PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	A double masked randomised 4-week, placebo-controlled study in the US, Thailand and Taiwan to compare the efficacy of oral valganciclovir and topical 2% ganciclovir in the treatment of cytomegalovirus anterior uveitis: study protocol
AUTHORS	Takhar, Jaskirat; Joye, Ashlin; Somkijrungroj, Thanapong; Laovirojjanakul, Wipada; Lin, Chang-Ping; Lietman, Thomas; Porco, Travis; Keenan, Jeremy; Gebreegziabher, Elisabeth; Seitzman, Gerami; Rose-Nussbaumer, Jennifer; Doan, Thuy; Acharya, Nisha; Gonzales, John

VERSION 1 – REVIEW

REVIEWER	Antoine Rousseau APHP, Université Paris-Sud
REVIEW RETURNED	04-Sep-2019

GENERAL COMMENTS	Takhar et al. here describe a study protocol to compare oral VGCV versus topical GCV in the management of CMV anterior uveitis in immunocompetent patients. The primary criterion is the decrease in the AC viral load at D7. Secondary criterion is the clinical response to treatment. First, this study aims at answering an important question, as long as no consensus exist on the treatment of CMV anterior uveitis. The protocol is clear and well written. The dosing of drugs and judgement criteria have been chosen according to previously published data, and are clearly stated, so is the statistical methodology. Informed consent document and MOP are complete. Overall, it is a well-designed study. However, I have a few questions / comments / concerns: 1) regarding the participants: can they have a history of previously diagnosed CMV anterior uveitis ? 2) There may be an issue with the delay between Exam #0 and 1 : 7 days without treatment seem unacceptably long for some patients. Especially, in case of severe inflammation or ocular hypertension, or even more in patients with past history of proven CMV anterior uveitis. This delay should be reduced as much as possible. Why not start empiric treatment at exam #0 and then exclude patients with negative PCR ? 3) Exclusion criteria: Apparently, the author did not plan to exclude patients with severe glaucoma (consequence of previous bouts of CMV uveitis or POAG) and/or very severe inflammation. It seems quiet risky to include these patients in the study, as long as they could be randomized in

	the “no treatment” group. 4) Page 10, line 36: In the clinical response to therapy, the authors state that “IOP must be controlled without the addition of new IOP medication”. This criterion should be amended, as long as despite good clinical response, new IOP medications could be necessary in case of steroid induced hypertony. 5) regarding the masking: the authors did their best to mask the treatment to the patients. However, I may have some concern about a very different local tolerance between BSS and 2% GCV eyedrops… If patients of the protocol get in contact, they may unmask the treatment based on the local side effects… In order to limit this risk, the authors may try to avoid as much a possible contact between enrolled patients in a given center. 6) Table 3: timeline Delay between Exam #0 and 1 should be written in the table 3 (according to point 2)

REVIEWER	Manabu Mochizuki Miyata Eye Hospital Japan
REVIEW RETURNED	04-Oct-2019

GENERAL COMMENTS	This international, multicentred, double masked randomised 4-week, placebo-control study to compare the efficacy of oral valganciclovir and topical 2% ganciclovir in the treatment of cytomegalovirus anterior uveitis is a challenging and important study and the proposed study protocol is well planned and described. The study will provide useful information for the management of CMV anterior uveitis. However, there are a few issues unclear and recommended to be clarified as follows. Most of them are some discrepancy between text of study protocol and manual of operations & procedures (MOP) or informed consent documents (ICD). Major (1) According to the title of the study and the statement at page 25 of appendix 1 (ICD) as well as the Table 4 in page 17 of MOP, the treatment is 4-week(or 28 days), but this is not clearly written in the text of study protocol. It is recommend to clarify these issues in the text of protocol. (2) Similarly it would be nice to document the management after the 4-weeks study treatment in the study protocol like the statement at page 25 of appendix 1. (3) Although "Protocol Deviation" is written in the MOP (page 16), such statements are not written in the text of the study protocol. It is recommended to add such statements in the study protocol. (4) CMV is known to cause corneal endothelial cell damages in the long clinical course of CMV anterior uveitis and CMV endotheliitis. This study includes a group treated with inactive anti-viral drug (placebo, group 3), and no one knows what will happen in the corneal endothelial cells of those patients in the future. Although this may not be relevant to the subjects of the current study of the therapy of CMV anterior uveitis in its acute stage for relatively short period, is it possible to measure the corneal endothelial density as the base line for the future? Minor (1) As for dosing of 2% topical ganciclovir (or placebo drops), it is

	recommended to use either "6 drops daily" or "every 2 waking hours", but not both. Every 2 waking hours depends on patients' life style and may cause some confusion; it may be 6 times in some patients, but also 8 time in other patients. It is recommended to give clear and definite instruction.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Comment 1) regarding the participants: can they have a history of previously diagnosed CMV anterior uveitis?

Response: Participants may have a previously diagnosed CMV anterior uveitis. However, to qualify for enrollment, a participant must have active inflammation. Moreover, a potential participant would need to agree to have an anterior chamber (AC) paracentesis prior to being considered for enrollment to confirm that there is demonstrable virus associated with the currently active inflammation and to quantify the viral load as the viral load prior to treatment randomization will be compared to viral load after 7 days of treatment randomization (obtained from another anterior chamber paracentesis). We have added the following statement under the Recruitment section on page 6 to clarify this issue: “Participants who have a history of previously diagnosed CMV anterior uveitis are also eligible to participate in the study. However, like other participants, their participation in the trial would require that they agree to an AC paracentesis to confirm that their current flare has demonstrable CMV

present and to quantify the current flare’s viral load to which it would be compared at 7 days post-randomization.”

Comment 2) There may be an issue with the delay between Exam #0 and 1:

7 days without treatment seem unacceptably long for some patients. Especially, in case of severe inflammation or ocular hypertension, or even more in patients with past history of proven CMV anterior uveitis. This delay should be reduced as much as possible. Why not start empiric treatment at exam #0 and then exclude patients with negative PCR ?

Response: On Exam 0, participants have an unknown etiology for their inflammation. Additionally, it is possible that the results of the anterior chamber paracentesis reveal no viral pathogens on polymerase chain reaction. Thus, empiric therapy without knowledge or confirmation of infectious or non-infectious etiology is not routinely performed. Additionally, it is standard of care to prescribe topical corticosteroids to reduce the severity of intraocular inflammation in patients with anterior uveitis as well as manage elevated intraocular pressure with pressure-lowering eyedrops. Indeed, all patients seen prior to enrollment will have their intraocular inflammation and pressure managed with topical corticosteroids (prednisolone acetate 1% 4 times daily) and topical pressure-lowering drops (treating ophthalmologist may use best medical judgement to use any eye drop and frequency deemed necessary) at exam #0. To clarify this, we have added the following statement in the manuscript on page 8 under Intervention, paragraph 5. “Patients requiring management of elevated intraocular pressure (IOP) will be prescribed IOP-lowering medication according to treating ophthalmologist’s discretion and best medical judgment.” Additionally, we have clarified this point in Table 3 such that the pre-study visit (Exam #0) now outlines that potential participants suspected of having a viral aetiology for their uveitis be prescribed topical corticosteroid and intraocular pressure-lowering drops:

> “Patients will be prescribed topical corticosteroid (prednisolone acetate 1%) to be used 1 drop in affected eye 4 times daily (this is typical standard of care)

- Patients requiring management of elevated intraocular pressure (IOP) will be prescribed IOP-lowering medication according to treating ophthalmologist's discretion and best medical judgment"

Comment 3) Exclusion criteria:

Apparently, the author did not plan to exclude patients with severe glaucoma (consequence of previous bouts of CMV uveitis or POAG) and/or very severe inflammation. It seems quiet risky to include these patients in the study, as long as they could be randomized in the "no treatment" group.

Response: We thank the reviewer for requesting clarification regarding the management of glaucoma. In fact, participants will be allowed to have their glaucoma managed according to standard of care (using any intraocular pressure-lowering medication). We have revised the text in the manuscript and table 3 to indicate that any intraocular pressure-lowering medication may be used.

Comment 4) Page 10, line 36:

In the clinical response to therapy, the authors state that "IOP must be controlled without the addition of new IOP medication". This criterion should be amended, as long as despite good clinical response, new IOP medications could be necessary in case of steroid induced hypertony.

Response: We thank the reviewer for requesting clarification regarding the management of intraocular pressure. The study does not disallow the use of IOP medications if necessary. The treating ophthalmologist may use any glaucoma medication to manage IOP according to standard of care and according to his or her best medical judgment and discretion. Rather, the definition of "controlled inflammation", which is a clinical outcome measure, requires that anterior chamber inflammation be graded at 0.5+ cell or less and that intraocular pressure is controlled (as elevated intraocular pressure may be a feature of active CMV anterior uveitis). Thus, if a participant is exhibiting elevated IOP and must have additional IOP lowering medications added to their regimen, the participant will be classified as "uncontrolled inflammation". However, this classification will not preclude the participant from receiving treatment of their IOP (having additional IOP-lowering medications added to their regimen). To this end, we have clarified the Outcome Assessments Section (Clinical Response to Therapy sub-section on page 11) to read, "Since active inflammation can feature elevated IOP, if IOP is not controlled at a study visit, the participant will be considered as "not quiescent". This designation, however, does not preclude the participant from receiving additional IOP-lowering medication and the treating ophthalmologist may institute additional IOP-lowering medications as deemed necessary." We have further clarified the terms "quiescent" and "not quiescent" as clinical outcome measures by including quotations around these terms.

Comment 5) regarding the masking: the authors did their best to mask the treatment to the patients. However, I may have some concern about a very different local tolerance between BSS and 2% GCV eyedrops… If patients of the protocol get in contact, they may unmask the treatment based on the local side effects… In order to limit this risk, the authors may try to avoid as much a possible contact between enrolled patients in a given center.

Response: We will make every effort to limit contact between enrolled participants and disclosure of their study treatment. We have modified the statement in the manuscript on page 7 in METHODS AND ANALYSIS under “Masking” to the following statement to further address this concern. “Before bringing participants to the study doctor, the study coordinator will remind participants not to disclose any information concerning their treatment to their study ophthalmologist or any other participants they may come across.” In the event that unmasking occurs, a protocol deviation form will be completed.

Comment 6) Table 3: timeline

Delay between Exam #0 and 1 should be written in the table 3 (according to point 2)

Response: We have included the number of days between exam 0 and exam 1 in Table 3. We have added “Exam #1 (Day 1 of study (7 days after Exam #0))” under exam visit in Table 3.

Reviewer: 2

Major

Comment 1) According to the title of the study and the statement at page 25 of appendix 1 (ICD) as well as the Table 4 in page 17 of MOP, the treatment is 4-week (or 28 days), but this is not clearly written in the text of study protocol. It is recommend to clarify these issues in the text of protocol.

Response: We have added the statement “All groups will receive their assigned treatment for 28 days” on page 7 under “Study overview” within the “METHODS AND ANALYSIS” section.

Comment 2) Similarly it would be nice to document the management after the 4-weeks study treatment in the study protocol like the statement at page 25 of appendix 1.

Response: We have added the following statement on page 8 within the “Intervention” section, paragraph 6. “Once participants have finished 28 days of treatment, including the final clinic visit and evaluation, they will have completed the study. The treating ophthalmologist will determine whether any continued treatment is necessary.”

Comment 3) Although "Protocol Deviation" is written in the MOP (page 16), such statements are not written in the text of the study protocol. It is recommended to add such statements in the study protocol.

Response: We thank the reviewer for making this recommendation. We have now added the following section on page 10 in the “METHODS AND ANALYSIS” section:

> “**Protocol Deviation**
>
> In rare cases, study ophthalmologists may determine that a deviation from protocol is necessary. This is at the discretion of the treating ophthalmologist and could be undertaken for a variety of reasons including rescue treatment and treatment discontinuation due to intolerability or safety. Subjects that experience deviations in treatment protocol will continue in their initially assigned treatment group and their data will be analyzed accordingly.”

Comment 4) CMV is known to cause corneal endothelial cell damages in the long clinical course of CMV anterior uveitis and CMV endotheliitis. This study includes a group treated with inactive anti-viral drug (placebo, group 3), and no one knows what will happen in the corneal endothelial cells of those patients in the future. Although this may not be relevant to the subjects of the current study of the therapy of CMV anterior uveitis in its acute stage for relatively short period, is it possible to measure the corneal endothelial density as the base line for the future?

Response: We agree with the reviewer that assessing the corneal endothelium is an important measure. Indeed, this trial will be assessing the corneal endothelium using confocal

or specular microscopy (depending on availability of the particular imaging modality at each centre). We have added the following statement on page 8 within the “Intervention” section, paragraph 4. “In addition, corneal endothelium will be assessed using confocal or specular microscopy (depending on availability of the particular imaging modality at each centre) and will be used to measure endothelial cell morphology and density on Day 1 and 28.”

Minor

Comment 5) As for dosing of 2% topical ganciclovir (or placebo drops), it is recommended to use either "6 drops daily" or "every 2 waking hours", but not both. Every 2 waking hours depends on patients' life style and may cause some confusion; it may be 6 times in some patients, but also 8 time in other patients. It is recommended to give clear and definite instruction.

Response: We thank the reviewer for this clarification suggestion. As suggested, we have removed “every 2 waking hours” and revised the statement on page 8 under intervention (paragraph 3) as “Dosing will be 4 tablets daily (900mg PO BID) for oral medication and 6 drops per day for topical.”

VERSION 2 – REVIEW

REVIEWER	Antoine Rousseau Department of Ophthalmology Hopital Bicetre Paris-Saclay University France
REVIEW RETURNED	22-Nov-2019

GENERAL COMMENTS	I thank the authors for their answers and clarification. I wish them all the best for this important study.

REVIEWER	Manabu Mochizuki Miyata Eye Hospital, Tokyo Medical and Dental University Japan
REVIEW RETURNED	14-Nov-2019

GENERAL COMMENTS	The authors revised to research protocol as this review suggested. The revised research protocol becomes now very clear and one can expect suitable results.