Tacrolimus Prevents the Development of Laryngo-tracheal stenosis in the Novel Rat model

Koji Araki, Daisuke Mizokami, Taku Yamashita, Nobuki Tanaka, Masayuki Tamifuji, and Akhiro Shiotani
Department of Otolaryngology-Head and Neck Surgery, National Defense Medical College, Japan.

ABSTRACT

[Background] Acquired laryngo-tracheal stenosis (LTS) is challenging problems for otolaryngologists. Several studies suggested Tacrolimus might potentially have inhibitory effects on airway stenosis as seen in coronary drug eluting stents (DES). The objective of the present study is to determine whether Tacrolimus modulate the wound healing of airway mucosa and prevent obstructive airway disease in an acute injury animal model.

[Methods] The authors recently reported the novel reliable LTS model in rats, whose laryngo-tracheal mucosa was scraped with a nylon brush through the tracheostoma. Tacrolimus (0.2 or 1.0 mg/kg i.m.) were systemically administered for 5 days. The pathological changes at the airway mucosa and the tracheal lumen were assessed at 10 days after the scraping. The percentage of stenosis was calculated by an image analysis software.

[Results] Both hyperplasia of airway epithelium and thickened submucosal layer with extensive fibrosis, angiogenesis, and collagen deposition provoked lumen stenosis. There was significant preventive effect on airway stenosis in the lower dose of Tacrolimus (0.2mg/kg) compared to brushing only group (p<0.05). The high dose of Tacrolimus group (1.0mg/kg) also showed a trend to potential protection of airway stenosis.

[Conclusions] This study suggests that the systemic immunosuppressive agent, Tacrolimus, has preventive effect on LTS from mucosal injury of the airway.

Introduction

Re-stenosis after surgical intervention is major problem to resolve in treating LTS. Modulating the wound healing of airway mucosa is the key component to prevent re-stenosis. DESs with immunosuppressants as Tacrolimus, calcineurin inhibitors which have antiproliferative effects, have been dominant for the treatment of coronary artery diseases in the interventional cardiology owing to their efficacy in significantly reducing restenosis. The aim of this study is to determine whether Tacrolimus prevents LTS in an acute injury animal model.

MATERIAL and METHODS

Fig. 1: Establishment of the laryngotracheal stenosis 4. The laryngotracheal mucosa above the tracheostoma was scraped ten times with a nylon brush through the tracheostoma (a). The nylon brush is 1.8 mm in diameter, 7.5 mm in length (b). The tracheostoma was kept open.

Fig. 2: Protocol of Tacrolimus administration

RESULTS

Fig. 5: There was significant preventive effect on airway stenosis in the lower dose of Tacrolimus (0.2mg/kg) compared to brushing only group (p<0.05). The high dose of Tacrolimus group (1.0mg/kg) also showed a trend to potential protection of airway stenosis.

Fig. 6: Immunohistochemical staining showed that interleukin-2 (IL-2) and nuclear factor of activated T cell (NFAT) was positive especially in the lymphocytes or fibroblasts in the submucosal tissue whereas down-regulated at the restructuring and organization stage, which stimulates inflammation or proliferation stage, via calcineurin/NFAT/IL pathway.

DISCUSSION

Calcineurin (CaN) is the target of calcineurin inhibitors, tacrolimus, which is the key for T cells of the immune system. CaN activates nuclear factor of activated T cell (NFAT), a transcription factor, by dephosphorylating it. The activated NFAT is then translocated into the nucleus, where it up-regulates the expression of interleukin 2 (IL-2), which stimulates the growth and differentiation of T cell response.

REFERENCES


SUMMARY

1. Calcineurin inhibitor, tacrolimus, effectively prevented the LTS in acute injury rat model.
2. Tacrolimus may prevent the early stage of the wound healing, inflammation or proliferation phase, via calcineurin/NFAT/IL-2 pathway.