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Letter to the Editor- **Treatment of Active Crohn's Disease With an Ordinary Food-based Diet That Replicates Exclusive Enteral Nutrition**

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We read with great enthusiasm the article by Svolos *et al* reporting the response of active Crohn's disease (CD) to a specific ordinary food-based diet, the CD-TREAT diet[1]. The authors present layered data from a rat model, longitudinal human study and small-scale clinical outcomes. Experimental data from the adult volunteers showed evidence for similar microbial changes in the CD-TREAT diet to those seen in exclusive enteral nutrition (EEN). There was reduction in ileitis severity in rats and the potential for induction of remission in a small number (3/5) of paediatric CD patients.

Dietary therapy in paediatric CD is well established, with the major drawback to it's routine use, especially in older age groups, being the palatability/acceptability[2]. The potential to treat patients with an exclusion diet as opposed to a polymeric or elemental feed would open dietary therapy up to routine use in adult CD, where currently it is largely redundant. The promise of reducing corticosteroid use would be a step forward in inflammatory bowel disease treatment.

Notwithstanding the clear impact of this study there are specific areas to be built upon, mentioned by the authors, requiring further investigation. The effect of both EEN and the CD-TREAT diet on the human microbiome at the mucosal level has not been explored, due to issues with serial endoscopies to obtain tissue samples. The faecal microbiome is known to poorly replicate the mucosal microbial community, largely due to differing oxygen levels and host immune impact[3]. The ability of the diet to alter faecal microbes is rapid (within days) and well established, but it's impact at the mucosal level is less well known. It would seem logical that any change would be slower at the mucosal level and therefore this change may result in slower induction of remission, something which is observed in patients treated with EEN vs those treated with intravenous or oral corticosteroids[4]. Whilst the bacterial composition in CD is now well reported the microbiome is moving into an era of functional potential, with metagenomic and metatranscriptomic studies recently shedding further light at both a stool and mucosal level[5,6]. It is possible that the key to entering remission is restoring key anti-inflammatory functions or removing pro-inflammatory bacterial metabolic processes at a mucosal level (something which has been demonstrated serially in

faecal samples), rather than changing specific bacterial species[7]. Exploring functional potential, either through inference with *in silico* modelling of 16S data (such as PiCRUST) or through metagenomic sequencing would be an obvious addition to future work. Where Svolos *et al* do provide extremely valuable data is in the measurement of stool metabolites, including short chain fatty acids, in both humans and rats. The statement that these are altered in the same direction as seen in EEN is of great interest and provides a context to move the CD-TREAT diet forward to a larger trial.

The observations of clinical response in four out of the five patients treated with the CD-TREAT diet is encouraging, but must be interpreted with some caution. It may be that a specific exclusion diet is better utilised in selected CD patients, perhaps based on their microbial or stool metabolite profiles at diagnosis. The targeted approach to therapy, termed personalised or precision medicine, may provide an opportunity to improve remission rates with a specific diet through selected use in patients who have a microbiome, gene expression profile or underlying genetic variation, amenable to this specific treatment[8]. Several studies have already identified microbial or gene expression profiles that are associated with therapeutic response to treatment[5,8]. Part of the group publishing this paper, alongside collaborators, have described metagenomic microbial profiles that more accurately predict response to therapy when compared to 16S sequencing[5]. These data suggest that mucosal metagenomic data can more accurately stratify patients by treatment response than 16S sequencing. The combination of single-time point mucosal metagenomic profiles alongside serial faecal 16S data, plus the potential of the CD-TREAT diet, provide the framework to move the microbiome to being a clinically useful tool in CD. There is potential to further refine CD-TREAT with the additional opportunity to move to personalised exclusion diet based on microbiome/metabolite response to treatment, although this is not yet possible. However in a multi-faceted, heterogeneous condition such as CD the ability to incorporate host genetic/immune features to this personalisation is vital. We look forward to the clinical progression of this work, and remain vigilant and enthusiastic for the opportunity to participate in a future randomised trial for CD-TREAT vs EEN.

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