



Effect of nicotine on gut mucosal microbiota in ulcerative colitis: a study proposal

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> Aleksandra Turp is a fifth year medical student at Christchurch School of Medicine. She has a research background in epigenetics and maintains a keen interest in medical research. This essay has won the Robin Carrell prize for an innovative research proposal, awarded by the Department of Pathology at the University of Otago.

Introduction

Ulcerative colitis (UC) is an inflammatory condition involving mucosa of the rectum variably extending to the colon. It has a complex aetiology, which involves genetic predisposition, environmental factors, immune dysfunction, and changes in the normal gut microbiota. One of the environmental factors associated with UC is smoking. Interestingly, smoking has been proposed to result in a more benign progression of UC. Compared to non-smokers, smokers experience fewer flare-ups and lower hospitalisation and colectomy rates.¹ Furthermore, smoking cessation also aggravates the condition.¹ Fewer clinical findings, including lower stool frequency, less episodes of rectal bleeding, and a lower histologic disease activity index, were seen in the population of patients with active UC who were administered nicotine patches on top of the usual treatment, compared to those receiving placebo.² This suggests that nicotine may have a direct effect on the progression of the disease. Although the precise bacterial phyla associated with UC when compared to healthy subjects vary between different studies, UC is firmly associated with a reduced microbial diversity.³ Smoking cessation has been found to induce profound changes in the composition of intestinal microbiota in healthy subjects, with an increase in Firmicutes and Actinobacteria and a decrease in Bacteroidetes and Proteobacteria phyla. Furthermore, microbial diversity increased after smoking cessation.^{4,5} It is likely that smoking cessation and uptake of smoking would also result in changes to the composition and diversity of microbiota in patients with UC. Given the beneficial effects of the nicotine patches on the progression of the UC, it would be interesting to know whether nicotine by itself can have an impact on the composition of the human microbiome in UC.

Proposal or hypothesis

This research aims to investigate whether nicotine administration can alter the composition of gut mucosal microbiota in patients with UC. It will also test whether the potential changes to microbiota induced by

nicotine administration are associated with the severity and progression of the disease.

Methods of testing

A cohort of 50 non-smoking patients with mild to moderate UC will be recruited for the study. This will be a pilot study that will help with refining of the methods and inform on the size of the future patient cohort needed to detect a statistically significant effect. Subjects with active UC will be assessed and given a score based on severity level, taking into account their clinical symptoms and sigmoidoscopy results according to the protocol described before.² Patients with positive pathogenic stool cultures and those on antibiotic treatment will be excluded from the study. In addition to the normal clinical treatment, including 5-aminosalicylic acid and steroid treatment, patients will be randomly allocated to either nicotine replacement therapy in the form of a nicotine patch (22 mg for three weeks, based on a previous study which has shown a promising effect) or a placebo patch.^{2,6} Treatment and placebo groups will be matched for disease severity, smoking history, and treatment. Microbiota identification will be carried out according to a protocol described previously.³ In short, stools will be collected from both treatment and placebo groups before and after the nicotine treatment. DNA will be extracted from faecal pellets and the variable region V1–V2 of the 16S ribosomal RNA gene will be amplified. Each polymerase chain reaction product will be tagged with a unique identifier and purified on agarose gel for high throughput next-generation Illumina MiSeq sequencing. Taxonomy of the microbiota from each sample will be assigned by comparison against the Ribosomal Database Project (RDP) release 10. Changes to the composition and diversity of microbiota will be assessed in the individual patients before and after the nicotine therapy, and collectively in the treatment versus placebo group. The effects of nicotine therapy on the composition and diversity of microbiota will also be compared with the progression of

active disease by a follow up sigmoidoscopy and gathering of clinical history from the treatment and placebo group. A standardised score, as described above, will be used to monitor disease progression over time and to compare the outcomes of the nicotine and placebo treatment.

Significance of results

This study aims to explore the relationship between nicotine therapy and changes in the intestinal microbiota, and whether this accompanies an improvement of symptoms of UC. The results of this pilot study will inform a larger study evaluating the above. A long-term goal of this research is to provide further support for nicotine therapy as one of the treatments for active UC. Nicotine replacement therapy is cheap and easy to administer. It counteracts the negative effects of tobacco smoking, whilst still preserving the benefits described above. The results will also add to further elucidation of how microbiota changes are implicated in the pathogenesis of UC.

Ethics

The Health and Disability Ethics Committee will be approached to gain the consent for the study proposed above.

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Conflict of Interest

Aleksandra Turp is the NZMSJ Editor-in-Chief. This article has gone through a double-blinded peer review process applied to all articles submitted to the NZMSJ and has achieved a standard required for publishing. The author has no other conflict of interest.