Clinics and Research in Hepatology and Gastroenterology (2016) xxx, xxx–xxx

Available online at ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com/en

ORIGINAL ARTICLE

The efficacy of tyrosine kinase inhibitor dasatinib on colonic mucosal damage in murine model of colitis

Güray Can [a,*], Süleyman Ayvaz [b], Hatice Can [c], İhsan Karaboğa [d], Selim Demirtaş [d], Hasan Akşit [e], Bülent Yılmaz [f], Uğur Korkmaz [a], Mevlüt Kurt [a], Turan Karaca [d]

[a] *Department of Gastroenterology, Abant İzzet Baysal University, Faculty of Medicine, Gölköy, 14280 Bolu, Turkey*
[b] *Department of Pediatric Surgery, Trakya University, Faculty of Medicine, Edirne, Turkey*
[c] *Department of Internal Medicine, Abant İzzet Baysal University, Faculty of Medicine, Bolu, Turkey*
[d] *Department of Histology and Embryology, Trakya University, Faculty of Medicine, Edirne, Turkey*
[e] *Department of Biochemistry, Balıkesir University, Faculty of Veterinary, Balıkesir, Turkey*
[f] *Department of Gastroenterology, Selçuk University, Faculty of Medicine, Konya, Turkey*

Summary

Background and objective: Ulcerative colitis is an inflammatory condition of the colon in the gastrointestinal system. Currently, the most potent medications used for ulcerative colitis produce no response in 20–30% of cases. There is a need for more efficient and reliable medications. Tyrosine kinase inhibitors have shown efficacy in some inflammatory diseases. Although dasatinib, a tyrosine kinase inhibitor, suppresses proinflammatory cytokines in colonic tissue, there are a few cases of hemorrhagic colitis with dasatinib. There is no study investigating the effect of dasatinib on experimental colitis. We aimed to investigate the effect of dasatinib in a colitis model induced with acetic acid in our study.

Methods: In the study, 24 male Sprague-Dawley rats randomly distributed into 4 groups of 6 rats each as control, dasatinib, colitis and dasatinib + colitis groups. For colitis induction, 4% acetic

Abbreviations: Ab, Abelson; CD, Crohn's disease; CML, Chronic myeloid leukemia; DAI, Disease activity index; DC, Dentritic cell; IBD, Inflammatory bowel disease; IL, Interleukin; LGL, Large granular lymphocytosis; MDA, Malondialdehyde; MPO, Myeloperoxidase; NFκβ, Nuclear factor kappa beta; PDGFR, Platelet derived growth factor receptor; SFK, Src family kinases; SOD, Superoxide dismutase; Syk, Spleen tyrosine kinase; TNFα, Tumor necrosis factor-alpha; TK, Tyrosine kinase; UC, Ulcerative colitis.

* Corresponding author.
E-mail addresses: dr_guraycan@yahoo.com (G. Can), suleyayvaz@yahoo.com (S. Ayvaz), yailaslan@yahoo.com (H. Can), ihsankaraboga@gmail.com (İ. Karaboğa), selimdemirtas@trakya.edu.tr (S. Demirtaş), vethas@hotmail.com (H. Akşit), dr.yilmazbulent@gmail.com (B. Yılmaz), drkorkmazugur@yahoo.com (U. Korkmaz), dr.mevlutkurt@gmail.com (M. Kurt), turankaraca@trakya.edu.tr (T. Karaca).

http://dx.doi.org/10.1016/j.clinre.2015.12.006

Please cite this article in press as: Can G, et al. The efficacy of tyrosine kinase inhibitor dasatinib on colonic mucosal damage in murine model of colitis. Clin Res Hepatol Gastroenterol (2016), http://dx.doi.org/10.1016/j.clinre.2015.12.006

acid was used. Sacrificing of the rats was performed on the seventh day. Disease activity, morphologic and histological injury, superoxide dismutase, myeloperoxidase and malondialdehyde activity, TNFα and CD3 expression were assessed in colonic tissue.
Results: Apart from malondialdehyde, significant difference in all parameters between the control and colitis groups was determined. Difference between the colitis and colitis + dasatinib groups was not significant in only weight loss and biochemical parameters. Though dasatinib does not fully resolve the changes in colitis, there was significant regression.
Conclusions: Dasatinib decreased the inflammation in a rodent model of colitis. It may be provide this effect by the suppression of TNFα. Dasatinib may be one of the treatment options for ulcerative colitis.

Introduction

Ulcerative colitis (UC) is a recurring, inflammatory and multifactorial disorder limited to the colon in the digestive system, characterized by continuous and superficial ulcers from the rectum toward the proximal colon [1]. Though the etiopathogenesis of UC has not been completely resolved, it is thought that the disease occurs due to the effect of complex interactions of genetic, environmental and immunological factors [2]. In individuals with genetic background, there is an uncontrolled and pathological immune response to still unknown luminal antigens by the adaptive and innate immune system in the intestinal mucosa. This immune response forms the basis of the pathological mechanisms causing the occurrence of inflammatory bowel disease (IBD). The proinflammatory mediators in chronic inflammation resulting from activation of dendritic cells (DC) and infiltration of neutrophils, macrophages and lymphocytes disrupts the mucosal integrity causing macroscopic ulcers in IBD [3,4].

Generally treatment of UC begins with 5-aminosalicylic acid. Depending on the severity, type and clinical progress of the disease, antibiotics, corticosteroids and immunomodulator medications may be added to treatment. In resistant cases, biological agents or surgical treatment may be considered as an alternative [5]. There is nearly 20% resistance rate even to biological agents, the most potent medications currently. With use, there is a reduction in efficacy over time [6]. When current treatment choices are considered, there is a need for more potent medications, with minimum side effects, that will allow more efficient remission including mucosal healing and change the clinical course of the disease [7,8].

During the inflammatory response, many different signal pathways are activated that control the synthesis of proinflammatory mediators led by DC, macrophages and T lymphocytes. Among these, molecules belonging to the tyrosine kinase (TK) family play a central role in many stages including the innate and adaptive components of intestinal inflammation [9]. TKs are enzymes playing a role in normal cell functions, metabolism, development, differentiation and apoptosis [10]. Receptor TKs have a place in transmembrane signal transmission with intracellular TK providing transmission of the signal to the nucleus. TKs generally suppress Abelson (Abl) and c-kit proto-oncogenes, tumor necrosis factor-alpha (TNFα), platelet derived growth factor receptor (PDGFR) [11]. Dasatinib, imatinib and nilotinib, used for treatment of chronic myeloid leukemia (CML), are the best known TK inhibitors. Though these are known as anticancer medications, recently they have been mentioned for use in non-neoplastic proliferative diseases and inflammatory conditions [11]. Together with the increase in TK activity in many inflammatory diseases, TK inhibition suppresses the synthesis of proinflammatory cytokines like TNFα, interleukin 1 (IL-1) and IL-6 [12]. There is some evidence supporting the idea that TKs may be effective in the pathophysiology of IBD. It was reported that protein TK activity in colonic mucosa of UC patients has increased, and in another study, spleen TK (Syk) activity in an experimental colitis model has increased [13,14]. At the same time, with Syk inhibition colitis was reported to regress [14]. UC has been shown to be related to tyrosine kinase-2 gene polymorphism [15]. A patient with Crohn's disease (CD) using imatinib for CML was reported to remain in remission for 3 years without treatment [16]. Cuzzocrea et al. in an experimental colitis model induced with dinitrobenzene sulphonic acid, found that the TK inhibitor tyrphostin AG126 reduced the development of colitis, while in another experimental colitis model induced with trinitrobenzene sulphonic acid (TNBS) the potent TK inhibitor of nilotinib was shown to increase mucosal healing [10,17]. Among TKs dasatinib also suppresses SFK (Src family kinases), unlike to imatinib and nilotinib. SFK increases survival, angiogenesis, proliferation, motility, invasion in cancer cells and vascular permeability. At the same time SFK's interact with signal transducer and activator of transcription 3 (STAT3) and nuclear factor kappa beta (NF-κβ) having a central role in the pathogenesis of IBD [18]. In patients with active UC, there is an increase in vascular permeability together with Src kinase activity in colonic tissue while a reduction of vascular permeability was observed with inhibition of Src kinase activity [19]. Though dasatinib inhibits salt-inducible kinases suppressing inflammatory cytokines, there are some CML and Philadelphia chromosome (+) acute lymphoblastic leukemia cases reporting acute hemorrhagic colitis related to dasatinib use [20–28]. There are no studies found evaluating the effect of dasatinib on mucosal inflammation in an experimental colitis model even though dasatinib inhibits Src kinase additionally when compared to the other TK inhibitors of imatinib and nilotinib, which have been studied for efficacy in colitis. It is aimed to investigate the efficacy of dasatinib in a murine colitis model in this study.

Please cite this article in press as: Can G, et al. The efficacy of tyrosine kinase inhibitor dasatinib on colonic mucosal damage in murine model of colitis. Clin Res Hepatol Gastroenterol (2016), http://dx.doi.org/10.1016/j.clinre.2015.12.006