capacity resulting from probiotic treatment, as shown in Fig. 1, clinically relevant? I would like to know a true \( p \) value rather than \( p < 0.05 \). In Fig. 2 showing the change in TLR-9 expression level, it appears that each pretreatment level decreased at the end of the study. I wonder why there is no statistical difference between pre- and post-treatment expression levels of TLR-9. Recent findings suggest that Gram-positive bacteria, their components or products, and their receptors such as TLR-2 and TLR-9 rather than endotoxin and TLR-4 have more important roles in the development of bacterial infection associated with cirrhosis [3].

Next, I would like to raise an issue regarding the method for \textit{ex vivo} endotoxin-stimulated cytokine production. The endotoxin concentration used for the study appears extremely high, more than 1000-fold higher than endotoxaemia observed in patients with cirrhosis. I would like to ask the authors the reason for using clinically irrelevant high dose endotoxin in the study. In the section of discussion, the authors mention that the lack of adverse events associated with the administration of probiotic preparation is evidenced by no change in clinical and laboratory parameters during the study. I think that no alteration in hepatic function during the study period may have to be attributed to the insufficient clinical efficacy of probiotic administration.

As well as with liver cirrhosis, bacterial overgrowth and reduced barrier function in the gut are associated with severe acute pancreatitis, predisposing to the development of infectious complications. In 2008, a randomised clinical trial (RCT) assessing the effects of probiotic prophylaxis in 296 patients with predicted severe acute pancreatitis resulted in unexpected increased 90-day mortality associated with probiotic administration (16% versus 6% in control patients) [4]. Although the exact mechanism is uncertain, fatal bowel ischaemia contributed to increased deaths in the probiotic group. I agree with the need for RCT to evaluate the efficacy of probiotics or probiotic cocktails in cirrhosis, but it should be done with caution.

References


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Probiotics for patients with liver cirrhosis: Reply

To the Editor:

We would like to thank Dr. Fujita for critically reading our paper about the effect of the probiotic, \textit{Lactobacillus casei} Shirota on innate immune function in patients with alcoholic cirrhosis. We would like to take the opportunity to answer the questions raised in this Letter to the Editor. Five points were raised.

1. \textit{Significance of a 25\% increase in phagocytic capacity:} We feel that a complete normalization of phagocytic capacity observed in our study from a level that represented only 75\% of the normal level is likely to be clinically important [1]. Several studies in diseases other than cirrhosis have shown that even a small increase in neutrophil phagocytosis is clinically relevant. Healing of diabetic foot infections was associated with a 14.8\% absolute increase in phagocytic capacity [2].

Treatment with granulocyte-colony-stimulating factor improved phagocytic capacity by 4.1–13.8\% in various clinical conditions (neutropenic children, septic patients, severe burns, diabetic foot infections, surgical patients on intensive care) which was associated with clinical benefits [3–8]. However, we agree with Dr. Fujita that further studies in larger patient cohorts are warranted to ultimately prove the clinical significance of our observation. The exact \( p \)-value for phagocytic capacity before and after supplementation with \textit{Lactobacillus casei} Shirota for 4 weeks was \( p = 0.045 \).

2. \textit{TLR 9 expression:} Dr. Fujita is right that there is a trend towards a decrease in TLR9 expression, however, with the correct statistical test (paired-\( t \)-test) only a \( p = 0.17 \) could be achieved. This is likely to be due to the relatively small sample size. We also agree that our
results do not show that endotoxins are the only factor contributing to neutrophil dysfunction in alcoholic cirrhosis. Indeed, we state in the discussion that our data suggest the presence of increased microbial products in the bloodstream of patients with alcoholic cirrhosis which is in accordance with previously published data on evidence of bacterial DNA in cirrhosis [9,10].

3. Ex vivo endotoxin stimulation: We have chosen this concentration because it has been used previously in a study investigating monocyte function in patient with acute-on-chronic liver failure [11]. It is correct that measured endotoxin concentrations in patients’ plasma are significantly lower, however it is also well known that plasma contains various inhibitors of endotoxin, which makes the analysis and interpretation of absolute endotoxin levels difficult [12].

4. The type of probiotic used: As we stated in the paper, in our study we did not observe any adverse events and we also saw no change in white blood cell count or C-reactive protein, indicating to us that Lactobacillus casei Shirota does not exert any proinflammatory stimulus in our patients. With respect to liver function, one would not expect to see changes over a short period in patients with stable cirrhosis. However, in our study one patient improved from Child class C to B and another from Child class B to A. Patient numbers are of course too small to draw any conclusion from this. ALT levels were normal in most of the patients at the beginning and throughout the study, indicating that we have chosen truly stable cirrhotic patients.

5. Safety of probiotics: We are aware of the discussion on safety of probiotics following publication of the study in patients with severe pancreatitis earlier this year [13]. In this publication, a combination of six different probiotic strains was administered twice daily over a nasojejunal tube. This protocol is completely different to our protocol where a single probiotic bacterial strain was consumed three times a day as a milk drink. Therefore these two studies cannot be compared easily. However, we agree that in trials with probiotics, safety has to be studied carefully, as with every other medication.

References


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