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REGULAR ARTICLE

Dose-escalation study of rivaroxaban (BAY 59-7939) — an oral, direct Factor Xa inhibitor — for the prevention of venous thromboembolism in patients undergoing total hip replacement

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Abstract

Introduction: Rivaroxaban (BAY 59-7939) is a novel, oral, direct Factor Xa inhibitor in clinical development for the prevention of thromboembolic disorders. The aim of this study was to demonstrate proof-of-principle for rivaroxaban. *Materials and methods:* This was an open-label, dose-escalation study to assess the efficacy and safety of rivaroxaban, relative to enoxaparin, for the prevention of venous thromboembolism (VTE) after total hip replacement surgery. Patients were randomized in a 3:1 ratio to rivaroxaban (2.5, 5, 10, 20 and 30 mg twice daily [bid] or 30 mg once daily [od] starting 6–8 h after surgery) or enoxaparin (40 mg od starting the evening before surgery). Therapy continued until mandatory bilateral venography was performed 5–9 days after surgery.

Abbreviations: VTE, venous thromboembolism; DVT, deep vein thrombosis; PE, pulmonary embolism; LMWH, low molecular weight heparin; bid, twice daily; od, once daily; ITT, intention-to-treat; PP, per-protocol; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal.

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Results: A total of 625 patients received therapy, of whom 466 patients were eligible for the per-protocol efficacy analysis. The primary efficacy endpoint – deep vein thrombosis (DVT), pulmonary embolism (PE) or all-cause mortality – occurred in 22.2%, 23.8%, 20.0%, 10.2%, 17.4%, 15.1% and 16.8% of patients receiving rivaroxaban 2.5, 5, 10, 20, 30 mg bid, 30 mg od and enoxaparin, respectively. The dose-response relationship with rivaroxaban for the primary efficacy endpoint was not statistically significant ($p = 0.0504$), although major VTE (proximal DVT, PE and VTE-related death) decreased dose dependently with rivaroxaban ($p = 0.0108$). Major, post-operative bleeding increased dose dependently with rivaroxaban ($p = 0.0008$), occurring in 0–10.8% of patients, compared with 0% in patients receiving enoxaparin.
Conclusions: This study demonstrated proof-of-principle for rivaroxaban for the prevention of VTE after total hip replacement surgery.

Introduction

The risk of venous thromboembolism (VTE; including deep vein thrombosis [DVT] and pulmonary embolism [PE]) is high after major orthopaedic surgery, such as total hip or knee replacement surgery [1]. Prophylactic anticoagulant therapy is recommended to reduce the risk, and has become the standard of care [1]. Due to the various shortcomings of the currently available anticoagulants [2], there is an unmet need for an oral anticoagulant with a rapid onset of action, predictable pharmacokinetics and pharmacodynamics and a low propensity for food or drug interactions [2].

Major orthopaedic surgery is a suitable setting for benchmark studies in the development of novel anticoagulants, for numerous reasons [3]: patients undergoing this type of surgery are a large, well-defined group, and the level and duration of the risks of VTE or bleeding complications are well characterized, and can be quantified and controlled easily in a hospital environment [4]. There is also an abundance of clinical trial data regarding the expected incidence of VTE and bleeding events in the usual comparator group — low molecular weight heparins (LMWHs). Furthermore, the incidences of outcome events are relatively high, and they can be measured by validated screening techniques and reliable central adjudication. As a result, relatively small dose-finding studies to demonstrate the efficacy and safety of anticoagulants can be conducted [1].

Direct inhibition of individual proteases within the coagulation cascade, such as Factor Xa – a key protease – has emerged as an attractive approach to anticoagulation [5,6]. Rivaroxaban (BAY 59-7939) is an oral, direct Factor Xa inhibitor that reversibly inhibits the active site of Factor Xa [7]. In healthy subjects, rivaroxaban had high oral bioavailability (~80%), dose-proportional pharmacokinetics and pharmacodynamics, and was well tolerated [8,9]. It has a rapid onset of action, a half-life of 5–9 h, and a dual mode of excretion, being excreted predominantly via the kidneys, but also via the faecal/biliary route [9,10].

This phase IIa, open-label study investigating rivaroxaban in patients undergoing total hip replacement surgery was the first time rivaroxaban was administered to patients. The study followed an active-comparator-controlled, dose-escalation design, with five twice-daily (bid) rivaroxaban doses and one once-daily (od) rivaroxaban dose. The aim of the study was to demonstrate proof-of-principle for rivaroxaban for the prevention of VTE after major orthopaedic surgery by assessing the efficacy and safety of rivaroxaban relative to a standard regimen of the LMWH enoxaparin.

Materials and methods

Study design

This was a randomized, open-label, active-comparator-controlled, European, multinational, dose-escalation study. It was designed to explore the dose-response relationships for efficacy and safety with rivaroxaban, relative to the LMWH enoxaparin, for the prevention of VTE in patients undergoing total hip replacement surgery. If rivaroxaban was found to reduce the incidence of VTE and increase bleeding rates, this would provide 'proof-of-principle' for rivaroxaban. The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, and with the approval of the local independent ethics review committee. Patients provided written, informed consent before participation.

Patients

Males aged ≥18 years and post-menopausal females scheduled for elective, primary, total hip replacement surgery were eligible for the study. Exclusion