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Pharmacokinetics of oral cladribine (Mylinax®) after administration in patients with multiple sclerosis

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Background: Intravenous (IV) cladribine produces clinical benefits in multiple sclerosis (MS) patients. Since oral administration would have advantages over the IV route, the bioavailability and pharmacokinetics of an oral cladribine formulation were assessed.
Method: In a randomized 3-way crossover manner, 26 confirmed MS patients (mean age 44.1 years, mean weight 72 kg) each received 3 single fixed cladribine doses separated by ≥5 days: 3mg and 10mg orally (Mylinax-Serono/Ivax), and 3mg by 1-h IV infusion (Leustatin®-Janssen-Cilag). Blood samples were obtained before administration and repeatedly over 1 day thereafter. Plasma concentrations were measured by HPLC/MS.
Results: Achieved 0.5–0.6h after oral administration, peak concentration (C_{max}) averaged (geometric mean) 5608 pg/mL and 21242pg/mL after 3mg and 10mg orally, respectively, compared with 21425pg/mL after 1-h IV infusion. Areas under the concentration-time curve (AUC) with 3mg and 10mg orally were 20159h·pg/mL and 76690h·pg/mL, respectively, and 58528h·pg/mL following IV infusion. Mean absolute bioavailability was 35% and 39% following 3mg and 10mg orally, respectively. Variability was well controlled, with a coefficient-of-variance of <20% intra-patient and 30–35% inter-patient, on AUC. There was no evidence of clinically important pharmacokinetic nonlinearity after oral cladribine at either dose. Tolerability was good: the only reported adverse events occurred after 3mg orally: a mild headache in one patient, moderate headache and vomiting in a second; none were considered treatment-related.
Conclusion: Oral cladribine has favourable pharmacokinetic and safety profiles following administration of a single dose in MS patients: a Phase III trial with oral cladribine is underway.

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Influence of Immunomodulatory Therapies on Anti-Myelin-Antibodies in Multiple Sclerosis (MS)

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Background: Antimyelin antibodies seem to play a role in RRMS patients. Own previous data suggested an influence of interferon-beta on those antibodies, measured at a single time point, in 261 MS patients.
Objectives: This prospective study investigated the influence of disease modifying-drugs (DMD) on the antibody response against MOG and MBP after one year of treatment.
Methods: We have analyzed IgG, IgM and IgA serum antibodies against MOG and MBP in 49 RRMS patients receiving various DMT (16 Betaferon, 11 Avonex, 6 Rebif, 7 glatiramer acetate, 9 intravenous immunoglobulins) before and after one year of therapy. 14 RRMS patients without DMD served as controls. None of the patients had a relapse or received corticosteroids within one month before blood sampling. EDSS was assessed every three months for two years, relapses had to be confirmed. Antibodies were detected by semiquantitative Westernblot.
Results: We found a significant influence of DMD on anti-MBP IgM antibodies after one year of treatment ($p = 0.035$). The change of the relapse rate after two years of treatment with DMD differed significantly in patients positive for anti-MBP IgM antibodies compared to anti-MBP IgM negative patients measured at month 12 of treatment ($p = 0.002$).
Conclusion: MBP is quantitatively the major myelin protein. Antibody responses to this antigen might reflect the extent of inflammation and tissue destruction in MS patients. Although number of patients and the follow up period have to be extended we suggest that anti MBP antibodies may serve as a biomarker for monitoring indirectly the effectiveness of DMD.

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The critical role of pro- and anti-apoptotic mediators in patients with multiple sclerosis

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Background: Multiple sclerosis (MS) is a chronic neurological disorder characterized by myelin destruction and a variable degree of oligodendrocyte death. Programmed cell death (apoptosis) is critical for the normal development and homeostasis of the immune system. Apoptosis of autoreactive T cells in the CNS is likely to be important in preventing the development of MS. CD95/CD95L interaction results in activation-induced apoptosis and their abnormal expression together with NF-kB and Bcl-2 may be involved in the pathogenesis and the clinical course of MS.
Aim: To study the role of pro- and anti-apoptotic mediators in MS patients.
Methods: we studied the level and expression of Fas, Fa-L, NF-kB and Bcl-2 using RT-PCR, morphological changes of apoptosis in peripheral blood mononuclear cells, DNA fragmentation in 16 patients with MS divided into 3 groups, relapsing, remitting and chronic cases. In addition, a group of 16 healthy cases served as controls.
Results: we found that Fas & Fas-L were significantly decreased in patients with MS compared with healthy controls. While NF-kB and Bcl-2 were significantly increased in patients compared with controls.
Conclusion: Fas, Fas-L, Nf-kB and Bcl-2 play an important role in the pathogenesis of MS.

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Cognitive dysfunctions and fatigue in newly diagnosed multiple sclerosis patients and in the early stage of the disease

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Background: Cognitive dysfunctions and fatigue are frequent symptoms in the course of multiple sclerosis (MS). There are some long-term studies which show stability or slow progression at any time of the course. No study investigated cognitive dysfunctions as well as fatigue at the time of diagnosis.
Method: The cognitive performance of 50 patients with newly diagnosed multiple sclerosis was compared with that of 33 control subjects, matched for sex, age and education. The test-battery included tests of reasoning, verbal and nonverbal memory, alertness, divided and focused attention. Tests were applied at diagnosis, a half, one and three years later. Fatigue was measured subjectively by the Modified Fatigue Impact Scale and objectively by a test of vigilance. Physical disability (EDSS) and depression (BDI) were controlled.
Results: Patients had an average age of 35 years, a mean EDSS-score of 1.8. 92% suffered from a relapsing-remitting MS. At baseline 50% of the patients were cognitively unimpaired, 38% showed mild and 12% moderate cognitive deterioration. Patients performed significantly poorer than controls in nonverbal memory and reaction-time. No differences were found in reasoning and verbal memory. Three years later no improvement in cognitive performance was found. Fatigue was reported in 63% at baseline and one year later. After three years only 47% suffered from it. Throughout testing the BDI-score was significantly correlated with subjective fatigue.
Conclusion: Cognitive dysfunctions and fatigue were frequent symptoms already in newly diagnosed MS patients. After three years the cognitive performance as well as the reported fatigue did not increase.