

**A proof of concept pilot trial of probiotics in symptomatic oral lichen planus (CABRIO).**

Erni Marlina<sup>1,2</sup> Richard N. Goodman<sup>3</sup> Valeria Mercadante<sup>1</sup> Martina Shephard<sup>4</sup> Roddy McMillan<sup>1,4</sup> Tim Hodgson<sup>4</sup> Rachel Leeson<sup>1,4</sup> Stephen Porter<sup>1</sup> Julie A. Barber<sup>5</sup> Stefano Fedele<sup>1,6</sup> Andrew M. Smith<sup>1</sup>

<sup>1</sup>University College London, Eastman Dental Institute, UK.

<sup>2</sup>Department of Oral Medicine, Faculty of Dentistry, Hasanuddin University, Makassar, Indonesia

<sup>3</sup>Department of Tropical Disease Biology, Liverpool School of Tropical Medicine, Liverpool, UK

<sup>4</sup>UCLH, Eastman Dental Hospital, UK.

<sup>5</sup>Department of Statistical Science, UCL, UK.

<sup>6</sup>NIHR UCLH Biomedical Research Centre, UK.

**Correspondence**

Andrew M Smith,  
Eastman Dental Institute, Microbial Diseases  
Royal Free Campus  
Rowland Hill Street  
London, NW3 2PF  
UK  
Email: [andrew.m.smith@ucl.ac.uk](mailto:andrew.m.smith@ucl.ac.uk)

## **Abstract**

**Objective:** To preliminary evaluate the clinical effects of probiotics in individuals with symptomatic oral lichen planus, and the possible mechanisms of action.

**Subjects and Methods:** 30 individuals with symptomatic oral lichen planus were recruited in a double-blind parallel group randomised controlled (1:1) proof-of-concept pilot trial of probiotic VSL#3 vs placebo. Efficacy outcomes included changes in pain numeric rating scale, oral disease severity score and the chronic oral mucosal disease questionnaire. Adverse effects, home diary, and withdrawals were assessed as feasibility outcomes. Mechanistic outcomes included changes in salivary and serum levels of CXCL10 and IFN- $\gamma$  and in oral microbial composition.

**Results:** The probiotic VSL#3 was safe and well tolerated. We observed no statistically significant change in pain, disease activity, quality of life, serum/salivary CXCL10 or oral microbial composition with respect to placebo. Salivary IFN- $\gamma$  levels demonstrate a trend for a reduced level in the active group ( $p=0.082$ ) after 30 days of probiotic consumption.

**Conclusions:** The present proof-of-concept study provides some weak not convincing indication of biological and clinical effects of probiotic VSL#3 in individuals with painful oral lichen planus. Further research in this field is needed, with the current study providing useful information to the design of future clinical trials.

## **KEYWORDS**

Probiotic, VSL#3, Oral lichen planus, CABRIO

## References

- Abdel-Haq, A., Kusnierz-Cabala, B., Darczuk, D., Sobuta, E., Dumnicka, P., Wojas-Pelc, A., & Chomyszyn-Gajewska, M. (2014). Interleukin-6 and neopterin levels in the serum and saliva of patients with Lichen planus and oral Lichen planus. *J Oral Pathol Med*, 43(10), 734-739. doi:10.1111/jop.12199
- Akpinar Kara, Y. (2017). The measurement of serum TNF- $\alpha$  levels in patients with lichen planus. *Acta Dermatovenerologica Alpina Pannonica et Adriatica*, 26(4). doi:10.15570/actaapa.2017.26
- Carrozzo, M., Porter, S., Mercadante, V., & Fedele, S. (2019). Oral lichen planus: A disease or a spectrum of tissue reactions? Types, causes, diagnostic algorithms, prognosis, management strategies. *Periodontology 2000*, 80(1), 105-125. doi:10.1111/prd.12260
- Deng, S., Xu, Y., Wang, X., Liu, M., Li, L., Yu, X., . . . Cong, B. (2020). Study on the Role of Salivary Flora and NF-kappaB Inflammatory Signal Pathway in Oral Lichen Planus. *Inflammation*. doi:10.1007/s10753-020-01185-1
- Di Lernia, V. (2016). Targeting the IFN-gamma/CXCL10 pathway in lichen planus. *Med Hypotheses*, 92, 60-61. doi:10.1016/j.mehy.2016.04.042
- Douglas, A. G. (1990). *Practical statistics for medical research*: Chapman & Hall.
- Eldrige, S. M., Chan, C. L., Campbell, M. J., Bond, C. M., Hopewell, S., Thabane, L., & Lancaster, G. A. (2016). CONSORT 2010 statement: extension to randomized pilot and feasibility trials. *Bmj*, 355, i5239. doi:10.1136/bmj.
- Escudier, M., Ahmed, N., Shirlaw, P., Setterfield, J., Tappuni, A., Black, M. M., & Challacombe, S. J. (2007). A scoring system for mucosal disease severity with special reference to oral lichen planus. *Br J Dermatol*, 157(4), 765-770. doi:10.1111/j.1365-2133.2007.08106.x
- Gardner, M. J., & Altman, D. G. (1986). Confidence intervals rather than P values: estimation rather than hypothesis testing. *Br Med J (Clin Res Ed)*, 292(6522), 746-750. doi:10.1136/bmj.292.6522.746
- Gonzalez-Moles, M. A., Warnakulasuriya, S., Gonzalez-Ruiz, I., Gonzalez-Ruiz, L., Ayen, A., Lenouvel, D., Ramos-Garcia, P. (2020). Worldwide prevalence of oral lichen planus: A systematic review and meta-analysis. *Oral Dis*. doi:10.1111/odi.13323
- Iheozor-Ejiofor, Z., Kaur, L., Gordon, M., Baines, P. A., Sinopoulou, V., & Akobeng, A. K. (2020). Probiotics for maintenance of remission in ulcerative colitis. *Cochrane Database Syst Rev*, 3, CD007443. doi:10.1002/14651858.CD007443.pub3
- Jiang, C., Wang, H., Xia, C., Dong, Q., Chen, E., Qiu, Y., Chen, T. (2019). A randomized, double-blind, placebo-controlled trial of probiotics to reduce the severity of oral mucositis induced by chemoradiotherapy for patients with nasopharyngeal carcinoma. *Cancer*, 125(7), 1081-1090. doi:10.1002/cncr.31907
- Jontell, M., & Holmstrup, P. (2015). Red and white lesions of the oral mucosa. 12<sup>th</sup> eds. In *Burket's oral medicine* (pp. 77). Hamilton: BC Decker Inc.
- Julious, S. A. (2005). Sample size of 12 per group rule of thumb for a pilot study. *Pharmaceutical Statistics*, 4(4), 287-291. doi:10.1002/pst.185
- Kaur, L., Gordon, M., Baines, P. A., Iheozor-Ejiofor, Z., Sinopoulou, V., & Akobeng, A. K. (2020). Probiotics for induction of remission in ulcerative colitis. *Cochrane Database Syst Rev*, 3, CD005573. doi:10.1002/14651858.CD005573.pub3
- Ke, Y., Dang, E., Shen, S., Zhang, T., Qiao, H., Chang, Y., Wang, G. (2017). Semaphorin4D drives CD8+ T cell lesional trafficking in oral lichen planus via CXCL9/CXCL10 upregulations in oral keratinocytes. *J Invest Dermatol*. doi:10.1016/j.jid.2017.07.818
- Keller, M. K., & Kragelund, C. (2018). Randomized pilot study on probiotic effects on recurrent candidiasis in oral lichen planus patients. *Oral Dis*. doi:10.1111/odi.12858

- Lear, J. T., & English, J. S. C. (1995). Erosive and generalized lichen planus responsive to azathioprine. *Clinical and Experimental Dermatology*, 21, 56-57. doi:doi:10.1111/j.1365-2230.1996.tb00015.x.
- Li, Y., Shao, F., Zheng, S., Tan, Z., & He, Y. (2020). Alteration of Streptococcus salivarius in Buccal Mucosa of Oral Lichen Planus and Controlled Clinical Trial in OLP Treatment. *Probiotics Antimicrob Proteins*, 12(4), 1340-1348. doi:10.1007/s12602-020-09664-5
- Lodi, G., Manfredi, M., Mercadante, V., Murphy, R., & Carrozzo, M. (2020). Interventions for treating oral lichen planus: corticosteroid therapies. *Cochrane Database Syst Rev*, 2, CD001168. doi:10.1002/14651858.CD001168.pub3
- Lu, R., Zhang, J., Sun, W., Du, G., & Zhou, G. (2015). Inflammation-related cytokines in oral lichen planus: an overview. *J Oral Pathol Med*, 44(1), 1-14. doi:10.1111/jop.12142
- Mansourian, A., Najafi, S., Nojumi, N., Parhami, P., & Moosavi, M. S. (2018). Salivary Cortisol and Salivary Flow Rate in Clinical Types of Oral Lichen Planus. *Skinmed*, 16(1), 19-22.
- Mariman, R., Tielen, F., Koning, F., & Nagelkerken, L. (2014). The probiotic mixture VSL#3 dampens LPS-induced chemokine expression in human dendritic cells by inhibition of STAT-1 phosphorylation. *PLoS One*, 9(12), e115676. doi:10.1371/journal.pone.0115676
- Marshall, A., Celentano, A., Cirillo, N., McCullough, M., & Porter, S. (2017). Tissue-specific regulation of CXCL9/10/11 chemokines in keratinocytes: Implications for oral inflammatory disease. *PLoS One*, 12(3), e0172821. doi:10.1371/journal.pone.0172821
- Mora, D., Filardi, R., Arioli, S., Boeren, S., Aalvink, S., & de Vos, W. M. (2019). Development of omics-based protocols for the microbiological characterization of multi-strain formulations marketed as probiotics: the case of VSL#3. *Microb Biotechnol*. doi:10.1111/1751-7915.13476
- NHS, G. s. a. S. T. Disease activity scoring sheet [Press release]
- Ni Riordain, R., Hodgson, T., Porter, S., & Fedele, S. (2016). Validity and reliability of the Chronic Oral Mucosal Diseases Questionnaire in a UK population. *J Oral Pathol Med*. doi:10.1111/jop.12425
- Ni Riordain, R., & McCreary, C. (2011). Validity and reliability of a newly developed quality of life questionnaire for patients with chronic oral mucosal diseases. *J Oral Pathol Med*, 40(8), 604-609. doi:10.1111/j.1600-0714.2011.01021.x
- Ni Riordain, R., Meaney, S., & McCreary, C. (2011). Impact of chronic oral mucosal disease on daily life: preliminary observations from a qualitative study. *Oral Dis*, 17(3), 265-269. doi:10.1111/j.1601-0825.2010.01734.x
- Nibaldi, L., Fedele, S., D'Aiuto, F., & Donos, N. (2012). Interleukin-6 in oral diseases: a review. *Oral Dis*, 18(3), 236-243. doi:10.1111/j.1601-0825.2011.01867.x
- Osipoff, A., Carpenter, M. D., Noll, J. L., Valdez, J. A., Gormsen, M., & Brennan, M. T. (2020). Predictors of symptomatic oral lichen planus. *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology*, S2212-4403(2220)30005-30005. doi:10.1016/j.oooo.2019.12.019
- Plaza-Diaz, J., Gomez-Llorente, C., Fontana, L., & Gil, A. (2014). Modulation of immunity and inflammatory gene expression in the gut, in inflammatory diseases of the gut and in the liver by probiotics. *World J Gastroenterol*, 20(42), 15632-15649. doi:10.3748/wjg.v20.i42.15632
- Plaza-Diaz, J., Ruiz-Ojeda, F. J., Vilchez-Padial, L. M., & Gil, A. (2017). Evidence of the Anti-Inflammatory Effects of Probiotics and Synbiotics in Intestinal Chronic Diseases. *Nutrients*, 9(6). doi:10.3390/nu9060555
- Quinque, D., Kittler, R., Kayser, M., Stoneking, M., & Nasidze, I. (2006). Evaluation of saliva as a source of human DNA for population and association studies. *Anal Biochem*, 353(2), 272-277. doi:10.1016/j.ab.2006.03.021
- Rad, M., Hashemipoor, M. A., Mojtahedi, A., Zarei, M. R., Chamani, G., Kakoei, S., & Izadi, N. (2009). Correlation between clinical and histopathologic diagnoses of oral lichen planus based on modified WHO diagnostic criteria. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*, 107(6), 796-800. doi:10.1016/j.tripleo.2009.02.020
- Rapoport, L., & Levine, W. I. (1965). Treatment of oral ulceration with lactobacillus tablets. Report of forty cases. *Oral Surg Oral Med Oral Pathol*, 20(5), 591-593.

- Senn, S., Stevens, L., & Chaturvedi, N. (2000). Repeated measures in clinical trials: simple strategies for analysis using summary measures. *Stat Med*, *19*(6), 861-877. doi:10.1002/(sici)1097-0258(20000330)19:6<861::aid-sim407>3.0.co;2-f
- Sun, A., Wang, J. T., Chia, J. S., & Chiang, C. P. (2005). Serum interleukin-8 level is a more sensitive marker than serum interleukin-6 level in monitoring the disease activity of oral lichen planus. *Br J Dermatol*, *152*(6), 1187-1192. doi:10.1111/j.1365-2133.2005.06497.x
- Suresh, S. S., Chokshi, K., Desai, S., Malu, R., & Chokshi, A. (2016). Medical Management of Oral Lichen Planus: A Systematic Review. *J Clin Diagn Res*, *10*(2), Ze10-15. doi:10.7860/jcdr/2016/16715.7225
- Tao, X. A., Li, C. Y., Rhodus, N. L., Xia, J., Yang, X. P., & Cheng, B. (2008). Simultaneous detection of IFN-gamma and IL-4 in lesional tissues and whole unstimulated saliva from patients with oral lichen planus. *J Oral Pathol Med*, *37*(2), 83-87. doi:10.1111/j.1600-0714.2007.00593.x
- Tasli, L. M., C.; De Simone, C.; Yasici, H. (2006). Lactobacillus lozenges in the management of oral ulcers of bechet's syndrome. *Clin Exp Rheumatology*, *24*(Suppl 42), S83-86.
- Vickers, A. J., & Altman, D. G. (2001). Statistics notes: Analysing controlled trials with baseline and follow up measurements. *Bmj*, *323*(7321), 1123-1124. doi:10.1136/bmj.323.7321.1123
- Wang, X., Zhao, Z., Tang, N., Zhao, Y., Xu, J., Li, L., . . . Fan, Y. (2020). Microbial Community Analysis of Saliva and Biopsies in Patients With Oral Lichen Planus. *Front Microbiol*, *11*, 629. doi:10.3389/fmicb.2020.00629
- Wee, J. S., Shirlaw, P. J., Challacombe, S. J., & Setterfield, J. F. (2012). Efficacy of mycophenolate mofetil in severe mucocutaneous lichen planus: a retrospective review of 10 patients. *Br J Dermatol*, *167*(1), 36-43. doi:10.1111/j.1365-2133.2012.10882.x
- Wilkins, T., & Sequoia, J. (2017). Probiotics for gastrointestinal conditions: A summary of the evidence. *American family physician*, *1*(96), 170-178.
- Yang, H., Wu, Y., Ma, H., Jiang, L., Zeng, X., Dan, H., . . . Chen, Q. (2016). Possible alternative therapies for oral lichen planus cases refractory to steroid therapies. *Oral Surg Oral Med Oral Pathol Oral Radiol*, *121*(5), 496-509. doi:10.1016/j.oooo.2016.02.002
- Zucoloto, M. L., Shibakura, M. E. W., Pavanin, J. V., Garcia, F. T., da Silva Santos, P. S., Maciel, A. P., . . . Motta, A. C. F. (2019). Severity of oral lichen planus and oral lichenoid lesions is associated with anxiety. *Clin Oral Investig*. doi:10.1007/s00784-019-02892-2