プロテアーゼ活性化受容体1阻害薬はACSおよびCADにおいて有望である

J-LANCELOT：新たなプロテアーゼ活性化受容体1阻害薬はACSおよびCAD患者の重篤な心有害事象を減少させる

J-LANCELOT: New protease-activated receptor 1 inhibitor reduces major adverse cardiac events in ACS and CAD patients

新たなプロテアーゼ活性化受容体1阻害薬（E5555）は、急性冠症候群（ACS）および冠動脈疾患（CAD）において重大な出血事故を増加させることなく重篤な心有害事象（MACE）を減少させる可能性があることを、2つのJ-LANCELOT（トロンビンの細胞効果拮抗から日本が学んだこと：Japanese Lessons from Antagonizing the Cellular Effect of Thrombin）トライアルがそれぞれ示した。このプラセボコントロールトライアルはACS患者（不安定狭心症または非ST上昇MI、241人）および高リスクCADを有する患者(263人)を調査した。治験薬（E5555として知られる）の用量を増大させるにつれ出血件数が増加する傾向が認められたが、統計学的に有意ではなかった。CADトライアルおよびACSトライアルにおいて、実薬群ではプラセボ群よりもMACE（主に心筋梗塞および再発性心筋虚血）の発現数が少なかった（それぞれ1.0%対4.5%、P=0.066；5.0%対6.6%、P=0.73）。E5555はPAR-1遮断により血小板凝集を強力に阻害した。両スタディ群において、100mgおよび200mgの用量ではトラフレベルでの平均血小板凝集が90%以上であり、50mgでは20～60%であった。このトライアルの結果はESC2010ホットラインセッションで発表された。

Full Text

Aspirin and thienopyridine antiplatelet therapy (such as clopidogrel) are standard care in the treatment of acute coronary syndrome (ACS) and even in stable coronary artery disease (CAD) after coronary intervention with stent. However, effective antiplatelet agents are needed which do not increase the risk of bleeding. Two J-LANCELOT (Japanese Lessons from Antagonizing the Cellular Effect of Thrombin) trials were designed to evaluate a new protease-activated receptor 1 (PAR-1) inhibitor known as E5555 in Japanese patients; the primary purpose of the trials was to assess the safety and tolerability of E5555, and secondary purpose to determine its effects on major adverse cardiac events (MACE) and platelet aggregation in ACS and CAD. The trials were presented at a Hotline session at ESC 2010.

Principal investigator Professor Shinya Goto from Tokai University School of Medicine, Japan, reported that the two trials separately showed that E5555 may have the potential to reduce MACE (CV death, MI, stroke, or recurrent ischemia) with no increase in serious bleeding events even with addition to standard care in both ACS and CAD patients.

ACS patients (unstable angina pectoris or non-ST elevation MI, n = 241) received a loading dose of 400 mg E5555 on day 1, followed by 50 mg, 100 mg, 200 mg E5555 or placebo per day for 12 weeks (>90% of patients also received aspirin and a thienopyridine). Patients with high-risk CAD (n = 263) received placebo, and 50 mg, 100 mg, or 200 mg E5555 once daily for 24 weeks (all patients were on aspirin and approximately 40% thienopyridine).

Bleeding was assessed according to CURE ("clopidogrel in unstable angina to prevent recurrent events") and TIMI ("thrombolysis in MI") criteria. Though there was a numerical trend towards an increase in any bleeding incidence with increasing treatment dose of E5555, this was not statistically significant. Clinically significant bleeding consisting of TIMI major, minor and minimal bleeding requiring medical attention was almost the same between the placebo and combined active groups, 1.5% vs. 1.5% in CAD and 6.6% vs. 5.0% in ACS patients, respectively.

There was a numerically lower incidence of MACE in the active group than in the placebo group in the CAD trial (1.0% vs. 4.5%, p=0.066) and in ACS trial (5.0% vs. 6.6%, p=0.73). The MACE events seen in these trials were predominantly driven by MI and recurrent ischemia. While not powered to establish the efficacy in both patient groups, all active groups demonstrated a numerically lower incidence of MACE events relative to placebo. However, the overall number of events was very low.

E5555 produced strong inhibition of platelet aggregation via PAR-1 blockade. At trough levels, over 90% mean inhibition of platelet aggregation was achieved with doses of 100 mg and 200 mg, and 20-60% inhibition was achieved with a dose of 50 mg E5555 in both study groups.

Professor Goto said: "E5555 was generally well tolerated with regard to bleeding complications and has potential for reduction of MACE in patients with ACS or high risk CAD. While E5555 did not increase the incidence of clinically significant bleeding, there was a dose-dependent trend for increased minimal bleeding.

"From these results, PAR-1 receptor antagonism may be an attractive pathway in the treatment of atherothrombosis. But we need further adequately powered trials to determine the efficacy and safety of E5555."

Conference News