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Simplifying Monitoring with Oral Anticoagulants

San Diego - The choice of oral anticoagulants has expanded with the introduction of agents that do not require therapeutic drug monitoring. In new comparative data with warfarin, these agents are continuing to demonstrate advantages in a growing array of indications. As reported here at ASH, one of these newer agents was associated with an average 1-day reduction in hospital stay attributed to eliminating the necessity of establishing a therapeutic international normalized ratio (INR). While INR monitoring in patients on warfarin is needed to avoid both the risk of suboptimal levels of anticoagulation and excess bleeds, the predictability of benefit with oral agents appears to be at least similar to that of injectable low molecular-weight heparins.

Chief Medical Editor: Dr. Léna Coïc, Montréal, Quebec

Oral anticoagulants that offer predictable pharmacokinetics and relatively low response variability have been rapidly adopted for clinical practice because of the cumbersome demands imposed by injectable agents and warfarin, the only oral anticoagulant previously available. The data providing support for the efficacy and safety of the direct thrombin inhibitor dabigatran and the direct factor Xa inhibitor rivaroxaban continue to grow with new studies presented at the 2011 ASH meeting. The recent findings, building on the phase III studies, are demonstrating the advantages in the real-world setting.

"These agents, I think, are an important advance because of the burden of maintaining warfarin in the therapeutic range," reported Dr. Bengt I. Eriksson, Sahlgrenska University Hospital, Gothenburg, Sweden. An investigator on 2 studies designed to evaluate dabigatran safety parameters, Dr. Eriksson mentioned that there are numerous reports in the literature regarding the difficulties and the inconvenience of monitoring international normalized ratio (INR) in patients on chronic warfarin.

INR Issues

New data from the ongoing Canadian ROAM (Resource utilization associated with Oral Anticoagulation Management) study reinforced that perception. It is the first prospective assessment of the burden of care from monitoring long-term oral anticoagulant therapy in routine medical care in Canada. All patients in ROAM are receiving anticoagulation for non-valvular atrial fibrillation (NVAF). The 48-week study is monitoring an array of variables, including how quickly and how well INR results are communicated to patients, who are keeping diaries.

At ASH, 180 of the 600 patients planned for inclusion from centres in 9 provinces had completed the 48-week follow-up. In preliminary results, approximately 13 INR tests were performed on average over 48 weeks on each patient. The average time patients spent in the desired INR therapeutic range of 2.0 to 3.0 was 67%. The average delay between obtaining the INR and communicating the result to the patient was 1.4 days, but 28% of patients did not record any INR values over the course of the study and only 4% of patients reported INR dates and values completely matched the physicians' records.

"The majority of patients undergo telephone monitoring, with a delay in reporting results back to patients and frequent miscommunication of results," stated Dr. Rita Selby, Sunnybrook Health Sciences Centre, Toronto, Ontario.

Reducing Hospital Stay

While these results support some of the well-known problems with INR monitoring, there is evidence that a newer oral agent can reduce hospital stay principally by avoiding INR monitoring. In a large cohort study in patients receiving dabigatran or warfarin, all hospitalizations over a 3-month period for NVAF were evaluated. In either group, about 45% received their oral anticoagulant as a monotherapy. In the rest, patients had also received a low molecular-weight heparin (LMWH) or unfractionated heparin (UFH) during their course of hospitalization.

"After controlling for an array of variables, the hospitalizations were about 1 day shorter among patients with NVAF who received dabigatran when compared to those receiving warfarin," observed Eileen Fonseca, Health Economics and Outcomes Research, Plymouth Meeting, Pennsylvania. In this study, which had data on 1320 hospitalizations involving use of dabigatran and 22,395 hospitalizations involving warfarin, "average length of stay was also significantly shorter [$P<0.05$] for dabigatran when comparing all the various anticoagulant regimens. These ranged from a 0.5-day on monotherapy to 2.3 days for patients who also received UFH."

Efficacy and Safety of Oral Anticoagulants

Attributed to the ability of dabigatran to reach a steady anticoagulant state more rapidly, the shorter hospital

stay would be predicted to substantially increase its cost efficacy relative to warfarin. Its efficacy and safety were not assessed in this study, but comparable efficacy to warfarin for stroke prevention in NVAF patients was previously confirmed in a phase III study (Connolly et al. *N Engl J Med* 2009;361:1139-51). At a dose of 110 mg, dabigatran was equivalent to warfarin for stroke prevention but reduced the risk of major hemorrhage. At a dose of 150 mg, it was more effective than warfarin for stroke prevention with a similar bleeding risk.

In new data with rivaroxaban, which can also be prescribed in a fixed dose without INR monitoring, comparison was conducted with fondaparinux, an injectable factor Xa inhibitor, and with LMWH in patients undergoing major orthopedic surgery. In the retrospective review of 4807 patients, 1055 received rivaroxaban, 2069 received fondaparinux and 1683 received LMWH. Relative efficacy and safety were both superior on the oral anticoagulant relative to the comparators. The end points were the rate of venous thromboembolism (VTE) and safety.

As reported by Dr. Jan Beyer-Westendorf, Dresden University Clinic, Germany, the oral factor Xa inhibitor "was significantly more effective for preventing symptomatic VTE relative to fondaparinux or LMWH, mostly due to significantly lower rates of distal VTE." In addition, it also provided lower rates of surgical revisions and of severe bleeding complications. Specifically, the rates of all VTE for rivaroxaban, fondaparinux and LMWH were 2.5%, 5.5% and 3.9%, respectively ($P<0.0005$ vs. fondaparinux and $P<0.05$ vs. LMWH). The rates of severe bleeding were 7.4%, 11.2% and 14.9%, respectively ($P=0.001$ vs. fondaparinux and $P<0.0005$ vs. LMWH).

HEMOCLOT Assay

With all anticoagulants, protection against thrombotic events is balanced against risk of bleeding, which confers the predictability of the newer anticoagulants with a particular advantage when consistent antithrombotic effect is most important. Although newer agents do not require INR monitoring, a one-time assay may be valuable in measuring anticoagulant levels in an emergency setting. New data presented by Dr. Eriksson suggest that a direct thrombin assay called HEMOCLOT can confirm that drug concentrations are appropriate.

"The HEMOCLOT direct thrombin inhibitor assay is suitable for the precise quantitative determination of dabigatran in citrate plasma samples," reported Dr. Eriksson, who was involved in testing this assay in plasma samples from patients participating in a trial with dabigatran. The accuracy of the concentrations was compared against liquid chromatography/tandem mass spectrometry. The results demonstrated that "the accuracy is acceptable for the intended use of the assay, which is to confirm that dabigatran concentrations are in the therapeutic range."

In patients being considered for the assay, such as those with a delicate balance between the benefits and risks of anticoagulation, this test needs only to be administered once, rather than periodically, because of the expectation of a persistent dose-to-dose effect, but it may be helpful for optimal titration of the therapeutic level. However, Dr. Eriksson emphasized that the predictability of dabigatran and rivaroxaban is among their strongest features and such testing was not undertaken in the comparative trials.

Of the comparative trials, new pooled data were evaluated from the 4 phase III studies comparing dabigatran to the LMWH enoxaparin for preventing VTE after major orthopedic surgery. The purpose of this new analysis was to compare acute coronary syndrome (ACS) events, such as myocardial infarction, unstable angina and ischemic cardiomyopathy. According to Dr. Eriksson, who presented these data, overall event rates were low and not different in the 2 treatment arms.

"There are now 4 trials in the analysis with more than 10,000 patients, and there were no significant differences in ACS-related adverse event rates between dabigatran and enoxaparin," Dr. Eriksson told delegates. He considers these reassuring results another piece in a large collection of evidence that the newer oral anticoagulants should be a prominent option for patients at risk of thrombosis.

Summary

New oral anticoagulants are being rapidly incorporated into the same indications previously conferred on warfarin. The key advantage is that these agents are demonstrating an efficacy and safety comparable to warfarin when an appropriate INR is maintained. The consistency of activity also appears to be similar to that of injectable anticoagulants including LMWH. The ability to control thrombotic risk with an oral agent that does not require periodic monitoring has implications for benefit, safety, use of health care resources and patient convenience. □

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