P < .0001$) and remained stable at 6 months (0.44 ± 0.1 logMAR), 12 months (0.48 ± 0.1 logMAR), and 24 months (0.42 ± 0.11 logMAR) ($P < .0001$ compared to baseline, for all time points). At baseline, BCVA was ≥20/40 in 24.2% of eyes (8/33 eyes, 8/25 patients), increasing to 57.6% after 3 months of treatment ($P < .0001$); thereafter, rates were 66.7% at 6 months, 54.5% at 12 months, and 63.6% at 24 months (Figure 7). Although minor fluctuations were observed, the visual acuity was relatively stable after the initial improvement. Only 3 eyes had a BCVA worse than 20/200 at baseline; all improved during follow-up. They included 1 eye each of a patient with pars planitis, epiretinal membrane, and retinal vasculitis; a patient with idiopathic intermediate uveitis and vitreoretinal traction; and a patient with juvenile idiopathic arthritis and cataract at baseline. A final BCVA of ≥20/40 was achieved in 75.2% of patients with subretinal fluid and 90.6% of patients without subretinal fluid, and in 70.4% of patients with intraretinal cysts and 100% of

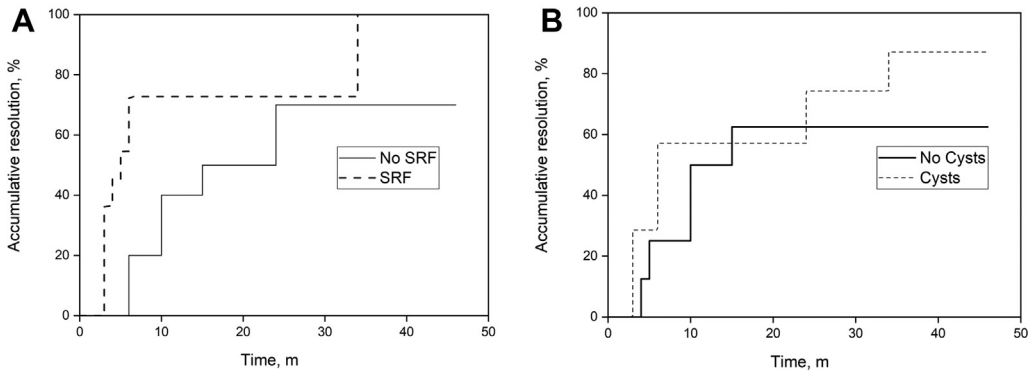

FIGURE 4. Rate of macular edema (ME) resolution in relation to ME structure. (A) The presence of subretinal fluid (SRF) at baseline was associated with a trend toward faster resolution of ME (5 months vs 24 months for eyes with and without subretinal fluid, respectively, $P = .11$). (B) The presence of intraretinal cysts at baseline was also associated with a trend toward faster ME resolution (median 6 months vs 10 months for eyes with and without cysts, respectively, $P = .48$).

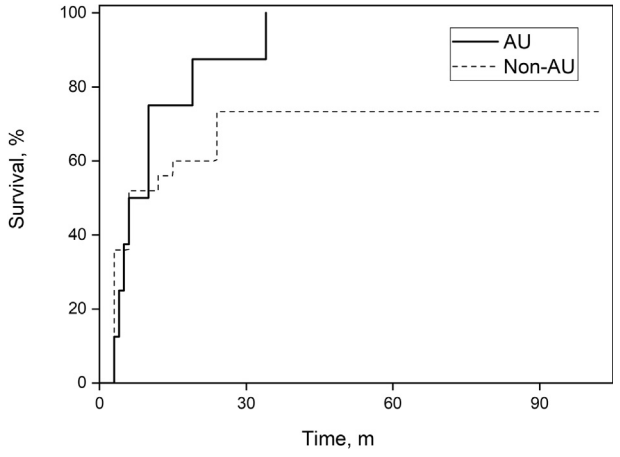

FIGURE 5. Rate of macular edema resolution in relation to the underlying cause of uveitis. Median time to resolution was 6 months, both for patients with (7 patients) and without (18 patients) anterior uveitis (AU; 95% CI 3–4, $P = .23$, log-rank test).

patients without; neither of these between-group differences was significant.

Treatment of ME was started no later than 3 months after diagnosis in all patients. Treatment regimens included local corticosteroid injections or dexamethasone implants in 20 eyes (14 eyes received periocular injections, 3 received dexamethasone implants, and 3 received both), systemic corticosteroids in 22 eyes (16 patients, 66.7%), antimetabolite immunosuppressive agents in 16 eyes (12 patients, 48.5%) (methotrexate in 14 eyes, 10 patients [1 patient also received azathioprine]; mycophenolate mofetil in 2 eyes, 2 patients), and anti–tumor necrosis factor (TNF)-α agents in 9 eyes (6 patients, 27.3%) (infliximab in 7 eyes, 4 patients; and adalimumab in 7 eyes, 5 patients, including 5 eyes switched from infliximab). Four of the eyes treated with periocular steroid injections (28.57%) had cataract progression and 5 eyes developed glaucoma (35.71%). Two of the eyes that received dexamethasone implant had cataract progression (66.67%) and none developed glaucoma. Owing to the small number of cases it was not possible to compare side effect rates. No correlations were found between ME resolution and the specific treatment strategy used. ME resolution occurred respectively in 62.5% and 80.0% of patients who were treated or not with systemic steroids (OR = 0.59, 95% CI 0.24–1.45, $P = .25$); in 53.8% and 75.0% of patients who were treated or not with the addition of immunosuppression (OR 0.65, 95% CI 0.26–1.64, $P = 0.36$); in 72.7% and 61.1% of patients who were treated or not with the addition of biologic therapy (OR 0.73, 95% CI 0.34–2.15, $P = 0.73$); and in 65.5% and 80% of eyes treated with or without local injections, respectively (OR 0.52, 95% CI 0.17–1.58, $P = .25$). Cataract progression during the study period was noted in 5 of 23 eyes with previously undocumented cataract (21.74%) and new-onset glaucoma was documented in 5 of 31 eyes with no previous glaucoma (16.13%).

DISCUSSION

IN THE PRESENT STUDY OF CHILDREN WITH ME SECONDARY to different types of chronic noninfectious uveitis, most of the cohort had a favorable clinical and functional outcome. ME resolved in 75.8% of eyes during 24 months of follow-up. CRT improved by ≥20% in 7 eyes (21.2%) at 3 months from diagnosis and in 9 eyes (27.3%) at 6 months. In most of the refractory cases, a structural complication was observed. BCVA improved significantly as early as 3 months after treatment was started, when 57.6% of the patients had BCVA ≥20/40, and remained stable thereafter. The underlying cause of uveitis, specific features of

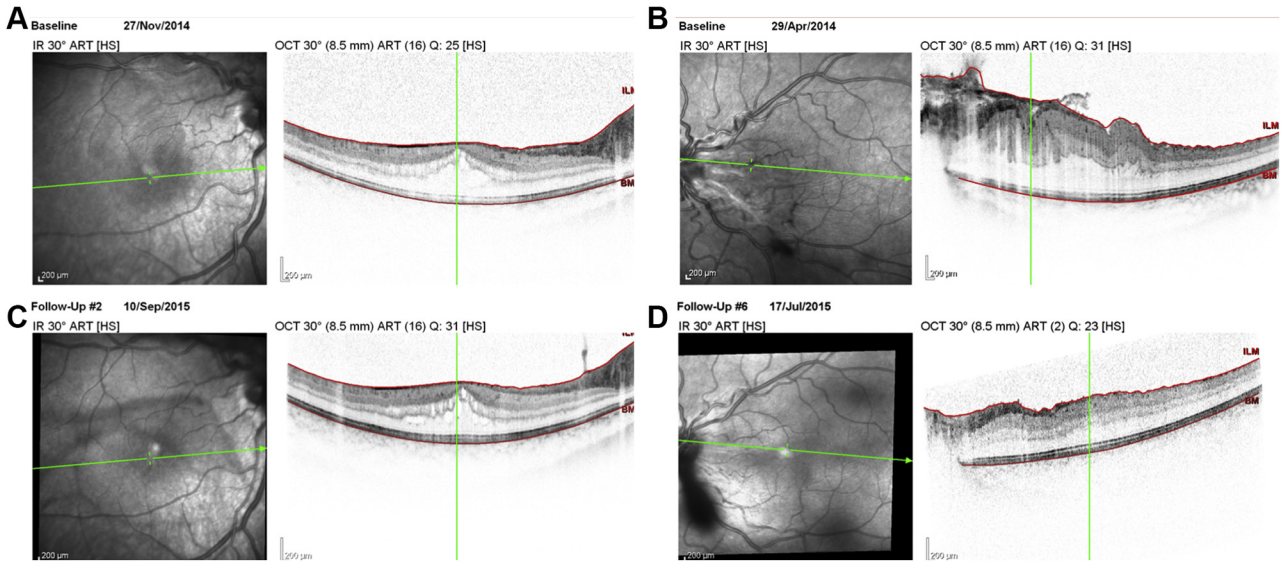

FIGURE 6. Macular optical coherence tomography showing epiretinal membrane limiting macular edema (ME) resolution in 2 patients. (A and C) A 7-year-old girl with pars planitis who failed to respond to treatment. (A) Before treatment. (C) Ten months after treatment. (B and D) A 6-year-old boy with pars planitis partial in whom ME resolved with treatment, accompanied by spontaneous resolution of the tractional component. (B) Before treatment. (D) After treatment.

ME, and specific treatment regimen had no significant effect on the rate of resolution of ME or on the final BCVA. There was a trend toward faster resolution in patients with subretinal fluid, although the difference was not statistically significant.

Most of the studies in the literature that focused on ME in noninfectious uveitis were performed in adults.[9] In children, the focus was mainly on the effect of treatment on inflammation; the effect on ME was evaluated in some, but only as a secondary finding.[10–15] The mainstay of treatment of adult uveitic ME is corticosteroids, local or systemic.[15,16] Immunosuppressive drugs including methotrexate,[17] anti-TNF-α agents,[18] interferon-β,[19] and anti–vascular endothelial growth factor (VEGF) agents[20] have also shown a favorable effect. However, children pose a therapeutic challenge for several reasons: intravitreal injection of corticosteroids or anti-VEGF agents frequently necessitates general anesthesia[7]; the ocular hypertensive response to topical corticosteroids is more frequent, rapid, and severe[21]; and long-term treatment with systemic steroids is associated with adverse effects such as growth retardation.[22] Furthermore, the current literature on visual outcome of noninfectious uveitic ME in children is limited to small (1–16 eyes) retrospective and noncomparative case series with a relatively short follow-up time.[2,7,22–26] In several studies, treatment was given for uveitis and only part of the cohort had ME. All studies reported favorable results in terms of VA and central macular thickness on OCT, usually after different corticosteroid regimens. Lei and Lam[7] noted an improvement in VA and central macular thickness at a median of 12 weeks after injection of dexamethasone intravitreal implant (Ozurdex); however, by 52 weeks, VA had improved from baseline in only in 2 of 5 eyes. Sella and associates,[23] in a study of 14 eyes with ME, found that 10 showed an improvement in central macular thickness and BCVA after 1–3 months of Ozurdex injections. Sallam and associates[22] reported complete resolution of ME in 5 of 6 eyes (94%) after a median of 3 weeks' treatment with intravitreal triamcinolone. This was accompanied by significant improvement in VA at a median follow-up of 4 weeks; in 56% of eyes, best VA was increased by 0.4 logMAR after 15 months. In a study of 19 uveitic eyes, including 11 with ME, treated with periocular corticosteroid injection, Habot-Wilner and associates[24] found that ME resolved and VA improved in 5 eyes each by 6 weeks. Slabaugh and associates used topical difluprednate to treat 9 of 26 eyes with ME, with a 78% improvement rate after a mean interval of 4 weeks,[2] along with improved vision. One case report described bilateral improvement in central macular thickness and VA 1 week after bevacizumab injection in a single eye.[25] The results were maintained to the end of the 16-week follow-up. Finally, Trittibach and associates[26] examined the influence of pars plana vitrectomy on ME outcome and found a significant reduction in VA in 8 of 10 eyes at 12 months postoperatively. The improvement in VA was not associated with the resolution of ME.

A number of studies of visual outcome of ME after different treatment regimens were performed in mixed adult and pediatric populations. The MUST-CME trial[9]

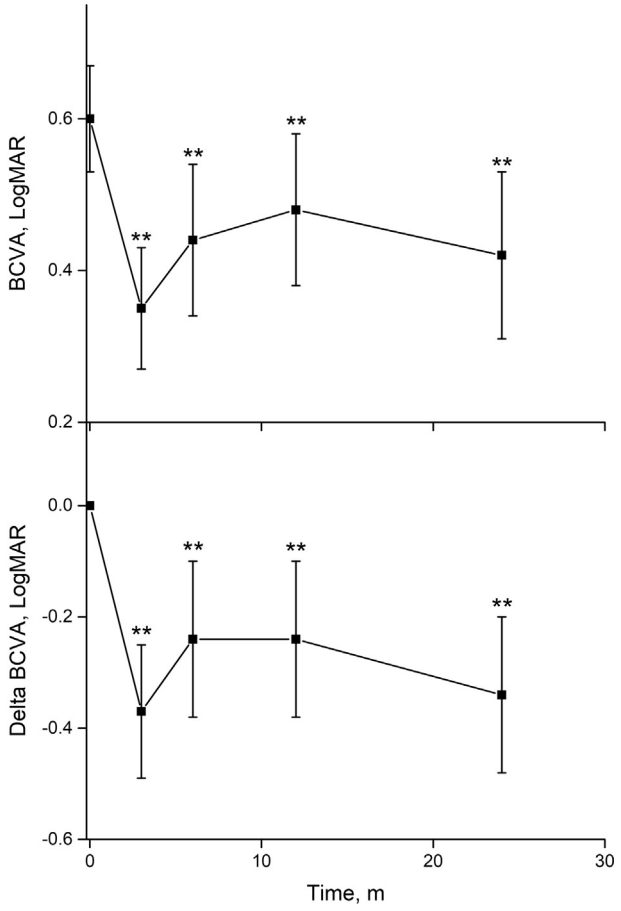

FIGURE 7. Percentage of eyes with best-corrected visual acuity (BCVA) ≥20/40. BCVA was ≥20/40 at baseline in 8 eyes (24.2%), increasing to 57.6% after 3 months of treatment ($P < .0001$) and remaining stable thereafter.

included patients from age 13 years and showed that central macular thickness and BCVA improved in about two thirds of eyes treated with dexamethasone implant or systemic corticosteroids. The only predictive factor for ME improvement was leakage on fluorescein angiography. Schaap-Fogler and associates[18] showed that anti-TNF-α and conventional immunosuppressive therapy resulted in significant improvement in central macular thickness and VA after 3 months in all age groups. At 12 months, the effect was reduced. In the study by Sohn and associates,[27] peripheral cryotherapy for the management of pars planitis was associated with a faster time to ME resolution than corticosteroids; the difference was statistically significant at 6 months. VA improved over time in the cryotherapy group but decreased in the controls.

Overall, treatment regimens were effective in resolving ME and improving VA in children with ME. The time to improvement of central macular thickness and VA ranged from 1 week to 12 months in the majority of patients.[2,7,9,18,22,23,25–27] All the studies conducted to date evaluated a single treatment regimen, alone or compared to systemic corticosteroids. The results are in line with the present study, which included children with different types of uveitis and ME treated with different regimens. We found that ME resolved and VA improved after 3 months of treatment, with no difference in outcome by the specific treatment used. Regarding the difference between periocular corticosteroid injections and dexamethasone implants, owing to the small sample size it was not possible to conclude on differences in efficacy or side effects.

A few studies attempted to correlate structural characteristics of ME with visual outcome. Macular thickening and specifically the presence of retinal cysts were correlated with different degrees of visual impairment.[28–30] Iannetti and associates[30] reported a correlation between serous retinal detachment and disruption of the ellipsoid zone and visual loss. By contrast, in our cohort, ME structure and features did not affect ME resolution and final BCVA, with the possible exception of subretinal fluid and intraretinal cysts, which may have had some beneficial effect. However, the determination of retinal structure is subject to interexaminer bias, so comparisons between studies are limited.

Despite the small sample size, this is, to the best of our knowledge, the largest outcome study of pediatric ME to date, with the longest follow-up, and the first to compare treatment regimens in the "real-life" clinical setting. The study was limited by the difficulty in differentiating treatment for uveitis from treatment for ME; the heterogeneous treatment regimens; the small cohort; the retrospective design; and the heterogenous disease entities.

In conclusion, our findings suggest that early and intensive treatment of noninfectious uveitis–related ME can lead to a favorable outcome in terms of ME resolution and VA. The specific treatment regimen may be left to the discretion of the physician, with consideration of the patient's systemic condition. Larger randomized controlled trials are needed to corroborate our findings and evaluate potential differences among the treatment regimens.

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