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Andexanet Response

To the Editor:

We read with interest the *Annals* Journal Club entry on andexanet alfa by Radecki and Spiegel.[1] There are several issues with the discussion that we would like to address. First, the authors state that the preclinical work for idarucizumab was extensive enough arguably to make a placebo arm in the ReverseAD trial unethical. By implication, the authors contend andexanet had no such preclinical work and therefore the lack of a control arm in the ANNEXA-4 study was unethical. This is inaccurate. The development programs for both drugs had extensive preclinical programs in animals and cohorts of nonbleeding human beings.[2-5] The approval pathways were discussed with the Food and Drug Administration and thought leaders at the White Oak campus at the same meeting in 2014, the results of which were published.[6]

Both trials, ReverseAD and ANNEXA-4, were launched shortly thereafter. This was only a few years after the approval of dabigatran in 2010 and rivaroxaban in 2011. At that point, only 2 published human studies,[7,8] 2 healthy normal cohorts of a total of 22 patients, had examined prothrombin complex concentrate for direct oral anticoagulant reversal. There were equally "valid" alternatives to idarucizumab and andexanet if one is to be compelled by such a paucity of evidence. Off-label use of prothrombin complex concentrates for dabigatran and factor Xa inhibitors began because there were no other options for patients bleeding to death who received these drugs. There was little structure to the accumulation of evidence and no regulatory oversight. The use of prothrombin complex concentrate in dabigatran or factor Xa inhibitor bleeding also lacks a reasonable hypothesis underpinning it. How can prothrombin complex concentrate reverse the anticoagulant effect, given the low concentration of factor Xa molecules in even a large dose of prothrombin complex concentrate relative to the concentration of circulating inhibitors? Although one can hypothesize that the substantial prothrombin provided by prothrombin complex concentrate is sufficient to "overwhelm" the anticoagulant effect, this excess is unlikely to be of benefit, given that uninhibited factor Xa is needed to convert it to thrombin. There were 2 small prospective uncontrolled cohorts of prothrombin complex concentrate for factor Xa inhibitor reversal of 84 and 66 patients published while ANNEXA-4 was ongoing.[9,10] As ANNEXA-4 investigators noted in the full-cohort publication,[11] this led to a perception, rightly or wrongly, of clinical equipoise during the trial period that did not exist before it.

This makes Radecki and Spiegel's assertion on the ethics of ANNEXA-4 puzzling. To suggest that a single-arm ANNEXA-4 trial was unethical is confusing the events of the past decade. It is holding investigators accountable for knowledge that did not exist at trial design and was not published until years later.

Because dabigatran use has decreased and factor Xa inhibitor use has skyrocketed in the United States, the cost of andexanet has received much attention. A single

low dose of andexanet costs $24,000, which is the dose 85% of the patients in the trial received. Essentially, the only patients who received a high dose ($48,000) were those who received higher doses of factor Xa inhibitors less than 8 hours before andexanet dosing. Andexanet is by no means cheap, but calling it a $50,000 drug is misleading. Cost-effectiveness and number needed to treat are problematic to calculate without control groups for both andexanet and prothrombin complex concentrate. But this should not conflate the evidence for efficacy alone. Andexanet has a reasonable mechanism and underlying hypothesis by stoichiometrically sequestering the factor Xa inhibitor drug, allowing native factor Xa to function in the clotting cascade. It has an extensive preclinical program, including several animal models and hundreds of healthy and older adults. It has a prospective cohort study with well-defined outcomes in 352 patients with major bleeding, with academic oversight and adjudication of safety and efficacy and regulatory oversight. It has Food and Drug Administration and European Medicines Agency approval, and a randomized trial is in progress to address potential uncertainties in benefit:risk. Prothrombin complex concentrate makers have not embarked on this lengthy and costly path, and we will probably never know whether prothrombin complex concentrate is either safe or effective.

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FDA Approval of Andexanet Alfa Based on a Single-Arm Trial: If There Is a Villain, Who Is It?

To the Editor:

A recent *Annals* Journal Club piece critiqued ANNEXA-4, sponsored by Portola Pharmaceuticals, the manufacturer of andexanet, arguing that it was unethical to conduct a single-arm trial, and that a placebo-controlled design should have been used.[1,2] I was a coauthor on the critiqued article and chaired the sponsor's Medical Advisory Panel that preceded Food and Drug Administration (FDA) approval and the drug's launch, for pay.

The Journal Club piece suggests that something nefarious is afoot in the commercialization of andexanet. If so, who's the villain? People use "structural violence" to refer to harm from social structures, rather than ill intent of individuals. "Structural violence is one way of describing social arrangements that put individuals and populations in harm's way," said Paul Farmer.[3] I suggest that we are dealing with a "structural" problem in drug development.