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JAK inhibitor, a new player for treatment-refractory microscopic colitis

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Microscopic colitis (MC), including collagenous colitis (CC) and lymphocytic colitis (LC), has emerged as a common cause of chronic diarrhea with an annual overall incidence of 4.14 per 100,000 person-years (CC) and 4.85 per 100,000 person-years (LC), respectively.[1] While most patients experience an indolent disease course with occasional relapses, it undeniably affects their quality of life. No curative therapy exists, but most patients respond well to budesonide, which represents the treatment of choice with up to 90% achieving clinical remission after induction therapy. However, in a European multicenter prospective registry, 49% of 381 patients had persistent activity or frequently relapsing (≥2/year) disease when budesonide was stopped.[2] A minority (3% of >14,000 patients) definitely had budesonide-refractory disease in a Danish cohort study and 18% of patients have a continuous suboptimal response to budesonide needing more than one prescription per year beyond the 1st year (CC: 21.8% and LC: 13.8%).[3] Such patients may be candidates for immunosuppressive advanced therapies as used for other forms of inflammatory bowel disease. Emerging data describe anti-tumor necrosis factor (anti-TNF) or anti-integrin therapy for budesonide-refractory MC, prior to surgical intervention.[4]

We report the case of a 39 years old lady with a history of watery diarrhea up to 10 times daily and peripheral arthritis. Informed consent has been obtained. Rheumatoid arthritis was diagnosed and treated conventionally with steroids, nonsteroidal inflammatory drugs and methotrexate. A decreased vascular colonic pattern was observed during endoscopy while histologic evaluation showed both an increased number of inflammatory cells within the lamina propria and increased intraepithelial CD3 positive lymphocytes revealing a diagnosis of LC. Nonsteroidal therapy was reduced when the diagnosis of LC was made. She was not receiving any other medication. Budesonide and systemic corticosteroids (prednisolone up to 20 mg/day) had no effect on the diarrhea. After 12 months, anti-TNF therapy was started for her rheumatoid arthritis but this also had no impact on the diarrhea. Diarrhea persisted, with a substantial effect on her quality of life, as did LC, confirmed histologically (no fewer than 5 procedures over 4 years), until her rheumatoid arthritis lost response to anti-TNF therapy. To offer better control of the rheumatoid condition, she was then switched to upadacitinib (UPA), a selective Janus kinase inhibitor-1 (JAK 1) inhibitor (15 mg once daily) and unexpectedly, her diarrhea resolved within days. Endoscopic evaluation 5 months after UPA initiation revealed a normal mucosa and complete normalization of the histologic lesions. Sixteen months after initiation, the patient remains free of diarrhea and continues UPA 15 mg/day.

The etiology and pathophysiology of MC are not well understood but MC shows a T-helper 1 (Th1) mucosal cytokine profile. Interferon-γ (IFN-γ) is the dominant cytokine in CC, but TNF-α in LC, together with increased mRNA levels of interleukin (IL)-8 and IL-15.[5] There is also evidence of a mixed

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Th17/Tc17 and Th1/Tc1 mucosal cytokine profile and mRNA levels of IFN-γ, IL-12, IL-17A, IL-21, and IL-22 have been reported to be up-regulated compared to controls.[6] JAK1 is involved in IL-2, IL-4, IL-6, IL-15 and IFN signalling.[7] The rapid onset of action, together with its reported safety profile[8] makes UPA an attractive option for new indications such as budesonide-refractory MC. Randomized studies should be considered.

ADDITIONAL INFORMATION

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Conflict of Interest

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Author Contributions

Data curation: Druez A, Rahier JF. Writing - original draft: all authors. Writing - review & editing: all authors. Approval of final manuscript: all authors.

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REFERENCES

1. Tong J, Zheng Q, Zhang C, Lo R, Shen J, Ran Z. Incidence, prevalence, and temporal trends of microscopic colitis: a systematic review and meta-analysis. Am J Gastroenterol 2015;110:265-276.
2. Verhaegh BP, Münch A, Guagnozzi D, et al. Course of disease in patients with microscopic colitis: a European prospective incident cohort study. J Crohns Colitis 2021;15:1174-1183.
3. Weimers P, Vedel Ankersen D, Lophaven S, et al. Disease activity patterns, mortality, and colorectal cancer risk in microscopic colitis: a Danish nationwide cohort study, 2001 to 2016. J Crohns Colitis 2021;15:594-602.
4. Boivineau G, Zallot C, Zerbib F, et al. Biologic therapy for budesonide-refractory, -dependent or -intolerant microscopic colitis: a multicentre cohort study from the GETAID. J Crohns Colitis 2022;16:1816-1824.
5. Tagkalidis PP, Gibson PR, Bhathal PS. Microscopic colitis demonstrates a T helper cell type 1 mucosal cytokine profile. J Clin Pathol 2007;60:382-387.
6. Münch A, Langner C. Microscopic colitis: clinical and pathologic perspectives. Clin Gastroenterol Hepatol 2015;13:228-236.
7. De Vries LC, Wildenberg ME, De Jonge WJ, D'Haens GR. The future of Janus kinase inhibitors in inflammatory bowel disease. J Crohns Colitis 2017;11:885-893.
8. European Medicines Agency. EMA recommends measures to minimise risk of serious side effects with Janus kinase inhibitors for chronic inflammatory disorders [Internet]. European Medicines Agency; 2022 [cited 2023 Apr 24]. https://www.ema.europa.eu/en/news/ema-recommends-measures-minimise-risk-serious-side-effects-janus-kinase-inhibitors-chronic