Rolofyllineは急性心不全に効果がなかった

PROTECT Study：Rolofyllineは急性心不全患者において有効性を示すことができなかった

PROTECT Study: Rolofylline does not demonstrate efficacy for patients with acute heart failure

PROTECTパイロットスタディでは有望な結果が認められたにもかかわらず、大規模なPROTECTトライアルではrolofyllineとプラセボとで非代償性心不全（HF）患者において差が認められなかった。24～48時間後の中等度から著明な呼吸困難の改善はrolofylline群の方がプラセボ群よりも多くの患者において認められたが、これは、永続的な腎機能障害に対する有効性の欠如により相殺された。このトライアルは、体液過負荷、腎機能障害（推定GFR 20～80ml/min）および血漿BNPまたはNT-proBNPレベル上昇（それぞれ>500pg/mLまたは>2,000pg/mL）の徴候発現後24時間以内にHFとして入院した患者2,033人に対するrolofyllineの効果を評価したものである。治療に成功したのはrolofylline群患者の40.6%に対し、プラセボ群患者では36.0%であり、治療無効と分類されたのはrolofylline群患者の21.8%に対し、プラセボ群患者では19.8%であり、その他の患者は不変であった（オッズ比=0.92、95%CI 0.78～1.09；p=0.348）。60日以内の死亡または心血管疾患および腎疾患による再入院は、rolofyllineおよびプラセボ患者でそれぞれ30.7%および31.9%であった（ハザード比および95%CI 0.98、0.83～1.17、p=0.861）。永続的な腎機能障害はプラセボ群患者の13.7%およびrolofylline患者の15.0%にそれぞれ発現した。重大な神経学的イベントはrolofylline群患者において多く認められた。

Full Text

Despite the promising findings of the PROTECT Pilot study, the larger PROTECT trial found no difference with rolofylline versus placebo with respect of the primary and main secondary end-points of the study. Although more rolofylline patients than placebo patients experienced moderate or marked dyspnea improvement at 24 and 48 hours from randomization, this was counterbalanced by a lack of effect on persistent renal impairment. Lastly, the risk of important neurological events was increased in patients on rolofylline.

Acute heart failure (HF) is the most common cause of hospitalization for patients over 65 years. Its prevalence continues to rise as the population ages. It carries a high cost and a dismal prognosis with an in-hospital mortality rate of 3-8%, a 60-90 day mortality rate of 9-13%, and a short-term re-hospitalization rate of 25-30%. Despite this, there have been no significant recent advances in medical treatment. The cornerstones remain intravenous diuretics to manage congestion, often in conjunction with morphine and intravenous vasodilators, such as nitrates, to relieve dyspnea.

Many patients hospitalized for HF have underlying chronic kidney disease or worsening renal function on admission or during their hospital course. Worsening renal function (WRF) and resistance to loop diuretics are consistently associated with poorer outcomes, including longer length of stay, higher in-hospital and post-discharge mortality rates, and increased readmission rates. Recently, adenosine has been implicated as an important mediator of both WRF and diuretic resistance as it causes a reduction in renal blood flow and glomerular filtration rate (GFR) and decreases sodium excretion. In the previously published PROTECT-Pilot study1, rolofylline treatment, at the 30 mg dose, was associated with trends toward better symptom improvement, lesser WRF, and fewer deaths or readmissions for HF or renal dysfunction over the next 60 days.

PROTECT (A Placebo-controlled Randomized study of the selective A1 adenosine receptor antagonist KW-3902 for patients hospitalized with acute HF and volume Overload to assess Treatment Effect on Congestion and renal function Trial) was aimed at the assessment of the effects of rolofylline on symptoms, renal function and short-term morbidity and mortality in 2,033 patients hospitalized for HF within 24 hours with signs of fluid overload, impaired renal function (estimated GFR 20-80 ml/min) and high BNP or NT-proBNP plasma levels (>500 pg/mL or >2000 pg/ml, respectively). Patients were randomized 2:1 to rolofylline 30 mg/day or placebo, administered as a 4 hours daily infusion repeated for 3 days. Dyspnea was assessed on a 7-point Likert scale daily for the first 7 days (or until discharge, if earlier) and then at 14 days, after enrollment. Blood samples for measurements of serum creatinine were collected daily until day 7 (or until discharge, if earlier) and at day 14 after enrollment. Deaths were captured to day 180 and rehospitalizations were captured up to day 60 after enrollment.

The primary end-point of PROTECT was a three category ordered outcome of treatment success, patient unchanged, or treatment failure. Treatment success was defined as a moderate to marked better dyspnea at 24 and 48 hours after the start of study drug compared to baseline, in the absence of any criteria for treatment failure. Treatment failure included any of the following criteria: death or readmission for HF any time through Day 7; or worsening symptoms and/or signs of HF occurring >24 hours after the start of study drug to Day 7 or discharge, whichever occurred first, or persistent renal impairment as defined by a serum creatinine (SCr) increase of≥ 0.3 mg/dL from randomization to Day 7, confirmed at Day 14, or the initiation of hemofiltration or dialysis through Day 7. Patients were categorized as unchanged if they did not meet criteria for either treatment success or treatment failure.

Secondary end-points were: time to death or rehospitalization for cardiovascular or renal causes through Day 60 and the proportion of subjects with persistent renal impairment defined as a SCr increase of ≥ 0.3 mg/dL from randomization to Day 7, confirmed at Day 14, or the initiation of hemofiltration or dialysis or death through Day 7.

Enrollment in PROTECT was concluded in January 2009 and the main results became available in June 2009. Six hundred seventy seven patients were randomized to placebo and 1,356 patients received rolofylline (placebo to rolofylline 1:2 randomization). The placebo and rolofylline groups were well balanced with respect to the main baseline characteristics. Follow-up was complete in all but 1 patient at 60 days and 4 patients (0.2%) at 180 days.

No significant difference was found between rolofylline and placebo with respect to the primary end-point. Treatment success was achieved by 40.6% patients on rolofylline, compared with 36.0% of the patients on placebo, 21.8% of the patients were classified as treatment failure with rolofylline versus 19.8% with placebo, the remainder being unchanged (OR=0.92, 95% CI=0.78-1.09; p=0.348). There were no significant differences between the treatment groups in either secondary endpoint. Death or rehospitalization for cardiovascular or renal causes at day 60 occurred in 30.7% and 31.9% of the rolofylline and placebo patients (hazard ratio and 95% CIs, 0.98, 0.83-1.17, p=0.861). Persistent renal impairment occurred in 13.7% of placebo patients and 15.0% of rolofylline patients, respectively.

With regards to the components of the primary end-point, moderate or marked better dyspnea at both 24 and 48 hours was observed in 52.0% of patients in the rolofylline treated group versus 45.4% of patients in the placebo group. However, this was partially counterbalanced by the higher rate of persistent renal impairment in the rolofylline group.

Serious adverse events (SAE) occurred in 13.8% of rolofylline and 14.7% placebo patients and cardiac SAEs occurred in 7.2% and 9.0%, respectively. The rate of central nervous system SAEs was 1.5% in the rolofylline group versus 0.6% in placebo, including more patients experiencing seizures.

In conclusion, despite the promising findings of the PROTECT Pilot study, the larger PROTECT trial found no difference with rolofylline versus placebo with respect of the primary and main secondary end-points of the study. Although more rolofylline patients than placebo patients experienced moderate or marked dyspnea improvement at 24 and 48 hours from randomization this was counterbalanced by a lack of effect on persistent renal impairment. Lastly, the risk of important neurological events was increased in patients on rolofylline.

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