

SUMMARY

Background. The exact etiology and the mechanisms of inflammatory bowel disease (IBD) are still unknown. Recent advances in the understanding of the pathophysiological conditions of IBD have provided new therapeutic targets. In the last decades animal studies suggested the role of ion transport mechanisms in intestinal colonic crypts in the pathogenesis of ulcerative colitis (UC). Despite the comprehensive animal studies, there are only scarce available data on the ion transporter activities of the normal and inflamed human colon. The **aim** of our study was to characterize the segmental differences of ion transport mechanisms (namely Na^+/H^+ exchangers [NHE1-3], the epithelial sodium channel [ENaC] and the SLC26A3 $\text{Cl}^-/\text{HCO}_3^-$ exchanger downregulated in adenoma [DRA]) in human colonic epithelial cells and to examine the activities of these transporters in UC. We also evaluated the efficacy of the infliximab induction therapy in Crohn's disease (CD) and assessed the safety and long-term applicability of infliximab treatment in patients with IBD. **Materials and methods.** 128 healthy controls and 69 patients suffering from active UC were involved in the first part of the study. Primary colonic crypts were isolated from human biopsy and surgical samples. The expressional and functional characteristics of NHE1-3, ENaC and DRA were determined by using fluorescence, patch clamp and real time RT PCR techniques. In the second part of the study one year review was undertaken of all CD patients who achieved remission or fistula closure with 3 infusions of infliximab. We evaluated the clinical response, the estimated CD Activity Index (CDAI), the number of draining fistulae, the dosages of steroid and immunosuppressive drugs at 6 and 12 months after the last infusion, and the needs for hospitalization and surgical intervention during this period. For the evaluation of the long term applicability and safety of infliximab therapy, data of 127 IBD patients were analyzed. A total of 733 infusions were administered, the mean number of infliximab infusions was 5.8/patient. The mean length of follow up was 2.3 years. **Results.** The activities of electroneutral (via NHE3) and the electrogenic Na^+ absorption (via ENaC) are in inverse ratio to each other in the proximal and distal colon. No significant differences were detected in the activity of NHE2 in different segments of the colon. Surface cell $\text{Cl}^-/\text{HCO}_3^-$ exchange is more

active in the distal vs. the proximal part of the colon. Importantly, both sodium and chloride absorptions are damaged in UC, whereas, NHE1 which has been shown to promote immune response is up-regulated by 6-fold. Infliximab induction therapy without retreatment resulted in a beneficial effect lasting for at least 1 year in 44% of the patients. 57.9% of the patients with luminal disease remained in steroid-free complete remission, while the fistulas persisted closed in only 35.5% of the patients. 12.6% of the patients had 31 episodes of acute, 5.5% patients had 9 episodes of delayed infusion reaction. 68.8% of those with acute reaction were on concomitant immunomodulator and/or corticosteroid treatment. Listeria meningoencephalitis, sepsis, pulmonary tuberculosis and lymphoma in two cases were the most severe infectious complications. The mortality rate was 3.1%. The beneficial effect of infliximab was also confirmed by two unusual cases. Infliximab maintenance therapy led to complete mucosal healing in severe refractory pouchitis and rectal instillation of infliximab was also successful in severe proctitis. **Discussion.** The experimental results of our comprehensive human study demonstrated the differences in the various ion transport mechanisms between the different parts of the colon. We also revealed that both sodium and chloride transport is damaged, whereas NHE1 is up-regulated in UC. With selective inhibition of NHE1 and/or stimulation of NHE3, ENaC and DRA our results may open up new therapeutical targets in UC. Infliximab induction therapy alone may result in sustained remission mainly in patients with luminal CD, while fistulizing disease requires maintenance infliximab therapy. The rate of serious adverse events is less than 5%, confirming infliximab therapy safe in the long-term.