


Long-Term Outcome of Treatment with 2% Topical Ganciclovir Solution in Cytomegalovirus Anterior Uveitis and Corneal Endotheliitis

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Purpose: This study aimed to evaluate the therapeutic efficacy and long-term outcomes of treatment with topical 2% ganciclovir solution in immunocompetent patients with aqueous humor polymerase chain reaction (PCR)-proven cytomegalovirus (CMV) anterior uveitis and corneal endotheliitis.

Methods: We retrospectively reviewed the findings for immunocompetent patients diagnosed with CMV uveitis or endotheliitis based on clinical manifestations and polymerase chain reaction (PCR) examination results and treated with topical 2% ganciclovir solution at National Cheng Kung University Hospital. Clinical outcome measurements included evaluations of the response rate, relapses, resolution of anterior chamber inflammation, visual acuity, and intraocular pressure.

Results: The study included 38 eyes of 32 patients. Long-term administration of topical 2% ganciclovir significantly decreased keratic precipitates ($p = 0.001$), anterior chamber cells ($p = 0.001$), and reduced intraocular pressure ($p < 0.001$). Only one eye was unresponsive to topical ganciclovir treatment, and the recurrence decreased to 0.13 relapses per year. The presence of keratic precipitates and higher intraocular pressure at the initial presentation were significantly associated with recurrence ($p = 0.036$ and $p = 0.001$, respectively).

Conclusions: Long-term use of topical 2% ganciclovir solution is effective, safe, and applicable when commercialized ganciclovir gel is not available.

Keywords: cytomegalovirus, endotheliitis, ganciclovir, uveitis

Introduction

Cytomegalovirus (CMV) ophthalmic infection has been identified as an etiological factor for Posner-Schlossman syndrome (PSS), Fuchs heterochromic iridocyclitis, retinitis, corneal uveitis, and endotheliitis.^{1–8} CMV infections involving the anterior segment are characterized by blurred vision, inflammation in the anterior chamber, the presence of keratic precipitates (KP), elevated intraocular pressure (IOP), and corneal endothelial cell damage.^{1,4}

At present, the treatment for CMV anterior uveitis and endotheliitis involves the continuous application of antiviral agents. Since systemic antiviral therapies are associated with various adverse reactions, recent studies have recommended treatment with topical antiviral agents as initial and maintenance therapy to address the high recurrence rates.^{9,10} In this regard, ganciclovir gel (0.15%, Zirgan®) was approved for acute herpetic keratitis with dendritic ulcers by the US Food and Drug Administration (FDA) in 2009 and was also reported to be eligible for CMV ocular infections in previous studies.^{11–13} Koizumi et al showed that all CMV patients responded to 0.15% ganciclovir gel,¹² and Pavan-Langston et al reported a case refractory to systemic antiviral therapy that improved after application of topical 0.15% ganciclovir gel at 2-h intervals.¹⁴ However, 0.15% ganciclovir gel is not available in many countries, including Taiwan. Clinically, a topical 2% ganciclovir solution has been used as a substitute for commercialized ganciclovir gel. However, the long-term

efficacy of topical 2% ganciclovir has not been fully studied. Therefore, in this study, we aimed to investigate the long-term efficacy, safety, and predictive factors for CMV uveitis and endotheliitis recurrence treated with 2% ganciclovir solution therapy.

Method

Patient Selection

This retrospective study was approved by the Institutional Review Board of the National Cheng Kung University Hospital (NCKUH). The informed consents were obtained from the study participants prior to the study commencement. Anterior chamber tapping was performed in patients with suspected CMV infection, and the aqueous samples were subjected to polymerase chain reaction (PCR) for analysis of herpes simplex virus (HSV), varicella-zoster virus (VZV), Epstein–Barr virus (EBV), and CMV. We retrospectively reviewed the medical records of patients with positive PCR results for aqueous CMV who had been treated with 2% ganciclovir solution between April 2012 and April 2021 at NCKUH, Tainan, Taiwan.

Inclusion and Exclusion Criteria

All patients were immunocompetent, diagnosed with CMV uveitis or endotheliitis with positive PCR results for the aqueous humor, and treated with 2% ganciclovir solution during initial and maintenance therapy. Patients with a follow-up duration of at least one year were included in the study. We excluded patients showing concurrent infection with HSV, VZV, or EBV and who were lost to follow-up for more than one year.

Treatment Protocol

All patients were treated with 2% ganciclovir solution prepared with intravenous ganciclovir and sterile distilled water. The storage condition of 2% ganciclovir solution was at a temperature between 2°C–8°C, sun exposure should be avoided, and the expiration date was 3 months. The 2% ganciclovir solution treatment was initiated at a dosage frequency of 2 h. The frequency was modified according to the clinical response and maintained at four times daily. Topical steroids (1% prednisolone, 0.1% betamethasone, or 0.1% fluorometholone) and anti-glaucoma medications (carbonic anhydrase inhibitors, alpha-2 adrenergic agonists, or beta-blockers) were prescribed based on the clinical presentation. Similar to previous study,¹⁵ if anterior chamber inflammation improved compared to last visit and IOP reduced below 21 mmHg, topical steroids were tapered off according to the clinical response and were finally stopped.

Outcome Measurements

In this study, we set patients to be followed up every three months during maintenance therapy. The follow-up endpoint and primary outcomes were the response to antiviral therapy, resolution of anterior chamber inflammation, intraocular pressure, and the cumulative relapses at the final visit. Response was defined as the resolution of anterior chamber inflammation, including reduction of the anterior chamber cell count, KP, and IOP. Recurrence was defined according to the Standardization of Uveitis Nomenclature (SUN) working group, which was defined as repeated episodes of active inflammation (two-step increase in the level of inflammation or increase from grade 3 to 4), corneal edema, endothelial KP, and elevated IOP separated by periods of 3 months.¹⁶ Patients with relapses during maintenance therapy would be classified into the recurrence group. Secondary outcomes were measured using changes in corrected-distance visual acuity (CDVA). All adverse effects were recorded.

Statistical Analysis

Statistical analysis was performed using Statistical Product and Service Solutions (SPSS) software, version 17 (IBM, Armonk, NY, USA). Data are presented as mean \pm standard deviation (SD) for quantitative variables and frequencies for categorical variables. Quantitative variables were compared using the independent *t*-test, paired *t*-test, and Mann–Whitney *U*-test. Categorical variables were evaluated using the chi-squared test and McNemar's test. *P* values less than 0.05 indicated statistical significance.

Results

Forty-four patients tested positive for CMV in the aqueous humor and were regularly followed up. All patients were treated with a topical 2% ganciclovir solution after diagnosis. Seven patients underwent follow-up assessments for less than one year. One patient each showed concurrent infections with VZV and HSV in the PCR results for the aqueous humor. Two patients were initially treated with oral antiviral medication without a topical 2% ganciclovir solution. One patient with CMV retinitis was immunocompromised and treated with Humira. These patients were excluded to obtain the long-term outcomes of topical 2% ganciclovir solution in isolated CMV anterior uveitis and endotheliitis.

Thirty-two immunocompetent patients with 38 affected eyes were enrolled, and 38 infected eyes were included in this study. The patients' characteristics are listed in Table 1. Disease recurrence was reported in 17 eyes (44.7%). The study population included 28 male participants (73.7%), and the mean age at diagnosis was 55.68 ± 12.43 years (range, 36 to 83 years). The mean follow-up duration was 45.68 ± 28.47 months (range, 12–105 months). CMV uveitis was diagnosed in 34 eyes (89.5%), and CMV endotheliitis was diagnosed in 4 eyes (10.5%).

Comparisons of characteristics between the recurrence and non-recurrence groups are summarized in Table 1. The recurrence and non-recurrence groups showed no significant differences in age ($p = 0.79$), sex ($p = 0.70$), follow-up period ($p = 0.056$), and diagnosis ($p = 0.40$ in uveitis and endotheliitis). At baseline, most patients reported at least 1–2 uveitis or endotheliitis episodes per year.

As shown in Table 2, the CDVA was 0.41 ± 0.27 (logMAR, ranging from 0 to 1.1), and the cell amount was 1.14 ± 0.73 (+, ranging from 0 to 2) at initial diagnosis. KP was present in 83% of infected eyes. The mean IOP was 27.67 ± 12.46 (mmHg, ranging from 12 to 60). The most affected eyes were treated with topical steroids (86.8%) and topical IOP-lowering agents (84.2%). Only a small proportion of eyes were prescribed systemic IOP-lowering medications, including oral acetazolamide (26.3%) and intravenous mannitol (18.8%).

At the last follow-up, only one uveitic eye was unresponsive to topical 2% ganciclovir solution and required further surgical intervention with trabeculectomy. Another eye underwent trabeculectomy due to intractable ocular hypertension when the disease relapsed 19 months after initiation of topical ganciclovir treatment. Both patients showed no episodes of IOP spikes after trabeculectomy. One patient with CMV endotheliitis experienced corneal decompensation and subsequently underwent keratoplasty. AC inflammation parameters and treatment modalities were compared between the time

Table 1 Patient Demographics

Variable	Overall Enrolled Eyes (N = 38)			Recurrence (N = 17)	Non-Recurrence (N = 21)	p value
	Mean or N	Median	Range	Mean or N	Mean or N	
Age (years)	55.68 ± 12.43	52	36–83	55.06 ± 12.75	56.19 ± 12.46	0.79 ^a
Gender						0.70 ^b
Male	28 (73.7%)			16 (76.2%)	12 (70.6%)	
Female	10 (26.3%)			5 (23.8%)	5 (29.4%)	
Medical history						
Diabetes mellitus	4			1	3	
Hypertension	7			4	3	
Coronary artery disease	2			1	1	
Asthma	2			0	2	
Follow-up duration (month)	45.68 ± 28.47	41	12–105	54.65 ± 27.87	38.43 ± 27.47	0.056 ^c
Diagnosis						
Uveitis	34 (89.5%)			16 (94.1%)	18 (85.7%)	0.40 ^b
Endotheliitis	4 (10.5%)			1 (5.9%)	3 (14.3%)	

Notes: ^aIndependent t-test, age difference between recurrence and non-recurrence group. ^bDouble tailed Chi-square test, gender and diagnosis difference between recurrence and non-recurrence group. ^cMann-Whitney U-test, follow-up duration difference between recurrence and non-recurrence.

Table 2 Treatment Outcomes: Comparison of Primary and Secondary Outcome Parameters in Initial Treatment and Last Follow-Up

Variable	Initial Treatment (N = 38)			Last Follow-Up (N = 38)			p value
	Mean or N	Median	Range	Mean or N	Median	Range	
Response (Yes/No)							
Yes				37			
No				1			
Recurrence number				21			
Recurrence (relapse/year)				0.13			
Clinical findings							
CDVA (LogMAR)	0.41 ± 0.27	0.4	0–1.1	0.27 ± 0.30	0.25	0–2	0.023 ^a
Cell (+)	1.14 ± 0.73	1	0–2	0.30 ± 0.53	0	0–1	0.001 ^{b, c}
Keratic precipitates							0.001 ^{*b}
Present	32 (84.2%)			15 (39.5%)			
Absent	6 (15.8%)			23 (60.5%)			
IOP (mmHg)	26.47 ± 11.86	23	12–60	14.49 ± 3.00	15	7–19	<0.001 ^{*a}
Treatment							
2% ganciclovir	38 (100%)			38 (100%)			
Topical steroid	33 (86.8%)			25 (73.7%)			0.039 ^b
Topical glaucoma therapy							0.075 ^a
No treatment	6 (15.8%)			9 (23.7%)			
Monotherapy	16 (42.1%)			18 (47.4%)			
Dual therapy	8 (21.1%)			10 (26.3%)			
Triotherapy	8 (21.1%)			1 (2.6%)			
Oral acetazolamide	10 (26.3%)			0 (0%)			<0.001 ^{*b}
IV mannitol	6 (18.8%)			0 (0%)			<0.001 ^b

Notes: ^aDouble-tailed paired *t*-test, treatment efficacy, difference between paired initial and last follow-up in continuous parameters. ^bMcnemar's test, difference between paired initial and last follow-up in categorical parameters (binomial distribution used). ^cCell was measured with Mcnemar's test by divided into 2 groups (0–0.5+ as less inflammation group and 1+–2+ as more inflammation group). *Statistical significance.

Abbreviations: CDVA, corrected distance visual acuity; IOP, intraocular pressure.

of diagnosis and last follow-up (Table 2). By the last follow-up, there were 21 relapses and 0.13 relapses/year, and significant differences were observed in KP resolution ($p < 0.001$), the decrease in IOP ($p < 0.001$), and a reduction in the use of oral acetazolamide ($p = 0.008$).

The results of the recurrence analysis are shown in Table 3. We attempted to identify the predictive parameters for recurrence by comparing the initial parameters between the recurrence and non-recurrence groups. Only the initial presence of KP and a higher IOP were significantly different ($p = 0.036$ and $p = 0.03$, respectively). Adverse effects of ganciclovir treatment were also recorded. One patient had punctate epithelial erosion, which was suspected to be related to ganciclovir toxicity, and one patient had allergic conjunctivitis of uncertain etiology.

Discussion

In this study, we used topical 2% ganciclovir solution that was initiated at a frequency of 2 h and maintained at 4 times daily, similar to a previous study.¹⁷ Using a literature review, we have summarized the findings of previous studies that evaluated topical 2% ganciclovir solution therapy (Table 4). In comparison with previous reports, our study had the longest follow-up period and the lowest rate of relapses per year with long-term efficacy and recurrence analysis of topical 2% ganciclovir in aqueous PCR-proven CMV infection.

CMV infection recurrence has been mentioned in several studies, especially when antiviral therapy was discontinued.^{13,18} In this study, we reported 21 relapses with a total follow-up duration of 1736 months, with 0.13 relapses per year on average. Accorinti et al reported 23 relapses over 714 months of follow-up,¹⁹ while Wong et al reported 0.88 episodes per person-year.¹¹ The better results obtained in our study may be due to the long-term

Table 3 Recurrence Analysis: Comparison of Initial Findings in Recurrence and Non-Recurrence Group

Variable	Recurrence (N = 17)			Non-Recurrence (N = 21)			p value
	Mean or N	Median	Range	Mean or N	Median	Range	
Initial findings							
CDVA (LogMAR)	0.33 ± 0.22	0.30	0.5–0.7	0.51 ± 0.30	0.52	0–1.1	0.061 ^a
Cell (+)	1.17 ± 0.80	1	0–2	1.11 ± 0.70	1	0–2	0.803 ^{b, c}
Keratic precipitates							0.036 ^{ab}
Present	16 (94.1%)			16 (76.2%)			
Absent	1 (5.9%)			5 (23.8%)			
IOP (mmHg)	34.93 ± 12.89	35	12–60	20.55 ± 6.40	20.5	13–33	0.001 ^{ab}
Initial treatment							
2% ganciclovir	17 (100%)			21 (100%)			
Topical steroid	14 (82.4%)			19 (90.9%)			0.461 ^b
Topical glaucoma therapy							0.208 ^b
No treatment	2 (11.8%)			4 (19.0%)			
Monotherapy	5 (29.4%)			11 (52.4%)			
Dual therapy	6 (35.3%)			2 (9.5%)			
Tritherapy	4 (23.5%)			4 (19.0%)			
Oral acetazolamide	8 (47.0%)			1 (4.8%)			0.001 ^b
IV mannitol	5 (29.4%)			1 (4.8%)			0.624 ^b

Notes: ^aIndependent t-test. ^bDouble tailed Chi-square test. ^cCell was measured with double tailed Chi-square test by divided into 2 groups (0–0.5+ as less inflammation group and 1+–2+ as more inflammation group). *Statistical significance.

Abbreviations: CDVA, corrected distance visual acuity; IOP, intraocular pressure.

Table 4 Literature Review of Topical 2% Ganciclovir Solution in Patients with CMV Anterior Segment Infection

Reference	Eyes	Initial Therapy	Maintenance Therapy	Treatment Duration (weeks)	Follow-Up Duration (Months)	Study Design
Keorochana, 2017 ²¹	11	Q2H	Nil	-	12	Efficacy and safety of 2% ganciclovir solution evaluated monthly over a 12-month follow-up period
Su, 2013 ¹⁰	7	Q2-3H	Q4H	Throughout follow-up	17.29±2.12	Clinical and immunological characteristics in 7 penetrating keratoplasty cases after topical 2% ganciclovir applied
Su, 2014 ¹⁷	68	Q2-3H	Q4H	Throughout follow-up	39.79±14.96	Comparison of therapeutic outcome of 126 Posner-Schlossman syndrome patients with CMV-positive (68 eyes) and CMV-negative (58 eyes)
Sheng, 2021 ⁹	36	QID	TID-QID	5.13 ± 3.66	36	Prognosis of 98 eyes with Posner-Schlossman syndrome and therapeutic outcomes of 36 CMV-positive eyes proven by IgG ratio of aqueous humor and serum samples
Sheng, 2022 ¹⁵	46	QID	QID	6.50 ± 4.67	1.5	Comparison of the 2% ganciclovir efficacy in the treatment of Posner-Schlossman syndrome relapses with and without CMV intraocular reactivation by IgG ratio of aqueous humor and serum samples

Abbreviation: CMV, cytomegalovirus.

application of topical antiviral therapy, but considering the small sample size, the results need to be confirmed in further large-scale studies to obtain more reliable conclusions. The recurrence episodes decreased significantly, and the repeated relapses after antiviral therapy might be attributable to the virostatic rather than the virucidal effect of ganciclovir.¹³ Moreover, the recurrence could have resulted from the low intracameral inhibitory dose when topical ganciclovir was titrated.^{12,20} Keorochana et al reported that the recurrence group tended to be present with poorer visual acuity, fewer cells, and more KP, but the differences failed to reach statistical significance.²¹ In our study, significant differences were observed in the presence of KP and elevation of IOP in recurrence group. However, contrary to a previous study,²¹ we found that patients with more anterior chamber cells tended to experience recurrence. Therefore, elimination of CMV anterior segment infection remains a challenge, but the reduction of relapse episodes is proof of efficacy, and long-term application of antiviral therapy for virostatic effects still remains the current consensus for CMV uveitis and endotheliitis treatment.^{15,22}

To better understand CMV treatment, we reviewed the findings obtained for previous treatment modalities and outcomes other than topical ganciclovir solution (Table 5). Systemic ganciclovir and valganciclovir treatment is known to cause infertility and bone marrow suppression and can result in severe neutropenia or thrombocytopenia.²³ In contrast, topical ganciclovir is less toxic and has shown no obvious side effects.^{11,21} Thus, topical ganciclovir has been reported to be a safe treatment modality and can ensure better compliance due to the non-invasive nature of treatment and the convenient mode of application. Although oral valaciclovir has been reported to be a successful treatment option for CMV anterior uveitis by Sira and Murray,²⁴ no consensus has been achieved for the use of valaciclovir in patients with CMV. Most studies still focus on the outcomes of oral valganciclovir or different modalities of ganciclovir as antiviral therapy.^{3,11,13,17,18,25–28} Van Bortel et al reported five cases of CMV uveitis that were successfully treated with oral valganciclovir for 3 to 12 months.³ Sobolewska et al showed favorable results with combination therapy using topical ganciclovir ophthalmic 0.15% gel (Zirgan®) and oral valganciclovir for a mean duration of 20 months.²⁷ Harada et al used oral valganciclovir followed by 1% ganciclovir eye drops due to the unavailability of the 0.15% gel in Japan.²⁹ Markomichelakis et al reported two cases of acyclovir-resistant CMV uveitis that were controlled by oral ganciclovir without recurrence.²⁶ Treatment with intravitreal ganciclovir injection has also been reported, and it showed reduction of CMV DNA copies and resolution of anterior chamber inflammation.²⁸ Chee et al reviewed four types of ganciclovir therapy, including intravenous, implant, intravitreal, and gel (0.15%, Zirgan® gel), and noted responses in 36 out of 47 patients.¹³ Among the treatments, intravitreal injection of ganciclovir was not suggested due to the higher rate of treatment failure. Meanwhile, a relatively lower recurrence rate was found in the topical ganciclovir gel group.¹³ Foscarnet was also applied and but was limited to cases with CMV retinitis.²⁵

Although our study revealed promising therapeutic and preventive effects of topical 2% ganciclovir solution, the retrospective nature of the study was a limitation, and the parameters for the analysis were also limited. Moreover, NCKUH is a tertiary referral medical center, and patients who had more complicated symptoms or were refractory to prior treatments at local ophthalmic clinics were referred to this center, which may have resulted in a selection bias. Furthermore, previous study has demonstrated the correlation between viral load and IOP, number of glaucoma medications, and future recurrences.³⁰ However, in this retrospective study, the viral load was not routinely examined in all patients. Besides, we performed paracentesis only once for diagnosis, and no further data from aqueous tapping were obtained to evaluate the therapeutic intracameral level of 2% ganciclovir solution. However, all our patients had PCR-positive results, completed at least one year of follow-up, and had the longest follow-up period in the literature; therefore, the results can be expected to contribute to the current body of knowledge regarding the treatment of CMV infections.

In summary, the long-term application of topical 2% ganciclovir solution was effective, safe, and non-inferior to other treatment modalities. This might be a treatment option when commercialized topical ganciclovir gel is not available. Further large-scale prospective studies are required to evaluate the long-term efficacy and safety of topical 2% ganciclovir solution.

Table 5 Literature Review of Other CMV Treatment Modalities and Outcomes

Studies	Eyes/ Treatment Episodes	Initial Therapy	Maintenance Therapy	Treatment Duration (m)	Follow-Up Duration (m)	Results
Sira and Murray, 2007 ²⁴	1	Oral VCV 1 g twice daily	-	11	11	No recurrence
Van Boxtel, 2007 ³	5	Oral valGCV 900 mg twice daily for 3 weeks	Oral valGCV 900 mg once daily	8.0±3.6	94.8±87.6	Uveitis quiescent within a few weeks, 1 recurred after cessation of antiviral therapy
Sobolewska, 2014 ²⁷	11	Oral valGCV 900 mg twice daily for 3 weeksTopical 0.15% GCV gel 5 times daily	Oral valGCV 450 mg twice daily	20.5±10.1	-	7/11 (63.6%) responsive, 2 recurrences after cessation of antiviral therapy
Harada, 2018 ²⁹	17	Oral valGCV 900 mg twice daily for 3 weeks Topical 1% GCV solution 6 times daily	Oral valGCV 450 mg twice daily	6.1±5.5	36.7±22.9	All patients (100%) responsive, 6/12 (50%) recurred during tapering or termination of anti- CMV therapy
Markomichelakis, 2002 ²⁶	2	Oral GCV 1000 mg three times daily	-	18±8.5	-	Asymptomatic under antiviral therapy
Chung and Chua, 2005 ²⁸	1	Intravitreal GCV	-	-	-	Uveitis quiescent and CMV DNA copies reduced after 2 weeks
Chee, 2010 ¹³	19	Intravenous GCV 5 mg/kg twice daily, oral GCV 1 g 3 times daily or oral 900 mg valGCV twice daily for 6 weeks	450 mg twice daily for 6 weeks	3	4.9–54.8	17/19 response, 14/17 recurred
	4	GCV implant: 4.5 mg GCV	-	-	-	4/4 response, 4/4 recur
	7	Intravitreal GCV 2 mg/0.1ml weekly	-	3	-	4/7 response, 4/4 recur
	17	Topical 0.15% GCV gel 4 times daily	-	3	-	11/17 response, 5/11 recur
De Schryver, 2006 ²⁵	5	Intravenous GCV or foscarnet at least 2 weeks	Oral valGCV 450 mg twice daily for 2 months	2.5	14.8±6.9	2 patients recurred after cessation of therapy
	1	Oral valGCV 450 mg twice daily for 2 months	-	2	24	Recurrence after cessation of therapy
Koizumi, 2017 ¹²	7	Topical 0.15% GCV gel 6 times daily	-	3	3	Inflammation controlled and no clinical recurrence at 12-week administration
Pavan-Langston, 2012 ¹⁴	1	Topical 0.15% GCV gel every 2 hours	Topical 0.15% GCV gel twice daily	4.5	≥24	Rapid resolution of uveitis but relapse after discontinuation
Fan, 2016 ²²	10	Topical 0.5% GCV every 2 hours	Topical 0.5% GCV four times daily	Throughout follow-up	48.1±25.1	All responsive with clear graft or cornea, 1 had recurrence once

Abbreviations: CMV, cytomegalovirus; GCV, ganciclovir; VCV, valcyclovir; valGCV, valganciclovir.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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