New drugs

Andexanet alfa for reversal of direct factor Xa inhibitor anticoagulation

Approved indication: provisionally approved for adult patients treated with a direct factor Xa inhibitor (apixaban or rivaroxaban) when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding

Andexxa (AstraZeneca)
20 mL vials containing 200 mg andexanet alfa as a powder for solution (10 mg/mL after reconstitution), for intravenous administration

Andexanet alfa is a specific reversal agent designed to neutralise the anticoagulant effect of factor Xa (FXa) inhibitors. Direct FXa inhibitors, such as apixaban and rivaroxaban, are oral anticoagulants that are increasingly used for a wide range of approved indications. While they have some benefits over older oral anticoagulants such as warfarin (e.g. fixed dosing without the need for routine anticoagulation monitoring), they are associated with bleeding events, which can be life-threatening. Replacement clotting factor therapies, such as prothrombin complex concentrates, are sometimes used to manage major bleeding associated with FXa inhibitors, but they are not approved for FXa inhibitor reversal and there is little mechanistic evidence supporting their use for this indication.[1]

Andexanet alfa is a recombinantly produced, inactive form of FXa that acts as a decoy to bind and sequester the FXa inhibitor, thereby reducing the free plasma concentration of the FXa inhibitor.[1]

Andexanet alfa has haemostatic efficacy, but its effect on clinical outcomes (e.g. mortality and functional outcomes) compared with usual care is unclear. Placebo-controlled studies were conducted in healthy volunteers dosed with direct FXa inhibitors.[1] There was only one pre-registration study in patients with acute major bleeding following direct FXa inhibitor administration.[1] This was an open-label, single-arm clinical trial of 479 patients, most of whom had an intracranial (69%) or gastrointestinal (23%) haemorrhage. It reported a decrease in anti-FXa activity of up to 94% from baseline, and haemostatic efficacy at 12 hours post-infusion in 80% of patients.[2] The lack of a control arm in this study creates uncertainty regarding the extent to which andexanet alfa contributed to the efficacy outcome, and its impact on clinical outcomes.[1]

Andexanet alfa was approved in the USA in 2018 for life-threatening or uncontrolled bleeding, but is not routinely used due to its high cost and uncertain clinical benefits.[3] Recent nonrandomised, observational studies from the USA have compared outcomes in patients treated with andexanet alfa versus 4-factor prothrombin complex concentrate, following an FXa-related major bleed. These studies reported lower in-hospital and 30-day mortality in patients who received andexanet alfa.[3,4]

The Therapeutic Goods Administration (TGA) has provisionally approved andexanet alfa in Australia (for reversal of apixaban or rivaroxaban anticoagulation in patients with life-threatening or uncontrolled bleeding) on the basis of haemostatic efficacy and reduction in anti-FXa activity. Continued approval depends on verification of the efficacy and safety of andexanet alfa compared to usual care in a confirmatory randomised controlled trial in patients presenting with acute life-threatening bleeding who were taking a direct FXa inhibitor.[1,5] A confirmatory study was underway at the time of TGA assessment, recruiting patients with an acute intracranial haemorrhage. This trial has since been terminated early by its independent data and safety monitoring board, based on the achievement of prespecified criteria for haemostatic efficacy.[6] The full, peer-reviewed results of the trial are not yet available.

Because of insufficient supporting data, andexanet alfa is not approved for reversing the anticoagulant effect of FXa inhibitors prior to surgery and other invasive procedures, treating FXa inhibitor overdose, or reversing the anticoagulant effect of indirect FXa inhibitors such as enoxaparin.[1]

The safety of andexanet alfa is not well established. The placebo-controlled studies were conducted in healthy subjects who did not require anticoagulation and did not have active bleeding, and hence would be expected to have a more favourable safety profile than the proposed treatment population.[1] In addition to binding to FXa inhibitors, andexanet alfa binds to, and inhibits, tissue factor pathway inhibitor. This can increase tissue factor–initiated thrombin generation, inducing a procoagulant effect.[5] In the uncontrolled open-label clinical study, thromboembolic events occurred in 10.4% of patients. The patients in this study had a high underlying risk of thromboembolic events

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given their age, medical comorbidities and withdrawal of medically indicated anticoagulation. In the absence of a control arm, there is uncertainty regarding the extent to which andexanet alfa contributed to thromboembolic events.[1] Non-thromboembolic adverse effects included headache, nausea and infusion reactions (rigors, chills, hypertension, oxygen desaturation, agitation and confusion).[5]

Andexanet alfa is administered in either a low-dose or high-dose regimen, based on the patient's apixaban or rivaroxaban dose and when the last dose was taken. Both andexanet alfa regimens consist of a bolus dose, immediately followed by a 2-hour continuous infusion.[5] Resumption of anticoagulation is recommended as soon as medically appropriate, based on individualised risk of thrombosis from the underlying condition.

Andexanet alfa provides a new option for managing major bleeding associated with rivaroxaban and apixaban; however, its high cost and uncertain clinical benefits compared to current management make its place in treatment uncertain at this time.

T manufacturer provided the AusPAR and the product information. The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA, the European Medicines Agency and the Therapeutic Goods Administration.

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