Shedding Some Light on Crohn's Disease: Birth Month and Vitamin D?

To the Editor:

Van Ranst et al[1] found that being born in June is associated with a reduced risk of the later development of Crohn's disease. They mentioned seasonal infection rates as a possible cause. There is an additional possibility that might be worth considering.

Vitamin D modulates the immune system.[2,3] The hormonally active form of vitamin D, $1,25(OH)_2D_3$, binds to the vitamin D receptor (VDR), which in turn regulates gene expression through vitamin D responsive elements (VDREs) in the promoter regions of target genes. Many different types of immune cells contain VDRs, enabling $1,25(OH)_2D_3$ to play multiple roles in the regulation of the immune system. This includes the development of self-tolerance.

The modulation of the immune system by $1,25(OH)_2D_3$ may play a role in susceptibility to Crohn's disease, as evidenced by the findings of a linkage between a VDR polymorphism and the risk of developing Crohn's disease.[4]

Individuals born in June might get higher than average exposure to sunlight during the first few months after birth. This might play a role in the development of self-tolerance with respect to susceptibility to Crohn's disease.

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Saccharomyces Boulardii in Crohn's Disease: Effect on Anti-*Saccharomyces Cerevisiae* Antibodies and Intestinal Permeability

To the Editor:

The commensal gut flora plays a pivotal role in the triggering and the maintenance of inflammation seen in Crohn's disease (CD) and biotherapeutic agents are studied with increasing intensity in inflammatory bowel diseases with promising results. Two pilot studies with the probiotic *Saccharomyces boulardii* (Perenterol®), given at a dose of 750 to 1000 mg daily for up to 6 months, indicated a significant decrease in relapse of Crohn's disease.[1,2] Although case-reports have mentioned a risk of fungemia during this therapy,[3–5] this was mainly in hospitalised patients with intravenous catheters and in general Perenterol® is considered to be safe and well tolerated.

Given that S boulardii shows 99.3% up to 100% resemblance in sequence homology with *S cerevisiae,* it has been suggested that *S boulardii* should be recognized as a member of *S cerevisiae* and not as a separate species. This is of interest, since ±60% of Crohn's disease patients carry antibodies in the serum against *Saccharomyces cerevisiae* (ASCA) for yet unknown reasons.[7] ASCA are directed against the mannoses of the cell wall of the yeast. It is not known if ASCA is really induced against *S cerevisiae* or if this represents cross-reactivity to another commensal or pathogen. The most accepted hypothesis is that yeast mannan oligomannosides correspond to epitopes shared by other micro-organisms.[8] It is not known if *S boulardii* treatment could induce ASCA in patients with CD.

Crohn's disease is associated with gut barrier dysfunction in a proportion of patients and intestinal and colonic increased permeability for macromolecules may play an important role in the pathogenesis of IBD. A study with *S boulardii* in enteropathogenic *Escherichia coli* associated disease suggested a protective effect on the barrier function.[9] It is not known whether the intestinal permeability in Crohn's disease could be altered by the intake of biotherapeutics.

Therefore, we investigated if *S boulardii* intake in patients with CD is able to induce ASCA and secondly, if gut permeability in patients with CD is altered with this treatment.

We studied 12 CD patients (6 females and 6 males, mean age 39.8 years (26–57 years) and 7 healthy volunteers (5 females and 2 males, mean age 36.6 years (24–54 years) (sex and age matched), whom were administered *S boulardii* (Perenterol®, Biodiphar, Belgium-France) 3 × 250 mg/day orally during 3 months. At the start of the study, patients were in remission or had only mild disease activity. Intestinal permeability was measured through 24 h urine collection after the intake of 50 μCi ^{51}Cr-EDTA (0–6 hrs urine collection only for small bowel permeability) and was expressed as % urinary recovery of ingested ^{51}Cr-EDTA dose.[10] ASCA was determined by a standardised ELISA assay (Medipan GmbH, Selchow, Germany). Both tests were performed and blood cultures were taken at baseline, after 6 weeks and after 3 months. The use of antibiotics or probiotics (less than 4 weeks prior to the study) by the participants was an exclusion criterion in this study. The ethical committee of the Catholic University Leuven approved the study and all participants gave written informed consent.

Two out of the 12 CD patients had to stop their participation in study due to a severe relapse of their disease after

5 and 8 weeks, respectively. ASCA prevalence at the start of the study was 75% (9/12) in the CD patients compared to 0% (0/7) in the healthy controls ($p = 0.003$). Neither ASCA status nor ASCA titters of the subjects changed during the intake of *S boulardii* (median ASCA titters in CD: 1.99 (IQR: 1.03–3.74), 2.02 (IQR: 1.02–3.14) and 2 (IQR: 0.90–3.04) at baseline, 6 weeks and 3 months respectively). Except for 2 patients, intestinal permeability was normal at baseline and they did not vary during the study period. One of these 2 patients stopped the study after 5 weeks due to a severe relapse of the disease. The median small bowel permeability of the CD patients was 1.09 (IQR: 0.83–1.57) %, 0.95 (IQR: 0.75–1.68) % and 1.03 (IQR: 0.76–1.38) % at baseline, 6 weeks and 3 months, respectively, and the median colon permeability was 0.99 (IQR: 0.69–1.19) %, 1.17 (IQR: 0.81–1.86) % and 0.89 (IQR: 0.59–1.30) % at baseline, 6 weeks and 3 months, respectively. The blood cultures of all participants remained negative during the course of the study and no side effects were reported. The treatment was well tolerated.

Based on the present study, we believe the intake of *S boulardi* in CD patients is safe and does not induce antibodies against *S cerevisiae*. Most CD patients had already tested positive for ASCA at the start of the study and did not change their antibody status. However, none of the ASCA negative patients at baseline developed ASCA. We can conclude that although both species share up to 100% sequence homology, they do not appear to induce antibodies in CD patients. We could not observe an influence on the gut permeability of CD patients or healthy volunteers. Only CD patients in remission or with mild disease activity were included in this study. Since inflammation and gut permeability are related, it is not surprising that except for one patient, all permeability values were normal at baseline. Finally, no development of fungemia during the treatment with *S boulardi* was observed and no other side effects were reported.

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