REVIEW ARTICLE

Clinical importance of nonsteroidal anti-inflammatory drug enteropathy: the relevance of tumor necrosis factor as a promising target

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The pathogenesis of nonsteroidal anti-inflammatory drug (NSAID) enteropathy is still unclear, and consequently, there is no approved therapeutic strategy for ameliorating such damage. On the other hand, molecular treatment strategies targeting tumor necrosis factor (TNF) exerts beneficial effects on NSAID-induced intestinal lesions in rodents and rheumatoid arthritis patients. Thus, TNF appears to be a potential therapeutic target for both the prevention and treatment of NSAID enteropathy. However, the causative relationship between TNF and NSAID enteropathy is largely unknown. Currently approved anti-TNF agents are highly expensive and exhibit numerous side effects. Hence, in this review, the pivotal role of TNF in NSAID enteropathy has been summarized and plant-derived polyphenols have been suggested as useful alternative anti-TNF agents because of their ability to suppress TNF activated inflammatory pathways both in vitro and in vivo. (Translational Research 2016;175:76–91)

Abbreviations: ATP = adenosine triphosphate; CE = capsule endoscopy; DBE = double-balloon endoscopy; FDA = Food and Drug Administration; GI = gastrointestinal; GTPase = guanosine triphosphatase; H2RAs = histamine 2 receptor antagonists; IL = interleukin; LPS = lipopolysaccharide; MPTP = mitochondrial permeability transition pore; NADPH = nicotinamide adenine dinucleotide phosphate; NOD2 = nucleotide-binding oligomerization domain 2; NSAIDs = nonsteroidal anti-inflammatory drugs; PGs = prostaglandins; PPIs = proton pump inhibitors; RA = rheumatoid arthritis; RAC1 = ras-related C3 botulinum toxin substrate 1; RIRR = ROS-induced ROS release; ROS = reactive oxygen species; TLR = toll-like receptor; TNF = Tumor necrosis factor

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Institutional Communication Reference Number: PERD430815.

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Submitted for publication January 12, 2016; revision submitted March 18, 2016; accepted for publication March 21, 2016.

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1931-5244/$ - see front matter

http://dx.doi.org/10.1016/j.trsl.2016.03.014

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) represent one of the most commonly used prescription and over-the-counter class of medications globally.[1] Although, NSAIDs are extremely efficacious drugs,[2] but, their usage is linked with a variety of adverse reactions in the kidney, heart, liver, skin, and gastrointestinal (GI) tract.[3] A recent meta-analysis that included 31 trials and 116,429 patients revealed an increase in rates of myocardial infarction, stroke, and cardiovascular death in patients taking either selective or nonselective NSAIDs.[4] The GI adverse effects of NSAIDs have also been well documented in several studies,[5-9] meta-analysis[10,11] and Cochrane reviews.[12] The ability of NSAIDs to cause ulceration and bleeding in the upper GI tract was first documented by the endoscopic study of Douthwaite and Lintott as early as 1938.[13] However, much later, in the year 1993, Bjarnason et al[14] reported that NSAIDs have the ability to induce significant small intestinal injury (enteropathy) also. The term NSAID enteropathy has been used to describe the small intestinal toxicity of NSAIDs.[15] In context to the severity and importance of NSAID enteropathy, based on their studies, Lanas et al made an important observation that "over the years, NSAID-induced lower GI complications are increasing, whereas upper GI complications are decreasing".[16] Indeed, past decade has seen a decreasing trend in NSAID-induced symptomatic GI events in rheumatoid arthritis (RA) patients[17] and, in line with that, in hospitalizations due to upper GI complications, but lower GI complications have shown an apparent increasing trend.[18-20] McCarthy[21] expressed similar concern, pointing out that in the Vioxx Gastrointestinal Outcomes Research trial,[22] small intestine was the major site of ulceration and bleeding caused by NSAIDs (naproxen and rofecoxib).

The clinical impact and severity of lower GI events has actually been greater than those in the upper GI tract.[23] NSAID-induced small intestinal injury includes bleeding (leading to iron deficiency anemia), erosion, and ulceration[24,25]; however, serious complications may include massive bleeding, perforation, and strictures, sometimes leading to death.[26] These symptoms may persist even after the therapy is discontinued.[27] For example, the intestinal lesions reported by Leung et al[28] tended to persist for up to 3 months after the discontinuation of aspirin; however, in some cases, they have been reported to persist for up to 16 months after discontinuation.[27]

DIAGNOSIS OF NSAID ENTEROPATHY

Until recently, the clinical relevance or significance of NSAID enteropathy was largely underestimated.[29] The main reasons were the difficulty in making a diagnosis, as this damage occurs in regions beyond the reach of typical endoscopic examinations in contrast to the gastroduodenal damage and because of the subclinical nature of NSAID enteropathy (60%–70% cases).[29]

However, the availability and use of novel diagnostic tools such as capsule endoscopy and double-balloon endoscopy has enabled the identification of previously undetectable enteropathic damage in humans.[30,31] Indeed, available studies[25,32] have provided clear evidence that NSAIDs including aspirin can induce significant intestinal mucosal injury, with most denuded areas identified in the proximal part of the small intestine and all ulcers identified in the distal part.[30] According to a recent study, gross enteropathic damage was observed in 68% of healthy volunteers who were administered 75 mg of diclofenac for 2 weeks.[33] Hayashi et al[34] came out with the staggering figures of 100% intestinal damage with the use of NSAIDs such as diclofenac and either ampiroxicam, aspirin, or loxoprofen. Another report indicated that macroscopic small-bowel injury occurred in 80% of the patients who took low dose of aspirin (100 mg d^{-1}) for 2 weeks.[32] Unexpectedly, enteric-coated aspirin induces higher enteropathic damage in comparison to uncoated aspirin.[32] In addition, the frequency and severity of aspirin-induced enteropathic damage has been often under-recognized, particularly when aspirin is prescribed at low doses.[26]

Table I summarizes the recent diagnostic data of NSAID enteropathy. However, an important point worth mentioning here is, unfortunately, the operational cost of these novel diagnostic techniques is quite high, thus, limiting their widespread use, so NSAID enteropathy still remains to be underdiagnosed.[23] The true magnitude of the clinical implications of NSAID enteropathy could be much higher.[23]

UNDERSTANDING THE PATHOGENESIS OF NSAID ENTEROPATHY

The exact mechanisms underlying NSAID enteropathy are not fully understood[35] and consequently, there are no approved therapeutic strategies for ameliorating the intestinal damage caused by NSAIDs.[36,37] Thus, developing effective, preventative or curative therapies for NSAID enteropathy is an unmet challenge and requires proper understanding of the complicated pathogenesis of this disorder.

In recent years, pathogenesis of NSAID enteropathy has been widely investigated.[38] Importantly, deficiency of prostaglandins (PGs),[39] enterohepatic circulation of NSAIDs,[26] changes in intestinal permeability[40,41] and motility,[42] intestinal microbiome alteration,[43] mitochondrial dysfunction,[44] generation of reactive oxygen