

Hyperbaric oxygen therapy: More hope than hype for future treatment of perianal fistulizing Crohn's disease?

Perianal fistulas are a severe, disabling complication of Crohn's disease (CD) occurring in about 20% of patients within 20 years from diagnosis, with a significant impact on patients' quality of life and an increased risk of undergoing major abdominal surgery.^{1,2} A multimodal approach, that is a combination of a surgical approach along medical therapies, mainly infliximab ± antibiotics, represents the current standard of care for treatment of complex perianal disease.^{3,4} However, only a minority of patients achieve durable fistula remission, with high rate of recurrence, need for re-intervention or diverting stoma.^{5,6} The adjunctive topical treatment with expanded allogeneic adipose-derived mesenchymal stem cells has demonstrated interesting results in the randomized double-blind placebo-controlled adipose derived mesenchymal stem cells for induction of remission (ADMIRE) trial, with up to 50% of fistula remission at week 24.⁷ However, the partial beneficial effect, the selective access criteria (no concomitant active luminal disease or active severe proctitis or diverting stoma) and the cost of each treatment denote that novel therapeutic strategies are increasingly needed for complex perianal CD.

Hyperbaric oxygen therapy (HBOT), involving intermittent inhalation of 100% oxygen at pressures >1 atm, has shown encouraging results in several CD phenotypes, including inflammatory luminal disease, enterocutaneous fistulas, metastatic perianal disease and fistulizing perianal disease.^{8,9} The underlying involved mechanism seems to be related to the modulation of immune response and the promotion of tissue repair and wound healing mediated by hyperoxygenation.¹⁰

In the current study, Lansdorp et al. reported the long-term (week 60) follow-up of 20 patients enrolled in the HOT-TOPIC trial.¹¹ At enrolment, all patients had ≥1 actively draining high (defined as transversing the upper two-thirds of the external sphincter/puborectal muscle, regardless of the number of internal and external openings) medical-refractory perianal fistula for a median duration of 4 years (interquartile range 2–12 years). 16 patients (80%) were on concomitant biological therapy (14 on infliximab, one on vedolizumab and one on ustekinumab). Patients were treated with 40 daily sessions of HBOT on working days, for a total of 8 weeks.¹² The co-primary outcome was a comprehensive assessment of the fistula, with a clinical evaluation according to the perianal disease activity index (PDAI)¹³ and a magnetic resonance imaging (MRI) assessment through the modified Van

Assche Index¹⁴ at week 16 and 60. At both time-points, a significant reduction of the median PDAI score (8 vs. 4 vs. 4, $p < 0.001$ for both comparisons) and of the modified Van Assche Index (9.2 vs. 7.3 vs. 7.7, $p = 0.004$ and $p = 0.005$, respectively) was recorded compared to baseline. Moreover, at the end of follow-up, 12 patients (60%) were in clinical remission (defined as a PDAI score ≤4) and four patients (20%) had a fibrotic fistula complex at MRI. Conversely, the improvement in biochemical (both C-reactive protein and faecal calprotectin) and patient-reported outcomes measures achieved at week 16 was no longer present at week 60. During the study, only three patients (15%) required perianal surgical re-intervention. Overall, these results seem promising, especially considering the clinical features of the population enrolled. However, the greatest limit of this study is the absence of a control group to really assess the effect of the additive treatment with HBOT. As previously shown, in fact, in the ADMIRE trial where 34% of placebo-treated patients achieved remission, an appropriate surgical procedure (fistula curettage, surgical drainage, and internal orifice closure) plus concomitant medications alone can significantly improve the fistula outcome. To be honest, a small control group of 8 patients unwilling to undergo HBOT was included, but no comparisons were possible.

Assuming a potential diffusion of HBOT in clinical practice for perianal fistula, three aspects should be considered: (1) the direct cost for health/insurance system; (2) the indirect cost for patients, treated for 40 working days and (3) the HBOT chambers availability across the IBD centres.

In conclusion, complex perianal fistulas represent one of the most challenging aspects of treatment of CD. Hyperbaric oxygen therapy seems to be a potential advance for standard-of-care refractory patients. Future larger studies are required to verify the real additive benefit and the cost-effectiveness assessment of HBOT in this setting of difficult-to-treat patients.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

Alessandro Armuzzi¹ 

Daniela Pugliese²

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2022 The Authors. United European Gastroenterology Journal published by Wiley Periodicals LLC. on behalf of United European Gastroenterology.

¹Dipartimento Universitario di Medicina e Chirurgia Traslazionale,
Università Cattolica del Sacro Cuore, Rome, Italy
²CEMAD, IBD UNIT, Unità Operativa Complessa di Medicina
Interna e Gastroenterologia, Dipartimento di Scienze Mediche e
Chirurgiche, Fondazione Policlinico Universitario "A. Gemelli"
IRCCS, Rome, Italy

Correspondence

Alessandro Armuzzi, Fondazione Policlinico Universitario A, Gemelli
IRCCS - Università Cattolica del Sacro Cuore Largo A, Gemelli 8,
Rome 00168, Italy.
Email: alearmuzzi@gmail.com

ORCID

Alessandro Armuzzi  <https://orcid.org/0000-0003-1572-0118>

REFERENCES

1. Wewer MD, Zhao M, Nordholm-Carstensen A, Weimers P, Seidelin JB, Burisch J. The incidence and disease course of perianal Crohn's disease: a Danish nationwide cohort study, 1997–2015. *J Crohns Colitis*. 2021;15:5–13.
2. Eglinton TW, Barclay ML, Geary RB, Frizelle FA. The spectrum of perianal Crohn's disease in a population-based cohort. *Dis Colon Rectum*. 2012;55:773–7.
3. Torres J, Bonovas S, Doherty G, Kucharzik T, Gisbert JP, Raine T, et al. ECCO guidelines on therapeutics in crohn's disease: medical treatment. *J Crohns Colitis*. 2020;14:4–22.
4. Spinelli A, Armuzzi A, Ciccocioppo R, Danese S, Gionchetti P, Luglio G, et al. Management of patients with complex perianal fistulas in Crohn's disease: optimal patient flow in the Italian clinical reality. *Dig Liver Dis*. 2020;52:506–15.
5. Molendijk I, Nuij VJ, van der Meulen-de Jong AE, van der Woude CJ. Disappointing durable remission rates in complex Crohn's disease fistula. *Inflamm Bowel Dis*. 2014;20:2022–8.
6. Sebastian S, Black C, Pugliese D, Armuzzi A, Sahnun K, Elkady SM, et al. The role of multimodal treatment in Crohn's disease patients with perianal fistula: a multicentre retrospective cohort study. *Aliment Pharmacol Ther*. 2018;48:941–50.
7. Panés J, García-Olmo D, Van Assche G, Colombel JF, Reinisch W, Baumgart DC, et al. Expanded allogeneic adipose-derived mesenchymal stem cells (Cx601) for complex perianal fistulas in Crohn's disease: a phase 3 randomised, double-blind controlled trial. *Lancet*. 2016;388:1281–90.
8. McCurdy J, Siw KCK, Kandel R, Larrigan S, Rosenfeld G, Boet S. The effectiveness and safety of hyperbaric oxygen therapy in various phenotypes of inflammatory bowel disease: systematic review with meta-analysis. *Inflamm Bowel Dis*. 2021:izab098. <https://doi.org/10.1093/ibd/izab098>
9. Lansdorp CA, Buskens CJ, Gecse KB, D'Haens GR, Van Hulst RA. Wound healing of metastatic perineal Crohn's disease using hyperbaric oxygen therapy: a case series. *United European Gastroenterol J*. 2020;8:820–7.
10. Kirby JP, Snyder J, Schuerer DJE, Peters JS, Bochicchio GV. Essentials of hyperbaric oxygen therapy: 2019 review. *Mo Med*. 2019;116:176–9.
11. Lansdorp C, Buskens C, Gecse K, Löwenberg M, Stoker J, Bemelman WA, et al. 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. *United European Gastroenterol J*; 2022.
12. Lansdorp CA, Gecse KB, Buskens CJ, Löwenberg M, Stoker J, Bemelman WA, et al. Hyperbaric oxygen therapy for the treatment of perianal fistulas in 20 patients with Crohn's disease. *Aliment Pharmacol Ther*. 2021;53:587–97.
13. Irvine EJ. Usual therapy improves perianal Crohn's disease as measured by a new disease activity index. *McMaster IBD Study Group. J Clin Gastroenterol*. 1995;20:27–32.
14. Samaan MA, Puylaert CAJ, Levesque BG, Zou GY, Stitt L, Taylor SA, et al. The development of a magnetic resonance imaging index for fistulising Crohn's disease. *Aliment Pharmacol Ther*. 2017;46:516–28.