Tofacitinib for celiac disease and microscopic colitis: killing two birds with one stone

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Abstract

Microscopic colitis is a chronic inflammatory condition of the colon. Firstline treatment consists of budesonide, with the consideration of biological agents in refractory cases. Celiac disease is a chronic immune mediated and gluten-induced enteropathy, with treatment consisting of a gluten-free diet. There is an association between microscopic colitis and instead of xand celiac disease, especially in refractory cases they can coincide. In this manuscript, we report for the first time the efficacy of tofacitinib, a pan Janus kinase inhibitor, in the treatment of concomitant microscopic colitis and celiac disease, resulting in persistent clinical and histological remission. (Acta gastroenterol. belg., **2023,** 86, **374-376**).

Keywords: Janus kinase inhibitor, celiac disease, microscopic colitis, tofacitinib.

Introduction

Microscopic colitis is a chronic inflammatory condition of the colon. Diagnosis is based on specific microscopic features in the absence of endoscopic and radiologic abnormalities (1), with two major subtypes being defined: lymphocytic and collagenous colitis. Firstline treatment consists of budesonide, and beclomethasone diproprionate as an alternative. Due to lack of any randomized placebo-controlled trials and limited data in case reports/series, guidelines do recommend consideration of anti-TNF agents or vedolizumab in refractory cases (1).

Celiac disease is a chronic immune-mediated and gluten-induced enteropathy (2). Treatment consists of a gluten-free diet, with clinical improvement and reversal of pathologic findings in the majority of patients after complete gluten withdrawal.

Table 1. — **Modified Marsh classification according to Oberhuber for histopathological evaluation of celiac disease on duodenal biopsies (6)**

Class	Increased IEL*	Crypt hyperplasia	Villous atrophy
Type 0	No	No	No
Type 1	Yes	No	No
Type 2	Yes	Yes	No
Type 3a	Yes	Yes	Yes (partial)
Type 3b	Yes	Yes	Yes (subtotal)
Type 3c	Yes	Yes	Yes (total)

*IEL: intraepithelial lymphocytes (> 40 IEL per 100 enterocytes

Celiac disease and microscopic colitis are concomitantly prevalent, mainly in the subset of patients with either refractory diagnosis (4.5% prevalence of microscopic colitis in refractory celiac disease, and 6.7% inversely) (3). Meta-analyses suggest that celiac disease is 8 times more likely to be found in refractory microscopic colitis patients as compared to controls (3).

Tofacitinib is a Janus kinase (JAK) inhibitor, approved for treatment of ulcerative colitis and rheumatoid arthritis (4). There is case-based evidence reporting successful treatment of refractory celiac disease with tofacitinib (5). To our knowledge, no reports of the use of tofacitinib in microscopic colitis are available to date.

Case report

We report the case of a 66-year-old man diagnosed with lymphocytic colitis back in 2012. As the patient did not receive any drugs which could potentially provoke microscopic colitis, initial treatment consisted of multiple cycles of budesonide. Budesonide was stopped due to loss-of-response, with confirmation of active histologic disease (2017). Subsequently, infliximab was initiated for two years, after which it had to be withdrawn due to loss-of-response (2019). Biopsies confirmed active histologic disease despite adequate serum infliximab trough levels without anti-infliximab antibodies. Hence, the patient was treated with vedolizumab, resulting in clinical and histological remission (2019). Nevertheless, vedolizumab was discontinued because of interruption of a compassionate use program (2021).

Five months later, the patient presented at the emergency department with symptoms of weight loss, anorexia, abdominal bloating and watery diarrhea, requiring multiple admissions due to dehydration and acute prerenal insufficiency. Diagnostic work-up confirmed a flare of lymphocytic colitis (Figure A). However, duodenal biopsies also revealed the presence of villous atrophy (Figure B), compatible with concomitant celiac disease Marsh 3a (the patient was not on any

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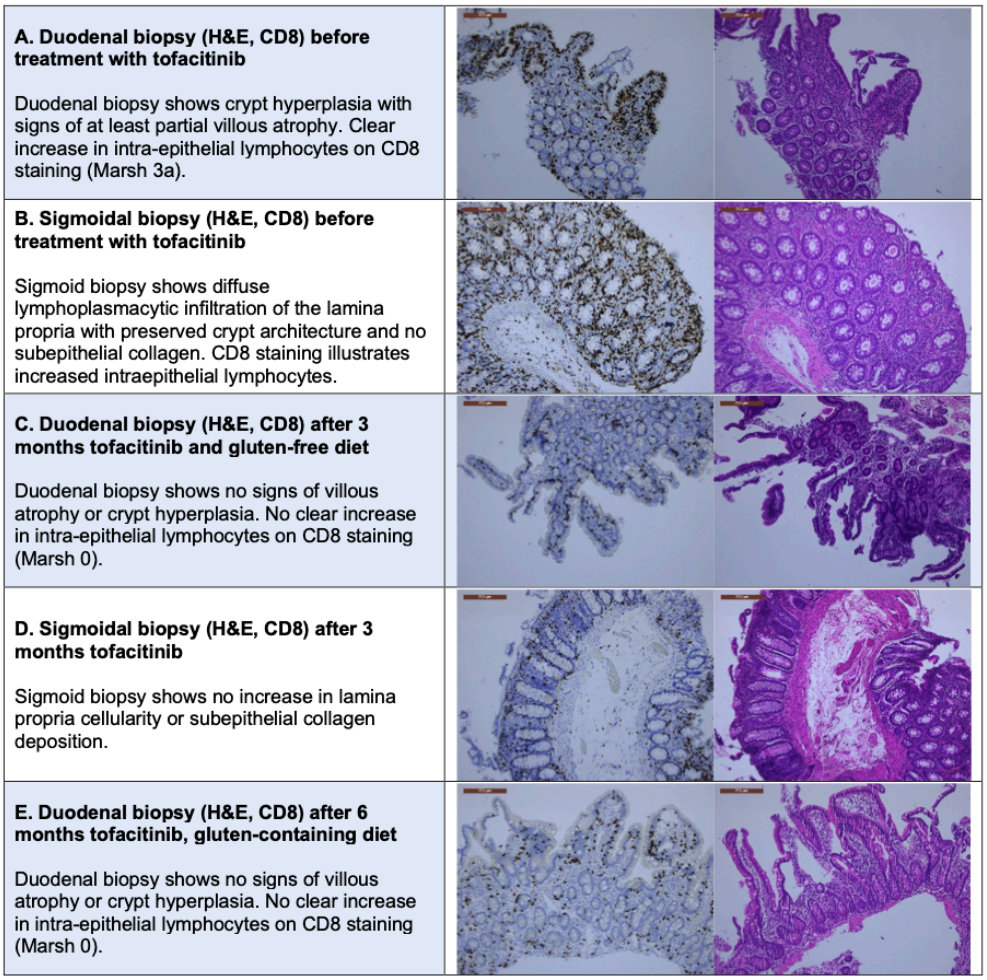

Figure 1. — A-E: evolution of sigmoidal and duodenal biopsies (Marsh classification, Table) during treatment with tofacitinib, including duodenal biopsies with gluten-free and gluten-containing diet. H&E: hematoxylin and eosin

medical therapy linked to a non-celiac villous atrophy). Although serologic tests were negative (anti-tissue transglutaminase IgA, with normal serum IgA level), additional genetic testing showed human leukocyte antigen DQ2/DQ8 positivity, a haplotype compatible with celiac disease.

Tofacitinib was initiated in a dosing regimen approved for ulcerative colitis: an induction dose of 10 mg twice daily for a period of 8 weeks, followed by a maintenance dose of 5 mg twice daily. In addition, the patient was started on a gluten-free diet under supervision of a dietician.

Follow-up investigations showed complete clinical and histological remission (Figure C-D), even after reintroduction of a gluten-containing diet 4 months later (Figure E).

Patient continued tofacitinib 5mg twice daily and remains asymptomatic to date.

Discussion

Microscopic colitis accounts for up to 20% of cases of chronic diarrhea in the population of patients above 65 years of age (7). Estimated incidence in North America and Europe varies widely between 6.8 and 24.7 per 100.000 person-years (7). A nationwide cohort study conducted in Sweden estimated the lifetime risk of developing microscopic colitis to be 1 in 115 in women and 1 in 286 in men (8). Instead, global prevalence of celiac disease varies based on ethnicity and geography with higher prevalence found in Caucasian and Nordic countries, although the incidence of celiac disease is increasing worldwide (9). Seroprevalence rate in Europe is estimated to be around 1.4% compared to a prevalence of biopsy-diagnosed celiac disease of 0.7% (9). Often wrongfully thought to be a pediatric or adolescent disease, celiac disease can develop at any age (9).

Microscopic colitis is associated with other immune mediated diseases, including celiac disease, autoimmune thyroid disease, psoriasis, and type 1 diabetes mellitus (7). Approximately 5% of patients have concomitant diagnoses of microscopic colitis and celiac disease (3). Gastroenterologists should be aware of this association, especially in case refractory symptoms persist despite adequate therapy. Besides colonic biopsies, duodenal biopsies should therefore be obtained in all patients with (refractory) microscopic colitis and persistent diarrhea.

In contrast to celiac disease which is treated by a gluten-free diet, microscopic colitis is primarily treated with budesonide (1), the only drug approved by the European Medicines Agency (8). However, guidelines do recommend consideration of biologicals in budesonide-refractory cases (1).

JAK inhibitors inhibit signal transducers and activators of transcription pathways, that regulate signaling by pro-inflammatory cytokines including interleukin-6, interleukin-15, and interferon-gamma (10), cytokines involved in the pathogenesis of microscopic colitis and celiac disease (11-12). Hence, there is an underlying pathophysiological rationale to consider JAK inhibitors for the treatment of both microscopic colitis and celiac disease.

Although there is case-based evidence for tofacitinib in refractory celiac disease (5), efficacy in microscopic colitis has not yet been reported. Recently, a single case of refractory microscopic colitis treated with upadacitinib, a selective JAK-1 inhibitor, was described (13). In contrast to the current tofacitinib case, the upadacitinib treated patient achieved clinical remission without histological confirmation of treatment success.

Conclusion

Given the unmet need for nondietary therapies in celiac disease and alternatives to corticosteroids in microscopic colitis, we believe that the use of JAK inhibitors deserves further study in both indications. Furthermore, physicians should be aware of the association between (refractory) microscopic colitis and celiac disease.

Conflicts of interest

Matthias Lenfant reports no conflicts of interest.

Gert De Hertogh receives fees for his activities as central pathology reader from Centocor and receives speakers' fees from Janssen.

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