THE ADMINISTRATION OF JAK AND TYK2 INHIBITOR SUCCESSFULLY AMELIORATED THE SEVERITY OF T CELL TRANSFER-INDUCED COLITIS IN MICE

Chunhui He, Yanping Yuan, Juan Wang, Dongye Jia, Xiangnan Qiang, Ruiqing Yan, Nan Xie.

1WuXi AppTec, Nantong, Jiangsu Province, China; 2WuXi AppTec, Shanghai, China; 3WuXi AppTec, Cambridge, MA, USA

Background Inflammatory bowel disease (IBD), which includes ulcerative colitis (UC) and Crohn’s diseases, is recognized as an autoimmune disorder characterized by chronic inflammation of the digestive tract. Although the pathophysiology of IBD is not yet fully understood, genetic, gut microbial and environmental factors are believed to be involved. IBD remains a problematic disease as it can repeatedly relapse despite clinical therapy. To better understand the mechanisms of IBD, various animal models have been developed for research, including erosive and self-limiting models, spontaneous chronic colonic inflammation models induced by targeted gene deletion, and T cell-induced chronic colitis and intestinal inflammation model. Among all these models, T cell transfer IBD model is significantly more relevant to human disease than other models in terms of immunological mechanisms and regulation of chronic disease.

Methods Spleens from female Balb/c mice were harvested and ground into cell suspension. CD4-positive T cells were isolated from centrifuged cell suspension. Flow cytometry was used to select CD4+CD45RBlow naive T cells for modelling and CD4+CD45RBhigh naive T cells for negative control. Tofacitinib and BMS-986165 were selected as the positive control in the study. The Disease Activity Index (DAI) score which is the sum of body weight loss, stool consistency, and bleeding subscores, was used to assess the severity of colitis. After 42 days treatment, colons were harvested, and the excess tissue such as mesentery and adipose tissue was carefully removed. The length and weight of the colon were measured to calculate colon density.

Results The body weight of the mice in the Vehicle group decreased significantly compared with that in the CD4+CD45RBhigh group. The DAI score of the mice in the Vehicle group significantly increased, confirming the successful establishment of the T cell transfer model. Both Tofacitinib and BMS-986165 treatment significantly increased the body weight and decreased the DAI score of the mice. The treatment also reduced the colon density compared to the CD4+CD45RBhigh group.

Conclusions The T cell transfer IBD model was successfully established, presenting symptoms such as diarrhea, hematochezia, served body weight loss and increased colon density. Treatment with Tofacitinib and BMS-986165 ameliorated the severity of T cell transfer-induced colitis in mice. This was evidenced by reduced weight loss, improved stool consistency, and enhanced colon density through the JAK and TYK2 pathways.

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