

## **Bifidobacterium Longum and Lactoferrin Exert Entero-Protective Effects In a Rat Model of Diclofenac-Induced Intestinal Injury**

1)Tirotta E. 2)Fornai M. 3)Gentile D. 4)Benvenuti L. 5)Pellegrini C. 6)Antonoli L. 7)Blandizzi C. 8)Colucci R.

*Dept. Pharm. and Pharmacological Sciences, Univ. of Padova*

**Introduction.** Nonsteroidal anti-inflammatory drugs (NSAIDs) can exert detrimental effects on the upper and lower digestive tract. Although the underlying mechanisms remain unclear, the involvement of enteric bacteria and mucosal inflammation has been suggested. Increasing evidence suggests also that appropriate manipulations of the enteric microbiome through probiotics and/or prebiotics could represent a useful strategy for the management of bowel disorders associated with inflammatory conditions. Based on this background, the present study examined the ability of the combination Bifidobacterium longum (BIF) and lactoferrin (LAC) of preventing mucosal damage in a rat model of diclofenac (DIC)-induced small bowel injury.

**Methods.** Enteropathy was induced in rats by intragastric DIC administration (4 mg/kg BID) for 14 days. Control animals received drug vehicle (1% methylcellulose). Subgroups of rats received BIF ( $2.5 \cdot 10^6$  CFU/rat/BID), LAC (100 mg/kg BID) or their combination 1 hour before DIC. Doses of BIF and LAC were selected on the basis of preliminary dose-finding experiments. At the end of treatments, were collected blood samples to evaluate hemoglobin (Hb) concentration (indirect index of digestive bleeding) and fecal samples to quantify the calprotectin content (index of intestinal inflammation). Small intestine was excised and the ileum processed for the evaluation of: 1) tissue myeloperoxidase (MPO) levels, as a marker of inflammatory neutrophil infiltration; 2) tissue malondialdehyde (MDA) concentration, as an index of lipid peroxidation.

**Results.** DIC-treated displayed a 40% mortality rate, while in groups treated with DIC+LAC the mortality rate was lower (13.3%). No deaths were observed in controls or rats treated with DIC+BIF or DIC+BIF+LAC. Treatment with DIC significantly decreased blood Hb levels (-38.3%). This effect was counteracted by the administration of LAC, BIF or their combination. MPO and MDA levels in the ileum from DIC-treated rats were significantly increased, as compared with controls (+223.3% and +102.8%, respectively). The administration of LAC, BIF or BIF+LAC to DIC-treated animals reduced significantly both MPO and MDA levels, as compared with DIC alone. In DIC-treated rats, fecal calprotectin levels were significantly increased, as compared with controls (+127.4%), while in rats co-treated with LAC, BIF or BIF+LAC were significantly decreased as compared to DIC alone.

**Conclusion.** BIF or LAC treatment significantly prevents DIC-induced intestinal damage, this entero-protective effect being associated with a decrease in tissue inflammation, oxidative stress and digestive bleeding. The combination of BIF+LAC does not appear to allow further improvements of the NSAID-induced intestinal injury.