Vidofludimus Inhibits IL-17 and Improves Hapten-Induced Colitis in Young Rats

L. R. Fitzpatrick1, Jeffrey S. Small1, R. Doblohefer2, Stefan W. Henning2, and A. Ammendola2

1Department of Pharmacology, Penn State College of Medicine, Hummelstown, PA 17036, USA; 24SC AG, 82152 Planegg-Martinsried, GERMANY

Background

- Vidofludimus (Vido), an inhibitor of dihydro-orotate dehydrogenase (DHODH) and interleukin-17 (IL-17A and IL-17F), is a novel oral immunomodulator in clinical phase II for IBD. Previously we showed that IL-17 inhibition by Vido in vitro is decoupled from its effects on lymphocyte proliferation Fitzpatrick et al., Inflamm Bowel Dis, 2010.

- The aim of this study was to evaluate the in vivo effects of Vido on IL-17 expression and colitis symptoms, in the presence or absence of concomitant uridine (Uri) dosing, by using our rat model of hapten-induced colitis (Fitzpatrick et al., JGPN, 2010).

- Vidofludimus is a small molecule drug candidate discovered and developed by 4SC AG (www.4sc.com).

Methods

- Young Wistar rats were dosed with either vehicle(s) (Phosal 50 PG [p.o.] or 0.9% saline [i.p.], Uri (500 mg/kg, i.p.), Vido (60 mg/kg, p.o.), or Vido + Uri for a six day period (days 0 to 5).
- On day 1, rats received a 150 µL enema of either PBS or TNBS (8 mg in 40% Ethanol/PBS). On day 6, a various morphometric, biochemical and histological indices of colitis were determined from the colonic tissue.

- Macroscopic colonic scores included observations on ulceration, adhesions, colonic thickness and diarrhea.

- IL-17 levels and STAT3 activation were measured with commercial ELISA kits and myeloperoxidase (MPO) was analyzed by the tetramethylbenzidine method. Colonic NF-κB (p65) was measured by western blot, from nuclear extracts. Histological scores and numbers of CD3+ T-cells (by immuno-histochemistry) were determined using coded slides.

Results

- In comparison to Vehicle/TNBS treated rats, smaller areas of ulceration were evident in the distal colons of animals treated with Vido alone or Vido ± Uri (fig 1A).

- A significant reduction (p < 0.05 vs. Vehicle/TNBS) in colonic ulceration was found with Vido treatment (fig 1B). In contrast, colonic ulceration in Vido + Uri treated rats (pink bar) was also reduced but not to the degree seen in rats treated with Vido alone (green bar). Uri treatment (blue bar) was ineffective for reducing colonic ulceration.

- Total macroscopic colonic score data (representing a combination of ulceration, adhesions, colonic width, and presence of loose stool/diarrhea) showed a very similar pattern to the colonic ulcer data (fig 2).

- Interestingly, a significant reduction (p < 0.05 vs. Vehicle/TNBS) in colonic NF-κB p65 expression was found with Vido treatment (fig 6). In contrast, p65 expression in Vido + Uri treated rats was also reduced but not to the degree seen in rats treated with Vido alone.

Conclusions

- Vidofludimus improved parameters of TNBS-induced colitis in young rats, including macroscopic pathology and colonic CD3+ T-cells. Vido treatment, in the presence of Uri, also improved these parameters, but not to the same degree as Vido alone. Of note, colonic STAT3 binding and IL-17 inhibition by Vido was not affected by combination with Uri.

- Thus, Vidofludimus appears to improve colonic inflammation by a dual mode of action, namely 1) inhibition of T-cell proliferation and 2) suppression of pro-inflammatory cytokines which is decoupled from the control of proliferation.

- This unique pharmacological profile supports further clinical testing of Vidofludimus in patients with IBD.