LONG TERM RESULTS ON TREATMENT OF INTERSTITIAL CYSTITIS WITH LOW DOSE CYCLOSPORINE A

Aims of Study
Patients with intractable symptoms of interstitial cystitis (IC) unresponsive to usual conservative treatments are considered as candidates for subtotal or total cystectomy. We have earlier described (1) in a pilot study a good effect in this group of patients resulting in relief of symptoms and increase of bladder capacity after 6 months treatment with cyclosporine A (CyA). CyA inhibits expression of inflammatory cytokines and suppresses lymphocytic inflammation which is known to be predominant type of inflammation in IC bladders. The resolution of IC symptoms may be due to this anti-inflammatory effect. The aim of this open study was to find out whether long term treatment with cyclosporine would be effective enough to keep the symptoms away and to spare the patients from major surgery.

Methods
20 patients with severe IC (16 women, 4 men) with mean age of 61 years (47-75 years) were treated with CyA. All patients met the NIDDK criteria of IC and had undergone multiple ordinary empiric treatment modalities before starting CyA. Additional inclusion criteria were normal creatinine clearance and blood pressure. Contraindications for immunosuppressive agents were excluded in all patients. Mean symptomatic time before administration of cyclosporine was 6 years (1-20 years). Actual micturition charts were obtained. Bladder pain was evaluated only subjectively. Cystoscopy was performed to all patients in anesthesia. Mean anesthetic bladder capacity was 438 ml (200-800 ml).

The initial CyA dose was 3-3.5mg/kg divided in two daily dosages. Serum creatine, blood pressure and CyA concentration were monitored at weekly intervals in the beginning up to 1 month. The follow up interval was lengthened gradually to 3 months and then to 6 months if no adverse effects occurred. The effect of treatment was monitored by micturition charts and subjective pain analysis. CyA dosage was lowered during treatment according to the clinical response to minimize possible harmful effects of the drug. Statistical analysis was made by paired t-test with SigmaStat commercial software program.

Results
Mean follow-up time is at present 49 months (12-108 months).
Mean frequency of daily voidings before treatment was 21.9 (SD=6). It was reduced after 3 months to 13.0 voids (SD=4.5) and after 6 months to 11.8 voids (SD=5.0).
Maximal bladder capacity according to micturition charts was before treatment 155 ml (SD=78). After 3 months of treatment bladder capacity was enlarged to 250 ml (SD=89) and respectively after 6 months to 299 ml (SD=120). Changes in frequency and maximal capacity are statistically highly significant (p<0.001).
The effect of treatment on micturition charts was maintained throughout the follow-up time.
Subjective evaluation of bladder pain showed improvement in all patients and 11/20 patients were completely free of pain. During cyclosporine treatment no additional analgesics were used.
No change in serum creatinine values was noted. During the treatment 3 patients had to start medication for raised blood pressure. A few patients had tickling feeling in their fingers in the first weeks of treatment. Four patients noticed facial lanugo hair growth. Gingival hyperplasia was treated by dentist in one patient.
During the treatment the dosage of medication could be lowered to half of the original one in all patients. Maintenance dosage could be as low as 1 mg/kg once daily.
Cessation of treatment lead to recurrence of symptoms in a few months time in 5 of 6 patients. The beneficial effects were reached again when CyA was restarted. One patient has so far been asymptomatic for one year without medication after treatment of 3.5 years with CyA.

Conclusions
Cyclosporine was highly effective in our patients with difficult IC. The effect on symptoms was maintained throughout the follow up period (up to 90 months). No serious adverse effects were recorded. The CyA dose could be gradually reduced to minimum to control the symptoms which improves patient compliance because of the high cost of the medicine. The amount of placebo effect cannot be measured in this study. It may be considerable because of the careful regular follow-up by the same individual urologists, but hardly explains the significant changes in the micturition charts. A placebo controlled study has not been possible due to unavailability of placebo for CyA. In our department we have restricted major surgery for IC.
only to patients who have contraindications for CyA treatment.