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Symposia and Free Communications**

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O139

Long-term follow-up of patients treated with glatiramer acetate: a multi-centre, multi-national extension of the European/Canadian double-blind, placebo-controlled, MRI-monitored trial

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Objective: To investigate the long-term evolution of clinical and MRI findings in patients with relapsing-remitting (RR) multiple sclerosis (MS) who participated in the glatiramer acetate (GA) 9003 trial, in order to explore the correlates of long-term GA treatment.

Background: GA is effective in reducing clinical and MRI activity in RRMS. Serial MRI data on a long-term basis were never obtained for large samples of GA-treated patients.

Design/Methods: The 9003 study consisted of two consecutive phases, each lasting nine months. The first treatment phase was randomized, double-blind and placebo-controlled. The second was an active treatment phase for all patients. Treatment consisted of daily administration of 20 mg GA subcutaneously. All patients underwent brain MRI at screening (to be included, they had to have one or more enhancing lesions), baseline, every month during the double-blind phase and every three months during the open-label phase. Clinical assessment included neurological visits with Expanded Disability Status Scale (EDSS) score rating. For the long-term follow-up (LTFU), dual echo, pre- and post-gadolinium T1-weighted brain MRI scans were obtained with the same acquisition scheme as for the original trial and a neurological assessment was performed. Total T2-hyperintense and T1-hypointense lesion volumes, as well as normalized brain volumes (NBV) and percentage BV changes (PBVC), were measured.

Results: One hundred and forty-two of 224 patients who completed the 9003 study (63.4%) underwent the LTFU after a mean period of 5.8 years. Seventy-three of them had been treated with GA since the study initiation. At 9003 baseline, there were no significant differences between patients who subsequently came at LTFU and those who did not. Among the former ones, MRI measures of disease burden and activity, as well as brain volume changes, at LTFU did not significantly differ between patients originally assigned to placebo and those who were always treated with GA. The proportion of patients who did not reach relevant locomotor disability (EDSS ≥ 6.0) at LTFU was significantly greater in patients treated with GA during the first nine months of the 9003 trial ($p=0.03$). PBVC between baseline and LTFU was significantly correlated with T2 lesion volume at study entry.

Conclusions: This study indicates that the earlier initiation of GA treatment in patients with active RRMS might have a favorable impact on the long-term disease evolution.

O140

A phase II randomised, double-blind, placebo-controlled study to evaluate the preliminary efficacy and safety of abatacept, a selective co-stimulation modulator, in patients with relapsing-remitting multiple sclerosis

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Background: Abatacept selectively modulates the co-stimulatory signal required for the full activation of T-cells expressing CD28. Abatacept has demonstrated efficacy in experimental autoimmune encephalomyelitis, a surrogate animal model thought to be predictive of human multiple sclerosis (MS).

Objective: To evaluate the efficacy and safety of abatacept in patients with relapsing-remitting MS (RRMS).

Methods: This was a randomized, double-blind, placebo-controlled cohort study in RRMS male and female patients aged 18–58 years. Patients had definite MS, an Expanded Disability Status Scale (EDSS) ≤ 6 (inclusive), at least 1 relapse in the preceding 2 years (clinically stable for 2 months prior to treatment) and at least 1 gadolinium T1 (GdT1) enhancing lesion on magnetic resonance imaging. Patients were randomized into 1 of 3 cohorts receiving: abatacept 2 mg/kg, abatacept 10 mg/kg or placebo by infusion on Days 1, 15, 29, and then every 4 weeks until Day 197.

Results: The study terminated early due to an increase in patients with ≥ 5 new GdT1 lesions in the abatacept 2 mg/kg group. The cohort design resulted in excess patients in the abatacept 2 mg/kg group with poor baseline prognostic factors; 80% of patients with > 10 GdT1 enhancing lesions were randomized to abatacept 2 mg/kg. A total of 127 of a planned 219 patients

were randomized and received ≥ 1 infusion of study medication. Compared with abatacept 2 mg/kg and placebo, abatacept 10 mg/kg-treated patients had fewer new (1.5 vs. 8.0 vs. 5.5) and total GdT1 enhancing lesions (3.0 vs. 13.0 vs. 8.5), fewer protocol defined exacerbations (20.6 vs. 56.6 vs. 30%), a lower mean annualized relapse rate (0.38 vs. 1.49 vs. 0.73), a greater proportion free from enhancing activity (12 (36, 4%) vs. 7 (13, 2%) vs. 6 (15%)) and with improved EDSS (44.1 vs. 17.0 vs. 25%).

Conclusions: The cohort design contributed to clinically important treatment group imbalances at baseline that precluded conclusive assessment of the safety and efficacy profile of abatacept in RRMS. However, while the abatacept 2 mg/kg group experienced more MS-related symptoms and relapses, data from the abatacept 10 mg/kg cohort were suggestive of reduced disease activity.

O141

FTY720 in relapsing MS: results of a double-blind placebo-controlled trial with a novel oral immunomodulator

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FTY720 is an oral immunomodulator (sphingosine-1 phosphate receptor (S1P) modulator) that reversibly sequesters tissue damaging T and B cells away from blood and the central nervous system to peripheral lymph nodes. FTY720 has demonstrated both preventive and therapeutic efficacy in several animal models of MS.

Methods: We report the clinical and MRI results of an international, multicenter, double-blind study to evaluate efficacy, safety and tolerability of two doses of FTY720 and placebo (PL). 281 patients with active relapsing MS were randomized to receive PL ($n=93$), 1.25 mg ($n=94$) or 5.0 mg FTY720 ($n=94$) q. d. for 6 months. Patients had monthly cranial MRI scans and 3-monthly neurological assessments by a neurologist otherwise not involved in their care.

Results: Clinical and MRI baseline characteristics were balanced amongst groups. The primary outcome, mean (median) total number of Gadolinium(Gd)-enhancing lesions in monthly post baseline MRI scans was 14.8 (5.0), 8.4 (1.0) and 5.7 (3.0) for PL, FTY 1.25 and 5.0 mg groups ($p < 0.001$ 1.25 vs. PL, $p = 0.006$ 5.0 vs. PL). Similar, clearly significant effects favoring both FTY720 groups vs. PL were found for Gd-enhancing lesion volume, new T2 lesions and change in T2 lesion volume (only 5 mg qd sign. better than PL). The proportion of relapse-free patients (70.0, 86.0 and 86%; $p = 0.007$ 1.25 mg vs. PL, $p = 0.008$ 5 mg vs. PL), annualized relapse rate (0.77, 0.35 and 0.36) and time to first relapse were significantly better in both FTY720 groups vs. PL. There was no compelling dose-related difference in efficacy on MRI or clinical endpoints. Treatment was generally well tolerated with 255 (91%) of patients completing study and 249 (89%) electing to continue into the extension phase where PL patients were rerandomized to one of the active drug dose groups. Adverse events were more common in the 5 mg group, with the most frequently reported ($> 15\%$ patients) being mild headaches and nasopharyngitis.

Conclusion: This proof of concept study demonstrated efficacy of FTY720 on both MRI and relapse-related endpoints. Both the efficacy and safety evaluations strongly suggest that FTY720 has the potential to be an efficacious disease modifying treatment for relapsing forms of MS with the additional benefit of once daily oral administration.

Study supported by Novartis Pharma AG Basel.

Session 23

Higher function disorders 1

O142

Interaction between CYP19-aromatase and butyrylcholinesterase genes increases Alzheimer's disease risk

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Background: Biological evidence suggests that the enzymes aromatase (CYP19) and butyrylcholinesterase (BCHE) play a role in disrupting the cholinergic neurotransmission observed in Alzheimer's disease (AD). CYP19 is a critical enzyme in the peripheral synthesis of estrogens, which