

# Andexanet alfa

Craig Hertz, DO FAAEM; Iosif Davidov, MD, PGY-2; and Dorjan Pantic, MD, PGY-6



**A**s our populations age, incurring increases in cardiovascular and neoplastic disease, the use of anticoagulants is bound to rise. Over the past

decade there has been a shift from vitamin K antagonists to more targeted anticoagulants, specifically factor Xa inhibitors (Xa inhibitors). Reasons behind this shift are numerous, with reduced potential for major bleeding being one. Despite the reduced bleeding risk, patients on Xa inhibitors who develop major bleeding require mitigation and anticoagulation reversal, previously accomplished with entities such as Prothrombin Complex Concentrates (4-factor (4F PCC), 3-factor, Activated or Inactivated). Now Coagulation Factor Xa (Recombinant), Inactivated-zhzo, or andexanet alfa, appears on the scene as an alternative under accelerated FDA approval.<sup>1</sup>

Andexanet alfa – approved in 2018 – is a Xa specific decoy molecule for patients afflicted by “life-threatening or uncontrolled bleeding” who are taking rivaroxaban or apixaban<sup>2</sup> and was approved under the Accelerated Approval Requirements by the Federal Drug Administration in accordance with rules for an unmet need in medical therapy/treatment.<sup>1,3</sup>

The Andexanet alfa, a Novel Antidote to the Anticoagulation Effects of Factor Xa Inhibitors (ANNEXA) studies (ANNEXA-R[ivroxaban], ANNEXA-A[pixaban]) and most recently ANNEX-4,<sup>4</sup> paved the way for accelerated approval and rapid acceptance as the primary therapeutic agent for patients with life-threatening bleeding on rivaroxaban or apixaban. As with any new agent, there are pros and cons.

## Pro

The andexanet alfa molecule is currently the only medication that acts as a decoy for Xa inhibitors rivaroxaban and apixaban.<sup>5</sup> Once bound, the ANNEXA-4 study demonstrated a 92% reduction in anti-factor Xa activity levels in patients on rivaroxaban or apixaban. Patients suffering from gastrointestinal bleeding (26% of study population) demonstrated

an 85% improvement<sup>6</sup> in hemostatic efficacy.<sup>4,7</sup> The impact of this effect was immediate – less than four minutes – and lasted up to four hours.<sup>4</sup> The half-life of rivaroxaban and apixaban is 9-12 hours<sup>8,9</sup> with previous therapy for major bleeding being 4F PCC, possibly adjunct agents (i.e. tranexamic acid) and give it time, thus a four hour window of improved hemostatic efficacy and reduced bleeding risk provides the bridge clinical practitioners and patients have been looking for.

Though no current study has compared the efficacy of andexanet alfa to 4F PCC, we can infer the potential benefit of andexanet alfa over 4F PCC from andexanet alfa’s 85% hemostatic efficacy<sup>6</sup> of bleeding risk in gastrointestinal (GI) bleeding and 80% hemostatic efficacy<sup>10</sup> in intracranial hemorrhage (ICH) volume expansion.<sup>4,7</sup> Mortality within a PCC study population study (70.4% ICH predominance) was higher at 32% compared to andexanet alfa (43% ICH predominance) mortality of 14% at 30 days.<sup>4,7,11</sup> Furthermore, a study using similar criteria to the ANNEXA-4 group, for evaluation of PCC was deemed 69.1% effective in hemostasis compared to andexanet alfa 82% hemostatic efficacy.<sup>4,7,11</sup>

Taking the above data in to account, several review articles on treatment of hemorrhage for patients taking rivaroxaban or apixaban have added andexanet alfa into the recommended repertoire. August 2019, *Emergency Medicine Practice* lists “Coagulation factor Xa (recombinant), inactivated-zhzo” as “first line” treatment in their flow to reverse Xa inhibitor hemorrhages.<sup>12</sup> The *CHEST* journal, September 2019 suggest andexanet alfa for reversal of major hemorrhage, as does the Emergency Medicine and Cardiac Research and Education Group.<sup>13,14</sup> Desai, et al., in *Hospital Practice*, July 2019 offer andexanet alfa as the primary reversal agent for “major or life-threatening” bleeding or “need for emergency surgery/procedure.”<sup>15</sup>

Putting it all together, biochemically and – by surrogacy – clinically, patients with major or life-threatening hemorrhage on rivaroxaban or apixaban, there is a reasonable argument andexanet alfa is the treatment of choice to reduce the risk of further bleeding and improve hemostatic efficacy.

**We must be stewards for our patients who may only read or hear about some new “FDA” medication. Andexanet alfa is a ~\$50,000 per high dose medication which temporarily reduces inhibition of Xa levels in patients on rivaroxaban or apixaban.**



Industry sponsorship aside, the ANNEXA-4 study provided us 249 patients in which only an efficacy arm was evaluated (60 GI Bleed, 168 ICH, 21 Other)—no control arm.<sup>7</sup> We concede the biochemical findings are impressive, though the use of a laboratory value as a surrogate for clinical improvement is inherently limited and potentially flawed. Furthermore, the primary endpoint in ANNEXA-4 changed to include laboratory value reduction as a *second* primary endpoint, with the original single primary endpoint of hemostatic efficacy “only tested if a change in anti-[factor]Xa active was *first* demonstrated.”<sup>7</sup> Therefore, could this additional primary endpoint reduce hemostatic efficacy testing – i.e. reduced denominator – skewing the hemostatic efficacy findings and artificially inflate improvements? In short, we have no evidence that andexanet alfa improves morbidity, mortality, or that it does so better than the current treatment(s), such as 4F PCC.

Although the current studies have not directly compared efficacy of 4F PCC versus andexanet alfa, we can pull upon the body of PCC literature and modestly say even PCC does not demonstrate the rapid, almost complete reversal of abnormal biochemical laboratory values.<sup>11</sup> If we are to use a biochemical test as surrogacy for clinical outcomes, how should we address the ~24% of patients being excluded – despite meeting bleeding criteria – due to their anti-factor Xa levels being “too low?”<sup>4</sup> While intuitively these patients would unlikely benefit – biochemically – from andexanet alfa, the exclusion of these patients yields a different population than we would encounter clinically. Furthermore, this exclusion, without demonstrating hemostatic efficacy and/or clinical improvement, raises concern for selection bias and whether or not such clinical end-points are achievable.

Andexanet alfa’s function is based on its decoy receptor property with limited duration- 4 hours- and concerns of rebound Xa levels after infusion.<sup>4,7</sup> Andexanet alfa also not eliminate Xa inhibitors in plasma—that is to say, the decoy binding is temporary and later releases the Xa inhibitors.<sup>4,7</sup> Based on the decoy properties, andexanet alfa is being touted as a reversal agent; while not untrue in a strict sense, it should be made clear andexanet alfa does not definitively remove the Xa inhibitors – unlike idarucizumab the reversal agent for dabigatran, which permanently binds dabigatran.

In contrast, PCC functions as a “replacement agent” by providing clotting factors involved in the clotting cascade, (i.e. factors X, IX, VII, II ), thus, allowing a dose-dependent circumvention of the inhibited Xa. Factor X’s half-life of 24-48 hours provides a longer duration of action compared to andexanet alfa<sup>16</sup> (4 hours). Baugh, et al., provides an excellent discussion on this topic, suggesting 4F PCC as first-line when andexanet alfa is not available.<sup>17</sup> At current it would appear andexanet alfa is a reversal agent of biochemical markers though is yet to be a proven one of active bleeding, a more clinically relevant end point. The FDA reiterated this:

“This approval requires you to study the biological product further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit...”<sup>1</sup>

Furthermore, Ryan Radecki in “Disutility, Thy Name is ANEXXA-4” quotes the ANEXXA-4 study:

“Reduction in anti-factor Xa activity was not predictive of hemostatic efficacy overall but was modestly predictive in patients with intracranial hemorrhage.”<sup>4,8</sup>

It should not go without mention andexanet alfa is associated with thrombosis of 10% within 30 days. This is a factor to consider when giving andexanet alfa in patients with unclear morbidity and potentially long-term mortality as a result of associated thrombotic risk. Thrombosis primarily occurred in patients in which anticoagulation was not restarted “immediately,”<sup>4,7</sup> though the thrombotic culprit remains unclear, and 10% appears unexpectedly high.

### As our populations age, incurring increases in cardiovascular and neoplastic disease, the use of anticoagulants is bound to rise.

Peled, H., et al., in a response to Lip, G., et al., in *CHEST*, suggested “The cost-benefit analysis of available treatments is critical in any health-care ecosystem. For patients who truly present with life-threatening non-vitamin K antagonist oral anticoagulant-associated bleeding, we felt the opportunity to save more lives warrants preference of specific reversal agents over PCCs.”<sup>19</sup> Thus, we must address the ~\$50,000<sup>20</sup> gorilla in the room... the approximate cost per patient who requires the high dose (800mg) andexanet alfa rather than the low dose 400mg.<sup>21</sup> Even with the Center for Medicare & Medicaid services offering a reimbursement program up to ~\$18,200<sup>22</sup> there is still a substantial cost burden to healthcare facilities and potentially patients. Haque, et. al., provides us an interesting perspective regarding the cost effectiveness of andexanet alfa, suggesting it is more cost-effective for GI bleeding than ICH by a factor of ~5 (\$40,718 GI bleed v \$211,056 ICH; cost-effectiveness ratio- andexanet alfa v standard of care).<sup>23</sup> Their work further expands the need for clinically relevant outcomes and comparative studies to current standards of care, especially considering Deitelzweig et al’s work suggesting the economic burden for “mean total all-cause healthcare cost” for ICH was ~\$90,000.<sup>24</sup> As evidence-based quality is at the forefront of healthcare, we must be aware of the cost burden to patients, caregivers, and communities.

What about the review articles suggesting use of andexanet alfa as the reversal agent of choice for life-threatening or major bleeding? Diving into them, take for example, Maher, et al., in *Emergency Medicine Practice*,<sup>13</sup> despite listing andexanet alfa as “first line” it is followed by stating it is “Class IV” evidence- defined as “indeterminate.”<sup>25</sup> Baugh, et al’s, *Annals of Emergency Medicine* expert panel publication recommends andexanet alfa, unless it is unavailable, or replacement of factors is felt warranted rather than reversal (i.e. dosing of andexanet alfa)- it should also be clear “the expert panel meeting was convened with funds from unrestricted educational grants from Portola Pharmaceuticals and Boehringer Ingelheim.”<sup>17</sup> Furthermore, several of these articles conflict one another and/or FDA sentiments, suggesting andexanet alfa for reversal in patients who need “emergency surgery/procedure.”<sup>15</sup> Only the National Institute for Health and Care Excellence (N.I.C.E) is slated to have a viewpoint in 2020,<sup>26</sup> other guideline agencies such as Cochrane and Emergency Care Research Institute (ECRI) had no information about andexanet alfa during the time of this writing.



CRITICAL CARE MEDICINE In an aim to improve the value of care: Value=Quality/Cost, driven by evidence-based practices, we cannot say that andexanet alfa has proven to improve value or quality, although it does increase cost. The lacking support for clinical improvements, with none due for another 4-10 years, is concerning when it comes to the rapid assimilation into articles suggesting andexanet alfa as “first line” therapy – more concerning when various articles continue to only cite one another, and consensus guidelines are industry sponsored. Based on the above, there is a reasonable argument andexanet alfa is not actually the treatment of choice to improve the value of care in major bleeding for patients on rivaroxaban or apixaban.

### Let's Be Real

We agree new medications, needed medications, and medications which can impact lives require a more streamlined approval, implementation, and reimbursement process. We caution clinical, administrative, and policy groups in rapid adoption, when the downstream impact is not fully elucidated. There are already over a hundred articles on andexanet alfa – including this one – which continually cite, sponsor, and quote one another. While several more clinical trials – randomized double blinded, comparison, etc. – are pending for andexanet alfa, none of these (at current) are due for completion until the mid-2020's. Using surrogate markers for clinical outcomes can be a stretch (i.e. pro-brain natriuretic peptide, D-dimer, troponins); we know this; we live this. We must be stewards for our patients who may only read or hear about some new “FDA” medication. Andexanet alfa is a ~\$50,000 per high dose medication which temporarily reduces inhibition of Xa levels in patients on rivaroxaban or apixaban. Based on the published literature this is all we can conclude. What has been extrapolated is: andexanet alfa is a medication which reverses Xa inhibitors and stops life-threatening bleeding. While it may or may not be true, we must be cognizant of the all the variables that play into providing cost effect, evidence based, patient partnered, quality care. ●

### References:

1. Accelerate Approval: BL 125586/0. U.S. Food and Drug Administration, FDA. May 3, 2018
2. ANEXXA® Prescribing Information. Revised 12/2018 Rivaroxaban and apixaban are the only two Xa inhibitors thus far tested
3. FDA Accelerated Approval: “Qualifying Criteria: Treats a serious condition that generally provides a meaningful advantage over available therapies. Features: Can approve on the basis of a surrogate or intermediate endpoint that is reasonably likely to predict a clinical benefit.” <https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/accelerated-approval>
4. Connolly, S.J., et al. Full Study Report of Andexanet alfa for Bleeding Associated with Factor Xa Inhibitors. *New England Journal of Medicine*, 380 (14): 2/7/2019; Updated Apr 18, 2019
5. It may bind others- edoxaban or betrixaban- to date, published studies and approval is based on apixaban and rivaroxaban
6. Not requiring further transfusion of blood products or <20% decrease in hemoglobin/hematocrit as compared to baseline over 12 hours; See footnote- 4,7
7. Connolly, S.J., et al. Full Study Report of Andexanet alfa for Bleeding Associated with Factor Xa Inhibitors. *New England Journal of Medicine*, 380 (14): 2/7/2019; Updated Apr 18, 2019- supplemental

8. Lexicomp, apixaban. Accessed 8/20/2019 <http://online.lexi.com/lco/action/search;jsessionid=084e4e198ff1e22a25b5bc132499?origin=api&t=globaid&q=512790&nq=true>
9. Lexicomp, rivaroxaban. Accessed 8/20/2019: <http://online.lexi.com/lco/action/search?q=rivaroxaban&t=name&va=rivaroxaban>
10. 85% efficacy in preventing more than 20% decrease in corrected hemoglobin and hematocrit at 12 hours, 80% efficacy 35% increase in intracranial hemorrhage volume expansion- see footnote 7
11. Majeed, A., et al. Management of rivaroxaban- or apixaban- associated major bleeding with prothrombin complex concentrates: a cohort study. *Blood*. 130(15): 10/12/2017. Pg 1706-1712
12. Maher, P., et al. Emergency Department Management of Patients Taking Director Oral Anticoagulant Agents. *Emergency Medicine Practice: An Evidence-Based Approach to Emergency Medicine*. 21(8); 8/2019
13. Rali, R., et al. Direct-Acting Oral Anticoagulants in Critically Ill. *Chest Journal*. 156(3): 9/2019. Pg 604-618
14. Fermann, G., et al. Management of Life-Threatening Bleeding in the Anticoagulated Patient in the Emergency Setting and the Impact of ANEXXA-4 on the Treatment of Patients Taking Factor Xa Inhibitors. *Emergency Medicine Cardiac Research and Education Group*. 8/2019
15. Desai, N., et al. Reversal Agents for Direct Oral Anticoagulants: Considerations for Hospital Physicians and Intensivists. *Hospital Practice*. 7/2019
16. Lexicomp, Prothrombin Complex Concentrate (Human) [(Factors II, VII, IX, X), Protein C, and Protein S]. Accessed 1/12/2020. [http://online.lexi.com/lco/action/doc/retrieve/docid/patch\\_f/1034779?cesid=4hRVhUoEBY5&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3Dkcentra%26t%3Dname%26va%3Dkcentra](http://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/1034779?cesid=4hRVhUoEBY5&searchUrl=%2Ffco%2Faction%2Fsearch%3Fq%3Dkcentra%26t%3Dname%26va%3Dkcentra)
17. Baugh, C., et al. Anticoagulant Reversal Strategies in the Emergency Department Setting: Recommendations of a Multidisciplinary Expert Panel. *Annals of Emergency Medicine*. 0(0). Published online 11/2019
18. Radeck, Ryan. Disutility, Thy Name is ANEXXA-4; updated 2/7/2019 <https://www.emlitofnote.com/?p=4384>
19. Peled, H., et al. Response- Prothrombin Complex Concentrate or Coagulation Factor Xa (Recombinant), Inactivated-zhzo. *CHEST Journal*. 155(6): 6/2019. pg 1308
20. Extracted from Analy\$ource 11.12.2019
21. High dose indications: Patient on Apixaban at >5mg or unknown dose, < 8 hours from last dose; Rivaroxaban >10mg or unknown dose, < 8 hours from last dose. Low dose: Apixaban ≤ 5 mg, ≥ 8 hours from last dose; Rivaroxaban ≤ 10mg, ≥ 8 hours from last dose. Lexicomp: Factor Xa (recombinant), Inactivated-zhzo. Accessed 1/12/2020. [http://online.lexi.com/lco/action/doc/retrieve/docid/essential\\_ashp/6671728#dosage-admin-nested](http://online.lexi.com/lco/action/doc/retrieve/docid/essential_ashp/6671728#dosage-admin-nested)
22. <https://www.andexxa.com/ordering#reimbursement>. Accessed 12.26.2019
23. Haque, M., et al. Beginning to Understand the Cost-effectiveness of Andexxa. *Georgetown Medical Review*. 3(1). 2019
24. Deitelzweig, S., et al. Incremental economic burden associated with major bleeding among atrial fibrillation patients treated with factor Xa inhibitors. *Journal of Medical Economics*. 20(12): 8/2017. Pg 1217-1223
25. See f.n. 13: Indeterminate: Continuing area of research; No recommendations until further researching: Evidence not available; Higher studies in progress; Results inconsistent, contradictory; Results not compelling
26. NICE Guidance. Andexanet alfa for Reversing Anticoagulation [ID1101]. Expected 6/2020. <https://www.nice.org.uk/guidance/indevelopment/gid-ta10440>