Enduring clinical remission in refractory celiac disease type II with tofacitinib: an open-label clinical study

Dieckman, T.; Schumann, M.; Beaumont, H.; Bontkes, H.J.; Koning, F.; Bouma, G.; Rcdii Tofacitinib Consortium C

Enduring Clinical Remission in Refractory Celiac Disease Type II With Tofacitinib: An Open-Label Clinical Study

Refractory celiac disease type 2 (RCDII) is a rare condition with high mortality because of a lack of effective treatment strategies. RCDII is caused by clonal expansion of intraepithelial lymphocytes (IELs). Gain-of-function *JAK1* mutations are frequently found in these cells.[1,2] In a previous in vitro study,[3] we demonstrated the potential of tofacitinib, a small-molecule *JAK1/JAK3* inhibitor, to control activity of the aberrant IEL population. Here, we report on an open-label prospective pilot study with tofacitinib in patients with therapy-refractory RCDII (EudraCT 2018-001678-10; onderzoekmetmensen.nl, NL-OMON25125). Between November 2019 and February 2022, 4 patients with an established diagnosis of RCDII[4] who had failed previous therapies were treated in the Netherlands with tofacitinib 10 mg twice-daily for 12 weeks (Methods; Supporting Documents). Two patients in Germany who fulfilled the inclusion criteria received similar treatment outside this protocol.

Baseline patient characteristics are available in Supplementary Table 1. All patients failed previous treatment regimens including cladribine. All patients showed signs of malabsorption, including weight loss, diarrhea/loose stools, abdominal pain, and/or hypoalbuminemia. Small intestinal biopsies displayed a median of 70%–90% (interquartile range [IQR], 27·38–90·50) aberrant cells of total IELs. Two patients had ulcerative jejunitis (UJ). Histologic classification for villous atrophy at baseline displayed Marsh 3 (n = 5) and Marsh 2 (n = 1) lesions. All patients were treated with 10 mg twice-daily for 12 weeks. One per-protocol treated patient had a dosage modification at Week 8 to 5 mg twice-daily.

All patients completed 12-week treatment with tofacitinib. In the 4 patients treated per-protocol, tofacitinib treatment led to a prompt resolution within 2–14 days of diarrhea/loose stools, disappearance of abdominal pain, and weight gain (median increase 12·30% [IQR, 7·55–17·13] at Week 12) (Figure 1*A*). One patient with severe UJ could discontinue total parenteral nutrition at Week 9. On discontinuation of treatment in the per-protocol treated patients, we observed rapid recurrence of symptoms including weight loss in all patients. Reinstitution of therapy again led to a rapid and complete clinical response (Figure 1*A*). Similar clinical observations were found in the 2 patients in the off-protocol treated group (weight gain 16·70% [TOF05], 3·10% [TOF06] at Week 12).

The primary immunologic end point, an absolute decrease of ≥20% aberrant IELs (of total IELs) from baseline to Week 12, was not met, neither in the per-protocol, nor in the off-protocol treated patients. Altogether, the median fraction of aberrant IELs at baseline was 70·90% (IQR, 27·38–90·50), whereas at Week 12 this was 72·00% (IQR, 24·73–83·55).

Improvement from baseline in histology scores for villous atrophy was a secondary end point. At Week 12, we observed mucosal improvement in 4 of 6 patients, whereas 2 per-protocol treated patients showed similar histologic scores (Figure 1*B*). Marked macroscopic mucosal improvement was observed in both UJ patients (Figure 1*C*).

Adverse events (AEs) occurred in all patients. Summary data of serious AEs are available in Supplementary Table 2. We observed 52 AEs, including 2 serious AEs in 1 patient. This per-protocol treated patient (TOF03) had a pulmonary embolism, which occurred during line sepsis with a *Staphylococcus epidermidis* bacteremia. Based on major clinical improvement in this patient, we decided on a dose reduction to 5 mg twice-daily and continued treatment with success. The most common AE was lymphopenia, which occurred in 4 of 6 patients (5 events) and was transient in 2 of 5 events at Week 12.

Per-protocol treated patients restarted treatment with 5 mg twice-daily on recurrence of symptoms. Off-protocol treated patients continued tofacitinib treatment at Week 12, with 5 mg twice-daily. Extended follow-up data over 2 years in 6 patients (median, 84 weeks; IQR, 50–113) revealed persistent clinical remission. Overall, a median weight gain of 19·80% (IQR, 11·10–20·38) was reported, an increase of 7·50% when compared with Week 12. Duodenal biopsies all showed further improvement in histologic scores (Figure 1*B*) without changes in the amount of aberrant cells. Capsule endoscopy showed complete resolution of ulcerations in UJ patient TOF03 at Week 63 (Figure 1*C*); near complete remission was observed in UJ patient TOF05 at Week 120.

Abbreviations used in this paper: **AE, adverse event; IEL, intraepithelial lymphocyte; IQR, interquartile range; RCDII, refractory celiac disease type II; UJ, ulcerative jejunitis.**

Most current article

1542-3565
https://doi.org/10.1016/j.cgh.2024.05.022

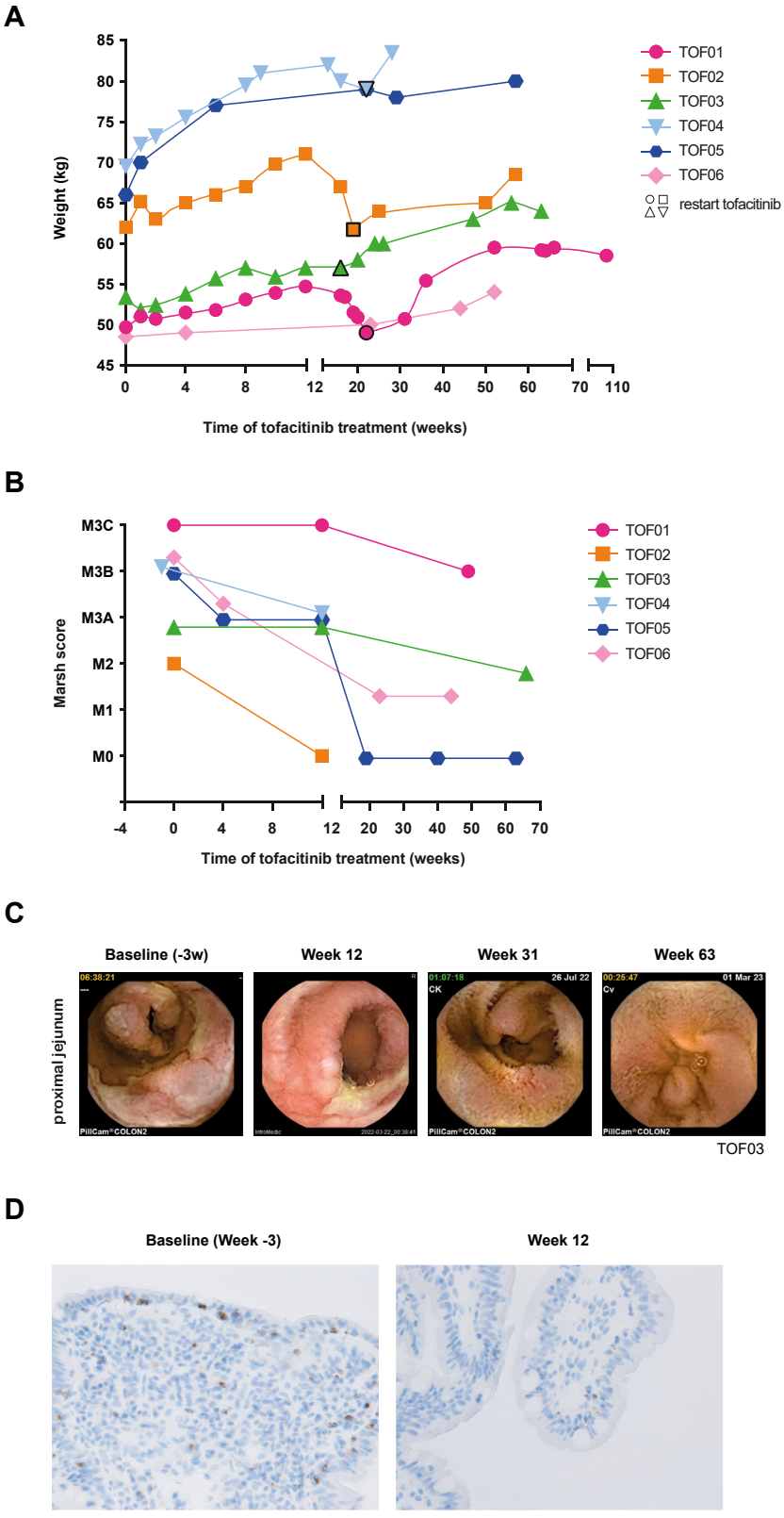

Figure 1. Response to tofacitinib treatment in RCDII patients. (*A*) Graph showing weight curves for per-protocol treated patients over time. *Symbol linings* indicate the timepoint of restart of tofacitinib treatment. (*B*) Graph showing Marsh scores (from M0 to M3C) for classification of villous atrophy in duodenal biopsies. Displayed are timepoints at baseline (Week 0), during, at end of study (Week 12), and during extended follow-up. (*A, B*) Distinct colors/symbols/TOF-numbers indicate RCDII patients treated with tofacitinib. (*C*) Images at site of the most severe ulcerative lesion, in the proximal ileum, from patient TOF03. Image at baseline is taken during anal double-balloon enteroscopy; images at Week 12 and during follow-up are taken during capsule endoscopy. (*D*) Immunohistochemistry staining for granzyme B in duodenal tissue retrieved from patient TOF03 at baseline (Week -3) and Week 12 of tofacitinib treatment (representative image). Positive staining is indicated by the color *brown*.

The marked clinical and histologic improvement in conjunction with persistence of aberrant cells suggests that tofacitinib has a functional effect on aberrant IELs rather than inducing apoptosis. In support of this, in an exploratory immunohistochemical staining experiment (Methods; Supporting Documents), we observed a clear decrease in granzyme B expression in 4 of 5 patients in the duodenal epithelium and lamina propria (representative image, Figure 1*D*) after 12 weeks of tofacitinib treatment.

This study describes the first targeted treatment strategy for RCDII patients showing prompt clinical remission

and histologic improvement. During extended follow-up, we observed enduring remission without safety concerns beyond those already known for tofacitinib. Despite age and clinical condition, no serious or opportunistic infections were seen. One patient in the per-protocol group developed a pulmonary embolism, but this occurred in the context of a catheter sepsis. A causal relationship with tofacitinib treatment can therefore be neither excluded nor proven. Nevertheless, this underlines the potential side effects of this category of drugs and should be weighed against other treatments for RCDII including cladribine[5] and autologous stem cell transplantation.[6] Prophylactic measures for the mentioned side effects should be considered per patient, such as herpes zoster vaccination and anticoagulants, particularly during treatment with 10 mg twice-daily. Finally and most importantly, we observed no progression to enteropathy-associated T-cell lymphoma in any of our patients.

This small study size warrants cautious interpretation. The consistent clinical responses, rapid recurrence of symptoms after discontinuation, and the effectiveness of reinstitution of therapy with extensive follow-up add to the robustness of our observations. Additionally, similar clinical observations were made in a recently published case report.[7] We believe that tofacitinib should be considered as a treatment option for patients who fail open-capsule budesonide[8,9] therapy. We anticipate that this study will change the future treatment landscape of RCDII.

TESSA DIECKMAN
Department of Immunology
Leiden University Medical Center
Leiden, the Netherlands, *and*
Department of Gastroenterology and Hepatology
Amsterdam UMC, Vrije Universiteit Amsterdam
Amsterdam Gastroenterology Endocrinology Metabolism
Amsterdam, the Netherlands

MICHAEL SCHUMANN
Division of Gastroenterology, Infectious Diseases and Rheumatology
Campus Benjamin Franklin, Charité Universitätsmedizin Berlin
Berlin, Germany

HANNEKE BEAUMONT
Department of Gastroenterology and Hepatology
Amsterdam UMC, Vrije Universiteit Amsterdam
Amsterdam Gastroenterology Endocrinology Metabolism
Amsterdam, the Netherlands

HETTY J. BONTKES
Medical Immunology Laboratory, Laboratory Specialized Diagnostics & Research
Department of Laboratory Medicine
Amsterdam UMC, Vrije Universiteit Amsterdam
Amsterdam, the Netherlands

FRITS KONING
Department of Immunology
Leiden University Medical Center
Leiden, the Netherlands

GERD BOUMA
Department of Gastroenterology and Hepatology
Amsterdam UMC, Vrije Universiteit Amsterdam
Amsterdam Gastroenterology Endocrinology Metabolism
Amsterdam, the Netherlands

RCDII TOFACITINIB CONSORTIUM

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at http://doi.org/10.1016/j.cgh.2024.05.022.

References

1. Cording S, et al. Gut 2022;71:497–508.
2. Ettersperger J, et al. Immunity 2016;45:610–625.
3. Kooy-Winkelaar YMC, et al. Proc Natl Acad Sci 2017;114:E980.
4. Cellier C, et al. Lancet Gastroenterol Hepatol 2019;4:960–970.
5. Tack GJ, et al. World J Gastroenterol 2011;17:506–513.
6. Al-toma A, et al. Blood 2006;109:2243–2249.
7. Grewal JK, et al. BMJ Case Reports 2022;15:e244692.
8. Brar P, et al. Am J Gastroenterol 2007;102:2265–2269.
9. Mukewar SS, et al. Am J Gastroenterol 2017;112:959–967.

Correspondence
Address correspondence to: Gerd Bouma, MD, PhD, Department of Gastroenterology and Hepatology, Amsterdam UMC, Vrije Universiteit Amsterdam, Boelelaan 1118, 1081 HZ, Amsterdam, the Netherlands. e-mail: g.bouma@amsterdamumc.nl.

Acknowledgments
RCDII Tofacitinib Consortium includes Valerie Byrnes,[1] Jane McCarthy,[1] Andra Neefjes-Borst,[2] Christoph Loddenkemper,[3] Jeroen van Bergen,[4] Marlous op de Weegh,[5] and KEA Lundin,[6,7]; from the [1]Department of Haematology and Gastroenterology, Galway University Hospital, Galway, Ireland; [2]Department of Pathology, Amsterdam UMC, location VU Medical Center, Amsterdam, the Netherlands; [3]Pathotres Gemeinschaftspraxis fur Pathologie, Berlin, Germany; [4]Department of Immunology, Leiden University Medical Center, Leiden, the Netherlands; [5]Department of Gastroenterology, Anna Ziekenhuis, Geldrop, the Netherlands; [6]Department of Gastroenterology, Oslo University Hospital, Riskshospitalet, Oslo, Norway; and [7]Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway. The authors thank all patients for participation in this study. They thank all gastroenterologists and endoscopy nurses for performing endoscopies and obtainment of patient samples. They thank research nurses Louis Schellekens, Inge van der Horst, and Renée Dierx for conducting in-patient visits. They thank Pfizer for providing tofacitinib for this study. They thank the RCDII Tofacitinib Consortium members for their contribution to this study.

Conflicts of interest
The authors disclose no conflicts.

Funding
Grant support by KWF Dutch Cancer Society (UL 2015-2850) and the Dutch Celiac Disease patient association (Nederlandse Coeliakie Vereniging, NCV). This investigator-initiated trial was funded by Pfizer in terms of drug supply through an independent Investigator Sponsored Research Grant (#53234095). Pfizer provided tofacitinib (Xeljanz) for patients treated per-protocol in the Netherlands. Michael Schumann is funded as a Berlin Institute of Health Clinical Fellow. None of the funding sources had a role in study design, collection, analysis, or interpretation of data.