The Infectious Uveitis Treatment Algorithm Network (TITAN) Report 1 – Global Current Practice Patterns for the Management of Herpes Simplex Virus and Varicella Zoster Virus Anterior Uveitis

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Running title: Global practice pattern of HSV and VZV AU – TITAN report 1

ABSTRACT

Aims: To present current expert practice patterns and to formulate a consensus for the management of HSV and VZV AU by uveitis specialists worldwide.

Methods: A two-round online modified Delphi survey with masking of the study team was conducted. Responses were collected from seventy-six international uveitis experts from 21 countries. Current practices in the diagnosis and treatment of HSV and VZV AU were identified. A working group (The Infectious Uveitis Treatment Algorithm Network [TITAN]) developed data into consensus guidelines. Consensus is defined as a particular response toward a specific question meeting ≥ 75% of agreement or IQR ≤1 when a Likert scale is used.

Results: Unilaterality, increased intraocular pressure (IOP), decreased corneal sensation and diffuse or sectoral iris atrophy are quite specific for HSV or VZV AU from consensus opinion. Sectoral iris atrophy is characteristic of HSV AU. Treatment initiation is highly variable, but most experts preferred valacyclovir owing to simpler dosing. Topical corticosteroids and beta-blockers should be used if necessary. Resolution of inflammation and normalisation of IOP are clinical endpoints.

Conclusions:

Consensus was reached on several aspects of diagnosis, choice of initial treatment, and treatment endpoints for HSV and VZV AU. Treatment duration and management of recurrences varied between experts.

Keywords: Anterior uveitis; diagnosis; Herpes Simplex Virus; TITAN (The infectious Uveitis Treatment Algorithm Network); treatment; Varicella-Zoster Virus

INTRODUCTION

Anterior uveitis (AU) is the most common inflammation in uveitis, accounting for more than half of uveitis.[1] Though most AU cases are idiopathic or associated with HLA-B27, herpetic AU contributes a significant proportion, making up 5-10% of the total number of cases[2,3] and a larger proportion in those above 60 years old.[1] These figures are supported by molecular identification from aqueous samples.[2] From an epidemiological perspective, both *Herpes simplex virus* (HSV) and *Varicella-Zoster Virus* (VZV) AU are currently regarded as important causes of infectious uveitis in both developed and developing countries.[4]

The clinical features of HSV and VZV AU are similar and can include diffuse fine, stellate, dendritiform, or granulomatous keratic precipitates (KPs). Increased intraocular pressure and iris atrophy are seen in more than half of herpetic AU cases.[5–7] While Cytomegalovirus AU (CMV AU) often presents differently (older patients, more diffuse KPs, higher IOP, and coexistence of corneal lesions), differentiating HSV and VZV AU based solely on clinical manifestation may be difficult as previous studies found no significant difference in herpetic AU types.[7,8] Obtaining aqueous samples for polymerase chain reaction (PCR) testing, although demonstrably important[9–12], may not be feasible in all settings.[9–12] Diagnostic and treatment strategies may therefore vary amongst experts in different centres.

Aside from varying diagnostic techniques amongst uveitis experts in different settings, there are also differing opinions on optimum treatment. From a published systematic review,[13] there is neither firm evidence nor clear guidelines for the management of HSV and VZV AU as the evidence base is limited. Of note, Herpetic Eye Disease Study (HEDS) results have provided us with a standard of care for managing herpetic eye disease, but with more significant attention to keratitis.[14] In

addition, their controlled trial study only included 50 iridocyclitis cases.[14,15] Apart from improving on the limited number of subjects from HEDS, our study elaborates on a variety of aspects that had not been covered.[14,15] The Infectious Uveitis Treatment Algorithm Network (TITAN) group was established to address these issues and develop comprehensive and practical information for ophthalmologists managing patients with infectious uveitis, including HSV and VZV AU. This study presents an expert global consensus for the diagnosis and management of HSV and VZV AU based on a two-round modified Delphi survey of a panel of uveitis experts worldwide.

METHODS

Study design and participants

We performed a two-round online modified Delphi survey regarding the diagnosis, treatment, follow-up, and complications of HSV and VZV AU. The Infectious Uveitis Treatment Algorithm Network (TITAN) working group consists of a core of 24 uveitis specialists based worldwide and three fellowship-trained uveitis specialists. One hundred uveitis experts (including the core committee) were co-opted by the TITAN steering committee based on their experience as uveitis specialists, acknowledged by membership in the International Uveitis Study Group or relevant published works on uveitis topic. Currently available evidence (Supplementary file 1) was provided, the level of evidence being graded using the Oxford Centre for Evidence-Based Medicine Levels of Evidence criteria.[16] The TITAN group was masked to participant identities. Ethics approval was obtained from the Postgraduate Institute of Medical Education and Research in North India (No: INT/IEC/2020/SPL-405), and the study was conducted according to the tenets of the declaration of Helsinki.

Survey questions

This study implemented a modified Delphi technique to capture the current practice of experts worldwide and to formulate consensus.[17,18] The first round consisted of 21 questions, comprising eight, nine, and four domains of diagnosis, treatment, and follow-up, respectively (Supplementary file 2). Open-ended spaces were also provided to accommodate the experts' thoughts on each question. Responses were captured using multiple-choice answers and the Likert scale, depending on the scenario presented. Responses collected from the first-round survey were analysed and discussed by the core team to construct questions for the second round. Items with less than 65% agreement and IQR >1 (for Likert-scale responses) were discarded. Twelve questions were then distilled for the second round of the modified Delphi survey (Supplementary file 3) using questions clarified by statistical feedback on the first-round results.

Data analysis

The most frequent responses to a particular question/statement were identified. Median scores for items with Likert scales and interquartile range (IQR) were used on some occasions to quantify agreement. We also performed thematic analysis for open-ended questions to identify participants' preferred practices. The median score and interquartile range (IQR ranging from 0-3) were presented for questions answered on a Likert scale. Consensus was achieved when a particular response reached ≥ 75% of agreement or IQR ≤1.[17] Statistical analysis was performed using IBM® SPSS® Statistics version 27.

RESULTS

Response rate

The response rate for the first round was 76% (76 out of 100 invited uveitis experts) and 68% (Supplementary file 4) in the second round. Participants had 21.7 ± 8.3 years of clinical experience as uveitis experts. The distribution of uveitis experts who participated in the first and second rounds (N=68) of the survey based on regions is shown in Table 1.

Diagnosis and initial investigations

Based on the provided list of common signs at presentation, several were considered quite specific, i.e, unilaterality, increased Intraocular pressure (IOP), decreased corneal sensation, and diffuse or sectoral iris atrophy. If several of these signs were present at presentation, sectoral iris atrophy was considered the most helpful for diagnosing HSV AU (76% agreement). When viral AU is suspected, approximately one-third of uveitis experts (36.4%) stated that they would sometimes perform aqueous tap (other choices with lower response percentages include: not available in my centre [2, 2.6%], never [0,0%], rarely [11, 14.3%], often [20,26.0%], and all the time [16, 20.8%]). However, if the classical skin lesion is present, most experts would not perform aqueous tap (64% for presumed HSV AU and 74% for VZV AU). If aqueous tap is requested, multiplex qualitative PCR was selected by 73%. Further exploration of the importance of quantitative PCR for suspected HSV or VZV AU in the second round of the survey found that quantitative PCR was unavailable for 37% of the experts even though they stated quantitative PCR is relevant to herpetic AU management. Meanwhile, 35% of experts will not perform quantitative PCR because it is useless. Performing Goldman-Witmer Coefficient

(GWC) testing was not considered as this was used by fewer than a quarter of participants, typically because of the lack of availability of the test. For the serological test, the commonest response was experts would rarely perform the serological test for suspected HSV or VZV AU (never: 23, 29.9%; rarely: 31, 40.3%; sometimes: 11, 14.3%; often: 5, 6.5%; all the time: 7; 9.1%).

Treatment

Consensus was achieved (66/76 experts, 87% agreement) to start both antiviral and anti-inflammatory treatments for both HSV and VZV AU in the absence of confirmatory testing. There was also consensus (HSV 62/76, 82%; VZV 61/76, 79%) that clinical follow-up without repeat PCR was sufficient, and treatment decisions were based on clinical appearance (Table 2).

First episode; initial treatment: Systemic antiviral therapy without topical antiviral was the choice of 44 experts (58%) for HSV AU and 46 experts (60%) for VZV AU. There was consensus that topical corticosteroids should not be administered without systemic or topical antiviral cover (79% for HSV and 75% for VZV). There was consensus that the duration of treatment should depend on the treatment endpoint as defined by resolution of clinical signs of inflammation (KPs, cells, flare) and IOP normalisation (75/76, 99% for both HSV and VZV AU). However, the use of resolution of corneal oedema as a treatment endpoint was considered appropriate by fewer experts (HSV AU 52/76, 68%; VZV AU 53/76, 70%). Refinement in the second round of the modified Delphi survey revealed that 56% would continue treatment if significant corneal oedema persisted, even if intraocular inflammation was no longer present. Prednisolone acetate 1% was the primary choice of 69%; dosage and

duration varied from 2-3 hourly to 4 times a day for 1-2 weeks for both HSV and VZV AU. There was consensus that maintenance topical corticosteroids should be slowly tapered until there has been no inflammatory activity for up to 12 months (3-12 months). The vast majority of experts (79%) will use topical beta-blocker as the selected IOP lowering agent.

Oral valacyclovir was chosen as the first-line systemic antiviral treatment by 67% for HSV AU and 73% for VZV AU based on our pool of respondents. However, this did not reach the threshold for consensus. Further exploration revealed the main reason for drug choice was mainly due to the simpler dosing regimen of valacyclovir (76%). More than half (59%) also stated that they believed it was more effective. Either valacyclovir 1 g twice or three times daily for 10-14 days or acyclovir 400-800 mg five times per day for 10-14 days were used for HSV AU (67%) and valacyclovir 1g three times daily for 10-14 days or acyclovir 800 mg five times per day for 10-14 days for VZV AU (70%). Geographical variation among experts on this topic, along with cycloplegic use, is summarised in Supplementary file 5**.**

Maintenance treatment: Once the initial endpoint had been achieved, maintenance systemic antiviral therapy varied in dose and duration between different practices. . 50% opted for Valacyclovir 500mg two to three times per day for 3-12 months, for both HSV and VZV AU. Other choices, including regional differences, are listed in Supplementary file 5.

Chronic or recurrent AU: Treatment plans varied for both chronic and recurrent hypertensive AU secondary to HSV or VZV. For chronic HSV AU and chronic VZV AU, long-term maintenance with oral antivirals with or without topical corticosteroids

was suggested by 39 experts (51%) and by 34 experts (44%) respectively. For episodic hypertensive HSV and VZV AU, maintenance antiviral treatment would be used by 15 experts (19%) and 14 experts (18%) respectively. If there are two or more episodes of hypertensive uveitis per year, 35 experts (51%) would use long-term maintenance of oral antivirals ± topical corticosteroids ± IOP lowering drops). If there was corneal involvement (keratitis), topical antiviral treatment would be added by 29 experts (43%). In addition, 65% and 63% would prescribe topical cycloplegic for HSV and VZV AU, respectively.

In the case of recurrence, 52 experts (68%) would restart the initial treatment but with a longer taper of antiviral treatment for both HSV and VZV AU. In this circumstance, antiviral treatment alone, without topical corticosteroid, would be used by 64 experts (83%) in HSV AU and 65 experts (84%) in VZV AU.

There was no consensus on the need for enhanced anti-inflammatory or antiviral therapy as prophylaxis for cataract or glaucoma surgery (supplementary file 5). For both HSV and VZV AU, 18 experts (24%) would start topical steroid 4-6 times daily two weeks before surgery and taper according to the postoperative inflammation. For HSV and VZV AU, perioperative oral acyclovir 400 mg twice daily was opted for by 19 experts (25%) and 18 experts (23%), respectively. Meanwhile, oral valacyclovir 500 mg twice daily was chosen by 13 experts (17%). There was, however, a strong consensus (94%) on the need to titrate topical corticosteroid dosage in the presence of viral keratitis (i.e. dosage decrease for epithelial keratitis and increase for stromal keratitis). While it did not reach consensus, it is useful to consider a referral to a cornea specialist for co-management, with 71% of experts opting for this. A summary of management principles is presented in Table 2.

DISCUSSION

Both HSV and VZV constitute a large proportion of infectious AU worldwide.[11,19,20] However, there are no clear guidelines on treatment and follow-up. There is a wide range of opinions amongst uveitis experts worldwide, which creates dilemmas in patient management. This first report from the TITAN study group involved uveitis specialists worldwide with expertise in the management of HSV/VZV AU. Where strong consensus was achieved, published guidance for ophthalmologists managing patients with HSV and VZV AU would be useful.

Based on consensus, clinical signs suggestive of herpetic AU are sufficient for diagnosis, and most experts would not perform an aqueous tap. This is supported by previous studies suggesting that a clinical diagnosis alone is sufficient to differentiate viral from non-viral AU.[21,22] Even though PCR from aqueous tap had a high positivity rate among AU patients in general, one report found that its low sensitivity could limit its use in ruling out viral entities. A twelve-year study in South Korea found that aqueous tap PCR in suspected infectious uveitis cases had a sensitivity of only 0.43, while the specificity was 0.98.[23] There are well established differences in clinical presentation between VZV and HSV. VZV AU more commonly affects older individuals compared to HSV AU.[24] When present, dermatomal distribution of skin lesions may also help differentiate a VZV infection from a HSV one.[25] However, since HSV and VZV AU have many overlapping features, it may be difficult to differentiate using clinical presentation alone.[7,8,11] In such indeterminate cases, PCR becomes useful in identifying specific pathogens and giving direction to the treatment regimen.[10–12,26] Notably, expert responses indicate that qualitative PCR is more accessible than quantitative in many settings..

Based on our survey, the GWC examination's high cost and relative unavailability in many settings limits its ability to reach a diagnostic threshold for initiating treatment. However, a previous study in Thailand shows its potential in diagnosing unexplained AU as the GWC examination can be positive in 3/4 (75%) of these patients .[27] On the other hand, although iris atrophy is generally considered an essential feature of herpetic AU, not all patients with GWC HSV positive had iris atrophy in that study.[27] Thus, even though GWC might not be considered necessary in clear cases of presumed HSV/VZV AU, it may still help detect possible herpetic causes among unexplained AU patients and guide appropriate treatment.

With the emergence of acyclovir resistance in HSV-1,[28] determining the preferred antiviral regimen in the initial and maintenance phases may become more challenging. Most experts chose to give only systemic antiviral treatment for HSV and VZV AU. Previously, it was thought that the penetration of topical acyclovir ointment was better than oral acyclovir.[29] However, a clinical comparison of these two delivery routes seemed to result in no significant difference.[13,29] Zandi et al proposed that oral acyclovir, valacyclovir, or famciclovir are currently the mainstay treatment for HSV and VZV AU.[3] We found consensus on the use of topical acyclovir for active corneal involvement (keratitis) when available, but optimal dosage and duration remains unclear.

Despite moderate variation for systemic antiviral selection to treat HSV/VZV AU, valacyclovir tended to be the drug of choice in our survey. Valacyclovir, a prodrug of acyclovir with 3-5 times higher bioavailability, potentially results in a higher ocular tissue concentration .[30] It is also the preferred choice for maintenance treatment. A pilot study by Miserocchi et al found that acyclovir 400 mg twice daily and valacyclovir 500 mg once daily were associated with similar recurrence rates during

12 months of observation of HSV eye disease patients.[31] Yet there are also published papers[13,32] that refute the 59% of respondents who believe valacyclovir is more efficacious than acyclovir. This is an interesting conundrum that exposes the possible areas for further research into HSV / VZV AU management. We hypothesised that healthcare financing, practitioner preference, local prescribing norms, drug availability, and bias from the respondents, who are Asian uveitis specialists, could all influence drug choice selection. Agreement on the antiviral regimen was similar across different regions (Supplementary file 5), indicating no potential difference in implementing this consensus. The previous HEDS clinical trial on anterior uveitis only used acyclovir,[15] which is no longer the systemic drug of choice based on our survey. Based on these findings, further study is needed to explore the efficacy of valacyclovir in herpetic AU management. While there was agreement on the dosages of systemic antivirals for HSV and VZV AU, we would like to highlight that these seemingly common indications remain off-label. The agreement on dosages probably stems from ophthalmologists directly translating the dosages of well-established herpetic mucocutaneous infection indications such as zoster and genital herpes rather than any formal clinical trial data.[33]

Another debatable issue in HSV/VZV AU treatment is determining the duration of treatment and deciding upon appropriate endpoints. In a recent systematic review, we defined quiescence as no cells in the anterior chamber (AC).[13] In another review, four weeks was considered a minimum duration for HSV and VZV AU suppressive treatment.[25] Even though consensus was not reached, we found that about two-thirds of experts would consider it necessary to include corneal oedema resolution as an endpoint, in addition to the resolution of inflammation and decreased IOP. This treatment approach appeared similar across all regions. Based on our findings, it is

worth further exploring whether herpetic AU recurrence could be related to discontinuing treatment when only inflammation, but not corneal oedema has resolved.

Consensus was achieved for topical beta-blocker as the first choice drug for IOP control. Concerns on the induction of inflammation may have contributed to this choice, and it has been suggested that prostaglandin analogues should be prescribed only when necessary based on the current evidence.[34] However, a study with 163 eyes found that prostaglandin analogues were potent IOP lowering agents without increased risk of anterior chamber inflammation or cystoid macular edema.[35] Moreover, Markomichelakis et al found that there was no difference between latanoprost and beta-blocker use in terms of inflammation recurrence when treating raised IOP among anterior uveitis patients in general; however it should be noted that this study included few with herpetic uveitis (what did the herpetic uveitis patients show).[36] We acknowledge that the study only sought to find out the first line IOP lowering medication and is not a comprehensive take on the complex topic of uveitic glaucoma, which may be better handled by a glaucoma subspecialist. The proposed management algorithm based on the consensus achieved for the first episode of HSV/VZV AU is illustrated in Figure 1.

Regarding perioperative therapy, no consensus was achieved on the dosage and duration of prophylactic pre-operative treatment in HSV/VZV AU, if any were to be used. It has been stated that oral acyclovir or valacyclovir could prevent relapse and that a combination of topical NSAID and corticosteroid may lessen the risk of recurrence.[37] Of note, NSAIDs were not supported as the first choice by experts in this consensus. We observed much variation in opinions on anti-inflammatory therapy or antiviral prophylactic treatment adjustment before and after procedures

such as cataract or glaucoma surgery. Some experts considered topical corticosteroid (4-6 times a day beginning two weeks before surgery) and oral antiviral therapy (acyclovir 400mg BD 3-7 days before and 2 weeks postoperative or valacyclovir 500 mg BD 1 week – 10 days preop up to 6 months postoperative) necessary.

Several limitations were encountered in this study. Although all participants were uveitis experts, the annual caseload of herpetic AU in particular was not quantified for each individual. Variability in experience might affect decisions on diagnosis, treatment, and follow-up. Moreover, obtaining an even distribution of participants from each region was difficult. Of note, only one expert from Africa (a region with few uveitis specialists) participated. In addition, we acknowledge that HSV and VZV AU patients are also not strictly the domain of uveitis subspecialists, especially when there are significant corneal and IOP complications. Also, general ophthalmologists may have significant expertise in the topic, which we have not sought in this particular study. However, we believe that the 68 uveitis experts who participated can be argued to adequately reflect both expertise and global variation in HSV and VZV AU management. Besides, given the robustness of the Delphi survey to generate consensus in the medical field, a wide variety of its implementations exist.[18] Giving a clinical scenario in the second round of the survey may have introduced bias from the core TITAN members. Nonetheless, we ensured anonymity and controlled feedback to retain the reliability of the study. Lastly, experts' practice experience and the selection of some ancillary tests, such as PCR and GWC, could be more influenced by geographic accessibility and cost rather than scientific consideration. The limited number of randomised trials on this subject makes consensus based on practice experience valuable.

In conclusion, this is the first report from TITAN describing the current global practice pattern in HSV and VZV AU management by uveitis specialists worldwide, with some important aspects reaching consensus, including the following: Several clinical signs help to distinguish herpetic AU. Experts do not routinely perform PCR and GWC. Systemic antiviral treatment is generally prescribed, with oral valacyclovir being the antiviral of choice owing to its simpler dosing regimen. Alongside the resolution of both AC inflammation and raised IOP, resolution of corneal involvement may be necessary as one parameter of the clinical endpoint. The summary table (Table 2) and flowchart included represent a current snapshot of the limited but important areas of consensus on HSV and VZV AU. There are, however, several areas of contention, especially regarding the specifics of treatment protocols, including duration and dosages for both topical and systemic antiviral therapy. These are important areas to further elucidate in further research to guide the management of HSV/VZV AU.

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TABLES

FIGURE