

Translational Research Center for Medical Innovation



NEW TREATMENTS FOR ULCERATIVE COLITIS ON THE CUSP OF APPROVAL

Ulcerative colitis is an inflammatory bowel disease characterized by chronic inflammation of the colon and rectum. It is thought to be an autoimmune condition triggered by a combination of genetic and environmental factors. Ulcerative colitis can develop at any age and both men and women seem to be equally affected. A recent report showed that it is more common in industrialized nations and that incidence of the disease is accelerating in developing countries¹. Researchers at Miyazaki University and Keio University are contributing to new therapeutics.

Current treatment approaches rely on corticosteroids and anti-inflammatory agents, in conjunction with anti-diarrhoeal agents and rehydration. However, around 1 in 4 patients are intolerant or unresponsive to existing medication and require immunosuppressants or surgical removal of the colon. Further understanding the underlying mechanisms of disease and the body's intrinsic protection is revolutionizing the treatment of intractable diseases, including ulcerative colitis.

Research on the vasodilating peptide hormone adrenomedullin and the herbal medicine indigo naturalis shows that they are both effective at reducing the severity of ulcerative colitis in mouse models and in patients.

Studies led by Kazuo Kitamura at the University of Miyazaki in Japan have shown that adrenomedullin is produced by the gastrointestinal tract in response to pro-inflammatory cytokines. Adrenomedullin reduces inflammation and stimulates mucosal regeneration in various animal models of colitis. The first patient with refractory ulcerative colitis to receive adrenomedullin experienced a dramatic improvement in their condition and no adverse effects,

apart from a slight reduction in blood pressure². A colonoscopic examination performed two weeks after treatment revealed significant mucosal regeneration and prompted further clinical studies to confirm the efficacy and safety of adrenomedullin.

A pilot study involving seven patients with ulcerative colitis showed that after two weeks of adrenomedullin therapy all patients experienced an improvement in symptoms (Fig. 1), exhibited a significant reduction in inflammation, and showed evidence of neovascularization and mucosal regeneration in their ulcerative lesions³. Adrenomedullin did not cause any adverse events and had a lasting effect — 12 weeks after initiating therapy the patients' ulcers had disappeared.

Although the mechanism of action of adrenomedullin is not fully understood, the colonoscopic effects observed suggest that it may not only inhibit the production of inflammatory cytokines, but also stimulate tissue regeneration through re-epithelialization and vascularization. This finding is consistent with previous studies showing that adrenomedullin has a role in maintaining microvascular integrity⁴.

Indigo naturalis, obtained from the *Persicaria tinctoria* plant and traditionally used to make blue dyes, has shown definitive clinical efficacy in people with ulcerative colitis⁵. Indigo stimulates aryl hydrocarbon receptors (AhR) and promotes mucosal healing by stimulating the production of interleukin 22 (IL-22). A recent trial led by Takanori Kanai, Keio University School of Medicine, involving 86 patients showed that orally administering 0.5 grams of indigo naturalis per day for 8 weeks significantly promoted mucosal healing and had comparable clinical effects to other approved treatments for refractory ulcerative colitis.

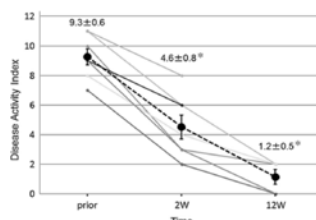


Figure 1: The clinical effectiveness of adrenomedullin. Total Disease Activity Index score measured at baseline (prior) and 2 weeks after (2 W) and 12 weeks after (12 W) adrenomedullin administration in seven patients. Values are the mean \pm SEM. * $p < 0.001$ versus baseline (ref. 3).

There are some concerns that indigo naturalis can cause reversible liver damage and, in a very small number of patients, pulmonary arterial hypertension. However, knowledge about the mechanism of action of indigo naturalis is contributing to the development of alternative and potentially safer approaches, such as manipulating the intestinal microbiome, to stimulate AhR and IL-22 signalling.

Stem-cell therapy is a promising treatment strategy for ulcerative colitis. Haematopoietic stem cells and mesenchymal stem cells are able to migrate to areas of injury and reset the immune system by regenerating T-cell populations. Ongoing clinical trials will determine whether stem-cell therapy will become a treatment option for patients with refractory disease.

Translational Research Center for Medical Innovation (TRI) is actively supporting the clinical development of adrenomedullin, indigo naturalis and stem-cell therapy for treating ulcerative colitis. The ability of adrenomedullin to restore microvascular integrity is particularly promising because it could potentially be used to treat other diseases in which the connective tissue barrier system is disrupted and lead to new curative therapies that exploit evolutionary conserved healing mechanisms.

ABOUT TRI

The Translational Research Center

for Medical Innovation (TRI), formerly known as Translational Research Informatics Center, was founded in 2002 by the Japanese Ministry of Education, Culture, Sports, Science and Technology (MEXT) Center for Medical Innovation (TRI), formerly known as Translational Research Informatics Center, was founded in 2002 by MEXT and Kobe city to promote academia-originated medical innovation. TRI established the Academic Research Organization (ARO) network in 2013, which is transforming into an Asian ARO network in conjunction with Korea, Taiwan and Singapore. We plan to expand the network globally to Europe and the United States. Our aim is to develop an infrastructure to support the launch of global clinical trials of academia-originated projects and to obtain regulatory approval worldwide.

REFERENCES

1. Ng, S. C. *et al.* Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *The Lancet* **390**, 2769–2778 (2017).
2. Ashizuka, S., Kita, T., Inatsu, H. & Kitamura, K. Adrenomedullin: a novel therapy for intractable ulcerative colitis. *Inflamm. Bowel Dis.* **19**, E26–E27 (2013).
3. Ashizuka, S., Inatsu, H., Kita, T. & Kitamura, K. Adrenomedullin Therapy in Patients with Refractory Ulcerative Colitis: A Case Series. *Dig. Dis. Sci.* **61**, 872–880 (2016).
4. García-Ponce, A., Cháñez Predes, S., Castro Ochoa, K. F. & Schnoor, M. Regulation of endothelial and epithelial barrier functions by peptide hormones of the adrenomedullin family. *Tissue Barriers* **4**, e1228439 (2016).
5. Naganuma, M. *et al.* Efficacy of Indigo Naturalis in a Multicenter Randomized Controlled Trial of Patients With Ulcerative Colitis. *Gastroenterology* **154**, 935–947 (2018).

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