A Commercial Probiotic Induces Tolerogenic and Reduces Pathogenic Responses in Experimental Autoimmune Encephalomyelitis

Previous studies in experimental autoimmune encephalomyelitis (EAE) models have shown that some probiotic bacteria beneficially impact the development of this experimental disease. Here, we tested the therapeutic effect of two commercial multispecies probiotics — Lactibiane iki and Vivomixx — on the clinical outcome of established EAE. Lactibiane iki improved EAE clinical outcome in a dose-dependent manner whereas Vivomixx treatment improved the motor coordination skills of EAE mice at the end of the experiment. Both commercial probiotics decreased central nervous system (CNS) demyelination and inflammation. The clinical improvement under Lactibiane iki treatment was related to the inhibition of pro-inflammatory responses in the CNS and the stimulation of immunoregulatory mechanisms in the periphery. Moreover, both probiotics modulated the number and phenotype of dendritic cells (DCs). Specifically, Lactibiane iki promoted an immature, tolerogenic phenotype of DCs that could directly induce immune tolerance in the periphery, while Vivomixx decreased the percentage of DCs expressing co-stimulatory molecules. Finally, gut microbiome analysis revealed an altered microbiome composition related to clinical condition and disease progression. This is the first preclinical assay that demonstrates that a commercial probiotic, Lactibiane iki, performs a beneficial and dose-dependent effect on EAE mice and one of the few that demonstrates a therapeutic effect once the experimental disease is established. Because this probiotic is already commercially available, these data could be rapidly translated into the clinic.

Multiple sclerosis (MS) is a chronic, degenerative, autoimmune, and demyelinating disease of the central nervous system (CNS) and one of the main causes of disability in young adults [1]. Its precise pathogenesis is not fully understood but it is thought that genetically predisposed individuals develop MS after being exposed to different environmental factors. Recently, as a result from research in experimental autoimmune encephalomyelitis (EAE) models, the commensal microbiota has been described as an essential player in triggering autoimmunity and demyelination [2] and, consequently, emerged as a novel environmental risk factor in MS. However, experimental data support the idea that some bacterial strains, far from being harmful, have a beneficial impact on the outcome of EAE [3-8,9,10]. Thus, the promotion of beneficial microorganisms via probiotics is being developed as an important therapeutic strategy involving the gut microbiota in EAE.

In the present study, we investigated the therapeutic impact of two commercially available probiotics — Lactibiane iki and Vivomixx — composed by different strains from bacteria genera Lactobacillus, Bifidobacterium, and Streptococcus, on the clinical outcome of established EAE. Lactibiane iki contains two probiotic strains that have previously proved their capacity of increasing immunoregulatory cytokine interleukin (IL)-10 in vitro and of diminishing clinical severity in experimental colitis [11]. Furthermore, Vivomixx treatment has also demonstrated to induce IL-10 in a mouse model of colitis [12] as well as to promote anti-inflammatory immune responses in experimental diabetes [13]. Recently, Weiner laboratory has described the anti-inflammatory effect of Vivomixx treatment in MS patients that seems to be related to monocyte and dendritic cell (DC) functions [14-15].

Our data show that the commercial probiotic Lactibiane iki improved the clinical outcome of EAE mice in a dose-dependent manner as a therapeutic approach whereas Vivomixx treatment improved the motor coordination skills of EAE mice at the end of the experiment. However, both commercial probiotics decreased CNS demyelination and inflammation. Moreover, Lactibiane iki treatment decreased the expression of the T helper (Th)17-defining transcription factor Rorγt in the spinal cord, revealing a reduction in this pro-inflammatory cell population in the CNS. Lactibiane iki-treated mice also presented an increase in the frequency of regulatory T (Treg) cells and a reduction in the frequency of plasma cells in the periphery. On the other hand, administration of either probiotic increased the number of DCs and modified their phenotype in the periphery. Specifically, Lactibiane iki promoted an immature or semi-mature DC phenotype that expressed the surface marker PD-L1, which has been characterized as a marker for tolerogenic DCs and exhibits a contact-dependent mechanism for modulating peripheral immune responses and tolerance induction. On the other hand, Vivomixx treatment decreased the population of DCs expressing the co-stimulatory molecule CD86, which would indicate an inefficient T cell activation profile. In addition, we described that both the clinical condition and disease
progression alter the gut microbiome composition. Interestingly, Lactibiane iki-treated mice exhibited a higher abundance of *Bifidobacterium* than mice in the other treatment groups, which was associated with a lower clinical score. Finally, vehicle treatment was correlated with a higher abundance of *Enterococcus*, connected to higher clinical scores. Our results emphasize that Lactibiane iki plays a noticeable role in the immune response and in the processes of CNS demyelination and inflammation in this EAE model, being capable of reverting already established clinical signs. Therefore, this probiotic could exert beneficial effects in MS patients and could be rapidly translated into the clinic since it is already a commercialized product.

Figure 1. Commercial multispecies probiotics improve the clinical outcome or the motor coordination abilities in experimental autoimmune encephalomyelitis mice. Lactibiane iki treatment promotes a tolerogenic phenotype of dendritic cells that could directly induce immune tolerance in the periphery. This immune cell population could be responsible for the stimulation of immunoregulatory mechanisms in the periphery and these, in turn, may be decreasing both encephalitogenic immune cells in the periphery and pro-inflammatory responses in the central nervous system. On the other hand, Vivomixx decreases the percentage of dendritic cells expressing co-stimulatory molecules, which would indicate an inefficient T cell activation profile. As a result, both experimental treatments decrease the central nervous system inflammation and demyelination and improve experimental autoimmune encephalomyelitis clinical or motor coordination outcome. Abbreviations: CNS: central nervous system; EAE: experimental autoimmune encephalomyelitis.

References
Keywords
gut microbiota; probiotics; immune regulation; experimental autoimmune encephalomyelitis; multiple sclerosis; adaptive immunity; antigen-presenting cells; gut microbiome; gut permeability

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