肺塞栓症に対するrivaroxabanの効果は標準治療の効果と同等である

EINSTEIN PE:新たな経口抗凝固薬rivaroxabanは肺塞栓症に対する標準的な治療法よりも安全である

EINSTEIN PE: New oral anticoagulant rivaroxaban safer than standard approach to treat pulmonary embolism

肺塞栓症の初回治療および長期治療における重要な安全性指標に関し、新たな経口抗凝固薬は標準的な注射薬治療よりも成績が優れていたとの研究結果が第61回American College of Cardiologyにおいて発表され、New England Journal of Medicineオンライン版に掲載された。EINSTEIN-PEトライアルは2,419人の患者をrivaroxaban群（15mg1日2回内服を3週間の後に20mg1日1回）および2,414人を標準治療群（体重1kg当り1.0mgのenoxaparin1日2回を5日以上継続しINR2.0以上が2日間以上持続し、それに加えビタミンK阻害薬を無作為化後48時間以内に開始しINRを2.0～3.0とするように用量調節した時点でenoxaparinを中止）に無作為に割り付けた。Rivaroxaban群の再発率は2.1%（50件）であったのに対し、標準療法では1.8%（44件）であり、有効性に関する非劣性が有意に認められた。出血に関する安全性評価に関しては、rivaroxabanの方がはるかに良好であった:重大なまたは臨床的に明らかな出血に関する主要な安全性評価では、10.3%であったのに対し標準治療では11.4%であった;重大な出血のみに関しては、1.1%であったのに対し標準治療では2.2%であった。一次エンドポイント発現率は患者背景に関係なく同等であった。

Full Text

A novel oral anti-coagulant outperformed the injected standard therapy on important safety measures for initial and long-term treatment of pulmonary embolism (PE) and showed comparable efficacy, according to data from the EINSTEIN-PE trial presented at the American College of Cardiology's 61st Annual Scientific Session.

Venous thromboembolism (VTE) is the third most common cardiovascular disease, and PE is the third most common cause of hospital-related death. EINSTEIN-PE is one of a series of large international phase III clinical trials of the anti-coagulant rivaroxaban to treat VTE or prevent a recurrence in patients with acute PE or DVT. The Food and Drug Administration has approved rivaroxaban as the only oral anti-coagulant for prevention of VTE in patients who have knee or hip replacement, procedures that carry clotting risks.

The trial compared rivaroxaban with standard therapy – injection of the anti-coagulant enoxaparin, followed by a vitamin K antagonist (VKA; either warfarin or acenocoumarol) chosen by each participating site – to demonstrate that the oral drug as a single agent is equivalent to the complicated two-drug standard therapy. In the standard regimen, enoxaparin must be given as an injection, and the VKA must be monitored with INR testing to make sure the dose is adequate and safe, because common drugs such as antibiotics, alcohol and some foods interact with VKAs: the higher the INR number, the higher the risk of bleeding.

"If you give standard treatment in the right way, it's a perfectly effective drug with almost 90 percent reduction in recurrent thrombosis, but it has to be well controlled," said Harry R. Buller, M.D., Ph.D., professor of vascular medicine at the Academic Medical Center, Amsterdam, The Netherlands, who chairs the program for the three EINSTEIN studies. "The reason people look for alternatives is that it's a nightmare to give. Rivaroxaban makes things easier for everybody – patients and physicians. Our major aim was to show that it's at least as good as standard care."

The study, conducted at 263 sites in 38 countries, randomly assigned 2,419 patients to the rivaroxaban arm and 2,414 to standard treatment. All enrolled patients had a primary diagnosis of PE, and 25 percent in both groups also had DVT. Patients were treated for three, six or 12 months (average, seven) as deemed appropriate by each clinician before randomization. The rivaroxaban group received 15 mg twice a day for three weeks followed by 20 mg once a day. In the standard-therapy arm, the regimen was enoxaparin at 1.0 mg per kg of body weight twice daily, continued at least five days and stopped when the INR was 2.0 or more for two consecutive days, plus a VKA started within 48 hours after randomization with dose adjustment to maintain an INR of 2.0 to 3.0.

Rivaroxaban's efficacy was highly significant for non-inferiority with 2.1 percent recurrences (50 events) vs. 1.8 percent (44 events) in the standard-therapy arm. On safety measures of bleeding, rivaroxaban did much better: principal safety measure of major or clinically relevant bleeding, 10.3 percent vs. 11.4 percent for standard treatment; for major bleeding alone, 1.1 percent vs. 2.2 percent for standard therapy. Rates for primary endpoints were similar in both study arms regardless of patient characteristics.

"Physicians want to know about major bleeding, the most important safety outcome, and rivaroxaban was highly significantly superior. This was our most astonishing finding," Dr. Buller said. "Rivaroxaban is just as good as standard treatment for PE – these data are pretty convincing – and this is an oral-only approach, which makes it very simple. The subcutaneous injections can be hazardous as well."

Researchers also will be doing a subgroup analysis of the 8,200 patients in the EINSTEIN-PE and EINSTEIN-DVT trials to see if they can identify a risk profile for patients who are likely to have bleeding problems on standard treatment or the new drug.

The trial was sponsored by Bayer HealthCare and Janssen Pharmaceuticals. Dr. Buller is reimbursed for patients who participate in the study, travel costs and administrative time, and those funds go to the hospital.

This study was simultaneously published online in the New England Journal of Medicine at the time of presentation and will appear in the April 2012 print edition.

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