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A randomized, double-blind, placebo-controlled study of oral hydrolytic enzymes in relapsing multiple sclerosis

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Oral administration of hydrolytic enzymes (HE), such as bromelain, trypsin and rutosid, may have beneficial effects on the clinical course of neurological symptoms related to multiple sclerosis (MS). This is supported by a complete protection by HE from experimental allergic encephalomyelitis, an animal model related to MS. Three hundred and one patients with relapsing MS were enrolled in a double-blind, placebo-controlled trial. No treatment effect between the placebo and the HE groups was found either for clinical or MRI parameters.
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Introduction

Anecdotal reports and uncontrolled trials lead to the assumption that hydrolytic enzymes (HE) could reduce the relapse rate and potentially halt progression of multiple sclerosis (MS).[1,2] Oral HE prevent experimental allergic encephalomyelitis in mice, an animal model related to MS.[3] HE induce a dose-dependent shift in T-cell proliferation from a Th_1-type, with predominant interferon-γ production, to a Th_2-type profile, with increased IL-4 and IL-5 production.[4–6]

Based on these experimental data and claims of efficacy, based on open label observational studies, we initiated a double-blind, placebo-controlled study to assess the safety and efficacy of orally administered HE in patients with relapsing MS.

Methods

Ambulatory patients in the age range of 18–50 years with clinical or laboratory-supported definite relapsing MS,[7] diagnosed at least 12 months prior to screening and Expanded Disability Status Scale (EDSS) scores of 1.5–5.5 were included (Table 1) if they had had at least one relapse during the preceding 12 months, and at least two relapses prior to inclusion in this study.

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The patients were randomized to receive either HE or placebo tablets. One HE tablet contained 90 mg bromelain, 48 mg trypsin and 100 mg rutosid. Twenty two centres from 11 European countries participated in this randomized, double-blind, placebo-controlled study. All efficacy and safety variables were assessed at baseline and at months 1 and 3, and then at three-monthly intervals. MRI examinations were performed at baseline and after 12 and 24 months.

The primary endpoint was the effect on three-month confirmed EDSS progression. Secondary endpoints included the number of patients progressing in the EDSS, time to EDSS progression, relapse rate, time to first relapse and various MRI parameters. MRI evaluation was performed at the Central MRI Analysis Centre, Neuroradiology Department, University of Basel, Switzerland, without knowledge of the treatment allocation or clinical status of the patient.

Results

Two hundred and ninety-three patients were included for the intention to treat analysis. In the HE group 126/145 patients, and in the placebo group 129/146 patients completed the trial (Figure 1).

A confirmed increase of the EDSS during the study according to the default criteria (≥ 1 point for $EDSS_{Baseline} \leq 5.0$ and 0.5 points for $EDSS_{Baseline} > 5.0$) was observed in 40/145 patients (28%) in the HE group and in 38/144 patients (26%) in the placebo group.

Relapses

During the treatment period the mean annual relapse rate in the HE group was somewhat lower than in the placebo

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Table 1 Baseline demographic and clinical characteristics of patients

Characteristics	*Hydrolytic enzymes* (n = *145*)	*Placebo* (n = *146*)
Age, years, mean ± SD	37.0 ± 8.0	35.6 ± 8.6
Sex, M/F	40/105	47/99
Weight, kg, mean ± SD	66.1 ± 11.4	66.8 ± 12.6
Disease duration, years, mean ± SD	5.7 ± 5.3	6.1 ± 6.0
EDSS, mean ± SD (median)	3.0 ± 1.0 (3.00)	2.8 ± 1.00 (3.00)
No. of relapses in the last 12 months, mean ± SD	1.4 ± 0.6	1.5 ± 0.7
Months since last relapse, mean ± SD	5.9 ± 4.5	5.1 ± 6.8

group (0.63 ± 1.00 versus 0.74 ± 1.01, n.s.). In the HE group 64/145 (44%) of patients, and in the placebo group 55/146 (38%) had no relapse in the course of the study. However, the mean number of relapses during the two-year study period was identical in both groups (HE group 1.1 ± 1.4 versus placebo group 1.1 ± 1.3).

MRI analysis

The two groups did not differ significantly in the baseline number of enhancing lesions on T1w scans and volumes of T2w lesion. The median relative change of T2w lesion volumes over the two-year period was −1% for both groups. The number of Gd-enhancing lesions decreased after 24 months without a significant difference between the groups. Both groups showed similar numbers of new lesions on T2w scans.

Treatment with the oral HE preparation had a similar safety profile to placebo assessed by self-reported side effects or laboratory measures.

Discussion

This is the first randomized, double-blind, placebo-controlled clinical trial on the safety and efficacy of orally administered HE in MS. Oral HE has no therapeutic effect on the clinical neurological symptoms of MS. No differences between the treatment groups were found with regard to the MRI parameters.

Although this study gave 'negative' results and was finished some time ago, we feel responsible to communicate these data. There are several reasons: HE is still prescribed by physicians and/or by request of patients for the treatment of MS.

The MS course in the placebo group differs substantially from other placebo-controlled trials, the relapse rate declined by 50% during the two-year study period. With regard to the mean baseline EDSS score, our placebo group was in the range of other studies, however the standard deviation in our study population was remarkably high. Under these circumstances, treatment effects are hard to establish. Based on the subanalysis of different centres, a specific centre effect can be excluded, however a general

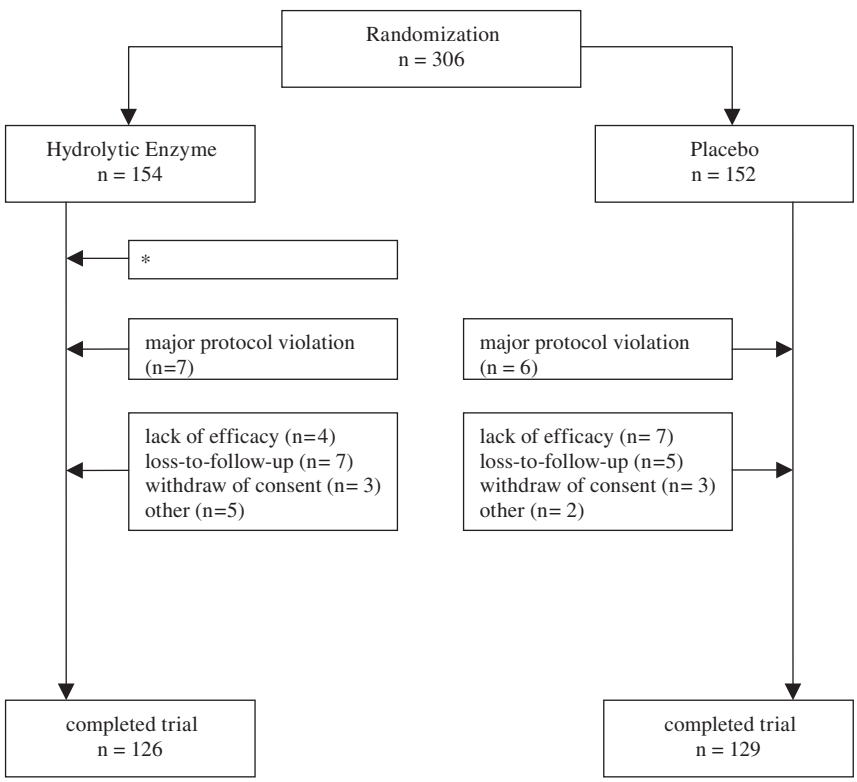

Figure 1 *Trial profile. *Did not receive study drug* (n = *2*).

selection bias for this study must be assumed. The start of our study coincided with the availability of beta-interferons as a first-line treatment for MS. Thus, it is reasonable to assume that investigators tended to include patients with a more stable course of the disease. This might have influenced the power of the study to detect a therapeutic effect.

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