Author's response to reviews

Title: A Systematic Review and Meta-Analysis to Compare the Efficacy of Acyclovir 3% Ophthalmic Ointment to Idoxuridine in Curing Herpetic Keratitis by Day 7 of Treatment

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Version: 2
Date: 7 March 2015

Author's response to reviews: see over
February 25, 2015

RE: A Systematic Review and Meta-Analysis to Compare the Efficacy of Acyclovir 3% Ophthalmic Ointment to Idoxuridine in Curing Herpetic Keratitis by Day 7 of Treatment [Author, et al]

Diane E. Balderson; Gengqian Cai; Michael A. Fries; David M. Kleinman; Megan M. McLaughlin; Trupti M. Trivedi; John I. Wurzelmann; Sheila B. Young

Dear Alice,

This manuscript has been submitted a second time as an original article. Although we received feedback from reviewers after the first submission, it took longer than expected for all authors to provide feedback on the reviewer’s comments. Thus, because of timing we are forced to resubmit as an original manuscript. Although the document is submitted for original review, we did diligently and thoroughly address the comments, suggestions, and questions of the reviewers previously, as detailed below. We provide this information for you in case you find it helpful, and we wanted you to know that we did take the reviewer’s comments seriously and fully addressed all issues to the best of our ability.

We feel that this work will contribute to the current body of literature because it demonstrates that treatment of herpetic keratitis with Acyclovir 3% ophthalmic ointment is generally safe, well tolerated, and effective in herpetic keratitis. The manuscript provides valuable information for ophthalmologists around the world faced with treating this serious condition.

If we can be of further assistance, please do not hesitate to contact me.

Sincerely,

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General comment

I think this meta-analysis comparing the efficacy of Acyclovir 3% Ophthalmic Ointment to Idoxuridine in Curing Herpetic Keratitis, does provide important information. A single time period is, however, selective and there are inaccuracies detailed below which need to be corrected and the analysis repeated where indicated. Many of the studies that have been included do not have day 7 as the endpoint and as such the extrapolations are weakened. It would therefore also be appropriate to do the same analysis for healing/failure by day 10 (or even day 14) and to compare the 2 results. For example, in the study by Collum, the number of days taken to heal in patients treated with acyclovir ranged from 2 to 9 days, compared with 3 to 17 days for patients treated with IDU. This would provide much more relevant information to the reader in comparing the efficacy of IDU and ACV.

Major Compulsory Revisions

1. Repeat analysis with correct numbers for Collum et al
2. Anaylze with healing/non-healing at another time point such as day 10
3. Review articles on IDU and natural history
4. Correct and provide more data in tables

Please see the response to specific comments below, as they address the comments above.

Introduction

In the introduction, reference needs to be made that epithelial ulceration is often associated with stromal disease and that they often coexist. Dendritic ulcers do heal without additional antiviral treatment and a brief account of the natural history of healing of dendritic ulceration is needed. The authors need to review the following papers and present a summary in both the introduction and discussion regarding the response to IDU:


Thank you for this suggestion, we have implemented it into the manuscript as follows: Herpetic Keratitis can be a self-limited condition and resolve without sequelae; however, untreated, such benign cases occur in a minority of outcomes. [10] Mechanical and nonspecific therapies such as debridement and chemical curettage were in use prior to the 1960’s to improve outcomes. Despite these interventions
signs of active HK were observed on the cornea for an average of 21 days, and HK remained one of the most important corneal diseases leading to loss of vision. [10] In 1962 Kaufman et al showed in an uncontrolled trial effectiveness of topical 5-ido-2'-deoxyuridine—(later called idoxuridine) in treating HK. Over the ensuing two years multiple authors reported on the efficacy of idoxuridine, including five controlled trials. Success, often defined as the resolution of staining, was reported in 50% to 90% of cases, and the time frame for the efficacy assessment was seven days for three of the five controlled trials. [10] [11] [12] [13] [14] Success rates for IDU generally fall in to the 75% rate based on review of these early studies.

**Methods and Results**

1. Further justification for selecting healing by day 7 is needed. The authors state 'The choice of Day 7 was influenced by the natural history of the disease, its use as a time point in head to head clinical trials, and the fact that resolution of HK in seven days is a favourable outcome and a reasonable therapeutic goal.' The authors need to re-address this in light of the natural history, previous studies on IDU and the end points used in the studies analysed.

We have extended the explanation in the results section of the manuscript based on the time for untreated HK to resolve, the time point used in many of the original IDU studies, as well add the mean time to healing as reported in the studies in the analysis as follows: Mean time to healing was reported in five of the seven studies [Colin 1981, Collum 1980, Hamard 1982, Kitano 1985, McCulley 1982]. The mean time to healing for ACV treated eyes ranged from 4.4 days [Collum 1980, Hamard 1982] to 7.5 days [Colin 1981] in 167 patients compared with 5.1 days [Hamard 1982] to 9.2 days [Collum 1980] in the IDU treatment groups totaling 168 patients. All 5 papers showed superiority for acyclovir ophthalmic ointment compared to IDU. The mean time to healing was statistically significantly shorter in 3 of these 5 reports [Colin 1981, Collum 1980, Kitano 1985], and numerically shorter in the other two [Hamard 1982 and McCulley, 1982]. One study [Klauber 1982] reported that mean time to healing was shorter for ACV treated eyes, but the means were not reported directly.

2. A comparison using 2 time points such as by day 7 and by day 10 would be much more informative and useful to the reader. This is particularly of relevance as the statements in the paper. 'Day 7 healing rates for ACV treated dendritic ulcers reached up to 27/28, or 96% [20]. Day 7 healing rates for IDU treated dendritic ulcers healing rates were as low as 4/20 or 20% [21]' This 20% is based on one study (I am not clear on the end point in that study) and the authors have not referred to the studies referenced above (1-5). Indeed using one study[21] suggests that IDU is worse than the natural history?

Thank you for this suggestion. We have extended the explanation for the choice of day 7. Specifically, we report the average healing time reported from the publications (unadjusted by meta analysis techniques). These suggest that 7 days is appropriate to highlight the difference between the two treatments, and that it is less likely to see significant differences at a later time point such as day 10 or 14. Although day 10 healing information is not provided in Kitano, where patients who were not healed at day 7 were crossed over to other therapy, we have added, briefly, day 10 results as follows: Per the reviewers suggestion this was further investigated by additional post hoc analysis examining 10 day healing rates. All sources, with the exception of Kitano 1985 had sufficient information to derive 10 day rates. Based on the result from the meta-analysis with the CMH method, in subjects with HK, the odds ratio (OR) of healing at Day 10 in the ACV treatment group is 2.99 times (95% CI: 1.68, 5.30; p-value:
<0.0001) higher than the OR in the IDU treatment group. Since the result based on HK was statistically significant at the 5% level, similar analyses were then sequentially performed for the two ulcer sub-types: dendritic ulcer and geographic ulcer and the results for the dendritic sub-types was statistically significant at the 2.5% level (for dendritic ulcer, OR 2.40 (95% CI: 1.06, 5.43; p =0.0237); and for geographic ulcer, OR 2.93 (95% CI: 0.71 12.15; p= 0.1129).

3. The comments regarding the study of Collum (1982) are inaccurate. 'In Collum, the healing rates observed with ACV (97%, 29/30) and IDU (21%, 6/29)' They withdrew patients if they had not shown improvement by day 4 and treated with 30/ ara-A ophthalmic ointment. This is important and very different from healing by day 7. As such 7 patients were withdrawn and one defaulted, leaving 22 patients. 6 of these 22 had had healed by day 7 and 13 of 22 by day 8. Thus if healing was taken as by day 8, an additional 7 patients would be included as success.

The defaulted subject is not included in the total of 29. In Collum, any subject that was not improved or had worsened by day 4 was planned to be withdrawn and treated with the rescue treatment ara-A ophthalmic ointment. Subjects that were treated with ACV, were at the same risk of being declared a failure by day 4, and if that had not shown improvement would have been treated as failures. Therefore, we submit that this difference is real and meets the pre-specified definition of failure and application of rescue medication within that trial.

In addition, treating those values as missing would not change the numbers, as we pre-specified in our analysis plan that subjects with missing day 7 healing outcomes would be classified as treatment failures. This criterion was equally applied to both treatments. Again, ACV treated subjects, if not showing improvement, would have been withdrawn and our analysis would have classified them as failures. We agree that if the endpoint had been day 8, 13/22 would have been a success, and the resulting difference with ACV would be smaller, although still substantial. This is partially addressed through the addition of the 10 day analysis, per your earlier suggestion.

A sensitivity analysis could be run considering alternate results for the 6 subjects that were withdrawn. If one takes the extreme case of assuming they were successes, again, 12/22 subjects would have been a success and the resulting difference with ACV, although smaller, would still be substantial and this would not change the conclusion.

4. More weight is need to those studies that actually measured daily healing.

Although this would be an interesting analysis, none of the studies specify daily assessment in their methods section.

5. More importance needs to be given to those studies, in which HSV had been isolated by culture or detected by PCR from lesions.

This is addressed in the revised text as follows: In keeping with many clinical trials assessing therapy for HK, the diagnosis in these studies was based on the clinical appearance of the cornea. Although it may appear optimal to only analyze cases in which the presence of herpes simplex was confirmed by culture or alternative laboratory testing, it wasn’t possible to break down the study results based on this parameter. For example, Coster 1980, Klauber 1982, and Hamard 1982 used clinical criteria only. In Colin 1981, a viral sample was taken for the majority of cases, but no culture results are reported. Collum 1980 showed recovery of herpes simplex virus type I in 19 (33%) of 54 conjunctival swabs while complement fixation antibody to HSV type I was present in 48 (96%) samples of sera. Collum 1980 also reported a
case by case analysis of recovery of virus and titer of complement fixing antibody. McCulley 1982 utilized virus cultures from the inferior cul-de-sac and showed a 19.9% positive culture rate. Kitano reported that virus was isolated in 61.5% of cases. None of these four studies that evaluated subjects for presence of virus separated out their aggregate results based on confirmation of virus. Of note, polymerase chain reaction testing was not available at the time these studies were conducted. It was felt that re-evaluating the Collum study, only, based on isolation of virus from the conjunctiva was not necessary. Furthermore, routine management of HK does not require laboratory confirmation prior to initiating therapy, thus the use of the broader population has clinical relevance.

6. Some form of reference is needed to the baseline size of both the dendritic and geographic ulcers at entry as clearly time to healing will be affected by the starting ulcer size.

We have added text to the document to address this concern, as follows: Ulcer size is another variable that can affect responses to antiviral therapy. Five studies provided useful information about baseline ulcer size. Coster 1980, Collum 1980, Colin 1981, McCulley 1982, and Hamard 1982 all presented a comparison of ulcer sizes between the ACV and IDU groups, and the treatment groups were not different based on analysis of the ulcer size between the groups. Kitano 1985 and Klauber 1982 did not describe subject ulcer size. It was not possible to reevaluate outcomes based on presenting ulcer size, but based on the similarities between study arms regarding ulcer size in the five studies that mentioned it, such an assessment was not necessary.

In addition, it is likely that most baseline characteristics should be balanced due to our requirement for randomized trials.

Discussion

1. There are many more up to date references, on HSV-1 corneal ulceration which should be included.

More references have been added.


2. The influence of 6 publications that were used to to support primary efficacy needs to be addressed. Colin 1981 [12]; Collum, 1980 [13]; Coster, 1980 [14]; Kitano, 1985 [15]; Klauber, 1982 [16]; and McCulley, 1982 [17]. Each of these studies have their limitations, as acknowledged by the authors: In Coster 1980 [14], The total numbers cured at Day seven had to be extracted from the cumulative time course plots of healing In Hamard 1982, no corresponding publication of these data was found. Total number of subjects cured at Day seven were extracted based on the cumulative frequency plot in the GSK report. In Klauber 1982 [16], the total number of subjects cured at Day seven was extracted based on the cumulative frequency plots in the publication. In fact it is only for McCulley 1982 [17], where day 7 is defined and where a comparison of ID and ACV is no particularly different: 19 of 30 for ACV and 18 of 34 for the IDU group.

The driving factor influence is a combination of observed effect and the size of the trial, per standard meta-analysis techniques. The jack-knife analysis establishes that the removal of any one trial does not impact the results. Per our analysis plan, any subject that was not reported as healed by day 7 was treated as a not healed by day 7.

3. Discussion of the relative concentrations of each agent within the cornea (directly or indirectly from AC measurement) is needed for this comparison and would provide the reader with relevant information particularly given the reports of resistant HSV ocular isolates to ACV via thymidine kinase.

This is now addressed in the text, as follows: Although knowing tissue drug concentration in drug development is important and would provide additional information relating to efficacy in these cases, neither corneal nor aqueous humor drug levels were provided in these studies. [28] Likewise, sensitivity testing for drug resistance was not performed.

4. Details from the end points is missing from table 1 e.g. 4 day cut-off for healing.
Additional detail has been added to table 1 as follows: Ulcers that did not show improvement by day 4 were treated with ara-A ophthalmic ointment and withdrawn.

In how many of the studies were patients examined on day 7? - this needs inclusion in table 7 and if not examined on day 7, the closest day to day 7
To clarify, any subject reporting healing prior to day 7 was considered healed by day 7. Any subject that was not reported as healed prior to or on day 7 was considered a failure on day 7. It is assumed that no preference was given during the conduct of the studies that would result on one arm with more frequent evaluations than the other arm. Therefore, although estimates may not be perfect, any bias in the healing rate estimates introduced should be systematic (ie both treatment arms should be biased similarly).

In order to clarify further, this limitation has been added to the discussion: … only McCulley 1982 reported planned evaluation on day 7, for subjects without a day 7 evaluation, healing prior to day 7 was deemed a success, and healing after day 7 was deemed a failure.

The figure in table 2 of 6/29 (21%) is not correct.
6/29 is the number we must use based on our pre-specified criteria for evaluation of healing. In addition, we think that is an accurate number for reasons provided earlier.

Table 3 needs to be updated with the data from other studies - e.g. from Collum it is 13/23 by day 8 and 14/23 for day 9 and 19/23 for day 10 for IDU.

Table 3 was not meant to illustrate healing across all studies, rather it was meant to illustrate the methodology used to determine the healing rates for Coster, 1980, were we had to carefully deduce the healing rates from the information provided relying on our pre-specified definitions and assumptions. One table with information from all studies would be too large (due to the number of distinct days which healing occurred), while one table for each study would not meet the publication specified limit on the number of tables.