FDA Consultation: Adnexanet (Part 1)
May 22, 2016
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1. In subjects anticoagulated with rivaroxaban, apixaban and edoxaban, andexanet caused a transient significant decline in anti-FXa activity during and shortly following a 2 hour infusion, which was followed by a return of anti-Xa levels to approximately 50% of initial levels with a subsequent decline as expected based upon the individual anticoagulant's half-life. a. Please comment on the adequacy of the observed duration of reversal in the treatment of intracranial hemorrhage (ICH) and to prevent further expansion of a subdural or parenchymal bleed.

   Response:

   In reviewing the literature, I noted that this question is on the minds of professionals who would ultimately implement this therapy http://www.ajhp.org/content/73/10_Supplement_2/S27.long

   Of the 9 illustrative cases presented, 8 were treated with the low dose protocol and 5/8 appeared to have good outcomes that neither corresponded to CT adjudication outcomes nor ICH volume at presentation. When bleeding progressed, it was noted either 1 hr. (2 cases of IVH) or 13 hrs. following infusion, at times when anti-Xa activity in normal volunteers was either rising again or naturally declining, but still 1.3 fold (apixaban) to 2 fold higher than the target threshold for bleeding risk. A single case was treated with the high dose protocol with a bad outcome, i.e., patient death due to interim stroke complicated by further hemorrhage at a time point when normal volunteers were shown to have intermediate levels of anti- Xa activity. The pathophysiology of good and bad outcomes is unclear in the absence of patient specific data on parameters of hemostasis (e.g., ETP) and activation of coagulation. Consequently the question is difficult to answer as posed. However, the case data do raise the following ancillary questions:

   1) *The surrogate marker data for this drug is impressive. However, is residual anti-Xa activity an effective surrogate marker in its own right for treatment duration when andexanet is use to stabilize or stop ICH? The Pernod reference recommends the ancillary not primary use of this parameter to guide intervention, contrary to the approach for emergency surgery.*
   2) *The reason for deciding on a standardized post-bolus two hour infusion as the therapeutic model for clinical trials is unclear to me. Was it determined on the basis of a risk-benefit analysis of hemostasis vs. re-thrombosis in animal or in vitro systems? What would be the risk or re-thrombosis or antibody formation associated with a longer infusion time in the case of ICH? The case studies suggest there may be a risk of both to be balanced in the case of ICH.*
   3) *Although the Phase I and II data provide an algorithm for initiating emergency anticoagulation (AC) reversal in the case of ICH, should the bolus dose /duration of therapy be monitored and guided for safety and efficacy by both CT and laboratory parameters of hemostasis (e.g., ETP) and activation of coagulation? Experience would suggest that each patient's threshold for bleeding and clotting must be individually ascertained. Therefore, should baseline steady-state hemostasis parameters (and PK?) be obtained as standard of care in patients on anti-Xa inhibitors who are at the highest risk of bleeding complications in order to guide emergency reversal?*
   4) *What are the reasonable expectations for the use of AC reversal agents for major bleeding stabilization and reversal? The mean time to bleeding cessation with idarucizumab is* (b) (4) .

The following questions refer to the proposed protocol for the Phase 3b/4 confirmatory study:

2. In the Phase 3b/4 confirmatory study, two subjects with intraparenchymal bleeds on baseline CT were found to have intraventricular hemorrhage (IVH) on follow-up imaging, resulting in higher than baseline total bleed volumes. Please comment on whether the adjudication methods used in this study to assess hematoma expansion for those subjects who experienced IVH on follow-up imaging are appropriate.

   Response:
   In the following study of ICH in patients on OAC the following was noted (Horstmann, J Neurol. 2013 Aug;260(8):2046-51):

   'Intraventricular hemorrhage (IVH) was quantified using the Graeb score. Within 19 months, 2,282 patients were admitted to our ER. 206 ICH patients were included. Overall, 24.8 % of all ICH were related to OAC. Compared to patients with spont-ICH, OAC-ICH patients were older (p = 0.001), more frequently had initial extension of ICH into the ventricles (p = 0.05) or isolated primary IVH (p = 0.03) and a higher Graeb score upon admission (p = 0.01). In contrast, initial ICH volume (p = 0.16) and ICH expansion (p = 0.9) in those receiving follow-up imaging (n = 152) did not differ between the two groups.'

   Consequently, although I am unsure about whether it should be included in the volumetric assessments of ICH progression, IVH should be included in the overall outcome assessment of morbidity, possibly by including the Graeb score in the EAC rating.

3. Please comment on the acceptability of the entry criteria (in terms of inclusion of an appropriate target population for whom immediate reversal of anticoagulation is necessary). Should there be specific criteria related to ICH (e.g., minimum volume/thickness of the lesion, imaging criteria that predict high-risk of hematoma expansion, specific symptoms)?

   Response:

   Based on the case studies presented in this dossier and my observations outlined in the response to question 1, I do not believe that the ICH criteria for subject inclusion should be further qualified beyond the current inclusion and exclusion criteria.

4. Following the start of andexanet treatment, subjects will be evaluated for the study efficacy endpoints, based on serial observations which include CT/MRI at baseline (defined as up to 4 hours prior to bolus), at 1 hour post infusion (defined as within 1 hour prior to and up to 3 hours following the end of the 2 hour andexanet infusion) and at 12 hours from the start of andexanet bolus with head CT and modified Rankin score (mRS) for ICH at 12 hours from the end of infusion.

a) Please comment on the adequacy of the timing of the imaging and clinical evaluations in the assessment of treatment success or failure.

   Response:
   Based on the case studies presented in this dossier and my observations outlined in the response to question 1, there is the potential for the 12 hr. EAC evaluation to be unrelated to the clinical outcome (subject (b) (6) *). Additionally, 30 day all-cause mortality will be assessed. Although there should be a limit in the # of CT scans to which patients are exposed for the purpose of clinical study, consideration should be given to extending the acute observations for safety and efficacy to the end of the risk period for DOAC-related bleeding based on PK/PD data (time to plasma anti Xa activity < 30 ng/ml) for the individual drugs with CT /MRI only for change in neuro status (i.e., expansion of the secondary objective of the proposed study). A longer observational period may also be able to assess time to hemostatic efficacy. Please see other comments in my response to question 1 regarding clinically relevant monitoring.*

b) Are the study design and proposed endpoints in the ongoing study adequate to assess efficacy of the study treatment in the ICH population?

Response:
In addition to the answers already provided, consideration should be given to including some assessment of neuro outcome (mRS or other).

c) Are there other clinically relevant endpoints that should be considered for the current and future studies?
Response:
See responses to other questions- nothing further to add

5. Given the heterogeneity in the eligible population (with regard to location and size of the bleed), please comment on the relevance and feasibility of reduction in ICH-related morbidity and mortality as a primary endpoint for a confirmatory study intended to assess the hemostatic efficacy of a reversal agent for the three anticoagulants.

a. Is there a relevant time-point to assess reduction in ICH-related mortality and morbidity (i.e., 30 days vs. a later time-point)?

Response:
Please see my response to question 4a. I am not expert enough in adult stroke to determine whether there might be a more relevant time point for neuro assessment.

b. The applicant has proposed a "Usual Care Cohort study" designed to serve as a comparator group for the assessment of the efficacy of andexanet in a population that is similar to the ongoing Phase 3b/4 confirmatory study (ANNEX 4 study).The study is an observational study in which patients receive the usual standard of care at their institution. There is no restriction of what treatments a patient may receive. The primary objective of the study is to evaluate a cohort of patients with acute major bleeding (that includes subjects with ICH) while on a fXa inhibitor, receiving usual care, in order to determine the feasibility of using this cohort as a comparator group to assess the efficacy of andexanet. A blinded adjudication process is planned to assess efficacy between the ANNEX 4 study and the "Usual Cohort Study". Is such a cohort study an appropriate control to evaluate the efficacy of andexanet in the ICH sub-group? Please also comment on the feasibility of conducting a randomized controlled study in patients with ICH for this indication.

Response:

A contemporaneous standard of care (SOC) population could be an effective control group if the observational study is conducted with a similar study design (including inclusion and exclusion criteria) and study objectives/ endpoints. For ICH, the timing and frequency of neuroimaging will be difficult to replicate. Also, since SOC will necessarily include laboratory monitoring, ideally this would be incorporated into the ANNEX 4 study as a point of comparison for the effectiveness of the SOC intervention and that of andexanet (ETP, AND coagulation activation parameters).
Given these considerations and the existence of clinical equipoise, an RCT incorporating some of the suggestions outlined in my response to question 1would be the better option.