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REVIEW OF ANDEXANET ALFA AND IMPLICATIONS FOR GLOBAL HEALTH

As direct oral anticoagulants (DOACs) are being more frequently prescribed, there is a pressing need for a reversal agent for these medications. Dabigatran was the first DOAC to have a specific reversal agent with the approval of idarucizumab (Praxbind®). A new reversal agent called andexanet alfa (Andexxa®), manufactured by Portola Pharmaceuticals and was approved by FDA in May 2018 for patients treated with rivaroxaban or apixaban that are experiencing life-threatening or uncontrolled bleeding. It is a modified recombinant form of the human factor Xa protein that is capable of reversing both direct and indirect factor Xa inhibitors.[1]

Andexanet alfa is produced following several chemical modification on factor Xa. The active site serine of human factor Xa, was substituted with alanine. This modification prevents the medication from activating prothrombin. Another modification was the elimination of the gamma-carboxyglutamic acid domain, which prevents the protein from assembling into the prothrombinase complex. In terms of mechanism, andexanet alfa functions by mimicking factor Xa and thus allowing the factor Xa inhibitors to bind to it rather than to the human factor Xa. Andexanet alfa also inhibits tissue factor pathway inhibitor, which leads to an increase in tissue factor-initiated thrombin generation.[1]

In terms of safety, andexanet alfa does have a Black Box Warning for serious and life-threatening effects such as arterial and venous thromboembolic events, ischemic events, cardiac arrest, and sudden deaths. Due to these risks, patients should be closely monitored and anticoagulation should be initiated only when medically appropriate. The most common adverse event based on clinical trial data was infusion-related reactions (frequency of 18%). These reactions included flushing, cough, dysgeusia, and dyspepsia. The symptoms were mild-to-moderate in severity and 90% of patients experiencing these effects did not require treatment.[1,2]

There are two dosing regimens available for andexanet alfa. The regimen used is based on specific factor Xa inhibitor given, the factor Xa inhibitor dose, and time since it was last administered. The low dose regimen is a 400mg IV bolus administered at a rate of 30mg/min, followed by a 4mg/min IV infusion for up to 120min. The high dose regimen is an 800mg IV bolus administered at a rate of 30mg/min, followed by an 8mg/min IV infusion for up to 120min.[1,2]

Each package of andexanet alfa contains four 100mg single-use vials, with a wholesale acquisition cost (WAC) of $11,000 per package. The WAC of each 100mg vial is $27,500. For the low dose regimen, the total cost of treatment would be $24,200 ($11,000 for the 400mg IV bolus, plus $13,200 for the maximum duration of the 4mg/min infusion). For the high dose regimen, the total cost of treatment would be $48,400 ($22,000 for the 800mg IV bolus, plus $26,400 for the maximum duration of the 8mg/min infusion).[3]

ANNEXA-A and ANNEXA-R are the two clinical trials that led to the approval of andexanet alfa in the U.S. The main objective of these trials was to evaluate the safety and efficacy of andexanet alfa in older healthy patients. The studies were conducted at two

clinical sites (Celerion in Tempe, Arizona for ANNEXA-A and West Coast Clinical Trials in Cypress, California for ANNEXA-R). There were 101 total participants (48 in ANNEXA-A, 53 in ANNEXA-R) with similar baseline characteristics. The primary outcome was the mean percent change in anti-factor Xa activity. In the ANNEXA-A trial, patients received 5mg of apixaban twice daily for 3.5 days. Three hours after the last dose of apixaban (day 4 of the trial), they received either a placebo or a 400mg IV bolus of andexanet alfa alone (part 1) or followed by a continuous infusion of 4mg/min for 120min (part 2). In the ANNEXA-R trial, patients received 20mg of rivaroxaban once daily for 4 days. Four hours after the last dose (day 4 of the trial), they received either a placebo or an 800mg IV bolus of andexanet alfa alone (part 1) or followed by a continuous infusion of 8mg/min for 120min (part 2). In both studies, anti-factor Xa activity was rapidly reduced (within 5 min) to a greater extent with andexanet alfa IV bolus compared to placebo (94±2% vs. 21±9% in ANNEXA-A and 92±11% vs. 18±5% in ANNEXA-R; $p<0.001$ in both groups). Anti-factor Xa activity was also reduced more than placebo when andexanet alfa was administered as an IV bolus followed by a continuous infusion (92±3% vs. 33±6% in ANNEXA-A and 97±2% vs. 45±12% in ANNEXA-R; $p<0.001$ in both groups). The reversal of anti-factor Xa activity with andexanet alfa persisted for 1-2 hours after the end of the infusion. Andexanet alfa also improved thrombin generation and reduced unbound anti-factor Xa plasma concentration significantly more than placebo ($p<0.001$ for both measures). No severe adverse events or thrombotic events were reported.[4]

There is an ongoing multicenter clinical trial called ANNEXA-4 that is being conducted for the purpose of evaluating the safety and efficacy of andexanet alfa in patients with acute major bleeding. This study is taking place in 20 centers in the US, 1 center in the UK, and 1 center in Canada. The trial began on April 10, 2015 and is still continuing. Patients are eligible to participate if they are at least 18 years old, received one of four factor Xa inhibitors (apixaban, rivaroxaban, edoxaban, or enoxaparin) within the past 18 hours, and present with acute major bleeding. Sixty-seven patients have been enrolled in the study (32 were taking rivaroxaban, 31 were taking apixaban, and 4 were receiving enoxaparin). For the efficacy analysis, the number was reduced to 47 patients (26 taking rivaroxaban, 20 taking apixaban, 1 taking enoxaparin) due to the other patients not meeting inclusion criteria. Baseline characteristics were similar between both groups. The primary outcomes are the percent change in anti-factor Xa activity and the rate of excellent or good hemostatic efficacy 12 hours after andexanet infusion. The study will continue to enroll participants until there are 162 patients available for the efficacy analysis, with an expected safety population of approximately 230 patients. Regarding the interventions, patients that had taken apixaban or rivaroxaban more than 7 hours before administration of andexanet alfa received an IV bolus dose of 400mg over 15-30min and an infusion dose of 480mg over 2 hours. Patients that had taken enoxaparin, edoxaban, or rivaroxaban 7 hours or less before andexanet administration, or at an unknown time, received an IV bolus dose of 800mg over 15-30min and an infusion dose of 960mg over 2 hours. In the preliminary analyses, anti-factor Xa activity was reduced by 93% in the apixaban group and by 89% in the rivaroxaban group. Additionally, 79% of the patients in the efficacy population (37/47) were determined to have good or excellent hemostasis 12 hours after the andexanet infusion. In terms of safety, thrombotic events occurred in 18% of patients (12/67). In terms of mortality, 15% of the patients died during the study (10/67). Six of these deaths were listed as cardiovascular

events and four as non-cardiovascular. There were no reported infusion reactions or antibodies developed against andexanet alfa.[5] Since this is an ongoing study, results will likely continue to change as more patients become enrolled. When the study has reached sufficient statistical power, further analyses will need to be performed to better establish the relationship between reversal of anti-factor Xa activity and clinical outcomes.

Although andexanet alfa has been approved in the US, it is still awaiting approval in other parts of the world. Between 2012 and 2016, Portola Pharmaceuticals entered into clinical collaboration agreements with manufacturers of the factor Xa inhibitors to support phase II and III trials of andexanet alfa in the US and the European Union, as well as to establish a clinical development program in Japan. The purpose of these agreements is to investigate the use of andexanet alfa as a universal antidote for factor Xa inhibitors. In February 2016, Bristol-Myers Squibb and Pfizer acquired licensing rights from Portola Pharmaceuticals for development and commercialization of andexanet alfa in Japan.[6] In December 2018, Portola Pharmaceuticals announced that the Committee for Medicinal Products for Human Use of the European Medicines Agency (EMA) has extended the review period for the company's marketing authorization application for andexanet alfa. An opinion by the EMA is now expected by February 28, 2019.[7] Andexanet alfa has patent protection and pending patents in countries

such as those of the European Union, China, Singapore, and New Zealand.[6] As clinical trials continue, andexanet alfa may soon become a key medication for reversing factor Xa inhibitors worldwide.

Andexanet alfa has shown significant reductions in anti-factor Xa activity without serious adverse effects in patients presenting with major bleeding. This new medication has the potential to improve global health by allowing factor Xa inhibitors to become safer options for patients who are indicated for them. This may increase the worldwide use of factor Xa inhibitors, which could lead to a global reduction of venous thromboembolism as well as stroke events. The availability of a reversal agent for factor Xa inhibitors would also help reduce the mortality from severe bleeding which may occur from using these agents. If andexanet alfa becomes approved in other countries, it could have a profound impact on health and current anticoagulant therapy practices in the world.

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