

## INTRAVESICAL HIGH-DOSE RESINIFERATOXIN FOR THE TREATMENT OF INTERSTITIAL CYSTITIS

### Hypothesis / aims of study

Vanilloid receptor agonists such as resiniferatoxin (RTX) desensitize C-fibers that transmit pain. It is hypothesized that such drugs will be effective in the treatment of interstitial cystitis (IC). However, a randomized, double-blind, placebo-controlled study with intravesical RTX at doses up to 0.10 microM [1] indicated that single administration of RTX at doses of 0.01 microM to 0.10 microM was not effective in patients with IC. However, no study with a higher dose than 0.10 microM of RTX in IC patients has been reported. In the present study, therefore, we evaluated the efficacy, safety, and tolerability of a higher dose (1 microM) of intravesical RTX in IC patients.

### Study design, materials and methods

The study enrolled nine women (aged from 42 to 78 year old) with IC met with NIDDK criteria [2]. The protocol has been approved by institutional ethics committees of each center. Written informed consent was obtained from all patients. RTX (R8756, Sigma-Aldrich Japan K.K., Tokyo) was dissolved with 100% ethanol at a concentration of 100 microM as a stock solution in a glass tube within 12 hours before treatment and 1 ml of the RTX stock solution was diluted with 99 ml of normal saline in a polypropylene bag for drip infusion to make 100 ml of 1 microM of RTX. The patients were received intravesical RTX instillation at the operation theatre. Before RTX instillation, 40 ml of 0.5 % of bupivacain was administered intravesically for 2 min into an emptied bladder through a transurethral silicon catheter, and to be hold for 20 min. After removal of the bupivacain, 100 ml of 10 microM as a 1% ethanolic solution was administered intravesically by drip instillation by holding the solution bag about 50 cm above the bladder level for 3-4 min. The RTX solution was kept in the bladder for 30 min, and the bladder was then drained. When patients complained of a severe burning suprapubic pain even after bupivacain instillation, general anesthesia with GO was applied additionally. The primary efficacy endpoint was a 10-point pain scale (0-9) at 4 weeks after treatment. Secondary efficacy endpoints included average voided volume calculated from a frequency/volume chart (F/Vc) recorded for at least 2 days. The volume at the first desire to void (FDV) and maximum cystometric capacity (MCC) were obtained from a filling cystometry at 4 weeks after treatment in selected patients. All patients were followed by the pain scale and F/Vc every 4 weeks interval until the effect of RTX disappeared and then the symptoms relapsed. Data was expressed as mean value  $\pm$ SD. A Student t-test was used for comparison of parameters between before and after RTX-treatment. Probability level of less than 0.05 was accepted as statistically significant.

### Results

RTX instillation caused a severe suprapubic pain 5-10 min after instillation, which required general anesthesia for all patients. But otherwise the treatment was generally well tolerated.

The pain scale improved in all patients at 4 weeks after treatment, and the average pain scale significantly improved from  $7.89 \pm 1.96$  before treatment to  $3.33 \pm 3.36$  ( $p=0.0015$ ) and  $3.67 \pm 3.46$  ( $p=0.0022$ ) at 4 and 12 weeks after treatment, respectively. However, the effect on the pain scale gradually attenuated, and the scale increased to  $5.17 \pm 4.42$  at 20 weeks after treatment. The suppressive effect on bladder pain lasted for at least 12 weeks in all but 1 patients. The average voided volume significantly ( $p=0.006$ ) increased from  $78.5 \pm 36.2$  ml to  $117.2 \pm 22.4$  ml at 4 weeks after treatment. Cystometric studies were carried out in six of the 9 patients before and 4 weeks after treatment. Neither FDV or MCC significantly increased at 4 weeks after treatment (FDV, from  $75 \pm 20$  ml to  $81 \pm 22$  ml; MCC,  $117 \pm 30$  ml to  $128 \pm 21$  ml).

### Interpretation of results

Intravesical RTX at a dose of 1 microM, which was 10-100 times higher than the highest concentration reported by the previous studies [1, 3], improved pain scale and increased average voided volume when evaluated at 4 weeks after treatment. Although suprapubic pain was induced during instillation, which required general anesthesia, no other adverse effects were reported during follow-up. Comparing to the improvement of bladder pain scale, the changes in voided volume and the cystometric parameters are not impressive. However, the present study suggest that even though RTX itself may not be a suitable agent for treating IC suppression of vanilloid receptors involved in bladder nociceptive transduction, for instance by TRPV1 antagonists, may be a promising way in the treatment of IC.

### Concluding message

The results of the present study with a high dose (1 microM) of intravesical RTX instillation indicate that the treatment can transiently relieve bladder pain in IC patients, and vanilloid-receptor (TRPV1)-mediated bladder nociceptive transduction may be a promising target for treating IC. Further studies on intravesical RTX with randomized control trial including high dose are needed to clarify this point.

### References

1. J Urol, 173, 1590-1594, 2005.
2. J Urol, 140, 203-206, 1988.
3. J Urol, 164, 676-679, 2000.

**FUNDING:** This study was supported by the Grant-in-Aid for Scientific Research C-2 from the Ministry of Education, Culture, Sport, Science and Technology of the Japanese Government (YI Grants 18591745).

**CLINICAL TRIAL REGISTRATION:** This clinical trial has not yet been registered in a public clinical trials registry.

**HUMAN SUBJECTS:** This study was approved by the Ethics Committee in Shinshu University, School of Medicine and Ethics Committee in Sapporo Medical University, School of Medicine and followed the Declaration of Helsinki Informed consent was obtained from the patients.