Oral anticoagulation with edoxaban

Focus on current phase III clinical development

I. Ahrens; C. Bode
Heart Center Freiburg University, Freiburg, Germany

Keywords
Edoxaban, oral anticoagulants, FXa inhibitor, thrombosis, atrial fibrillation, stroke, VTE, PE

Summary
Edoxaban (the former DU176b) an orally available direct factor Xa inhibitor has been engineered from DX-9065a, which was one of the first parenteral Xa inhibitors. Edoxaban has a time to peak plasma concentrations of 1–2 hours and a half-life of approximately 10 hours after multiple doses. Edoxaban is the third new oral anticoagulant in the group of direct factor Xa inhibitors that has gained clinical approval for the prevention of venous thromboembolism after major orthopaedic surgery. Currently, edoxaban is assessed in late stage clinical development for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (ENGAGE AF-TIMI 48, NCT00781391) and for the treatment and prevention of venous thromboembolism in patients with acute deep vein thrombosis and/or pulmonary embolism (HOKUSAI VTE, NCT00986154).
Both clinical phase III trials represent the largest single clinical studies in their entity so far with an enrolment of 21 107 patients in ENGAGE AF-TIMI 48 and a planned enrolment of 7500 patients in HOKUSAI VTE.
The pharmacological properties of edoxaban will be discussed along with the current late stage clinical development focusing on the prevention of stroke and venous thromboembolism.

Schlüsselwörter
Edoxaban, orale Antikoagulanzien, FXa-Inhibitor, Thrombose, Vorhofflimmern, Schlaganfall, VTE, PE

Zusammenfassung
Edoxaban (ehemals DU176b) ist ein oral verfügbarer direkter Faktor-Xa(FXa)-Inhibitor der von der Substanz DX-9065a, einem der ersten parenteralen FXa-Inhibitoren abgeleitet wurde. Edoxaban erreicht Plasmaspitzenspiegel nach 1–2 Stunden und hat eine Halbwertszeit von ca. 10 Stunden nach wiederholter Verabreichung. Edoxaban ist das dritte der neuen oralen Antikoagulanzien aus der Gruppe der direkten FXa-Inhibitoren, dass zur Prophylaxe venöser Thromboembolien nach großen orthopädischen Operationen zugelassen wurde. Zurzeit wird Edoxaban in Phase-III-Zulassungsstudien zur Prävention von Schlaganfall und systemischen Embolien bei Patienten mit nicht-valvulärem Vorhofflimmern (ENGAGE AF-TIMI 48, NCT00781391) sowie zur Behandlung und Prophylaxe venöser Thromboemolie bei Patienten mit akuter tiefer Beinvenenthrombose und/oder Lungenembolie (HOKUSAI VTE, NCT00986154) untersucht.
Beide Phase-III-Studien sind die bisher größten klinischen Studien in ihrer jeweiligen Indikation mit Einschluss von 21 107 Patienten in der ENGAGE-AF-TIMI-48-Studie und einem geplanten Einschluss von 7500 Patienten in der HOKUSAI-VTE-Studie.
Die pharmakologischen Eigenschaften von Edoxaban sowie die fortgeschrittene späte klinische Entwicklungsphase werden diskutiert mit Fokus auf Schlaganfallprävention und Prophylaxe venöser Thromboembolien.

Correspondence to:
Ingo Ahrens, MD
Heart Center Freiburg University
Hugstetter Str. 55, 79106 Freiburg, Germany
E-mail: ingo.ahrens@universitaets-herzzentrum.de

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Direct factor Xa inhibitors

A new class of oral anticoagulants

Factor Xa (FXa) has a central role in the coagulation system. As a part of the platelet-bound prothrombinase complex it catalyses the conversion of factor II (prothrombin) to factor IIa (thrombin) (1). The successful development of indirect factor Xa inhibitors as parenteral anticoagulants (low molecular weight heparins, fondaparinux) and the shortcomings of oral anticoagulation with vitamin K antagonists prompted the clinical development of the new group of oral direct factor Xa inhibitors as novel oral anticoagulants (1, 2).

Currently three oral direct FXa inhibitors have entered the market for novel oral anticoagulants. Among those rivaroxaban (Xarelto®, Bayer Healthcare) is the first substance that has gained approval for stroke prevention in atrial fibrillation. Edoxaban (Lixiana®, Daiichi-Sankyo) and Apixaban (Eliquis®, Bristol-Meyers-Squibb/Pfizer) have gained approval for the prevention of venous thromboembolism in 2011 and are currently in late stage clinical investigation for stroke prevention in atrial fibrillation.

Other members of the new family of direct factor Xa inhibitors (1) are

- Betrixaban (recently sold back from Merck to Portola Pharmaceuticals),
- Darexaban (Astellas, clinical development discontinued in 2011),
- Eribaxaban (Pfizer),
- TAK-442 (Takeda Pharmaceuticals),
- LY-517717 (Lilly).

Edoxaban

Pharmacology

Edoxaban (Lixiana®) is a small molecule direct factor Xa inhibitor with a molecular weight of 548 Da and inhibition constant

(Ki) of 0.56 nmol/l (3). Edoxaban, the former DU-176b was engineered from the parenteral FXa inhibitor DX-9065a (1). The current name of the drug is derived from EDO (in former times Tokyo was named Edo), XA for factor Xa, and the ending –BAN accounting for the group name of the novel direct Xa inhibitors.

Edoxaban is rapidly absorbed after a single oral dose with a time to peak plasma concentrations of 1–2 hours (4). Compared to rivaroxaban and apixaban, edoxaban has a lower protein binding capacity of 40–59% (4, 5). The elimination half-life of edoxaban is 6–11 hours after single doses and 9–10 hours after multiple doses (4, 5). Approximately 1/3rd of edoxaban is eliminated via renal secretion (4, 5). Therefore, a reduced dose of edoxaban will be administered in patients with a creatinine clearance of 50–30ml/min in a current clinical phase III trial (6). Like other oral Xa antagonists, edoxaban is substrate for P-glycoprotein (P-gp). Therefore, co-administration with strong P-gp inhibitors (e.g. amiodarone, dronedarone, verapamil) may increase plasma concentration and half-life (5).

Prevention of venous thromboembolism – edoxaban is superior to enoxaparin

In the Japanese population, edoxaban was assessed in two phase III clinical trials for the prevention of venous thromboembolism (VTE) after orthopaedic surgery (▶Tab. 1). The STARS (Studying Thrombosis After Replacement Surgery) E-3 trial (NCT 01181102) assessed a 30 mg once daily oral dose of edoxaban versus a twice daily subcutaneous dose of enoxaparin 20 mg in 716 Japanese patients undergoing total knee arthroplasty and the STARS J-5 trial (NCT011811167) did the same in 610 patients undergoing total hip replacement (7). Patients received edoxaban 6–24 h after surgery or enoxaparin 24–36 h after surgery. Both drugs were continued for 11–14 days post surgery. The primary endpoint was the composite of symptomatic and asymptomatic deep vein thrombosis (DVT) and pulmonary embolism (PE). The primary safety endpoint was major and clinically relevant non-major bleeding. In the pooled analysis of both trials, the primary endpoint occurred in 5.1% versus 10.7% of the edoxaban versus enoxaparin treated groups respectively ($p < 0.001$) (7). The primary safety endpoint occurred in 4.6% versus 3.7% of the edoxaban and enoxaparin treated patients respectively ($p = 0.427$) (7). Edoxaban gained approval for the prevention of VTE after major orthopaedic surgery in Japan in 2011, based on the superiority of edoxaban for the prevention of VTE after major orthopaedic surgery in the STARS trials. The 20mg twice daily choice of enoxaparin in the STARS trial is not commonly used outside Japan, therefore the results of the STARS trial may not compare to other populations.

Stroke prevention with edoxaban – ENGAGE AF-TMI 48

Edoxaban is currently being assessed for stroke prevention in patients with non-valvular atrial fibrillation compared to dose adjusted warfarin in the Effective aNticoaGulation with factor xA next GEneration in Atrial Fibrillation (ENGAGE AF-TIMI 48) trial (NCT00781391). ENGAGE AF-TIMI 48 is an event-driven, randomized, double-blind, double-dummy, trial in which patients are randomized into one of three treatment groups (6):

- 30 mg edoxaban once daily,
- 60 mg edoxaban once daily, or
- dose adjusted warfarin.

Patients aged 21 or older with documented atrial fibrillation within one year before randomisation and a $CHADS_2$-score of ≥ 2 are eligible for enrolment. The trial has completed enrolment of 21 107 patients in December 2010 – thereby making it by far the largest trial of stroke prevention with a novel oral anticoagulant – and is currently in the follow up phase (8). The estimated completion date is March 2012 (clinicaltrials.gov identifier: NCT00781391, accessed February 2012).

Patients were randomized on a 1:1:1 basis into the treatment arms edoxaban 60 mg, edoxaban 30 mg, and warfarin. Stratification to randomisation into the low (30 mg) or the high (60 mg) edoxaban treatment arm was based on the individual stroke risk ($CHADS_2$-score of 2–3 versus 4–6) and the likelihood of increased drug exposure determined by renal function, body weight and concomitant medication. Furthermore, unique to ENGAGE AF-TIMI 48 is the option that patients in the edoxaban treatment arm will receive dose adjustments throughout the whole period

Tab. Edoxaban: clinical phase III trials

trial	indication		treatment	duration	number of patients	outcome
STARS E3 (NCT01181102)	VTE prevention	total knee arthroplasty	30 mg QD edoxaban versus enoxaparin 20 mg subcutaneous BID	11–14 days post surgery	716 (Japan only)	pooled analysis of both trials: edoxaban superior to enoxaparin (5.1% vs 10.7%, $p < 0.001$ for composite of DVT and PE) (7)
STARS J-5 (NCT011811167)		total hip replacement			610 (Japan only)	
ENGAGE AF TIMI 48 (NCT00781391)	atrial fibrillation		15–60 mg QD edoxaban versus dose adjusted warfarin	24 months	21 107 (world wide)	currently in follow up phase (enrolment completed Dec 2012) (11)
HOKUSAI VTE (NCT00986154)	pulmonary embolism		60 mg QD edoxaban versus dose adjusted warfarin	12 months	7500 (world wide)	currently enrolling patients (estimated completion by Sep 2012) (5)

BID: bis in die (twice daily); DVT: deep vein thrombosis; QD: quoque die (once daily); VTE: venous thromboembolism

oft the study, depending on creatinine clearance and body weight or concomitant medication with strong inhibitors of P-gp (verapamile, quinidine, amiodarone, dronedarone) (6). In both edoxaban treatment groups, the dose will be reduced by 50% if creatinine clearance is 30–50 ml/min, if body weight is <60 kg, or if strong inhibitors of P-gp have to be administered as co-medication. The primary endpoint is the composite of stroke and systemic embolism and the primary safety endpoint is ISTH modified major bleeding (defined as bleeding leading to death, critical organ bleeding, transfusion adjusted drop in haemoglobin ≥2g/dl with every unit of packed red blood cells accounting for a drop in haemoglobin of 1 g/dl) (6).

When the design of the ENGAGE AF-TIMI 48 trial was published in October 2010, the baseline characteristics of 15 000 patients enrolled in the study were also presented. The mean age was 72 years, more than 1/3rd (39%) of the patients were older than 74 years, and 38% were females (6). The stroke risk in the enrolled population was predominately a $CHADS_2$-score 2–3 (81%) and therefore lies in between the risk of patients enrolled in the RE-LY trial (mean $CHADS_2$-score of 2.1) and the ROCKET AF trial (mean $CHADS_2$-score of 3.5) (6, 9). More than 1/3rd (39%) of the patients enrolled in ENGAGE AF-TIMI 48 were naïve to warfarin and half of the enrolled patients were diagnosed with permanent atrial fibrillation (6). The per protocol allowed dose adjustment in the edoxaban treated patients occurred at a rate of 25% in the overall study population with creatinine clearance being the predominant cause (19%) followed by bodyweight = 60kg (10%) or concomitant medication of either verapamil or quinidine (4%) (6). Presentation of the final results of the ENGAGE AF-TIMI 48 trial is expected later in 2012.

Edoxaban for the prevention and treatment of venous thromboembolism – HOKUSAI VTE

Edoxaban 60 mg once daily compared to dose adjusted warfarin is currently being assessed in the HOKUSAI VTE randomized, double-blind, double-dummy phase III clinical trial (NCT00986154) for the prevention and treatment of venous thromboembolism in patients with acute deep vein thrombosis (DVT) and/or pulmonary embolism (PE) after an initial 5 day heparin treatment period (either unfractionated heparin or low molecular weight heparin) (5). HOKUSAI VTE is also the largest single clinical trial for the treatment and secondary prevention of acute DVT and/or PE so far with a planned enrolment of 7500 patients (10). The primary endpoint is defined as the composite of DVT, non-fatal and fatal PE over a 12-month time frame from randomization. Treatment duration is pre-specified by the patient's individual risk for either 3, 6 or 12 months. The secondary endpoint is defined as the composite of symptomatic recurrent DVT, non-fatal symptomatic recurrent PE, all-cause mortality, and major or clinically relevant non-major bleeding during treatment (5). The estimated study completion date is September 2012 (clinicaltrials.gov identifier: NCT00986154, accessed February 2012).

Discussion

A carefully conducted phase II clinical development program led to the preferred selection of a once daily dose of either 30 mg or 60 mg edoxaban for the current phase III clinical assessment of edoxaban for the prevention of stroke and systemic embolism in the largest clinical trial (21 107 patients) conducted in this entity so far. In the phase II study in patients with non-valvular atrial fibrillation the twice daily dosing regimen (either 60 or 30 mg edoxaban) was found to be associated with a higher rate of bleeding compared to warfarin whereas the safety profile of once daily dose of either 60 mg or 30 mg edoxaban was similar to warfarin (11).

The results of the ENGAGE AF-TIMI 48 trial promise to address the clinical relevant question whether dose adjustments (the 60 mg dose will be decreased to 30 mg and the 30 mg dose will be decreased to 15 mg) in situations that are likely to result in increased drug exposure by changes in renal function, bodyweight or concomitant medication will ultimately lead to a reduction in bleeding events while preserving a safe anticoagulation for the patient.

Based on the results of the STARS trials, edoxaban is now approved in Japan as a superior treatment strategy to enoxaparin 20 mg twice daily for the prevention of venous thromboembolism in patients undergoing major orthopaedic surgery (7). Whether these results may be extrapolated to the common North American practice of enoxaparin 30 mg twice daily, or the European standard of enoxaparin 40 mg once daily, needs to be addressed by further clinical trials.

The HOKUSAI VTE clinical phase III trial, the largest single trial of a novel oral anticoagulant for the treatment and prevention of DVT and/or PE with a planned enrolment of 7500 patients, is currently investigating whether edoxaban 60 mg once daily is non-inferior to warfarin. While rivaroxaban has successfully been assessed as a fixed dose treatment regimen for the initial and continued treatment in the EINSTEIN clinical phase III studies (12) and apixaban is currently being evaluated in the AMPLIFY study (clinicaltrials.gov identifier: NCT00643201, accessed February 2012) as fixed dose therapy also for the initial and continued treatment, edoxaban in contrast is investigated as a subacute therapy following initial 5 days of heparin therapy in the HOKUSAI VTE trial (5).

Outlook

The development of novel oral anticoagulants is currently the focus of major cardiovascular clinical development programs of many major pharmaceutical companies. Rivaroxaban is the first of the new group of direct oral anticoagulants that gained approval for the prevention of VTE in patients undergoing major orthopaedic surgery, stroke prevention in patients with atrial fibrillation and the prevention of DVT. Now, with the recent approval of edoxaban and apixaban for the prevention of VTE in patients undergoing major orthopaedic surgery, the family of clinically available oral direct factor Xa inhibitors has grown. Depending on the regulatory authorities' evaluation of the results of the ARISTOTLE (apixaban) and ENGAGE AF-TIMI 48 (edoxaban) trials we may see the approval of these drugs for the prevention of stroke as

well. Ongoing clinical phase III trials will clarify whether apixaban (AMPLIFY trial) or edoxaban (HOKUSAI VTE trial) are non-inferior to warfarin for the treatment and prevention of DVT and PE.

The pharmacological properties of the oral direct factor Xa inhibitors are not too distinct from each other. Therefore, the place of the single substance in clinical settings requiring oral anticoagulation will initially largely depend on the design and the specific results of the relevant clinical trails leading to approval of the individual drug for a specific indication. Given the similarities between these drugs, the conduction of head to head trials is unlikely to occur. However, the clinical availability of these novel oral anticoagulant drugs and the increasing competition caused by the parallel clinical development of novel oral direct factor Xa inhibitors will be a major clinical benefit for those patients who suffered from the shortcomings of vitamin K antagonist in the past decades.

Conflict of interest

I.A. reports no conflict of interest.
C.B. received speaker's honoraries from Bayer Healthcare, Bristol-Myers-Squibb/Pfizer, Daiichi-Sankyo and Boehringer Ingelheim.

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