Reviewer's report

Title: Vascular Disrupting Agent for Neovascular Age Related Macular Degeneration: A Pilot Study of Safety, Tolerability, and Bioactivity of Intravenous Combretastatin A-4 Phosphate

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Reviewer: Stephan Michels

Reviewer's report:

Review on “Vascular Disrupting Agent for Neovascular Age Related Macular Degeneration: A Pilot Study of Safety, Tolerability, and Efficacy of Intravenous Combretastatin A-4 Phosphate (CA4P)” by Ibrahim and co-workers.

All comments are “Major Compulsory Revisions”.

1. Is the question posed by the authors well defined?
Primary and secondary outcomes are well defined.

2. Are the methods appropriate and well described?
Eight patients are clearly too few to draw profound conclusions on safety, tolerability and efficacy of the drug. This should be clearly stated. However such study provides a broad range experience on very frequent adverse events and efficacy.

The following key questions should be in addition answered by the authors:

a.) Why was the enrolment stopped with only 3 patients in the second cohort?
b.) Why was no further dose escalation performed? According to the authors no DLT occurred, which would have prevented further dose escalation
c.) At the time the study was conducted photodynamic therapy with Verteporfin and anti-VEGF therapy with Pegaptanib were the standard of care for most patients with neovascular AMD. Was standard of care a rescue treatment? Please clarify how the study could be conducted without a standard of care as control?
d.) The inclusion and exclusion criteria allowed the enrolment of patients with prior treatment only except thermal laser therapy (at that time standard of care only for extrafoveal lesions). How many patients were treatment naïve? How many patients had prior treatment? Please specify prior treatments and timing of these treatments prior to enrolment into the study.
e.) Definition of serious adverse events (SAE); one patient had two episodes of blood pressure increase to > 200/100 following the study drug administration. Such blood pressure increases are life-threatening, usually require hospitalization and require intervention to prevent permanent impairment or
damage. They are therefore consistent with an SAE. Also with regard to the Common Terminology Criteria for Adverse Events v3.0 (CTCAE) these events should have been graded as grade 3-4. Please comment.

f.) Only patients with negative cardiac stress test were enrolled. Is there data on how many typical neovascular AMD patients (age 75-80) have a negative cardiac stress test? Could this be an selection bias?

3. Are the data sound?

Key information regarding prior treatments of enrolled patients are missing. Since an effective treatment (standard of care: Verteporfin/Pegaptanib) was available and the study was uncontrolled, patient selection could have strongly biased the results. The authors do not provide statistics.

4. Does the manuscript adhere to the relevant standards for reporting and data deposition?

The classification of the hypertensive crisis of a patient (mentioned above) appears incorrect. The authors should address this topic and adjust their discussion and conclusion accordingly. OCT data should have been presented as the BP and QTc data.

5. Are the discussion and conclusions well balanced and adequately supported by the data?

Here seems to be the key limitations of the paper. If the manuscript would have been submitted in 2005, the discussion might have been adequate. However we are now in 2012 and the discussion on safety and efficacy in neovascular AMD has significantly changed.

Safety:
AMD is not a life-threatening disease, therefore the discussion on safety can not at all be compared to safety in cancer patients. The discussions on Ranibizumab and Bevacizumab have shown how relevant safety issues are considered today. In the reported study every patient (except one) had an increase in systolic and diastolic blood pressure (BP). For an AMD patient populations this is today not an acceptable safety profile. In addition the patients were already pre-selected by excluding those with unfavourable cardiac stress test. The question of safety with regard to QTc-prolongation cannot be answered in this study due to its small sample size. Again – despite pre-selection by cardiac stress test – at least one patient came close to the 500ms (474ms), which would have been an AE grade 3.

The authors should also go into more detail, why the frequency of the common CA4P associated AEs is so different form the results in the cancer populations. They report in the section background the descending order of AE in cancer patients with hypertension and QTc prolongation as the least common (in their study hypertension and QTc prolongation being the most common AEs). The comment that AEs are “consistent” with AEs in oncology trials cannot be
concluded from this study and is misleading.

Comparing CA4P to systemic anti-VEGF studies appears valuable, but the comparison should be done to the data in their manuscript rather than to oncology data (page 12), which appear not comparable. Comparing effects on BP, they appear similar with regard to extend but different with regard to onset and duration of the BP elevation. In addition systemic anti-VEGF therapy appears to have only an effect on systolic BP, different to CA4P which appears to have also an effect on diastolic BP. Very valuable for the discussion are the following papers:

1.) GEITZENAUER W, MICHELS S, PRAGER F. COMPARISON OF 2.5 mg/kg AND 5 mg/kg SYSTEMIC BEVACIZUMAB IN NEOVASCULAR AGE-RELATED MACULAR DEGENERATION Twenty-Four Week Results of an Uncontrolled, Prospective Cohort Study
Retina 2008;28;1375-86


Efficacy:
How do the authors explain that all but one patient showed increased or unchanged leakage on fluorescein angiography (FA)? What did FA of the fellow-eyes show? Were other lesion parameters measured (total lesion size)?
How can the discrepancy to FTH by OCT be explained? The discussion should go into more detailed comparison of functional and anatomic effects of CA4P vs. systemic anti-VEGF. Why is the FTH reduction much less pronounced than with anti-VEGF? How do the authors explain an increase in FTH up to day 10?
The discussion on efficacy of CA4P is well overestimated. The authors do not show any efficacy on FA. The effect of – 33microns in FTH is very little. We know that the Stratus OCT System has a variability of 10microns, the rest could be just do to chance. Throughout the paper no statistical analysis was performed confirming that the data is valuable. OCT FTH follow-up on each patient would be useful as well as clinical examples to convince the reader that there is some evidence for efficacy of CA4P in neovascular AMD.

6. Are limitations of the work clearly stated?
The authors should mention why the study was stopped midway through the second cohort.

7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished?
For the readers it would be valuable to get more insight on the molecule CA4P (size, half-life time…). Were any animal models conducted that showed efficacy
on ocular neovascularization following systemic CA4P? The readers would also be interested in more details on the mechanism of action and why CA4P is selective for abnormal vascular structures. The effect on BP could indicate that CA4P is actually not as selective. Please discuss.

8. Do the title and abstract accurately convey what has been found?

The conclusion of the abstract is misleading. The safety data is not convincingly consistent with oncology patients. The only evidence for efficacy was a minimal reduction in FTH by OCT (no statistics, no FTH curves for each patient, no convincing clinical cases), far less than seen by systemic anti-VEGF. The conclusion should be:

The level of systemic safety and efficacy indicates that systemic CA4P is not suitable as monotherapy for neovascular AMD, especially when compared to the overall safe and very effective intravitreal anti-VEGF therapy today. There might be a role for CA4P as add-on therapy when delivered intravitreally/topically.

9. Is the writing acceptable?

Yes

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

My institution obtained research grants from Novartis, Bayer, Allergan, Sucampo, Clanotech, Alcon