**Inhibitory effects of an orally active small molecule alpha4beta1/alpha4beta7 integrin antagonist, TR-728, on DSS-induced experimental colitis in mice and spontaneous colitis in HLA-B27 transgenic rats**

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**Background & Aims:** The successful treatment of inflammatory bowel disease (IBD) in humans with anti-alpha4 or anti-alpha4/beta7 integrin antibody has emphasized the clinical importance of alpha4 integrins that mediate leukocyte migration; however an increased risk for a rare brain disease, progressive multifocal leukoencephalopathy (PML) has been suggested for the anti-alpha4 integrin antibody. TR-728 is a novel orally active small molecule alpha4beta1/alpha4beta7 integrin antagonist and has different properties from the antibody, such as gut-dominant distribution and selectivity for the active form of alpha4beta1. The aim of this study was to evaluate the effect of TR-728 on two chronic colitis models resembling ulcerative colitis (UC) which is one of major types of IBD.

**Methods:** Chronic colitis was induced in BALB/c mice after three cycles of dextran sodium sulfate (DSS) application. TR-728 was orally administered twice daily over a 5-day period after the final dose of DSS. The effects of TR-728 on disease activity index and histological inflammation score were compared with those of anti-mouse alpha4 integrin antibody. Transgenic rats expressing human leukocyte antigen (HLA)-B27 and human beta2-microglobulin were used as these rats spontaneously develop chronic colitis. TR-728 was orally administered once daily after the development of colitis. Clinical score was assessed every few days during treatment with TR-728, and then the colons were excised for histological evaluations.

**Results:** In the DSS-administered mice, oral administration of TR-728 suppressed the increase in the disease activity index, and improved the loss of mucosal architecture in the colon in a similar manner to anti-mouse alpha4 integrin antibody. In the HLA-B27 transgenic rats, colitis symptoms were observed in about 80% of rats by 16 weeks of age. Oral administration of TR-728 after the development of colitis significantly reduced the clinical scores in HLA-B27 transgenic rats. Histological analysis demonstrated that TR-728 also suppressed colonic tissue damage.

**Conclusion:** These results suggest that TR-728 can be expected to be useful in the treatment of UC. Orally effective TR-728 with the unique distribution and mode of action may be more beneficial than anti-alpha4 integrin antibody.