Vitamin K antagonists, direct oral anticoagulants, and the rationale for reversal agents

Despite these advantages, clinicians have been concerned over the lack of specific reversal agents for use in the event of a life-threatening bleeding event or when an emergent interventional procedure is required. This concern may limit the use of DOACs, as warfarin can be reversed with the combination of a factor product (fresh frozen plasma or prothrombin complex concentrate) and phytonadione.

Idarucizumab, a dabigatran-specific reversal agent, was approved by the Food and Drug Administration (FDA) in October 2015 for use when reversal of the anticoagulant effects of dabigatran is needed (i.e., for emergency surgery, urgent procedures, or in the event of life-threatening or uncontrolled bleeding). Initial data from a Phase III trial of idarucizumab were published this year. At the time of writing, two more reversal agents—andexanet alfa and ciraparantag—were in clinical development. Both of these reversal agents have been granted accelerated FDA approval pathways. Phase III trials with andexanet alfa have been completed (NCT02220725 and NCT02207725) or are underway (NCT02329327). Ciraparantag is being evaluated in Phase II trials (NCT02206087 and NCT02207257). It is intended that these agents will offer healthcare providers the necessary tools to urgently reverse the anticoagulant effects in situations of life-threatening bleeds or emergent surgery in patients taking DOACs.

The three reviews in this supplement have been prepared to assist health-system pharmacists in understanding how specific reversal agents may be used to manage bleeding or facilitate invasive procedures in patients taking DOACs and how these situations are being currently managed for patients on DOACs and how that differs from those receiving warfarin. Current evidence concerning the mode of action, efficacy, and safety of each of the specific reversal agents is also reviewed, highlighting unresolved issues that require further research.

The pharmacology and mechanism of action of each reversal agent differs. Different dosages or dosing strategies will likely be required for different anticoagulants requiring reversal, and adjustments may be required based on how the patient responds (i.e., some reversal agents may need to be redosed). These agents may also have different indications, as they are being studied in different populations, (e.g., idarucizumab is approved for life-threatening bleeding and urgent surgery, whereas andexanet alfa is being studied only in patients with life-threatening bleeding). Furthermore, the use of agents such as ciraparantag, that can reverse the anticoagulant activity of traditional agents, as well as DOACs, may limit future options for reanticoagulation. Pharmacists are perfectly positioned not only to work in ensuring the appropriate use of these agents in direct patient care but also to develop anticoagulation reversal protocols, guidelines, and order sets to help clinicians care for these patients when a pharmacist cannot be at the bedside. Pharmacists can also help promote appropriate patient selection, recommending the use of these agents for DOAC reversal only when a bleeding event is critical or an urgent invasive procedure is required, as well as highlighting the need for other supportive measures that may still be required. Institutional pharmacists, therefore, have a crucial role to play in facilitating the optimal use of reversal agents for DOACs.
Acknowledgments
Editorial support was provided by Joanne Vaughan, B.Sc., of Envision Scientific Solutions, which was contracted and funded by Boehringer Ingelheim Pharmaceuticals. Boehringer Ingelheim Pharmaceuticals was given the opportunity to review the manuscript for medical and scientific accuracy as well as intellectual property considerations.

Disclosures
Dr. Gulseth received nonfinancial support from Boehringer Ingelheim during the development of this manuscript. Outside this submitted work, he has received personal fees from Bristol-Myers Squibb, Daiichi Sankyo, Portola Pharmaceuticals, Pfizer, and Janssen Pharmaceuticals, as well as personal fees and nonfinancial support from Boehringer Ingelheim.

References


