

Tacrolimus for prophylaxis of post-endoscopic retrograde cholangiopancreatography pancreatitis: a potential new target of old drug?

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See “Preventive effect of tacrolimus on patients with post-endoscopic retrograde cholangiopancreatography pancreatitis” by Harshvardhan B. Rao, Paul K. Vincent, and Priya Nair, et al., on page 665–673.

Tacrolimus is a macrocyclic lactone antibiotic that was first isolated in 1984 from the soil microorganism *Streptomyces tsukubaensis* in Japan.¹ This agent, which acts as a calcineurin inhibitor, has been the cornerstone immunosuppressive agent used to prevent graft rejection in organ transplant recipients for a long time.²

Acute pancreatitis, which is the most common complication of endoscopic retrograde cholangiopancreatography (ERCP) performed for the endoscopic management of biliary complications, frequently occurs after liver transplantation and can induce a systemic inflammatory response along with a painful local inflammatory reaction of the pancreas.³ Post-ERCP pancreatitis (PEP) can occur in up to 10% of cases, and most cases are not severe. However, some patients progress to severe pancreatitis, which can cause serious morbidity and complications and require long-term hospitalization and outpatient

treatment.³ Therefore, effective preventive drugs or interventional strategies for PEP, such as rectal indomethacin, an 8-hour protocol of aggressive lactated Ringer's solution, and pancreatic duct stenting, have been developed.⁴

It has recently been revealed that one of the key mechanisms of the inflammatory cascade leading to PEP is zymogen activation occurring early through the calcium-activated phosphatase calcineurin in acinar cells.⁵ After that, a calcineurin inhibitor, tacrolimus, has been suggested based on several previous pre-clinical and clinical studies.⁶⁻⁸

Rao et al.⁹ reported the results of a prospective pilot study that compared the PEP rate of the tacrolimus group and control group based on this recent emerging evidence. In this study, the authors reported that the incidence of PEP was reduced by nearly 50% in the tacrolimus group compared with that in the control group (8.3% vs. 15.7%). They suggested that tacrolimus might prevent the occurrence of PEP. Considering the main mechanism of PEP development, tacrolimus, which inhibits calcineurin, may theoretically be a suitable pharmacological measure. However, before accepting the positive results of the PEP-prevention effect of tacrolimus as evidenced in this study, the issues of this study must be pointed out.

First, this study was a small-scale, uncontrolled pilot study; there was a selection bias, and there was no analysis of PEP risk factors for the subjects. It is difficult to accept the results of this study as having a high level of evidence. In addition, even

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though this study was implemented in the average-risk PEP cohort, the PEP rate of both the control and tacrolimus groups was higher than that of the previous studies. One reason could be that the definition of difficult biliary cannulation (DBC) in this study was used in previous relevant studies. This definition differs from the new DBC definition that has been strengthened in the recently published European Society of Gastrointestinal Endoscopy guidelines about papillary cannulation.¹⁰ Applying the older definition of DBC while implementing ERCP to the subjects of this study may raise ethical concerns because it has already been shown that the chance of PEP incidence increases as the number of papilla attempts increases in previous studies.

Nevertheless, the results of this preliminary prospective study suggest that PEP has the potential to become a new target for tacrolimus, which has been used to prevent transplant rejection in organ transplant patients for over three decades. In addition, the results of the study are worth considering in the implementation of subsequent relevant studies that demonstrate the PEP preventive effect of tacrolimus and establish an appropriate therapeutic dosage that can have a preventive effect not only in patients at high risk of PEP but also in the average risk of the PEP cohort.

Conflicts of Interest

The author has no potential conflicts of interest.

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