World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
doi:10.3748/wjg.v19.i42.7487

World J Gastroenterol 2013 November 14; 19(42): 7487-7488
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

Rifaximin and Crohn's disease

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Received: July 3, 2013 Revised: September 2, 2013
Accepted: September 15, 2013
Published online: November 14, 2013

Abstract

In a recent article, Longman and Swaminath analyzed our paper on the use of rifaximin in patients with moderately active Crohn's disease (CD). Here we report some considerations concerning their article. The exploratory *post-hoc* subgroup analysis showed that early-stage disease and, differently from that written by Longman and Swaminath, also colonic involvement seemed to be associated with a significant higher efficacy of rifaximin-EIR 800 mg twice daily. Early-stage disease is generally considered as the more easily treatable phase of CD, and the better response to rifaximin in Crohn's colitis is in accordance with the high concentration of bacteria in the colon. In addition, patients with C reactive protein level > 5 mg/L achieved remission more significantly than patients with normal values, thus suggesting that the symptoms were probably caused by inflammation instead of by non-inflammatory causes. We also analyze the role of rifaximin against gut bacteria and the clinical situations that could obtain the best results from antibiotics.

Key words: Crohn's disease; Intestinal microbiota; Non-absorbable antibiotic; Rifaximin

Core tip: In this letter to the Editor we report some considerations concerning the article entitled "Microbial manipulation as primary therapy for Crohn's disease" written by Longman and Swaminath. In the article the authors analyzed our paper on the use of rifaximin as primary therapy in active Crohn's disease. The *post-hoc* analysis of our study showed that early-stage disease, colonic involvement and a C reactive protein level > 5 mg/L were associated with a significant higher efficacy of rifaximin. We also discuss the role of rifaximin against intestinal bacteria and the clinical situations to explore further in controlled studies with antibiotics.

Prantera C, Scribano ML. Rifaximin and Crohn's disease. *World J Gastroenterol* 2013; 19(42): 7487-7488 Available from: URL: http://www.wjgnet.com/1007-9327/full/v19/i42/7487.htm DOI: http://dx.doi.org/10.3748/wjg.v19.i42.7487

TO THE EDITOR

We would like to thank Doctor Longman and Swaminath from Columbia University for their interesting analysis of our article concerning the trial of rifamixin in Crohn's disease (CD)[1,2].

Their expert analysis entitled "Microbial manipulation as primary therapy for Crohn's disease" merits some considerations and one slight correction: (1) The *post-hoc* explorative subgroup analysis has certainly revealed that patients with an early disease (as defined as first diagnosis ≤ 3 years before enrollment in the study) are significantly more likely to achieve remission with rifaximin-EIR 800 mg twice a day compared to placebo, but, differently from what Longman and Swaminath have written, also colonic involvement, and a baseline C-reactive protein (CRP) level > 5 mg/L showed the same statistical significant superiority. The favorable effect of these three factors is biologically plausible. Elevated CRP values suggest that the symptoms, which increase the Crohn's disease activity index values, are probably caused by inflamma-

tion instead of by non-inflammatory causes such as irritable bowel, bile salt diarrhoea or previous surgery. Many previous studies with antibiotics have shown that Crohn's colitis responds better to this therapy than does that in the small bowel location, and this is in accordance with the higher microbial content in the colon. Finally, early disease is more easily treatable because the lesions are mainly inflammatory and the structural damage has usually not yet appeared; (2) Rifaximin is a non-absorbable antibiotic and consequently it should not work on the bacteria attached to the mucosa. Rifaximin can work against bacteria present in the lumen but not against adherent *Escherichia coli* (AIEC), and this fact could be particularly important if AIEC is one of the causes of CD[3]. At most rifaximin can reduce the attachment of enteroaggregative *Escherichia coli* by biologically altering the host cell, but it should not able to counteract the bacteria already adherent to the mucosa[4]. A study which explores the efficacy of one antibiotic together with a microbial analysis in order to ascertain which bacteria are involved in the inflammatory process, cannot be limited to investigating the stools flora, given that the bacteria found in the stools probably do not represent the adherent bacteria and could not be responsible for the inflammation; (3) From our study about 50% of the patients maintained clinical remission 12 wk after stopping rifaximin. It is probable, however, that a permanent change of the microbiota does not occur; and (4) Doctors Longman and Swaminath ask how to select patients who could obtain the best benefit from antibiotics. Crohn's colitis and elevated values of acute phase reactants seem the better clinical situation to explore further in controlled studies. Given the possible role of adherent bacteria in causing CD or, at least, in being responsible for symptoms, another very promising situation should be explored: immediately after surgery, when all the diseased tracts have been removed, antimicrobial therapy could obstruct the adherence of bacteria to the mucosa reducing the recurrence of lesions.

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P- Reviewer: Guslandi M **S- Editor**: Zhai HH
L- Editor: A **E- Editor**: Zhang DN

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Published by **Baishideng Publishing Group Co., Limited**
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E-mail: bpgoffice@wjgnet.com
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ISSN 1007-9327
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