


# Hyperbaric oxygen therapy for the treatment of perianal fistulas in 20 patients with Crohn's disease: Results of the HOT-TOPIC trial after 1-year follow-up

Corine A. Lansdorp<sup>1</sup>  | Christianne J. Buskens<sup>2</sup> | Krisztina B. Gecse<sup>3</sup> |  
Mark Löwenberg<sup>3</sup> | Jaap Stoker<sup>4</sup> | Willem A. Bemelman<sup>2</sup> |  
Geert R. A. M. D'Haens<sup>3</sup> | Rob A. van Hulst<sup>1</sup>

<sup>1</sup>Department of Anaesthesiology/Hyperbaric Medicine, Amsterdam UMC, Location AMC, Amsterdam, The Netherlands

<sup>2</sup>Department of Surgery, Amsterdam UMC, Location AMC, Amsterdam Gastroenterology Endocrinology Metabolism, Amsterdam, The Netherlands

<sup>3</sup>Department of Gastroenterology and Hepatology, Amsterdam UMC, Location AMC, Amsterdam, The Netherlands

<sup>4</sup>Department of Radiology and Nuclear Medicine, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands

## Correspondence

Corine A. Lansdorp, Amsterdam UMC, Location AMC, Department of Anaesthesiology/Hyperbaric Medicine, location H1-158, PO Box 22700, 1100 DE Amsterdam, the Netherlands.  
Email: [n.lansdorp@amsterdamumc.nl](mailto:n.lansdorp@amsterdamumc.nl)

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## Abstract

**Background:** Previously published short-term results (week 16) of this trial showed a significant improvement in clinical, radiologic and biochemical outcomes in Crohn's disease patients with therapy-refractory perianal fistulas after treatment with hyperbaric oxygen therapy.

**Objective:** To assess the long-term (week 60) efficacy, safety and feasibility of hyperbaric oxygen therapy in perianal fistula in Crohn's disease.

**Methods:** Crohn's disease patients with high perianal fistula(s) failing conventional treatment >6 months were included. Exclusion criteria were presence of a stoma, rectovaginal fistula(s) and recent changes in treatment regimens. Patients received 40 hyperbaric oxygen sessions and outcomes were assessed at week 16 and week 60.

**Results:** Twenty patients were included (median age 34 years). At week 16, median scores of the perianal disease activity index and modified Van Assche index (co-primary outcomes) decreased from 7.5 (95% CI 6–9) to 4 (95% CI 3–6,  $p < 0.001$ ) and 9.2 (95% CI 7.3–11.2) to 7.3 (95% CI 6.9–9.7,  $p = 0.004$ ), respectively. At week 60, the respective scores remained significantly lower than baseline: 4 (95% CI 3–7,  $p < 0.001$ ) and 7.7 (95% CI 5.2–10.2,  $p = 0.003$ ). Perianal disease activity index score of 4 or less (representing inactive perianal disease) was observed in 13 patients at week 16 and 12 patients at week 60. Using fistula drainage assessment, 12 and 13 patients showed a clinical response at week 16 and 60, respectively, and clinical remission was achieved in four patients for both time points. At week 16, a statistically significant biochemical improvement (C-reactive protein and faecal calprotectin levels) was found, but this effect was no longer significant at week 60.

**Conclusions:** The clinical and radiologic improvement of perianal fistula in Crohn's disease, that was found at week 16 after treatment with hyperbaric oxygen therapy, is maintained at 1-year follow-up.

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**KEYWORDS**

Crohn's disease, fistulising, hyperbaric oxygen therapy, inflammatory bowel disease, perianal fistulas, therapy-refractory

**INTRODUCTION**

Perianal fistulas are a common complication in Crohn's disease: every third patient has at least one fistulising episode during their disease course, and recent research shows that 8% of CD patients have a perianal fistula at a given time point.<sup>1,2</sup> Spontaneous fistula closure is rare, and most patients require medical and/or surgical intervention.

Treatment options for complex fistulas include medical treatment (mostly anti-tumour necrosis factor (TNF) therapy, with possible addition of an immunomodulator), surgical intervention aimed at fistula closure (including mucosal advancement flap and ligation of the intersphincteric fistula tract) and mesenchymal stem cells, with success rates of up to 60%.<sup>3-8</sup> However, even after multidisciplinary approach, long-term rates remain disappointing, with only one-third of patients with complex perianal fistulas achieving clinical remission at the end of follow-up (median 10 years) in a large epidemiological study.<sup>9</sup>

Hyperbaric oxygen therapy has been suggested as a potential adjunctive treatment for patients suffering from ulcerative colitis and Crohn's disease.<sup>10</sup> Treatment consists of breathing 100% oxygen under higher than normal atmospheric pressure: Hyperoxygenation and oxidative stress has been shown to result in anti-inflammatory effects, stem cell mobilisation and up-regulation of growth factors.<sup>10-12</sup>

Positive outcomes with hyperbaric oxygen therapy for treating perianal Crohn's disease have been reported previously in small case-series.<sup>10,13,14</sup> The HOT-TOPIC trial was designed in order to assess efficacy, safety and feasibility of the treatment in patients with therapy-refractory perianal fistulas.<sup>15</sup> Short-term results, assessed 2 months after treatment, were published previously and showed a significant improvement in clinical, radiological, biochemical and patient-reported outcomes after treatment with hyperbaric oxygen.<sup>16</sup> Here, we present the long-term outcomes of the HOT-TOPIC trial, assessed 1 year after treatment with hyperbaric oxygen therapy.

**METHODS****Study design**

The HOT-TOPIC study was a prospective interventional cohort study with a follow-up of 60 weeks. The outcomes of week 16 have been published previously.<sup>16</sup>

The study was performed in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. The protocol has been approved by the Medical Ethical Committee (METC 2017\_132) and has been published previously.<sup>15</sup> The trial has

**Key summary****Summary of the established knowledge on this subject**

- Perianal fistulas are a debilitating complication of Crohn's disease, and current treatment options have disappointing long-term success rates.
- Hyperbaric oxygen therapy has been suggested as a possible (adjunctive) treatment of perianal fistulas, and of inflammatory bowel disease (IBD) in general.
- This trial concerns 20 patients with therapy-refractory perianal fistulas in Crohn's disease that were treated with 40 sessions of hyperbaric oxygen therapy, and previously published short-term results have shown a significant improvement in clinical, radiologic, biochemical and patient-reported outcomes.

**What are the significant and/or new findings of this study?**

- The long-term outcomes presented here show that the initial clinical and radiologic improvement seen after treatment with hyperbaric oxygen therapy at week 16 is maintained at 1-year follow-up. The short-term improvements in biochemical and patient-reported outcomes, however, are not.
- Four patients (20%) achieved a fibrotic fistula complex and no other signs of activity on MRI, indicating deep healing. Furthermore, 60% of patients had inactive perianal disease as measured by the perianal disease activity index at week 60.
- Treatment with hyperbaric oxygen was feasible in this selected cohort of patients, and decision regret to undergo the treatment was consistently low during follow-up.

been registered at the Dutch Trial Registry (NL 6489/NTR 6676). All participants provided written informed consent.

**Population and treatment**

Detailed information on the study population and the treatment has been published previously.<sup>15,16</sup> Main inclusion criteria were: patients with a confirmed diagnosis of Crohn's disease and one or more actively draining high perianal fistula(s), failing standard care (medical and/or surgical, defined as persisting fistula drainage in the preceding

>6 months) or intolerance to standard treatment. Concomitant treatment regimens had to be stable for at least 6 weeks prior to starting hyperbaric oxygen treatment, that is no starting of antibiotics, no surgical intervention except for seton placement, no addition of immunosuppressants and/or no dose changes of biologicals. Exclusion criteria were unfit for hyperbaric oxygen therapy, stoma, rectovaginal fistula(s), anal stricture, fluid collection/abscess requiring surgical drainage, unwilling to undergo seton drainage of patients with a seton in situ >12 months, prior surgical procedure in the preceding 3 months and proctitis unless no deep ulcers were seen at endoscopy.

Eligible patients were treated with 40 daily hyperbaric oxygen sessions during workdays, that is for a duration of eight weeks in total. Seton removal was planned after 30 sessions (i.e., at week 6 after starting hyperbaric oxygen therapy) in order to allow for fistula closure. The medical treatment regimen patients received for their Crohn's disease remained unchanged in principle, but if necessary a change in medication could be made at the discretion of the primary physician.

Patients that were eligible to participate but did not wish to undergo hyperbaric oxygen therapy were asked to serve as a control group. Patients in the control group continued to receive standard care (medical and/or surgical) as deemed suitable by their primary physician.

## Endpoints, sample size and statistical analysis

The co-primary outcome parameters were changes in perianal disease activity index and MRI as measured by the (modified) Van Assche index at week 16 (i.e., 8 weeks after finishing hyperbaric oxygen treatment) and week 60 (i.e., 1 year after finishing the treatment).<sup>17,18</sup> Inactive perianal disease is defined as a perianal disease activity index score of 4 or less.<sup>19</sup>

Recently, a new MRI index (MAGNIFI-CD) has been published following a stringent development procedure and internal validation.<sup>20</sup> In addition to the original study protocol this index was also calculated at week 16 and 60.

Secondary outcome parameters included clinical response and remission at week 16 and week 60 as measured by the fistula drainage assessment, with clinical response defined as a reduction of  $\geq 50\%$  in the number of draining fistulas as compared to baseline, and clinical remission defined as the absence of draining fistulas upon gentle finger compression.<sup>21</sup>

Biochemical changes in C-reactive protein and faecal calprotectin levels were assessed at week 16 and week 60, as well as the proportion of patients with normal values of C-reactive protein (5 mg/l) and faecal calprotectin values below the cut-off score for remission of IBD (250  $\mu\text{g/g}$ ).<sup>22</sup>

For patient-reported outcomes, scores of a visual analogue scale (VAS), the IBD questionnaire (IBDQ) and a validated decision regret scale were assessed at baseline, week 16 and 60.<sup>23,24</sup> For the IBDQ, the proportion of patients with a relevant clinical

response (increase of  $\geq 27$  points) and the proportion of patients in remission (score of  $\geq 168$ ) were also assessed.<sup>25</sup> At week 16 and 60, patients were also asked to answer 'yes' or 'no' on the question if they felt their fistula(s) had improved due to hyperbaric oxygen treatment.

Changes in use of concomitant medication, re-interventions and adverse events during the hyperbaric oxygen treatment and study follow-up (60 weeks) were reported.

All outcomes except for MRI were also reported per protocol at week 34 to allow for assessment of intermediate changes. The results of this assessment are not included in this article but are available as a supplementary file (Table S1).

In the control group the same outcome measures were assessed, except for MRI and biochemical response. Reasons for refusal to undergo hyperbaric oxygen treatment were recorded. Assessment of outcome parameters was performed at the same time point as for the hyperbaric oxygen therapy group, at week 16 and 60.

Details on sample size and statistical analysis have been published previously.<sup>15,16</sup>

## RESULTS

### Inclusion, baseline characteristics and treatment

In total, 29 eligible patients were counselled and gave informed consent to participate: 21 patients accepted treatment with hyperbaric oxygen (72%) and eight patients were included in the control group. One patient in the hyperbaric oxygen therapy group was withdrawn from the study after five hyperbaric oxygen sessions because of inadequate seton drainage and was replaced by another patient. Twenty patients in the hyperbaric oxygen therapy group and eight patients in the control group completed the study and follow-up (60 weeks). A study CONSORT flowchart is available as a supplementary file.

Patient baseline characteristics for the hyperbaric oxygen therapy group are shown in Table 1, additional information on these characteristics, the hyperbaric treatment and seton removal has been published previously.<sup>16</sup>

### Co-primary outcome parameters: Perianal disease activity index and (modified) Van Assche index

Median perianal disease activity index and MRI indices scores are depicted in Figure 1 and Table 2. Individual changes in scores can be found in Figure S1 (perianal disease activity index) and Figure S2 (modified and original Van Assche index) in the supplementary files.

The median perianal disease activity index score decreased from 7.5 (95% CI 6–9) at baseline to 4 (95% CI 3–6,  $p < 0.001$ ) at week 16. At week 60, the median perianal disease activity index score remained the same as in week 16 (score of 4, 95% CI–3–7,  $p < 0.001$

**TABLE 1** Baseline characteristics of patients undergoing hyperbaric oxygen therapy

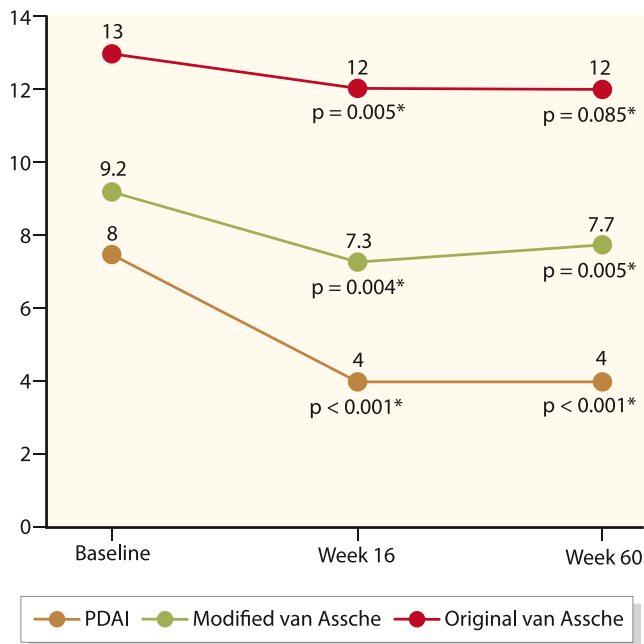
Characteristics	n = 20
Age (median age, IQR)	34 (24–49)
Gender at birth (number of patients)	
Male	13 (65%)
Active smoking (number of patients)	4 (20%)
Luminal disease activity present (number of patients)	5 (25%)
Concomitant use of medication	17 (85%)
Anti-TNF therapy with immunomodulator	9 (45%)
Anti-TNF monotherapy	4 (20%)
Anti-TNF with chronic antibiotic use	1 (5%)
Vedoluzimab	1 (5%)
Ustekinumab	1 (5%)
Mesalamine	1 (5%)
Years disease duration Crohn's disease (median, IQR)	12 (4–19)
Years disease duration perianal Crohn's disease (median, IQR)	7 (3–12)
Years disease duration current fistula (median, IQR)	4 (2–12)
Previous surgical closure (number of patients)	4 (20%)
Number internal openings (number of patients)	
1	15 (75%)
2	4 (20%)
3	1 (5%)
Number of external openings (number of patients)	
1	7 (35%)
2	5 (25%)
3	3 (15%)
4 or more	5 (25%)

Abbreviations: IQR, interquartile range; TNF, tumour necrosis factor.

compared to baseline). Inactive perianal disease, defined as a score of 4 or less, was achieved in 13 patients (65%) at week 16.<sup>19</sup> At week 60, 2 of these 13 patients deteriorated to a score of more than 4. Therefore, 11 patients showed persistent inactive perianal disease on both visits. One additional patient that did not achieve inactive disease at week 16 improved to a score of 4 at week 60. Consequently, at the end of follow-up, a total of 12 (60%) patients had inactive perianal disease.

Results of the perianal disease activity index at week 34 are available as supplementary material (Table S1).

The median modified Van Assche and original Van Assche scores decreased from 9.2 (95% CI 7.3–11.2) to 7.3 (95% CI 6.9–9.7,  $p = 0.004$ ) and from 13 (95% CI 12–15) to 12 (95% CI 10–13,  $p = 0.005$ ), respectively, at week 16. At week 60, the modified Van Assche index increased to 7.7 but remained significantly lower than baseline (95% CI 5.2–10.2,  $p$ -value 0.003). The median



**FIGURE 1** Median perianal disease activity index and (modified) Van Assche index scores at baseline, week 16 and week 60 in patients treated with hyperbaric oxygen therapy

original Van Assche index score at week 60 was the same as at week 16, but the difference compared to baseline was no longer significant (median of 12, 95% CI 10–14,  $p = 0.085$ ). At week 16, items of the MRI indices that were most reactive to change after hyperbaric oxygen treatment were inflammatory items (i.e., rectal wall involvement and inflammatory mass), as well as the dominant feature of the primary tract and extensions, with three patients having a predominantly fibrotic fistula complex at week 16. At week 60, items that changed compared to week 16 were the number of fistula tracts (more unbranched tracts, less branched or multiple tracts) and another patient achieved a predominantly fibrotic primary tract.

In addition to the original study protocol, scores of the MAGNIFI-CD index were also calculated. The median score at baseline was 16 (95% CI 13–18) and decreased to 14 (95% CI 13–16,  $p = 0.001$  as compared to baseline) at week 16. At week 60 the median score remained 14 (interquartile range [IQR] 9–16,  $p = 0.001$  as compared to baseline).

Counts and changes of the individual scoring items of the original and modified Van Assche index and MAGNIFI-CD index are available as supplementary material (Table S2).

### Secondary outcome parameters

#### Fistula drainage assessment

Twelve out of 20 patients showed a clinical response as measured by the fistula drainage assessment at week 16, with one additional patient achieving clinical response at week 60 (total of 13 patients,

**TABLE 2** Perianal disease activity index (modified) Van Assche index and patient-reported outcomes at baseline, week 16 and week 60 of patients treated with hyperbaric oxygen therapy

	Baseline		Week 16*			Week 60		
	Median	95% CI	Median	95% CI	p-value*	Median	95% CI	p-value*
Perianal disease activity index	7.5	6–9	4	3–6	<0.001	4	3–7	<0.001
Modified Van Assche index	9.2	7.3–11.2	7.3	6.9–9.7	0.004	7.7	5.8–10	0.003
Original Van Assche index	13	12–15	12	10–13	0.005	12	10–14	0.085
MAGNIFI-CD	16	(13–18)	14	13–16	0.001	14	9–16	0.001
C-reactive protein	4.2	1.6–8	2.2	0.9–4.3	0.003	4.0	1–13	0.687
Faecal calprotectin	399	52–922	31	16–245	0.001	94.0	50–353	0.198
VAS score	67.5	61–78	70	60–76	0.32	62	50–75	0.073
IBDQ score	169	141–191	183	167–199	0.001	166	150–191	0.965
Decision regret scale score	NA	NA	15	5–25	NA	12.5	0–28.75	NA

Abbreviations: CI, confidence interval; IBDQ, inflammatory bowel disease questionnaire; NA, not applicable; VAS, visual analogue score.

\*statistical significance as compared to baseline.

65%). Four out of 20 patients (20%) were in clinical remission at both week 16 and week 60. Of the 50 external fistula openings that were present at baseline, 24 were closed at week 16 (48%) and 21 at week 60 (42%).

### Biochemical response

The median C-reactive protein value at baseline was 4.2 mg/ml (95% CI 1.6–8 mg/ml) which decreased to 2.2 mg/ml (95% CI 0.9–4.3 mg/ml,  $p = 0.003$ ) at week 16, and increased to 4.0 (95% CI 1–13,  $p = 0.687$  as compared to baseline) at week 60. At baseline, 11 patients had normal (<5 mg/l) baseline C-reactive protein values. At week 16 and 60 this were 15 and 10 patients, respectively. For faecal calprotectin, the median value decreased from 399  $\mu\text{g/g}$  (95% CI 52–922  $\mu\text{g/g}$ ) to 31  $\mu\text{g/g}$  (95% CI 16–245  $\mu\text{g/g}$ ,  $p = 0.001$ ) at week 16, and increased to 94.0 (CI 95% 50–353,  $p = 0.198$  as compared to baseline) at week 60. Nine patients had values of faecal calprotectin indicating remission (<250  $\mu\text{g/g}$ ) at baseline, and 16 and 14 patients had these values at week 16 and week 60, respectively. The median C-reactive protein and faecal calprotectin values can be found in Table 2. Figure S3 of the supplementary files shows the individual C-reactive protein and faecal calprotectin values of patients at baseline and during follow-up.

### Patient-reported outcomes

The median VAS score increased from 67.5 (95% CI 61–78) to 70 (95% CI 60–76,  $p = 0.26$ ) at week 16, and decreased to 62 (95% CI 50–75,  $p = 0.073$  as compared to baseline) at week 60. The median IBDQ score at baseline was 169 (95% CI 141–191) and changed to 183 (95% CI 167–199,  $p = 0.001$ ) at week 16, to 166 (95% CI 150–

191,  $p = 0.965$  as compared to baseline) at week 60. Based on the IBDQ cut-off score of  $\geq 168$ , 11 patients were in clinical remission at baseline, 14 patients at week 16 and 10 patients at week 60. Four patients had a relevant clinical response at week 16 and 60, indicated by an increase in score of  $\geq 27$  points. The median score of the decision regret scale was 15 (IQR 5–25) at week 16 and 12.5 (IQR 0–28.75) at week 60, indicating low decision regret. Fourteen out of 20 patients (70%) answered “yes” on the dichotomous question if patients felt their fistula(s) had improved at week 16, and 13 (65%) patients at week 60. The median VAS, IBDQ and decision regret scale scores can also be found in Table 2.

Results of all secondary outcomes at week 34 are available as supplementary material (Table S1).

### Adverse events

#### Adverse events during hyperbaric oxygen therapy

Detailed information on adverse events related to hyperbaric oxygen therapy until week 16 has been published previously.<sup>16</sup> All these events were resolved at the end of the study, and no additional events occurred between week 16 and week 60.

#### Re-interventions and medical changes related to fistulas

During hyperbaric oxygen therapy and the first 16 weeks of the study there were no surgical (re-)interventions, including no drainage of abscess, seton placement or deviating colostomy. There were two medical changes: In one patient the infliximab dose was increased by an external gastroenterologist due to low trough levels, and in

another patient the thiopurine agent was stopped (at the request of the patient).

Between week 16 and week 60 there were four surgical re-interventions: one patient had ongoing luminal complaints for which an ileocaecal resection was performed. This patient's, perianal disease was inactive at week 16 and 60 as defined by the cut-off score of the perianal disease activity index of 4 or less. The other three patients had an examination under anaesthesia because of ongoing perianal complaints. These three patients were non-responders at week 16 and 60 as defined by the cut-off score of the perianal disease activity index. Setons were placed for two patients, in the third patient no fistulas could be identified. Two out of three patients also received a course of antibiotics because of their perianal complaints.

There were six additional changes in medication between week 16 and 60: Five concerning the dosage of biologics, and one switch from infliximab to ustekinumab. All of these changes were made because of low trough levels and/or luminal complaints, and not because of perianal complaints.

### Control group

The control group consisted of eight patients, five female and three male patients. The median age was 35 (IQR 24–41), and none of the patients were active smokers. The median disease duration was 6 years (IQR 1–24), and the median disease duration of the current fistula was 2 years (IQR 1–7). Five patients had one internal opening and three patients had two internal openings at enrolment.

Five out of eight patients had a surgical intervention during follow-up: Four patients had a ligation of the intersphincteric fistula tract, and one patient had a fistulotomy. Two out of four patients that had the ligation had ongoing perianal complaints caused by an intersphincteric recurrence. In both patients setons were placed at the end of follow-up, and they were scheduled for a subsequent fistulotomy.

Two patients had a medical intervention: one patient decreased the dose of adalimumab at his/her own discretion, and one patient was prescribed metronidazole ovules for luminal and perianal complaints.

The median perianal disease activity index for the control group decreased from 8.5 (95% CI 5–12) at baseline to 6 (95% CI 1–11,  $p = 0.046$ ) at week 16, and to 4 (95% CI 0–10,  $p = 0.035$  as compared to baseline) at week 60. At week 16 and week 60, three (37.5%) and four (50%) patients had inactive perianal disease as defined as a score of 4 or less, respectively. The median VAS score was 60.5 at baseline (95% CI 25–80), 63 at week 16 (95% CI 35–80,  $p = 0.599$ ) and 60 at week 60 (95% CI 38–80,  $p = 0.686$  as compared to baseline). The median IBDQ score was 145 at baseline (95% CI 78–198), 154 at week 16 (95% CI 86–214,  $p = 0.123$ ) and 159 at week 60 (95% CI 94–197,  $p = 0.069$  as compared to baseline).

## DISCUSSION

The HOT-TOPIC trial evaluated the efficacy, feasibility and safety of hyperbaric oxygen therapy in Crohn's disease patients with therapy-refractory perianal fistulas. At week 16, a significant improvement was found in the co-primary outcomes (perianal disease activity index and the modified Van Assche index), with 65% of patients having inactive perianal disease based on cut-off scores of the perianal disease activity index that were previously published.<sup>19</sup> Long-term follow-up (60 weeks) showed similar outcomes, implying a long-term effect of the treatment. Overall, hyperbaric oxygen treatment was well tolerated with acceptable low number of adverse events, demonstrating feasibility and safety.

At week 16, three patients had a fibrotic fistula complex with no other signs of activity of the fistulas on MRI. One additional patient achieved this endpoint at week 60, resulting in a total of 4 out of 20 (20%) patients with a fibrotic complex. This is an important finding, because deep remission on MRI is associated with a low chance of recurrence of perianal disease.<sup>26</sup> This long-term effect helps justify the duration and the cost of the treatment. Furthermore, a completely fibrotic fistula complex is a relatively rare outcome of treatment, especially for medical therapy. For example, in the study that evaluated the use of the modified Van Assche index in patients treated with anti-TNF, a fibrotic tract after treatment was seen in 3 out of 30 MRIs (10%).<sup>27</sup> Since the HOT-TOPIC study only included therapy-refractory patients, the percentage of fibrosis that was found here is promising, although these findings should be confirmed in a larger trial.

After the approval and registration of the initial trial protocol, which included assessment of MRI using the (modified) Van Assche index, the MAGNIFI-CD index was published.<sup>20</sup> This index was created following a stringent development procedure and internal validation, making it more robust than the original indices that were chosen as outcomes for this study. The MRIs of study patients were therefore also scored using the MAGNIFI-CD index. A similar statistically significant improvement as for the (modified) Van Assche index was found, which further supports the positive radiologic outcome.

Apart from the radiological healing, the clinical outcomes of the trial are also encouraging. The HOT-TOPIC trial included patients with difficult-to-treat fistulas, with a median disease duration of 4 years of the current fistula, that were highly therapy-refractory. Nevertheless, 60% of patients had inactive perianal disease defined by a perianal disease activity score of 4 or less at the end of follow-up (i.e., 1 year after hyperbaric oxygen therapy). This percentage, as well as the improvement in median perianal disease activity scores and clinical response and remission as defined by fistula drainage assessment, remained relatively stable between week 16 and 60, indicating a long-term effect of the treatment. However, some patients that had an inactive disease at week 16 had subsequent changes in concomitant medication during follow-up (all for luminal complaints), and it is possible that these changes also had an impact on the lasting improvement of the perianal fistulas.



At week 16, there was a significant improvement in biochemical and patient-reported outcome measures. This positive effect was no longer visible at week 60, indicating a discrepancy between these outcomes and the clinical and radiological fistula healing (for which an improvement was still seen at week 60). A possible explanation is that the anti-inflammatory effects of hyperbaric oxygen therapy wear off with time, while the positive effect on wound healing of the fistulas remains visible long-term. Furthermore, current biochemical markers (in this study: C-reactive protein and faecal calprotectin) and the patient-reported outcomes in itself have limitations in assessing activity of perianal fistulas and mucosal inflammation.<sup>28,29</sup> Recently, a patient-reported outcome measure that is designed specifically for perianal Crohn's disease was published, and the use of this scale in a future study could provide more insight into the long-term, patient-reported effects of hyperbaric oxygen therapy on perianal fistulas specifically.<sup>30</sup>

Due to the design of the control group (patient-preference) as well as the small number of patients that was included a meaningful comparison between groups could not be made. A future trial should include randomisation of patients to the active and control group so the (added) effect of the treatment can be assessed with more certainty. Although a traditional randomised controlled trial has several downsides when it comes to internal and external validity in fistula patients that often have a distinct preference for their treatment, a partially randomised patient-preference trial or Trial within Cohorts design could offer a solution to this problem.<sup>31-33</sup> It might also be interesting to investigate different approaches using hyperbaric oxygen therapy, such as treatment of patients with new fistulas (instead of therapy-refractory ones) or pre- and post-operative treatment with hyperbaric oxygen therapy around definitive surgical closure.

One of the strengths of this study is that a consecutive series of patients in a large IBD centre was included, and that a follow-up of 1 year assessed the durability of the results. Secondly, concomitant medication was kept stable at least 6 weeks before starting hyperbaric oxygen treatment and during the study period, which reduced the potential risk of measuring effects of other treatments/interventions prior to or during hyperbaric oxygen therapy. However, changes in concomitant medication were made in several patients after the completion of hyperbaric oxygen therapy, possibly introducing a bias in measuring the lasting effect. A limitation of the study is the relatively small number of patients that was included, and the lack of a randomised control group, which limits the ability to establish a true causal effect.

In conclusion, the long-term results of the HOT-TOPIC trial show that a clinical and radiological improvement of perianal fistulas is still seen 1 year after the treatment with hyperbaric oxygen therapy. The biochemical and patient-reported improvement in quality of life that was found at week 16 could not be established anymore at week 60. Future controlled trials are needed to confirm the findings and to determine the value (and place) of hyperbaric oxygen therapy for Crohn's perianal fistulas in daily clinical practice.

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## CONFLICT OF INTERESTS

Corine A. Lansdorp has no conflict of interests to declare. Christianne J. Buskens has received speakers honoraria from Takeda and Tillotts. She has an unrestricted grant from Boehringer Ingelheim, and is part of the advisory board of Johnson&Johnson energy devices. Krisztina B. Gece has received consultancy fees and/or speaker's honoraria from AbbVie, Celltrion, Ferring, Immunic Therapeutics, Janssen, Pfizer, Roche, Sandoz, Samsung Bioepis, Takeda and Tillotts. Mark Löwenberg has served as speaker and/or principal investigator for: Abbvie, Celgene, Covidien, Dr. Falk, Ferring Pharmaceuticals, Gilead, GlaxoSmithKline, Janssen-Cilag, Merck Sharp & Dohme, Pfizer, Protagonist therapeutics, Receptos, Robarts Clinical Trials, Takeda, Tillotts, Tramedico. He has received research grants from AbbVie, Merck Sharp & Dohme, Dr. Falk, Achmea healthcare and ZonMW. Jaap Stoker has a research agreement with Takeda on a non-related topic. Willem A. Bemelman has served as speaker for Takeda, Johnson and Johnson and Braun. He has received research grants from Braun and Vifor. Geert R.A.M. D'Haens has served as advisor for Abbvie, Ablynx, Active Biotech AB, Agomab Therapeutics, Allergan, Alphabiotics, Amakem, Amgen, AM Pharma, Applied Molecular Therapeutics; Arena Pharmaceuticals, AstraZeneca, Avaxia, Biogen, Bristol Meiers Squibb/Celgene, Boehringer Ingelheim, Celltrion, Cosmo, DSM Pharma; Echo Pharmaceuticals, Eli Lilly, Engene, Exelium Biosciences; Ferring, DrFALK Pharma, Galapagos, Genentech/Roche, Gilead, Glaxo Smith Kline, Gossamerbio, Pfizer, Immunic, Johnson and Johnson, Kintai Therapeutics, Lycera, Medimetrics, Takeda, Medtronic, Mitsubishi Pharma, Merck Sharp Dome, Mundipharma, Nextbiotics, Novonordisk, Otsuka, Photopill, ProciseDx, Prodigest, Prometheus laboratories/Nestle, Progenity, Protagonist, RedHill; Robarts Clinical Trials, Salix, Samsung Bioepis, Sandoz, Seres/Nestec/Nestle, Setpoint, Shire, Teva, Tigenix, Tillotts, Topivert, Versant and Vifor; received speaker fees from Abbvie, Biogen, Ferring, Galapagos/Gilead, Johnson and Johnson, Merck Sharp Dome, Mundipharma, Norgine, Pfizer, Samsung Bioepis, Shire, Millenium/Takeda, Tillotts and Vifor. Rob A. van Hulst has no conflict of interests to declare.

## ETHICS APPROVAL STATEMENT AND PATIENT CONSENT

The study was performed in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. The protocol has been approved by the Medical Ethical Committee

(METC 2017\_132). All participants provided written informed consent.

## AUTHOR CONTRIBUTIONS

Corine A. Lansdorp, Christianne J. Buskens, Krisztina B. Gecse, Mark Löwenberg, Jaap Stoker, Willem A. Bemelman, Geert R.A.M. D'Haens and Rob A. van Hulst contributed to the design and implementation of the research, to the analysis of the results and to the writing of the manuscript. All authors approved the final version of the manuscript.

## CLINICAL TRIAL REGISTRATION

The trial has been registered at the Dutch Trial Registry (NL 6489/NTR 6676).

## DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

## ORCID

Corine A. Lansdorp  <https://orcid.org/0000-0001-9395-4003>

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#### SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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