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News and views

The Dabigatran debate

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In the June 2013 issue of this Journal, we described compelling evidence for the use of three novel anticoagulants, including Dabigatran, on the basis of recent large multi-centre trials.¹ We acknowledged the approval of NOACs over warfarin in the ESC update and ACCP guidelines, and foresaw the greater usage of these newer, promising, therapies for stroke prevention in non-valvular atrial fibrillation.

In our review article, we also advised a degree of caution with NOACs, as 'experience with these drugs is relatively limited and that there are no currently available agents to reverse their effect in case of major complications, such as bleeding'. At the time, the concern centred around lack of reversal agents, which was discussed in a letter to the Editor, reflecting repercussions felt in the wider medical community.^{2,3}

We had examined and accepted the data from the RE-LY trial to show how NOACs were becoming more acceptable. In light of the emerging concerns regarding the RE-LY trial and Dabigatran, highlighted by a recent BMJ investigation, we review the debate to date, and ask whether or not we, alongside commissioning bodies, now need to retract support for the drug.

DABIGATRAN DEBATE

Dabigatran, the first novel oral anticoagulant to be used in mainstream clinical practice for non-valvular atrial fibrillation, emerged onto the market in 2010. Boehringer Ingelheim, the European manufacturer, promised an alternative to warfarin, which was marketed as 'effective, predictable and consistent anticoagulation with a low potential for drug-drug interactions and no drug-food interactions, without the need for routine coagulation monitoring or dose adjustment'.⁴

However, a recent BMJ editorial, published in July 2014, has raised some concerns over the development of the drug, approval process, and previous and emerging post-approval findings, which have brought the safety profile of dabigatran into question.⁵

THE RE-LY TRIAL

RE-LY (Randomised Evaluation of Long-Term Anticoagulation Therapy), a massive, multicentre trial spanning 951 centres in 44 countries with 18113 patients, comparing warfarin with two different doses of dabigatran, was published in 2009.⁶ It demonstrated that dabigatran reduced risks of ischaemic stroke and major bleeding events in comparison to warfarin, with a statistically significant absolute risk reduction of less than 1% per year. Boehringer asserts that RE-LY showed the superior efficacy of dabigatran over warfarin, as well as safety of the drug, without the use of an antidote or plasma level monitoring, which was its unique selling point.

FLAWS IN RE-LY

Several concerns have been raised about RE-LY. The 'open-label' study design of RE-LY meant that clinicians and trial patients knew which drug was being given. Potentially, this could lead to bias; transcript of the US Food and Drug Administration's (FDA) advisory committee shows that the US agency found "that knowledge of treatment arm [by clinicians and participants] may have led to important differences in the treatment of subjects," adding: "for example, if a subject experienced an ischemic stroke, TIA (a non-endpoint event) or minor bleed, she was more likely to have her study medication permanently discontinued in the dabigatran than the warfarin treatment arms."

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The FDA also questioned whether regular INR visits for patients on warfarin would have led to identification of clinical events not reported by the dabigatran arm.⁷

Analysis of the data also raised concerns. It took three reviews of the data to calculate the number of major and fatal bleeds among trial participants, as the FDA continually rejected trial data. There were also questions regarding the potential unblinding of “blinded” adjudicators, the use of concurrent warfarin-aspirin, the high and unequal rate of drop-outs; unaccounted drop-ins; high rates of major bleeds in warfarin-treated patients, despite being a low risk population; and the rates of major bleeds that do not match historic warfarin trials.⁸

POST- RE-LY CONCERNS

In 2012, the plot thickened. When Boehringer planned a new clinical trial for patients with mechanical heart valves it elected to use adjusted doses of dabigatran by assessing plasma concentrations of the drug; the company revealed that 17% of RE-LY patients were found to have plasma levels that were below target.⁹ Furthermore, the heart valve study, using dose adjustment, showed that at least 8% of participants had plasma levels below the target even when prescribed double the maximum approved dose of dabigatran. The heart valve study was stopped early, with Boehringer reporting “interim results showed an increased incidence of thromboembolic and bleeding events in patients treated with dabigatran compared to warfarin.”¹⁰

The approval process when licensing dabigatran has also raised concerns. The RE-LY trial benefited from an accelerated FDA review process as it was a ‘novel’ drug, despite only being studied in a single large phase III trial rather than in at least two trials, as is normally required for approval.⁷ During the FDA approval process, concerns were voiced by members of the committee about the huge variability in pharmacokinetics (up to a five-fold difference in plasma concentration), related to age, transient changes in renal function, and body weight. Boehringer brought this to the FDA’s attention, proposing to authorise a lower dose of dabigatran in patients aged over 80 years. The FDA rejected the proposal due to concerns regarding potential over-utilisation of the lower dose, placing patients at a greater risk of thromboembolism.⁹ The EMA also rejected a need for monitoring, despite Boehringer showing in 2010 to have “identified dabigatran concentrations not to be exceeded because of the increased risk of bleeding”.¹¹

Dabigatran continued to stir controversy post launch. The FDA published a post-approval review of bleeding risk using its ‘Mini-Sentinel’ system. The analysts concluded that the adverse event reports were the result of heightened awareness with a new drug.¹² Mixed messages from the FDA include a presentation at the 2013 American College of Cardiology (ACC) Scientific Sessions which suggested a much higher case fatality rate than that reported in other major clinical trials of the drug. However, it was stated that the figures ‘used in this analysis suffered from reporting bias, accuracy, and duplication problems and so should not be used to draw any definite conclusions.’¹¹

INCOMPLETE DATA

Litigation has centred on Boehringer’s perceived failure to disclose all the data from post-approval trials. This includes data that showed the number of people who died from bleeding was less than expected, according to internal documents made public in lawsuits over the product. The company did not share a second analysis showing a higher death rate, according to Bloomberg news.¹³ Calls for data transparency revolve around the limited value of analysis when all data is not disclosed.

The BMJ investigation in July 2014 echoes these concerns, but also report on apparent failure to disclose data on the potential benefits of monitoring anticoagulant activity and adjusting the dose to make sure the drug is working as safely and effectively as possible. The BMJ claims that previously unseen internal documents highlight questions about the safety raised by Boehringer’s employees. The company also withheld analyses that calculated how many major bleeds could be prevented by dose-adjustment. The company says that this information was not shared because the analysis did not provide a reliable prediction of patient outcomes.¹⁴ Furthermore, in the 2013 U.S litigation case, Boehringer was ordered to pay almost \$1million in lost files relating to dabigatran.¹³

BOEHRINGERS’S DEFENCE

For its part, Boehringer continues to deny any wrong-doing. In a reply to the BMJ article, it recalled that the data from the RE-LY trial, and post-marketing assessments recognised by the FDA and EMA,

have supported dabigatran as “an important medication that reduces the risk of stroke, when used as directed in appropriate patients with non-valvular atrial fibrillation (NVAF).” Importantly, RE-LY was conducted without the use of an antidote and without monitoring dabigatran plasma levels and demonstrated safety and efficacy in spite of this. The research shows that individual patient characteristics, such as age, renal function and bodyweight are the most critical factors in dosing decisions to help reduce the risk of bleeding. All data to support this conclusion was provided to the regulators.^{15–17} Models for bleeding events investigated post-approval, as well as monitoring of plasma level concentrations, were not supported by the rigors of “scientific and mathematical” analyses. The company deny “withholding of information”, as there were “no new data or conclusions to share”.¹⁵ Nevertheless, the company announced in May 2014 that it plans to settle 4000 lawsuits, “to avoid the distraction and uncertainty of lengthy litigation”.¹⁶

CONCLUSION

The example of dabigatran and the ensuing concerns has highlighted issues at a number of stages of its emergence into the public domain. Questions will continue to be asked on the potential flaws of RE-LY, the accelerated trial process for novel drugs, the regulatory bodies’ perceived value of convenience over safety, provision of incomplete data by drug companies to licensing committees, the process of licensing and statistical analyses made for data interpretation which has come under scrutiny for being subject to bias.

For a drug that has made over \$1.66 billion worldwide,¹⁸ and is prescribed for use in over 100 countries, the current debate looks set to continue. Although RE-LY appeared to demonstrate the benefit of taking dabigatran in patients with non-valvular atrial fibrillation, it is unclear whether RE-LY would have been accepted by commissioning bodies and Dabigatran approved, if all the data had been disclosed at the time of the approval process. It is also possible that the use of plasma concentrations as a guide to adjust the dose of dabigatran may have provided even better outcomes for patients. With all these unanswered questions, is it safe for a drug to remain under the current guidance in the public domain? At the very least, we call for commissioning bodies to acknowledge the new findings that have emerged into the public domain, since approval. We ask for current guidance to be updated for the safety of patients, given what we now know, which was not known in 2010.

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