Short Communication

Drug approval processes: A case study of rivaroxaban

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ABSTRACT

Rivaroxaban, a Xa inhibitor, was recently approved (March 2013) in the setting of post-acute coronary syndromes (ACS) by the European Medicine Agency. This is in contrast to not being approved by the Food and Drug Agency in the United States for the same indication in 2012 and 2013. The FDA's decision was based on a lack of follow-up data for the patients enrolled in the study based on the pivotal Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome (ATLAS-ACS 2-TIMI 51) trial. While both agencies have similar roles when functioning as drug regulatory bodies and goal of granting approval of safe and efficacious drugs, the difference in approval outcome in the case of rivaroxaban highlights the differences in drug review process when both agencies are presented with the same Phase 3 data to review.

INTRODUCTION

Rivaroxaban, aXa inhibitor, blocks the cascade of blood coagulation.[1] In the United States rivoraxaban was approved by the Food and Drug Administration (FDA) in July of 2011 as an anticoagulant used to prevent blood clots associated with deep vein thrombosis, atrial fibrillation, and pulmonary embolism.[2] In addition to all of the US approved indications, the European Medicines Agency (EMA) approved rivoraxaban in March of 2013 to prevent thrombotic events in patients with post-acute coronary syndrome.[3] Unlike vitamin K antagonists like warfarin, rivaroxaban does not require frequent monitoring, but is dosed-based on creatinine clearance and does not have a reversible antidote.

Pharmacological therapy plays a key role in the treatment of acute coronary syndromes (ACS). Patients who have had a recent ACS are still at risk for another cardiovascular event even though they are being treated with aspirin and a thienopyridine. The cause of this is thought to be related to excess thrombin generation, which continues after the presentation of ACS. Rivaroxaban inhibits factor Xa, therefore, preventing the final common pathway of the coagulation cascade which results in the production of thrombin. According to the 2013 American College of Cardiology/American College of Cardiology (ACC/AHA) ST-elevation myocardial infarction (STEMI) guidelines, a vitamin K antagonist should only be provided when there is another indication for anticoagulation such as atrial fibrillation with a $CHADS_2$ score ≥2, mechanical heart valves, previous venous thromboembolism or hypercoagulable disorder, due to a higher risk for bleeding.[4] These guidelines make no recommendation for use of the newer anticoagulants, such as rivaroxaban, in ACS patients due to a lack of robust data and only suggest usage if in patients if the risk for a thromboembolic event or stent occlusion exceeds the risk of bleeding.[4]

The European approval of rivaroxaban in prevention of thrombotic events in post-acute coronary syndrome patients helps highlight the differences and similarities of drug regulating agencies in Europe, the EMA, versus the regulating agency of the US, the FDA. Although the

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FDA and the EMA conduct overall similar processes for approval of novel therapeutic agents there are some key differences [Table 1].[5-9] An initial difference in the two agencies is in their power to approve the drug. The FDA is the sole regulator and approves new therapeutic agents for market availability, while the EMA is an evaluation board that reviews new therapeutic agents and gives advice on safety and efficacy.[5,6] The European Commission then permits or denies drug approval based on the EMA's evaluations. Another difference is in the preapproval application: When one applies for FDA approval they are applying for approval in all 50 states.[5] However, when one applies for EMA approval they may apply for approval of all states/countries of the European Union, filling out a centralized application, or they may apply for approval in one or some specific states/countries of the European Union, filling out a decentralized application.[7] A centralized application is required for therapeutic agents used to treat human immunodeficiency virus (HIV)/Acquired immunodefi ciency syndrome (AIDS), cancer, diabetes, neurodegenerative diseases, viral diseases, autoimmune and other immune disorders, and for orphan drugs.[7] A centralized application is also required for therapeutic agents derived from biotechnological processes and medications for advanced therapy, such as gene therapy.[6] In clinical trials and testing, the FDA requires a new therapeutic agent to be compared with a placebo drug.[5] Clinical trials evaluated by the EMA are preferably a new therapeutic agent as compared with another drug and a placebo, but can also be a new therapeutic agent only compared to another drug.[6] Another difference is in the median amount of time to review the drug and the amount of time it takes for the approved drug to appear on the market.[7,8] The FDA has a shorter review time at a median of 322 days per novel drug as compared to the EMA which has a median review time of 366 days per novel drug.[7,8] Out of 190 novel drugs approved by both the FDA and EMA, 121 (63.7%) were initially approved in the US at a median of 96 days earlier approval by the FDA than the EMA.[7,8] Therefore, drugs approved by FDA appear earlier on the market as compared to drugs approved by the EMA.

Although there are a number of differences between the regulatory and evaluation processes of the EMA and FDA, both have a common application for orphan drugs.[9] An orphan drug is defined as an uncommon condition affecting less than 200,000 people in the US or less than 10,000 people in the European Union.[8] This common application allows both parties to benefit in treatment of a rare condition. Also, both the FDA and EMA have similar stages of approval (e.g., preclinical testing stage and phase one, phase two, and phase three trials).[5,6] Furthermore, the ultimate goal of the FDA and EMA is same in providing safe and efficacious medication to improve public health.

Both the EMA and FDA evaluations of rivoraxaban for preventing thrombotic events in patients with post-acute coronary syndrome were based on the

Table 1: Comparison of the FDA and EMA drug approval process

	Food and drug administration	European medicines agency
Role of agency	Sole regulator Approves new therapeutic agents for market exposure	A part of a chain of regulators. Does NOT approve new therapeutic agents for market exposure
Pre-approval application	Applicant applies for approval in all states of the US	Centralized: Applicant applies for approval for all states/countries of the European Union (EU). Required for therapeutic agents used to treat HIV/AIDS, cancer, diabetes, neurodegenerative diseases, autoimmune and other immune dysfunctions, and viral diseases. Required for therapeutic agents derived from biotechnological processes and advanced therapy medications. Required for orphan drugs Decentralized: Applicant applies for approval in one or some of the members of the EU. Therapeutic agent does not fall under requirements for centralized application
Clinical trials	Drug A vs Control[a]	Drug A vs Drug B OR Drug A vs Drug B vs Placebo
Median time for review	322 days	366 days
Orphan drugs	Common application for FDA and EMA for rare diseases. An orphan drug application filed with the FDA can hold valid with the EMA and vice versa	

[a]Control can be set as placebo, dose-comparison, no-treatment, active-treatment, or historical control. HIV=Human immunodeficiency virus, AIDS=Acquired immunodeficiency syndrome, FDA=Food and drug administration, EMA=European medicines agency

Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome (ATLAS-ACS 2-TIMI 51) trial.[10] This phase 3, double-blind, multicenter (766 sites) study randomized more than 15,526 patients with ACS to rivaroxaban 2.5 mg rivaroxaban twice daily, 5 mg of rivaroxaban twice daily, or placebo, in addition to the standard dual antiplatelet therapy of a low dose aspirin (81 mg) with clopidogrel or ticlopidine. The primary endpoint in this study was death from cardiovascular causes, myocardial infarction (MI), or stroke (MEGA). The secondary endpoint was death from any case, MI, or stroke. The primary safety endpoint was major bleeding that was not related to coronary artery bypass grafting (CABG). The baseline characteristics were similar and 50.3% of the patients had a STEMI, whereas 25.6% of patients suffered an NSTEMI and 24% had unstable angina unstable angina (UA). Therapy with rivaroxaban was continued on average for 13.1 months. Discontinuation of the drug occurred in 26.9% (n = 5,174) of patients receiving the 2.5 mg dose, 29.4% (n = 5,176) of patients receiving the 5 mg dose, and 26.4% (n = 5,176) in the placebo. When the two doses were analyzed, the primary endpoint occurred in fewer patients receiving the 2.5 mg dose when compared to placebo (9.1 vs 10.7%, respectively; P = 0.02). The primary endpoint occurred in 8.8% in the 5 mg group compared to 10.7% in the placebo group (P = 0.03). The 2.5 mg dose reduced death from cardiovascular causes when compared with the placebo 2.7 vs 4.1%, respectively (P = 0.002) and reduced the risk of death from any cause (2.9 vs 4.5%; P = 0.002). The 5 mg dose of rivaroxaban did not reduce the risk of death from cardiovascular causes or any cause. Rivaroxaban significantly increased the rate of major bleeding that was not related to CABG when compared to placebo (2.1 vs 0.6%, P < 0.001). There were also more episodes of minor bleeds and bleeds requiring medical attention (1.3 vs 0.5%, P = 0.003 and 14.5 vs 7.5%; P < 0.001). Rivaroxaban did not show a significant difference in the rates of fatal bleeding when compared with placebo (0.3 vs 0.2%, P = 0.66). The rates of major bleeding were lower in the 2.5 mg dose compared to the 5 mg dose, but it was not significant different.[7]

The authors of the ATLAS-ACS 2-TIMI 51 trial concluded that rivaroxaban 2.5 mg twice daily showed a promising reduction in the rates of death of cardiovascular causes, MI, or stroke.[10] While the study had appropriate inclusion and exclusion criteria and the baseline patient characteristics were similar amongst the groups, there was a high rate of discontinuation of the rivaroxaban arm due to adverse events and other undisclosed reasons. The authors of the study did not provide follow-up data of long-term effects of rivaroxaban; however, the investigators did set out an intention to treat model that analyzes data from all subjects assigned to a treatment regardless of completion of the study and essentially measures the effectiveness of treatment. Advantages of an intention to treat model are that the analysis maintains randomization, mimics reality, and is a more conservative estimate of effect. However, because of dropout rates, a 'modified intention to treat' model was adapted to only include those patients who completed the trial. Such a model could lead to overestimation of the true effect of rivoraxaban, while simultaneously "hiding" potential adverse reasons why the patients chose to dropout of the study. It seems questionable that the 2.5 mg dose would provide a mortality benefit in comparison to the 5 mg dose. Finally, the reduction in the number of events does not seem convincing enough when compared to the significant increase in major bleeding events.

Janssen Pharmaceuticals, the manufacturer of rivaroxaban, has sought approval for this indication twice from the FDA and it has been denied each time. The FDA has turned down the new drug application for rivaroxaban in the prevention of stent thrombosis in patient post-ACS in May 2012 due to an incomplete follow-up, missing vital statuses, a number of uncounted deaths, concerns about increased risks of bleeding, and different rates of outcomes between the interim analyses in the ATLAS-ACS 2-TIMI 51 trial. (FDA website).[11] The FDA wants more data on treatment analysis because of questions of informative censoring on the manufacturer's part. The FDA has reason to believe that patients may have withdrawn from the ATLAS study due to adverse events associated with the use of rivoraxaban.[11]

Although similar in overall processes, the differences in the authorizing boards of drug approval in the United States and Europe can be seen played out with the case of approving rivaroxaban in the setting of post-acute coronary syndrome. While the FDA is requesting more safety and dropout data from the manufacturer to help make its final decision, the EMA in Europe felt that the data from the pivotal phase 3 trial was sufficient to grant an approval. It is understood that both agencies have the ultimate goal of granting the use safe and efficacious drugs to

the public, but it is important to recognize that their means to achieving this goal can vary and ultimately impact the approval of drugs, as seen by story of rivaroxaban.

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