Milvexian shows potential to reduce risk of ischemic stroke

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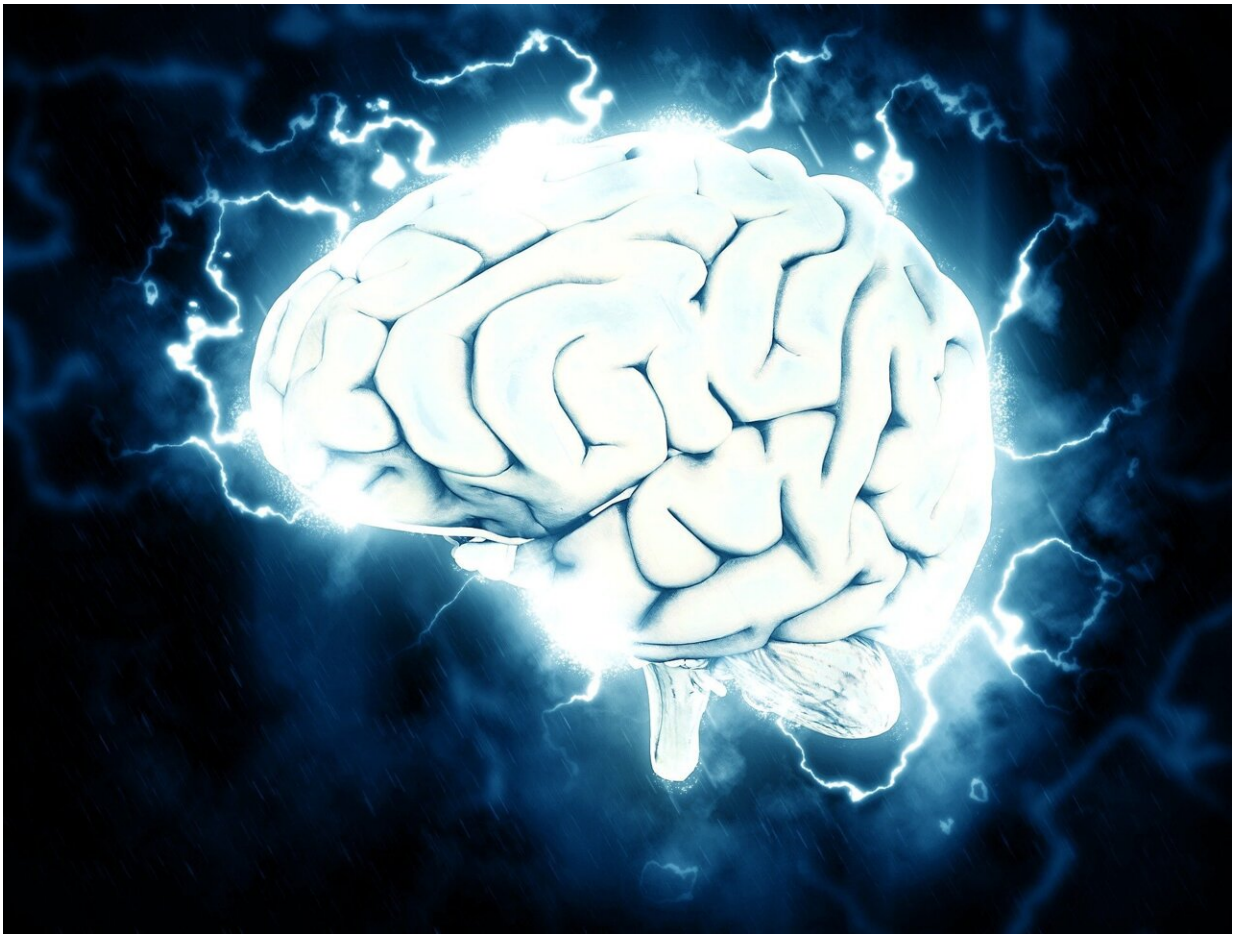

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A phase 2 trial in patients with a prior ischemic stroke or high-risk

transient ischemic attack (TIA) has indicated that milvexian should be further investigated for its ability to reduce the risk of ischemic stroke without a clinically important increase in bleeding. The late breaking research was presented in a Hot Line session on 28 August at ESC Congress 2022.

The risk of ischemic stroke in patients with a prior ischemic stroke or TIA is approximately 5–10% in the first few months. Efforts to reduce the early risk of recurrent stroke have focused on antiplatelets. Improvements in outcome have been observed with novel antiplatelet strategies, but a significant residual risk of ischemic stroke and the potential for major bleeding have limited the effectiveness of these options. Currently, no anticoagulants are approved for non-cardioembolic ischemic stroke prevention in the early phase. Factor XIa is a driver of thrombus growth and genetic studies have found that higher levels are associated with a greater risk of ischemic stroke. The phase 2 AXIOMATIC-TKR trial indicated that in patients undergoing knee arthroplasty, factor XIa inhibition with milvexian could prevent venous thromboembolism with a low risk of bleeding.

AXIOMATIC-SSP was the largest dose-finding trial of an anticoagulant in a stroke population. The study estimated the dose-response relationship of milvexian on stroke occurrence and bleeding in patients with a high risk of recurrent stroke and associated disability. Eligible patients were aged over 40, had a mild-to-moderate acute non-lacunar ischemic stroke (National Institutes of Health Stroke Scale score ≤7) or a high-risk TIA (ABCD2 score ≥6) with evidence of arterial atherosclerosis, and could be randomized within 48 hours of symptom onset. All participants had visible atherosclerotic plaque in a vessel supplying the affected brain region.

The study included 2,366 patients from 367 sites in 27 countries. The median age was 71 years and 64% were men. Patients were randomly

assigned to one of five doses of milvexian (25, 50, 100, 200 mg twice daily, 25 mg once daily) or placebo daily for 90 days. All participants received background treatment with open-label aspirin and clopidogrel for 21 days, followed by open-label aspirin from day 22 to 90. Magnetic resonance imaging (MRI) was performed at baseline and 90 days. The primary efficacy endpoint was a composite of ischemic stroke during treatment or incident infarct on brain MRI at 90 days. The main safety endpoint was major bleeding, defined as Bleeding Academic Research Consortium (BARC) type 3 or 5 bleeding.

The investigators found that while the rate of the primary efficacy endpoint was numerically lower at the 50 mg and 100 mg twice daily doses, there was no apparent dose-response (placebo 16.6%, 25 mg once daily 16.2%, 25 mg twice daily 18.5%, 50 mg twice daily 14.1%, 100 mg twice daily 14.7%, 200 mg twice daily 16.4%). Milvexian numerically reduced the risk of clinical ischemic stroke (excluding covert brain infarction) in the intention-to-treat population at all doses except 200 mg twice daily, with doses from 25 to 100 mg twice daily showing an approximately 30% relative risk reduction versus placebo (placebo 5.5%, 25 mg once daily 4.6%, 25 mg twice daily 3.8%, 50 mg twice daily 4.0%, 100 mg twice daily 3.5%, 200 mg twice daily 7.7%).

The incidence of major bleeding was low overall (placebo 0.6%, 25 mg once daily 0.6%, 25 mg twice daily 0.6%, 50 mg twice daily 1.5%, 100 mg twice daily 1.6%, 200 mg twice daily 1.5%). The rate of major bleeding for the milvexian 25 mg once daily and twice daily doses was similar to placebo, while a moderate increase was observed in the milvexian dose arms of 50 mg twice daily and above (the majority of which were gastrointestinal bleeds), with no apparent dose-response. There was no increase in severe bleeding (BARC type 3c or symptomatic intracranial hemorrhage) versus placebo, and there was no fatal bleeding in any arm of the study.

Principal investigator Dr. Mukul Sharma of McMaster University, Hamilton, Canada said, "Based on the observed efficacy signal for ischemic stroke, the bleeding profile, and the overall safety and tolerability, milvexian will be further studied in a phase 3 trial in a similar stroke population."

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