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NEUROCRITICAL CARE SOCIETY

VIEWPOINT

Key Points to Consider When Evaluating Andexxa for Formulary Addition

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In May 2018, Andexxa (coagulation factor Xa [recombinant], inactivated-zhzo or formerly andexanet alfa) received accelerated approval from the Food and Drug Administration (FDA) as a specific reversal for rivaroxaban- and apixaban-treated patients with life-threatening or uncontrolled bleeding despite not establishing improvement in hemostasis [1]. The recent publication of ANEXXA-4 and the wider availability for Andexxa in 2019 has led many hospital Pharmacy and Therapeutics (P&T) committees to discuss whether Andexxa should be added to formulary [2]. Currently, there are no studies comparing the safety and efficacy of Andexxa to the current standard of care. The ANNEXA-4 study and clinical trials with prothrombin complex concentrate (PCC) also have their limitations. Furthermore, the off-label use and FDA concerns, conflicting society recommendations, and financial impact add another challenging layer to this evaluation. In this article, we discuss key aspects to consider when evaluating Andexxa for formulary addition.

Pharmacology in Brief

Andexxa is a modified form of human Factor Xa which works by acting as a decoy that binds to factor Xa (FXa) inhibitors. It has been shown in vitro to rapidly reduce anti-FXa activity. The half-life of Andexxa is far shorter than the FXa inhibitors. Because of the short duration of action, anti-FXa activity starts to resume to baseline after the 2-hour infusion and goes back to the baseline by 4 hours after drug initiation. Andexxa also binds and inhibits tissue factor pathway inhibitor (TFPI). This off target effect can cause acceleration of the generation of FXa and thrombin which could promote thrombosis [3].

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Understand US Food and Drug Administration Concerns

The FDA clinical reviewers had concerns about the short half-life of Andexxa and the lack of correlation of in vitro activity with clinical efficacy. They also had safety concerns given the in vitro effects and clinical thrombosis rates of up to 18% in early studies. FDA clinical reviewer and supervisors recommended against approval of Andexxa because they believe the "safety and efficacy data for ANDEXXA are not adequate to support approval" [3]. However, the Director for the Office of Tissues and Advanced Therapies overruled the recommendation by the review team [4]. Due to the magnitude of the uncertainty of the benefit, the FDA did mandate randomized clinical trial against standard of care which is currently PCC. Approval for Andexxa may be withdrawn by the FDA if post-marketing studies fail to verify clinical benefit or not conducted with due diligence [5]. Again, this implies PCC is the standard of care for non-vitamin K oral anticoagulant (NOAC)-induced severe bleeding. Any committee deciding whether to add Andexxa to formulary should know the recommendation of the FDA clinical reviewers not to approve Andexxa whatsoever was overridden. Superiority claims over PCC or stating Andexxa as standard of care seem unwarranted given the FDA's assessment of clinical equipoise as well as the 59 centers listed as participating in the randomized control trial [6].

Weigh Surrogate Endpoint Correlation to Clinical Efficacy

There is extensive literature showing that surrogate endpoints often do not correlate with improved patient outcomes [7]. This has been shown in clinical trials for oncology drugs when progression-free survival often does not correlate with overall survival [8, 9]. Similarly, drugs reducing premature ventricular contractions, a

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marker for sudden cardiac death, actually increased mortality [10]. Lack of correlation between surrogate endpoint and clinical efficacy has also been well demonstrated in the field of neurocritical care. The FAST trial showed that Factor VII was associated with a statistically significant reduction in intracerebral hemorrhage (ICH) expansion but did not improve 90-day functional or mortality outcomes [11]. There were also more significant arterial thrombotic events in the Factor VII group ($P=0.04$). According to the ANNEXA-4 study, "there was no significant relationship between the hemostatic efficacy and a reduction in anti-factor Xa activity during andexanet treatment" despite the attractiveness of the concept [2]. Furthermore, the known off target binding to TFPI is a specific and unique mechanism to cause clinical thrombosis. We hope that limitations with surrogate endpoints will be thoughtfully applied today [12].

Evaluate ANNEXA-4 Unique Exclusion Criteria and Its Impact on Mortality as Compared to Real World Data

The ANNEXA-4 trial was an open-label trial of Andexxa that showed hemostatic efficacy of approximately 80% at 12 hours, rate of clinical thrombosis of 11% by day 30, and a 30-day mortality of 14% [2]. The ANNEXA-4 trial may have had a lower 30-day mortality due to its unique tight exclusion criteria—an effect of unknown magnitude. Patients expected to go to surgery were excluded which would tend to be those with the higher expected mortality such as the largest subdural, cerebellar, or large intraventricular hemorrhages. The study was subsequently amended early in the recruitment phase to also exclude patients if mortality from any cause is expected in less than one month [2, Supplementary Appendix]. Patients with intracerebral hematoma volumes greater than 60 cc were also excluded, a cutoff known to be associated with worse mortality [13]. The trial also excluded patients with Glasgow Coma Scale (GCS) less than 7. This study design systematically excluded patients with the highest expected mortality and led to a lower mortality than any comparison group that does not have these exclusions. Evaluating actual ICH volumes and GCS data from ANNEXA-4 and other clinical trials will confirm or support this hypothesis.

The ICH score is one of the most established and validated ways to predict mortality in the subset of intracranial hemorrhage with ICH [14]. In this study, the mean GCS score on admission was 10 with a mean ICH volume of 27 cc on initial computed tomography scan. Purrucker and colleagues evaluated the outcome of ICH related to NOAC in 61 patients and found a mean hematoma volume of 23.7 cc with a median of 10.8 cc [15]. This median is higher than the ANNEXA-4 trial and is artificially low due to excluding patients with hematoma evacuation prior to follow-up imaging. In comparison, ANNEXA-4 reported ICH volume < 10 cc or 11–60 cc with 61% of the ICH volumes less than 10 cc. Unfortunately, the exact distribution or mean in the 11–60 cc range is unknown or not published (e.g., how many greater than 30 cc). Nonetheless, ICH volume in ANNEXA-4 appears to be far smaller than real-world data. In addition, the mean GCS for the entire intracranial group is 14, which is considerably higher than the real-world study mentioned above.

Based on the ICH score system, ICH volume ≥ 30 cc receives one point which correlates with increased mortality rates. Therefore, the patients in the ANNEXA-4 study would expect to have a lower ICH score and should do better when compared to any group without this exclusion. Additionally, excluding patients going to surgery may lead to fewer infratentorial and intraventricular hemorrhages since those needing external ventricular drain or emergent decompression will be excluded. Excluding very low GCS will also lead to a group that by design can be expected to have lower ICH score. Given the very sharp change in expected mortality rates between ICH scores of 0, 1, 2, and 3, data for ICH score would shed light on the reported mortality despite the fact that the ICH score has been validated in ICH secondary to vitamin K antagonist and not specifically for NOACs [16]. A very large registry from the American Heart Association/American Stroke Association Get With The Guidelines-Stroke found a median National Institutes of Health Stroke Scale/Score (NIHSS) score of 8 and over one-third of NOAC-related bleedings with NIHSS > 14 [17]. We suspect the ANNEXA-4 patients had less severe strokes based on this objective method. It would be helpful to see the comparable data from ANNEXA-4 to confirm or repute our hypothesis that ANNEXA-4 patients were less clinically ill than real-world patients. Additionally, a small case series from a tertiary referral center reported 40% inpatient mortality with Andexxa even though some of the patients in this case series would have been excluded from the ANNEXA-4 trial [18]. The lack of comparison group in ANNEXA-4 and the unique set of exclusions not seen in any other trials preclude any certainty whatsoever in comparing Andexxa mortality rates to other studies or databases. The latest statistical analysis plan in the ANNEXA-4 trial protocol does describe the use of ICH score and data gathering to better characterize baseline prognosis [2, Protocol]. We look forward to the publication of this information. Making any decision to add Andexxa to formulary based on a mortality rate should await results of ongoing randomized controlled trial comparing Andexxa to standard of care.

Recognize Prothrombin Complex Concentrate Clinical Trial Limitations

The use of PCC for NOAC reversal is supported by many societies [19–21]. Andexxa, like PCC, has not been compared to placebo. Most of the studies with the use of PCC for NOAC-related bleeding are retrospective studies. Only a few studies are prospective, and no trials are randomized. A recent meta-analysis of 10 PCC studies estimated a hemostatic efficacy of 69%, 16% all-cause mortality, and 4% thromboembolism rate [22]. The quality of this meta-analysis is limited by variation in the type and dosing of the PCC and lack of standardization of protocols and definitions. The observed all-cause mortality of 16% was similar to the 14% in ANNEXA-4 although the PCC group had higher percentage of patients with ICH (74% versus 67%). Looking at the individual studies may elucidate the reported outcomes. Schulman et al. [23] did a prospective cohort study of 4-Factor PCC for FXa inhibitor-related bleeding, and 48% of the ICH bleeds had a volume of less than 10 cc. This is lower than the 61% of ICH volume < 10 cc in the ANNEXA-4 study. Additionally, the ICH group in the Schulman study had a 30-day mortality of 14%. They also excluded patients in whom a do not resuscitate (DNR) order had been given, similarly to another study performed by Majeed et al. [24]. In clinical practice, a DNR order exclusion is far less restrictive than an expectation to die from any cause in less than one month. The reason for the difference in mortality between the studies by Majeed (32%) and Schulman (14%) is unclear but also not explainable by exclusion criteria. Given the heterogeneity of the study inclusion criteria, mortality time frame definitions, and mortality rates, no definitive conclusions can be drawn from comparing PCC mortality rates to Andexxa. The magnitude of the difference in thromboembolic rates is notable and suggestive though cannot prove PCC has lower thromboembolic events. In relation to hematoma enlargement, Gerner et al. [25] found no difference in hematoma expansion with or without PCC with a mortality at discharge of 19.9%. However, there was no follow-up imaging in 20% of the patients and did not control for many possible confounders.

Address Off-Label Medication Use

Some clinicians may feel obligated to use Andexxa due to the FDA labeling for apixaban- or rivaroxaban-related severe bleeding rather than PCC which does not have the FDA labeling. However, the FDA does not limit or control how the medications are prescribed by physicians once the medications are available on the market. According to a recent United States appellate court case, "courts and the FDA have recognized the propriety and potential public value of unapproved or off-label drug use." [26]. The American Medical Association supports "the autonomous clinical decision-making authority of a physician and that a physician may lawfully use an FDA-approved drug product or medical device for an off-label indication when such use is based upon sound scientific evidence or sound medical opinion" [27]. Furthermore, "once a drug has been approved for marketing, a physician may prescribe it for uses or in treatment regimens or patient populations that are not included in the approved labeling" [28]. The FDA also states that "unapproved" or more precisely "unlabeled" uses may be appropriate and rational in certain circumstances. For an example, off-label use of intravenous amiodarone for atrial fibrillation is routine while most do not use quinidine or procainamide despite the FDA labeling. We encourage committees to get the explicit support of their risk or legal departments if they have concerns, so that clinicians feel fully supported in off-label use when an alternative FDA labeled drug is available.

Consider Conflicting Society Recommendations and Conflict of Interest

Currently, there are conflicting society recommendations regarding the management of NOAC-related bleeding. The American Society of Hematology explicitly states it has no clinical preference for Andexxa or PCC [19]. The American College of Cardiology (ACC) gives andexanet alfa a class 2 recommendation without comparing to PCC in its recent guideline updates [29]. The American College of Chest Physicians and others state a preference for Andexxa if available [30–32]. In a recent communication in CHEST, the guideline authors clarified that the recommendation in favor of Andexxa was merely a consensus statement and not a guideline recommendation [33, 34]. Furthermore, P&T committees should be aware of conflict of interest (COI) of guideline writers as well as carefully reviewing the grounds for their choices [35]. According to the Institute of Medicine, ideally no guideline writers should have COI [36]. However, the chair and majority of the committee members should not have COI if this is not feasible. This is also the policy of the ACC [37]. Recent American College of Physicians guidelines are even stricter regarding COI [38]. Any COI should be addressed because merely disclosing COI is probably not adequate [39]. This is to reduce unintentional or unconscious influence of judgment and not to challenge an individual's integrity. P&T committees need to assess if society recommendations address the issues discussed in this review and formulate their own conclusions regarding those recommendations. Clinicians with expertise in neurocritical care should be involved if possible.

Examine Financial Impact

P&T committees at hospitals are responsible for the issues relating to the safe and therapeutic use of medications. With the spiraling drug costs, healthcare systems are faced with the challenges of fulfilling their missions and obligations to use resources to best serve the good of the patients and community. The current average wholesale price for 4-Factor PCC is $1.62 per unit. Based on the average mean dose in a retrospective study of 4-Factor PCC in FXa inhibitor-related bleeding, it could cost around $4973 per treatment [40]. The costs of low dose and high dose of Andexxa are approximately $29,040 and $58,080, respectively. The average cost difference is well over $20,000 or $53,100 when compared to low or high-dose Andexxa to PCC. It is ethical and appropriate for P&T committee to consider the impact of a very high cost expenditure on the hospital's ability to provide quality services to all patients [41]. This is particularly true in the absence of sufficient data to show superiority over the less expensive agent.

Summary

We should be judicious in following consensus statements not based on head-to-head comparison with current best practice. A P&T committee that carefully deliberates on the issues raised above may choose whether or not to add Andexxa to the formulary. Additionally, facilities that have chosen to add Andexxa to formulary may reassess if they previously did not consider all the facts listed above. We hope this information can help healthcare institutions make the most informed decision that will be embraced by key stakeholders.

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Conflict of interest

All authors declare that they have no conflict of interest.

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References

1. ANDEXXA [Internet]. Fda.gov. 2018 [cited 2019 Sep 23]. Available from: https://www.fda.gov/media/113279/download.
2. Connolly SJ, Crowther M, Eikelboom JW, et al. Full study report of Andexanet Alfa for bleeding associated with factor Xa inhibitors. N Engl J Med. 2019;380:1326–35.
3. May 3, 2018 Summary Basis for Regulatory Action-ANDEXXA [Internet]. Fda.gov. 2019 [cited 2019 Sep 10]. Available from: https://www.fda.gov/media/113954/download. p. 1.
4. Bryan W. Office Director's Memo, May 2, 2018 [Internet]. Fda.gov. 2018 [cited 2019 Sep 4]. Available from: https://www.fda.gov/media/113960/download.
5. Malarkey M, Bryan W. May 3, 2018 Approval Letter - ANDEXXA. [online] Fda.gov. Available at: https://www.fda.gov/media/113285/download. Accessed 4 Sep. 2019. p. 2–3.
6. Trial of Andexanet in ICH Patients Receiving an Oral FXa Inhibitor—Full Text View—ClinicalTrials.gov [Internet]. Clinicaltrials.gov. 2019 [cited 2019 Sep 24]. Available from: https://clinicaltrials.gov/ct2/show/NCT03661528?cond=andexanet&rank=3.
7. Fleming TR, DeMets DL. Surrogate endpoints in clinical trials: are we being misled? Ann Intern Med. 1996;125:605–13.
8. Kemp R, Prasad V. Surrogate endpoints in oncology: when are they acceptable for regulatory and clinical decisions, and are they currently overused? BMC Med. 2017;15:134.
9. Miller K, Wang M, Graloq J, et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. N Engl J Med. 2007;357(26):2666–76.
10. Cardiac Arrhythmia Suppression Trial (CAST) Investigators. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. New N Engl J Med. 1989;321(6):406–12.
11. Mayer S, Brun N, Begtrup K, et al. Efficacy and safety of recombinant activated factor VII for acute intracerebral hemorrhage. N Engl J Med. 2008;358:2127–37.
12. Hall C, Mirski M, Palesch Y, Diringer M, Qureshi A, Robert C, et al. Clinical trial design in the neurocritical care unit. Neurocrit Care. 2012;16:6–19.
13. Broderick JP, Brott TG, Duldner JE, Tomsick T, Huster G. Volume of intracerebral hemorrhage: a powerful and easy-to-use predictor of 30-day mortality. Stroke. 1993;24:987–93.
14. Hemphill JC 3rd, Bonovich DC, Besmertis L, Manley GT, Johnston SC. The ICH score: a simple, reliable grading scale for intracerebral hemorrhage. Stroke. 2001;32:891–7.
15. Purrucker JC, Haas K, Rizos T, et al. Early clinical and radiological course, management, and outcome of intracerebral hemorrhage related to new oral anticoagulants. JAMA Neurol. 2016;73:169–77.
16. Houben R, Schreuder F, Bekelaar KJ, Claessens D, van Oostenbrugge RJ, Staals J. Predicting prognosis of intracerebral hemorrhage (ICH): performance of ICH score is not improved by adding oral anticoagulant use. Front Neurol. 2018;9:100.
17. Inohara T, Xian Y, Liang L, et al. Association of intracerebral hemorrhage among patients taking non-vitamin K antagonist vs vitamin K antagonist oral anticoagulants with in-hospital mortality. JAMA. 2018;319:463–73.
18. Culbreth S, Rimsans J, Sylvester K, Pallin D, Connors J. Andexanet alfa—the first 150 days. Am J Hematol. 2019;94(1):E21–4.
19. Witt D, Nieuwlaat R, Clark N, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: optimal management of anticoagulation therapy. Blood Adv. 2018;2(22):3257–91.
20. Frontera JA, Lewin JJ 3rd, Rabinstein AA, et al. Guideline for reversal of antithrombotics in intracranial hemorrhage: a statement for healthcare professionals from the neurocritical care society and society of critical care medicine. Neurocrit Care. 2016;24:6–46.
21. Tomaselli G, Mahaffey K, Cuker A, et al. 2017 ACC expert consensus decision pathway on management of bleeding in patients on oral anticoagulants. J Am Coll Cardiol. 2017;70(24):3042–67.
22. Piran S, Khatib R, Schulman S, et al. Management of direct factor Xa inhibitor-related major bleeding with prothrombin complex concentrate: a meta-analysis. Blood Adv. 2019;3:158–67.
23. Schulman S, Gross PL, Ritchie B, et al. Prothrombin complex concentrate for major bleeding on factor Xa inhibitors: a prospective cohort study. Thromb Haemost. 2018;118(5):842–51.
24. Majeed A, Agren A, Holmstrom M, et al. Management of rivaroxaban- or apixaban-associated major bleeding with prothrombin complex concentrates: a cohort study. Blood. 2017;130:1706–12.

25. Gerner ST, Kuramatsu JB, Sembill JA, et al. Association of prothrombin complex concentrate administration and hematoma enlargement in non-vitamin K antagonist oral anticoagulant-related intracerebral hemorrhage. Ann Neurol. 2018;83:186–96.
26. U.S v Caronia. 703 F.3d 149 (2d Cir. 2012).
27. Policy Finder AMA [Internet]. Policysearch.ama-assn.org. 2015 [cited 2019 Sep 14]. Available from: https://policysearch.ama-assn.org/policyfinder/detail/off-label?uri=%2FAMADoc%2FHOD.xml-0-201.xml.
28. Food and Drug Administration. Use of approved drugs for unlabeled indications. FDA Drug Bull. 1982;12:4–5.
29. January CT, Wann LS, Calkins H, et al. AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2019;74:104–32.
30. Christensen H, Cordonnier C, Kõrv J, et al. European stroke organisation guideline on reversal of oral anticoagulants in acute intracerebral haemorrhage. Eur Stroke J. 2019. https://doi.org/10.1177/2396987319849763.
31. Cuker A, Burnett A, Triller D, et al. Reversal of direct oral anticoagulants: guidance from the Anticoagulation Forum. Am J Hematol. 2019;94:697–709.
32. Lip GYH, Banerjee A, Boriani G, et al. Antithrombotic therapy for atrial fibrillation: CHEST guideline and expert panel report. Chest. 2018;154(5):1121–201.
33. Lip GYH, Ruff CT, Moores L, Panel CGE. Response Chest. 2019;155:1309.
34. Peled H, Dau NQ. Prothrombin complex concentrate or coagulation factor Xa (Recombinant), Inactivated-zhzo. Chest. 2019;155:1308.
35. Beauchamp T, Childress J. Principles of biomedical ethics. 7th ed. New York: Oxford University Press; 2013. p. 331.
36. IOM (Institute of Medicine). Clinical Practice Guidelines We Can Trust [Internet]. Washington DC: The National Academies Press; 2011 [cited 2019 Sep 10]. Available from: https://www.nap.edu/read/13058/chapter/6.
37. Relationships with Industry Policy—American College of Cardiology [Internet]. American College of Cardiology. 2016 [cited 2019 Sep 4]. Available from: https://www.acc.org/guidelines/about-guidelines-and-clinical-documents/relationships-with-industry-policy.
38. Qaseem A, Kansagara D, Lin JS, Mustafa RA, Wilt TJ, Clinical Guidelines Committee of the American College of Physicians. The development of clinical guidelines and guidance statements by the clinical guidelines committee of the American College of Physicians: update of methods. Ann Intern Med. 2019;170(12):863–70.
39. Jaeschke R, Guyatt GH, Schunemann H. Ten things you should consider before you believe a clinical practice guideline. Intensive Care Med. 2015;41:1340–2.
40. Smith MN, Deloney L, Carter C, Weant KA, Eriksson EA. Safety, efficacy, and cost of four-factor prothrombin complex concentrate (4f-pcc) in patients with factor Xa inhibitor-related bleeding:a retrospective study. J Thromb Thrombolysis. 2019;48(2):250–5.
41. Anderson JL, Heidenreich PA, Barnett PG, et al. ACC/AHA statement on cost/value methodology in clinical practice guidelines and performance measures: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures and Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63:2304–22.