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Review Article

Cytomegalovirus Uveitis: Taiwan expert consensus

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Cytomegalovirus (CMV) uveitis, a type of herpetic uveitis, is a major cause of infectious uveitis. Anterior and posterior CMV uveitis have diverse clinical presentations and treatment modalities. Based on expert consensus in Taiwan, this article provides suggestions regarding clinical manifestations, diagnosis, and treatment strategies for CMV uveitis based on clinical practice experience in Taiwan. CMV uveitis may have a distinct clinical presentation. Polymerase chain reaction (PCR) is an essential diagnostic tool to confirm a diagnosis. Antiviral therapy is the

Abbreviations: CMV, Cytomegalovirus.

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Uveitis

mainstay of treatment. Different agents, routes, and other supplemental treatments have been summarized and discussed in this article. Early diagnosis and appropriate treatment of CMV uveitis are crucial to avoid irreversible complications and vision loss. This consensus provides practical guidelines for ophthalmologists in Taiwan.

Introduction

Uveitis is an ocular disease that accounts for 2.8%–10% of the visual impairment worldwide.[1] Differential diagnosis is often challenging and is usually based on clinical presentation, laboratory information, and treatment course. The increased availability of molecular techniques for polymerase chain reaction (PCR) has enhanced the diagnosis of infectious uveitis, particularly herpetic uveitis.

Herpetic uveitis is a type of infectious uveitis caused by the Herpesviridae, a large family of double-stranded DNA viruses. The Herpesviridae family comprises more than a hundred viruses and some of which are recognized as common pathogens. These include herpes simplex virus (HSV), varicella-zoster virus (VZV), and cytomegalovirus (CMV). CMV uveitis consists of anterior uveitis (AU) and posterior uveitis (PU).

CMV AU is the most common ocular manifestation of CMV infection in immunocompetent individuals.[2] Recurrence and chronic status are common and may lead to irreversible vision loss. In contrast, CMV PU usually occurs in immunocompromised patients. In addition, direct damages from retinitis or indirect complications may negative visual prognoses. Thus, early diagnosis and prompt treatment are important for CMV AU and PU. Patient immune status, clinical manifestations, and comprehensive initial ophthalmic examinations are essential for diagnosis and follow-up. Treatment is individually tailored based on the patient's physical status, types of uveitis, and severity.

Although numerous treatment protocols are available regarding CMV uveitis worldwide, treatment strategies vary greatly among physicians, and treatment strategies may change with new advances in antiviral medications, surgical techniques, and health policies. The epidemiology of uveitis varies in different areas, such as CMV AU, more frequently in Asia and Taiwan.[3,4] A high CMV seroprevalence up to 87.28% was reported in Taiwan pregnant women.[5] CMV infection or uveitis is potentially a larger burden in Asian countries, especially in Taiwan. The style of CMV retinitis is changing owing to improved acquired immunodeficiency syndrome (AIDS) care. Therefore, an updated consensus is required. In addition to the diagnosis and appropriate treatment, associated complications and possible dilemmas are summarized. The purpose of this article was to provide a consensus on CMV AU and PU based on clinical practice experience and health policy in Taiwan.

Consensus development

This consensus statement was based on a panel discussion. This panel was organized by the Taiwan Ocular Inflammation Society (TOIS) and consisted of ten Taiwanese ophthalmologists with expertise in the management of uveitis. Panelists were invited to develop consensus recommendations for CMV uveitis. In addition, the panel reviewed the current literature and provided personal clinical experience focusing on the diagnosis and treatment of CMV uveitis.

A panel meeting was held at Kaohsiung, on April 10, 2021. Before the meeting, Dr. Hsi-Kung Kuo, Wei-Yu Chiang, and Wan-Hua Cho from Kaohsiung Chang-Gung Memorial Hospital raised several key questions. These questions were discussed and voted upon during the meeting, and a consensus was reached. Altogether, eight key questions were discussed (Table 1). The consensus was reached when 3/4 panelists agreed, while others did not reach a consensus that required evaluation of voting results to present different opinions. The consensus was presented at the TOIS meeting and opened to all members for further discussion. Thus, the final version was completed. CMV uveitis was divided into AU and PU, and the results are described in terms of clinical features, diagnosis, and treatment.

Result and discussion

CMV anterior uveitis

Clinical features

Common clinical features of CMV AU include conjunctival congestion, corneal edema, keratic precipitates (KPs), mild anterior chamber inflammation, iris atrophy, distorted pupil, elevated intraocular pressure (IOP), laterality, and reactivation.[2,9–14] Elevated IOP and secondary glaucoma are major complications of CMV AU.[2,14] Active and acute CMV AU share similar clinical features with Posner-Schlossman syndrome.[2]

HSV/VZV AU may have a history of keratitis or herpes/varicella zoster infection, ocular hyperemia pain, blurring of vision, ciliary injection, a relatively acute disease course, medium-to-large mutton-fat KPs, prominent stromal edema with haze and DM folds, cells and flare in the anterior chamber, and posterior synechia.[15,16] Compared to the AU of HSV and VZV, CMV AU exhibits the highest IOP level, lowest corneal endothelial cell density, and the mildest anterior chamber cells and flares and may also exhibit ring-shaped, coin-shaped, linear small-to-fine KPs, endotheliitis, less corneal stromal edema, diffuse iris atrophy, and more frequent glaucoma surgery, but posterior synechiae and macular edema are rarely observed.[2,12,14–17] CMV AU is a common and important type of AU in Taiwan.[4]

Table 1 Eight key questions and consensus statements.

Number	Key question	Consensus statement
1	How should we diagnose patients presenting with the typical clinical features of CMV AU, but negative PCR results?	1. Clinical course and therapeutic response can support the diagnosis 2. For cases with high clinical suspicion, repeated PCR tests are recommended to confirm the diagnosis.
2	What is the preferred treatment strategy in terms of loading and maintenance doses for CMV AU?	To avoid CMV AU recurrence, antiviral agents are preferred over steroids. Topical ganciclovir (20 mg/cc) is the preferred medication in Taiwan owing to its efficacy, safety, and convenience. Anti-glaucoma agents are considered in cases of poorly controlled IOP and disc damage.
3	How long should the treatment for CMV AU be maintained?	Currently there is no randomized control trial available to provide better evidence for the optimal treatment duration of CMV AU. The panel recommends antiviral treatment for 6 months in cases with an initial attack and no vision-threatening complications. An extended treatment duration of 12 months or longer may be indicated in cases who have recurrent attacks or present with vision-threatening complications. For cases who need an extended antiviral treatment, cornea and glaucoma consultations are crucial for detection and monitoring of vision-threatening complications. Because any relapse of CMV AU could cause further damage the corneal endothelium and/or the optic nerve, leading to irreversible visual loss. Thus, the treatment duration, even lifelong maintenance, is tailored individually by patients' age, visual acuity, corneal endothelial density, disc nerve fiber thickness, visual field, the fellow eye status, recurrence/relapse interval, the side effects or toxicity of treatment, and patients' compliance.
4	What are the roles of topical and systemic steroids in CMV AU treatment?	Steroids may cause CMV AU to become latent or refractory to treatment. However, the use of steroids in the acute stage of CMV AU remains debatable. Clinically, most patients received steroid treatment when referred to medical centers. Five out of ten panelists advocated the combined use of steroids, while five panelists opposed the use of steroids.
5	How should we manage ocular hypertension induced by CMV AU?	Aggressive control with topical and systemic IOP-lowering agents is initially used in ocular hypertension. Prostaglandin analogs is acceptable for CMV AU owing to its low inflammatory status. CMV AU commonly results in decreased corneal endothelial cell density; therefore, topical carbonic anhydrase inhibitors (CAI) are traditionally not recommended for use in patients with poor or even decompensated corneal conditions. However, based on several studies, the use of topical CAI had no influence on clinically meaningful changes of the cornea, including endothelial cells.[6–8] Topical CAI is still indicated in cases with refractory ocular hypertension. In addition to medication, the use of surgical intervention depends on IOP level, disc status, and visual field evaluation.
6	What are the preferred antiviral agents for CMV retinitis in clinical practice?	Systemic ganciclovir or valganciclovir has been suggested for vision-threatening cases. However, myelosuppression is also a common concern. IVI with ganciclovir constitutes a supplemental treatment in cases with the severe presentation, AIDS, and bone marrow transplantation. However, it is not recommended for mild cases because of the possibility of ganciclovir-induced maculopathy. Foscarnet (systemic or local use) is an alternative when ganciclovir/valganciclovir treatment fails, especially because of drug resistance (although generally rare, $<5\%$). Although Foscarnet is not available in regular practice in Taiwan, it is still accessible with applications and special permission.
7	How should efficacy be evaluated during the treatment course of CMV retinitis and when to quit treatment?	The intraocular and systemic conditions should be monitored to evaluate their efficacy. Inactive uveitis and regressed retinitis can be regarded as successful intraocular signs. Improved systemic immune status, such as a CD4+ count rising in HIV or cessation of immunosuppression therapy, is the key indicator for cessation of treatment. In general, CMV treatment is maintained for at least 3–6 months with inactive lesions and CD4+ count >100 cells/mm3 for 3–6 months in response to ART in HIV patients. Serum CMV DNA viral load can also be a supplementary indicator of treatment efficacy.
8	What is the strategy for prophylaxis of RD associated with CMV retinitis?	All panelists agreed that there is currently no suggested prophylaxis for RD associated with CMV retinitis.

Diagnosis

The panel agreed that no single clinical manifestation could be reliably used for the diagnosis. Therefore, objective laboratory assistance is essential to confirm the specific etiology, disease severity, and choice of treatment.

PCR or Goldmann-Witmer coefficient (GWC) assays using aqueous humor samples are preferred.[18–20] PCR on aqueous humor samples performed to detect infectious etiology, such as viral and Toxoplasma gondii-associated uveitis, demonstrated a sensitivity of 0.431, specificity of 0.985, and negative and positive predictive values of 0.506 and 0.980, respectively.[21] Sensitivity and specificity of real-time PCR for CMV uveitis were 84.2% and 95.5%, respectively; CMV retinitis showed significantly higher CMV DNA than other types of CMV infections.[22] GWC, calculated as (specific IgG in aqueous humor/total IgG in aqueous humor)/(specific IgG in serum/total IgG in serum), is also helpful for clinical diagnosis. PCR is appropriate to detect viral DNA within the first week of the disease. Antibodies detected using GWC may be maintained throughout the clinical course, but are more frequently detected later in the course of the disease; however, GWC is currently not available in Taiwan.[23]

The Standardization of Uveitis Nomenclature (SUN) Working Group developed the key criteria for CMV AU. The key criteria for CMV AU diagnosis[24] included unilateral AU with a positive aqueous humor PCR result for CMV; however, no clinical features can reliably diagnose CMV AU.

Key question 1

How should we diagnose patients presenting with the typical clinical features of CMV AU, but negative PCR results?

Consensus statement

1. Clinical course and therapeutic response can support the diagnosis
2. For cases with high clinical suspicion, repeated PCR tests are recommended to confirm the diagnosis.

Treatment of CMV AU

Treatment options for CMV AU include topical ganciclovir, oral valganciclovir, and intravitreal ganciclovir injection (IVI). The topical application of 2% ganciclovir solution is effective and safe.[25,26] A 0.15% topical ganciclovir gel decreases the frequency of CMV AU recurrences.[27] Oral valganciclovir is administered at a dose of 900 mg twice daily for 14 days as the loading dose, followed by 450 mg twice daily for maintenance.[28,29] IVI of ganciclovir (2 mg/0.05 ml) as a loading dose with or without subsequent administration of oral valganciclovir can effectively control inflammation, IOP and prevent a recurrence.[30,31] These three routes (topical, oral, and IVI) have been proven effective in treating CMV AU.[26,29,31] However, recurrence of CMV AU is common after cessation of maintenance therapy; thus, adequate induction and maintenance with escalated concentration and frequency are crucial to prevent recurrences.[25] The use of steroids is a controversial issue. Recently, two studies reported that combination of topical ganciclovir and corticosteroids as maintenance regimens could effectively preserve corneal endothelial function.[31,32]

The panel recommends that topical application of 2% ganciclovir solution should be preferred in Taiwan owing to its effects, safety, and convenience.[33] However, there are no commercialized eye drops available; thus, manufacturing and preservation are valid concerns. As commercial 0.15% gel is not available in Taiwan, our treatment experience is limited. Oral valganciclovir and IVI of ganciclovir are considered second or supplemental choices since oral valganciclovir commonly leads to systemic toxicities such as myelosuppression and IVI is an invasive intervention. An ongoing trial, The Systemic and Topical Control of Cytomegalovirus Anterior uveitis: Treatment Outcomes (STACCATO) trial, was designed as a multicenter, randomized, double-masked, placebo-controlled trial to compare the efficacy of oral valganciclovir, 2% topical ganciclovir, and placebo in treating PCR-confirming CMV AU.[34]

IOP control is crucial for CMV AU. Moreover, CMV AU exhibited the highest IOP and lowest corneal endothelial cell density compared with other herpetic uveitis cases. Thus, an ocular examination should focus on IOP and corneal and optic disc conditions.

The panel recommended a tailored therapeutic strategy in terms of medication, routes, and maintenance duration for the treatment of CMV AU. In addition, ophthalmologists should consider the side effects of drugs, their inflammatory status, and IOP. After the loading dose, the maintenance duration was determined based on the patient's ocular condition, compliance, and previous treatment experience. Recurrence is not uncommon after the treatment course since the pathogens are latent and not completely eradicated. Therefore, it is crucial to educate patients about being alert to the possibility of recurrence. Regular follow-up is recommended to detect of recurrence and evaluate the corneal endothelium, optic disc status, and visual field.

Key question 2

What is the preferred treatment strategy in terms of loading and maintenance doses for CMV AU?

Consensus statement

To avoid CMV AU recurrence, antiviral agents are preferred over steroids. Topical ganciclovir (20 mg/cc) is the preferred medication in Taiwan owing to its efficacy, safety, and convenience. Anti-glaucoma agents are considered in cases of poorly controlled IOP and disc damage.

Key question 3

How long should the treatment for CMV AU be maintained?

Consensus statement

Currently there is no randomized control trial available to provide better evidence for the optimal treatment duration of CMV AU. The panel recommends antiviral treatment for 6 months in cases with an initial attack and no vision-threatening complications. An extended treatment duration of 12 months or longer may be indicated in cases who have recurrent attacks or present with vision-threatening complications. For cases who need an extended antiviral treatment, cornea and glaucoma consultations are crucial for detection and monitoring of vision-threatening complications.

Because any relapse of CMV AU could cause further damage the corneal endothelium and/or the optic nerve, leading to irreversible visual loss. Thus, the treatment duration, even lifelong maintenance, is tailored

individually by patients' age, visual acuity, corneal endothelial density, disc nerve fiber thickness, visual field, the fellow eye status, recurrence/relapse interval, the side effects or toxicity of treatment, and patients' compliance.

Key question 4

What are the roles of topical and systemic steroids in CMV AU treatment?

Consensus statement

Steroids may cause CMV AU to become latent or refractory to treatment. However, the use of steroids in the acute stage of CMV AU remains debatable. Clinically, most patients received steroid treatment when referred to medical centers. Five out of ten panelists advocated the combined use of steroids, while five panelists opposed the use of steroids.

Key question 5

How should we manage ocular hypertension induced by CMV AU?

Consensus statement

Aggressive control with topical and systemic IOP-lowering agents is initially used in ocular hypertension. Prostaglandin analogs is acceptable for CMV AU owing to its low inflammatory status. CMV AU commonly results in decreased corneal endothelial cell density; therefore, topical carbonic anhydrase inhibitors (CAI) are traditionally are not recommended for use in patients with poor or even decompensated corneal conditions. However, based on several studies, the use of topical CAI had no influence on clinically meaningful changes of the cornea, including endothelial cells.[6–8] Topical CAI is still indicated in cases with refractory ocular hypertension. In addition to medication, the use of surgical intervention depends on IOP level, disc status, and visual field evaluation.

CMV posterior uveitis

Clinical features

CMV PU, especially retinitis, usually occurs in immunocompromised patients, including those with AIDS, organ transplantation, hematologic malignancies, and iatrogenic systemic or local immunosuppression.[35] The characteristic appearance includes retinitis progression along the vessels, hemorrhage with a circular appearance, and typically an absence of vitritis. There are two morphological variants of CMV retinitis: the fulminant or hemorrhagic form and the granular form.[36]

The incidence of CMV retinitis in HIV (human immunodeficiency virus) patients has dramatically decreased with antiretroviral therapy (ART).[35] CMV retinitis may also occur in immunocompetent hosts, and the increasing incidence of CMV retinitis in non-HIV patients was observed.[37] One report indicated that the overall visual prognosis and the clinical features of CMV retinitis do not differ between HIV and non-HIV patients.[38] Another report showed worse presenting vision in patients without HIV infection, most likely because of underlying hematologic malignancies and receiving intensive chemotherapy.[35] CMV retinitis in immunocompetent hosts resembles the aforementioned type in terms of clinical appearance, but possibly shows significant intraocular inflammation with vitritis, anterior chamber reaction, and predominantly arterial retinal vasculitis with nonperfusion.[35,39–41] Perivasculitis involving veins more often than arteries was described in AIDS associated CMV retinitis.[42]

Diagnosis

The diagnosis of CMV retinitis is primarily clinical and based on the characteristics of retinitis. PCR of the aqueous or vitreous humor can confirm the diagnosis, which is especially helpful in cases with atypical clinical presentations and in determining treatment strategies. However, treatment should not be delayed while awaiting PCR results.[43] Aqueous and vitreous humor PCR is sensitive and specific.[43]

The SUN Working Group developed key criteria for the diagnosis of CMV retinitis.[36] These included (1) necrotizing retinitis with indistinct borders due to numerous small satellites; (2) evidence of compromised immune status; and either (3) a characteristic clinical appearance, or (4) intraocular fluid PCR positive for CMV.

Treatment of CMV retinitis

Treatment of CMV retinitis consists of 5 mg/kg intravenous ganciclovir twice daily for 14 days for induction, followed by 5 mg/kg once daily for maintenance or 900 mg oral valganciclovir twice daily for 21 days for induction, followed by 900 mg once daily for maintenance.[39]

Bone marrow suppression is an important side effect of both ganciclovir and valganciclovir. Thus, IVI of ganciclovir (2 mg, one-four times per week as needed, followed by weekly administration) is an alternative for patients who cannot tolerate myelotoxicity associated with systemic therapy.

Key question 6

What are the preferred antiviral agents for CMV retinitis in clinical practice?

Consensus statement

Systemic ganciclovir or valganciclovir has been suggested for vision-threatening cases. However, myelosuppression is also a common concern. IVI with ganciclovir constitutes a supplemental treatment in cases with the severe presentation, AIDS, and bone marrow transplantation. However, it is not recommended for mild cases because of the possibility of ganciclovir-induced maculopathy. Foscarnet (systemic or local use) is an alternative when ganciclovir/valganciclovir treatment fails, especially because of drug resistance (although generally rare, $<5\%$). Although Foscarnet is not available in regular practice in Taiwan, it is still accessible with applications and special permission.

Key question 7

How should efficacy be evaluated during the treatment course of CMV retinitis and when to quit treatment?

Consensus statement

The intraocular and systemic conditions should be monitored to evaluate their efficacy. Inactive uveitis and regressed retinitis can be regarded as successful intraocular signs. Improved systemic immune status, such as a CD4+ count rising in HIV or cessation of immunosuppression therapy, is the key indicator for cessation of treatment. In general, CMV treatment is maintained for at least 3–6 months with inactive lesions and CD4+ count >100 cells/mm3 for 3–6 months in response to ART in HIV patients. Serum CMV DNA viral load can also be a supplementary indicator of treatment efficacy.

Key question 8

What is the strategy for prophylaxis of RD associated with CMV retinitis?

Consensus statement

All panelists agreed that there is currently no suggested prophylaxis for RD associated with CMV retinitis.

Closing comments

- CMV uveitis is a common and important differential diagnosis of infectious uveitis.
- Ocular hypertension is an important indicator of CMV AU. Laboratory PCR is an essential tool to confirm the diagnosis. It is also helpful in determining the treatment dosage and duration.
- Treatment should be individualized according to the clinical situation and systemic condition of the host.
- The evidence-based consensus developed by the experts is expected to provide the practical guidance for CMV uveitis in Taiwan.

Panel members

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Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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