New surrogate marker for ulcerative colitis (UC): PGE-major urinary metabolite (PGE-MUM)

Arihiro S*, Arai Y, Matsuura T, Okayasu I, Ito S and Fujiwara M**

1Division of Gastroenterology and Hepatology, Department of Internal Medicine, The Jikei University Katsushika Medical Centre, Japan
2Department of Laboratory Medicine, The Jikei University School of Medicine, Japan
3Division of Nutrition, Kiryu University School of Health Care, Japan
4IDAC Theranostics, Inc. Japan
5Department of Pathology, Nissan Tamagawa Hospital, Japan

Introduction

Ulcerative colitis (UC) is an intractable bowel disease with an unknown etiology. Although long-term curable treatment is required for UC, remission is a practical goal of the current therapeutic approach. Thus, patients live in fear of relapse.

Remission is evaluated using colonoscopic and pathologic evaluation of the lower digestive tract. However, undergoing frequent colonoscopic observations for monitoring is stressful for patients even for efficacy assessments. Furthermore, biopsies are more stressful. Therefore, in routine clinical practice, annual colonoscopic and pathological analyses are performed during follow-up.

Recently new agents, especially biologics (e.g., anti-tumor necrosis factor-α, anti-α4β7 integrin) and immune suppressors (JAK inhibitors) [1,2] and new biomarkers have been introduced as new treatment options [3,4]. Therefore, we may set “mucosal healing” as the treatment goal for UC [5].

Diagnostics to monitor treatment efficacy involves the replaceability of pathological precision and is quantitative rather than qualitative in nature. The recent introduction of fecal calprotectin (produced by neutrophils) as a new biomarker for assessing UC stage [6] gives us a new option for assessing treatment efficacy. However, its qualitative nature and variable factors are drawbacks in discussions of the degrees of real mucosal healing [7-9].

Pathological assessment is qualitative and involves sampling probability. In Japan, dysplasia cases are subjected to targeted rather than randomized biopsies [10]. Therefore, around 6 points of biopsy samples are subjected to pathological observation. In the clinical consideration of remission, some points exhibit active scores in pathological assessments [11]. A long duration of UC may lead to fibrosis caused by periodical inflammation and remodelling with a high risk of cancer [12,13]. This is why we must help patients achieve remission at an early phase as soon as possible. Frequent colonoscopy and pathological biopsy assessments are stressful for patients; therefore, a new biomarker utilizing less stressful methods for sampling is needed. A new biomarker, prostaglandin E–major urinary metabolite (PGE-MUM), was recently introduced to assess UC stage and activity [14]. This method is quantitative with daily reproducibility.

PGE-MUM

Prostaglandin E2 (PGE2) is a metabolite processed by cyclooxygenase-2, which is upregulated in inflammatory conditions. PGE2 has a short half-life in the blood; therefore, it may not be suitable for in-vitro diagnostic purposes [15,16]. However, its urinary metabolite (PGE-MUM) is stable and may be suitable for in-vitro diagnostics. Further, derivatizing into a bicyclic structure shows more stable characteristics for immunoassay recognized by specific antibodies to establish a radiolabelled immunoassay (RIA) [17]. Once the RIA system has been established, switching into the non-RIA style (enzyme-linked immunosorbent assay) is relatively easy. An automated system with a short assay time will also be introduced.

Because PGE2 is a biomarker of inflammation, the specificity of the inflamed organs is in question. However, only diseases with a wide range of inflammatory parts seem to reflect their inflammatory conditions on PGE-MUM. Thus, hepatitis and gastritis do not exhibit higher PGE-MUM values. Therefore, PGE-MUM is applicable for assessing UC activity evaluation in a practical fashion [18].

A report of the evaluation of adult UC showed that PGE-MUM assessments of children's UC activity showed good correlations with clinical activity [19]. Once monitoring usability of PGE-MU is established, its value for medical practice may indeed be appreciated. In a future comparative study, the practical value of fecal calprotectin and/or PGE-MUM for UC patients will give us valuable information for further clinical practice.

Necrotic enterocolitis (NEC) is a rare disease of neonates that shows extremely high PGE-MUM values compared to those of UC cases. Whether any decision of an urgent surgical request can be made by setting the PGE-MUM value in NEC cases is now a big question. However, such information, if established, seems to provide essential clinical value. One such study is ongoing, and its preliminary results have been submitted for publication [K. Konishi et al., in press. J. Pediatr. Surg.].

*Correspondence to: Mutsunori Fujiwara, MD. PhD, Department of Pathology, Nissan Tamagawa Hospital, Japan, E-mail: m-fujiwara@mbg.ocn.ne.jp

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Conclusion

After the diagnosis of UC is made, to determine whether PGE-MUM is considered a real new biomarker to assess colitis activity and treatment monitoring clinically further discussions with evidence of clinical practice are needed. However, the value of PGE-MUM must be discussed. This fact is essential for urine sampling, which is least stressful for patients, especially children and infants/neonates. In pediatrics, general anaesthesia is a condition of a UC diagnosis, which carries risk. Therefore, the practical value of urine sampling to monitor UC treatment should be emphasized.

Replacing colonoscopic and pathological assessments with urinary measurements would be appreciated by adult patients. This will lead to better treatment follow-up to achieve mucosal healing with better quality of life and reduced medical costs.

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