Andexanet to reverse apixaban or rivaroxaban anticoagulation

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Andexanet alfa (Ondexxya) is the first licensed antidote to the direct factor Xa inhibitors apixaban or rivaroxaban, for use when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding. This article summarises its indications, efficacy and safety.

The warm welcome for the new generation of anticoagulants, the direct oral anticoagulants (DOACs) rivaroxaban, dabigatran, apixaban and edoxaban, was tempered by concern that there was, at the time of their introduction, no means of antagonising their effects in the way that phytomenadione (vitamin K₁) was available to counter excessive bleeding associated with warfarin. In 2015, idarucizumab (Praxbind) was introduced for the rapid reversal of the effects of the direct thrombin inhibitor dabigatran; this is a monoclonal antibody specifically targeted at dabigatran and of no value for countering the effects of other DOACs.

Until the introduction of andexanet alfa (Ondexxya), treatment of bleeding due to the direct factor Xa inhibitors rivaroxaban, apixaban and edoxaban relied on reducing further gastrointestinal absorption by administration of activated charcoal and treatment with prothrombin complex concentrates or recombinant factor VIIa.

**Indication and dosage**

Andexanet alfa is a recombinant modified form of human factor Xa that acts as a decoy by binding with high affinity to a direct factor Xa inhibitor, blocking its anticoagulant activity. The European Medicines Agency (EMA) has given andexanet alfa a conditional marketing authorisation because of the lack of treatment options for excessive bleeding caused by direct factor Xa inhibitors.

The therapeutic indication is for adults treated with apixaban or rivaroxaban when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding. The indication does not extend to treating patients taking edoxaban.

Andexanet alfa is administered as an initial intravenous bolus of either 400mg (low dose) or 800mg (high dose) over 15 or 30 minutes respectively, followed by a continuous infusion of either 4mg per minute (low dose) or 8mg per minute (high dose) over 120 minutes. The choice of dose is dependent on the dose of apixaban or rivaroxaban the patient is taking and the timing of the last dose; full details are in the

**KEY POINTS**

- Andexanet alfa is a recombinant human factor Xa that binds to and blocks the activity of direct factor Xa inhibitor anticoagulants apixaban or rivaroxaban
- It has been given a conditional marketing authorisation to provide early access to treatment because there are few other options for excessive bleeding caused by a direct factor Xa inhibitor
- It is indicated for adults treated with apixaban or rivaroxaban when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding; there is insufficient data about its efficacy in reversing the effects of edoxaban
- It is administered as a bolus dose followed by an infusion over two hours in hospital; the dose of andexanet is determined by the dose of anticoagulant and time elapsed since the last dose
- In one clinical trial, andexanet alfa reduced anti-factor Xa activity by 92% in patients with acute major bleeding after taking rivaroxaban or apixaban; haemostatic efficacy was rated as good or excellent in 82% of patients
- A thrombotic event occurred in 10% of patients and mortality was 14% within 30 days follow-up
Summary of Product Characteristics. Administration is restricted to hospital use only. No dose adjustment is needed in elderly patients, or in renal or hepatic impairment.

NICE is evaluating andexanet in a technology appraisal, with publication expected in March 2020.

Efficacy
Andexanet alfa has been evaluated in the ANNEXA-4 trial. This included 352 adults with acute major bleeding within 18 hours of receiving apixaban, rivaroxaban or edoxaban at any dose, or the low-molecular-weight heparin enoxaparin at a dose of ≥1mg/kg/day. Patients with an estimated survival of less than one month, history of thrombosis within the previous two weeks or severe intracranial haemorrhage were excluded.

Andexanet alfa was administered as a bolus injection over 15 to 30 minutes followed by a two-hour infusion. The dose was determined by the anticoagulant received and the time of dosing. For apixaban, or for rivaroxaban taken more than seven hours previously, it was 400mg as a bolus dose over 15 minutes then a 480mg infusion; for enoxaparin, edoxaban, or for rivaroxaban taken seven hours or less previously or at an unknown time, it was 800mg over 30 minutes followed by a 960mg infusion.

The two co-primary efficacy endpoints were percent change from baseline in anti-factor Xa activity and the percent age of patients with excellent or good haemostatic efficacy 12 hours after the infusion. Efficacy was assessed in 254 patients. The primary safety outcomes were death, thrombotic events and the development of antibodies to andexanet alfa or to native factor X and factor Xa. Follow-up was 30 days.

Patients’ mean age was 77 years. The indications for anticoagulation were mostly atrial fibrillation (80%) or venous thromboembolism (17%). Other co-morbidities included myocardial infarction, stroke, heart failure and diabetes. Fifty-five per cent of participants had taken apixaban and 36% had taken rivaroxaban; few had been treated with edoxaban (3%) or enoxaparin (6%). The site of bleeding was mostly intracranial (64%) or gastrointestinal (26%).

The bolus administration of andexanet alfa reduced anti-factor Xa activity by 92% in patients treated with apixaban or rivaroxaban and 75% after enoxaparin. No specific efficacy outcomes were reported for edoxaban; only four patients in the efficacy population were taking this drug. Twelve hours after the andexanet infusion, anti-factor Xa activity was reduced by 38% from baseline for patients taking apixaban and by 62% for rivaroxaban. Haemostatic efficacy at 12 hours was rated good or excellent in 82% of patients overall; 85% in patients with gastrointestinal bleeding and 80% in those with intracranial bleeding.

There was no correlation between the reduction in anti-factor Xa activity after andexanet and haemostatic efficacy except in patients with intracranial haemorrhage, in whom haemostatic efficacy correlated with the maximum reduction in anti-factor Xa activity.

Safety
A thrombotic event occurred in 34 patients (10%) within the 30 days follow-up period, including myocardial infarction, ischaemic stroke, deep vein thrombosis and pulmonary embolism. About one-third of these occurred in the first five days, one-third in the following nine days and the remainder in the two weeks up to the end of follow-up. No patients developed antibodies to factor X or Xa, or to andexanet. Mortality within 30 days was 14%, with 71% being due to cardiovascular causes.

Sixty-two per cent of patients received at least one dose of any anticoagulant (oral or parenteral) during follow-up, of whom 2% subsequently had a thrombotic event; none of those restarted on an oral anticoagulant had a thrombotic event.

References

Declaration of interests
None to declare.

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