Qing-Dai is a Chinese herbal medicine containing indigo naturals and indirubin, which are compounds derived from the stems and leaves of several plant species and most commonly used in the manufacture of blue dyes. In China, Qing-Dai is traditionally used to treat various inflammatory diseases. In Japan, although Qing-Dai is not currently approved by the Pharmaceuticals and Medical Devices Agency, it is sometimes used by patients at their own discretion for the treatment of ulcerative colitis (UC) that has not responded to standard evidence-based therapy. In 2016, the INDIGO Study Group initiated a clinical trial to verify the efficacy of Qing-Dai in patients with UC; however, the trial was terminated early because of a report that a patient with UC being treated with Qing-Dai developed pulmonary arterial hypertension (PAH). In response to that trial, on 27 December 2016, the Japanese Ministry of Health, Labour and Welfare issued a public health warning regarding a possible association between Qing-Dai and the development of PAH. A subsequent Japanese national survey in 2017–2018 revealed that 1.8% of patients with UC were using Qing-Dai, and that the adverse effects experienced included, in order of frequency, liver dysfunction, gastrointestinal symptoms, headache, PAH, and intussusception, although no dose–effect relationship between Qing-Dai and these adverse events was identified. Based on the results of those reports, Qing-Dai was added to the list of drugs and toxins possibly associated with PAH at the 6th World Symposium on Pulmonary Hypertension in 2018.

Several mechanisms have been proposed for the development of PAH associated with Qing-Dai use: (1) indigo

Figure. Assumed relationship between duration of Qing-Dai use and development of pulmonary arterial hypertension (PAH). Ach, acetylcholine; AhR, aryl hydrocarbon receptor; BMP, bone morphogenetic protein.
Endothelial-dependent vascular relaxation, leading to the onset of heritable PAH in some patients; and mutations of genes in the BMP pathway are known to underlie the onset of heritable PAH in some patients; and (4) Qing-Dai and indigo attenuate acetylcholine-induced, endothelial-dependent vascular relaxation, leading to endothelial dysfunction.

Given these possible mechanisms, how should we treat patients with Qing-Dai-induced PAH? Clues to addressing this issue can be found in the article by Orihara et al in this issue of the Journal, as well as in 2 recent case reports from Japan. Orihara et al conducted a prospective study of 27 patients with UC treated with Qing-Dai, and report that none of the patients had developed PAH at 1 year follow-up, although pulmonary arterial systolic pressure was significantly decreased after discontinuation of Qing-Dai compared with patients with UC who continued Qing-Dai. The only predictive factor for increased pulmonary arterial systolic pressure in the continuous group was the duration of Qing-Dai treatment, and the cutoff was 20 months, which is consistent with previous case reports (Figure). Discontinuation of Qing-Dai and initiation of pulmonary artery dilators such as endothelin receptor antagonists, phosphodiesterase-5 inhibitors, and prostacyclin analogs was able to reduce pulmonary arterial pressure (PAP), and the pulmonary artery dilators could ultimately be withdrawn. However, it should be noted that Orihara et al did not measure mean PAP by right-heart catheterization, so care should be given when considering these findings.

Thus, according to the previous reports, the underlying cause of Qing-Dai-induced PAH is mainly reversible pulmonary vascular constriction, in the acute phase at least, probably followed by irreversible remodeling of the pulmonary artery due to high PAP in the chronic phase. Therefore, early detection of PAH and cessation of Qing-Dai are important steps to recovery from Qing-Dai-induced PAH. However, discontinuation of Qing-Dai may exacerbate the underlying UC and so this option may be rejected by patients. In such cases, the cardiologist has no choice but to initiate PAH therapy while the patient continues taking Qing-Dai. Whichever route is taken, a close relationship between cardiologists and gastroenterologists is needed to provide an environment in which refractory UC can be appropriately treated.

Further studies in UC patients taking Qing-Dai are needed to verify the efficacy of pulmonary artery dilators, elucidate important factors, including dose, that predict the development of PAH, and determine whether there is a point of no return in pulmonary arterial remodeling.

Disclosure
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References