Supplement 2 September 2004

Multiple Sclerosis

CLINICAL AND LABORATORY RESEARCH

20th Congress of the European Committee for Treatment and Research in Multiple Sclerosis

9th Annual Meeting of Rehabilitation in MS

October 6–9, 2004
Austria Center, Vienna, Austria

Multiple Sclerosis

CLINICAL AND LABORATORY RESEARCH

Volume 10 • Supplement 2 • September 2004

CONTENTS

Paper Abstracts

Poster Viewing I

Poster Viewing II

Multiple Sclerosis

Multiple Sclerosis (ISSN 1352-4585 print; ISSN 1477-0970 online) is published bi-monthly by Arnold, part of the Hodder Headline Group, 338 Euston Road, London NW1 3BH, UK. *Multiple Sclerosis* is affiliated with ECTRIMS and ACTRIMS.

Scope *Multiple Sclerosis* focuses on the aetiology and pathogenesis of demyelinating and inflammatory diseases of the central nervous system. It also deals with the application of these studies to scientifically based study.

Multiple Sclerosis is indexed by Academic Search Premier; Biological Abstracts; BIOSIS Previews Database; CSA Neurosciences Abstracts; Chemical Abstracts; Elsevier BIOBASE Current Awareness in Biological Sciences; EMBASE the Excerpta Medica Database; e-psyche; ISI Current Contents/Clinical Medicine; ISI Current Contents/Life Sciences; ISI Discovery Agent; Index Medicus/MEDLINE; Neuroscience Citation Index; Reference Update; Science Citation Index; Science Citation Index Expanded (also known as SciSearch); UK Health Centre Index.

Editorial Manuscripts (original plus 2 copies) and all editorial correspondence should be sent to:

Donald H Silberberg
Editor in Chief
3 Gates, HUP
University of Pennsylvania Medical Center
School of Medicine
Philadelphia
PA 19104, USA
Tel: +1 215 662 3386; Fax: +1 215 662 3353

Alan J Thompson
Co-Editor for Europe
University Department of Clinical Neurology
Institute of Neurology
Queen Square, London WC1N 3BG, UK
Tel: +44 20 7837 3611; Fax: +44 20 7813 6505

William Carroll
Co-Editor for Asia-Pacific
Department of Neurology
Sir Charles Gairdner Hospital
Nedlands, WA 6009, Australia
Tel: +61 8 9346 2471; Fax: +61 8 9346 2471

Publisher All business correspondence, advertisement enquiries, supplement enquiries, reprint orders and permission requests should be addressed to *Multiple Sclerosis*, Arnold Journals, 338 Euston Road, London NW1 3BH, UK. Tel: +44 20 7873 6339, Fax: +44 20 7873 6736, E-mail: arnoldjournals@hodder.co.uk.

WWW
Multiple Sclerosis' homepage is www.multiplesclerosis-journal.com. Editor's details, scope, subscription prices, reprint ordering, sample copy ordering, supplement information and contact names for the publishing, production, marketing and advertising departments are available for all Arnold journals.

2004 Subscription rates

Institutional subscriptions (print and online)	
US	$615
EU	£358
Rest of the World	£391
Individual subscriptions (print and online)	
US	$262
EU	£139
Rest of the World	£169
Privileged rate (print and online)	
ECTRIMS	£110 EU/£134 ROW
ACTRIMS	$214

Orders, payment and online access
Orders accompanied with payment should be sent directly to Extenza-Turpin Stratton Business Park, Pegasus Drive, Biggleswade, Bedfordshire, SG18 8QB, UK.
Tel: +44 (0) 1767 604 951. Fax: +44 (0) 1767 601 640

Customers should make payments by cheque in sterling payable (to Extenza-Turpin Distribution Services Limited) on a UK clearing bank or in US dollars payable on a US clearing bank. Back issues are also available from Extenza-Turpin. Periodical Postage is paid at Rahway, NJ, USA. Postmaster - please send address changes to Multiple Sclerosis, Turpin North America, 440 Creamery Way, Suite A, Exton, PA 19341, USA.

Once payment has been made, the online registration form should be completed at www.ingenta.com/home/fs_registernow.htm. Please have your customer number available. A username and password will be allocated to gain access to the Ingenta website. Alternatively, please contact www.ingenta.com

Typeset in Ireland by Datapage International Ltd., Dublin
Printed and bound in Great Britain by Alden Press, Oxford

relapse rate and the number of active lesions in MR-imaging in relapsing-remitting MS. The doses of ivIg used for treatment in relapsing-remitting MS have varied 10-fold and the optimal dose of ivIg for treating MS is still unknown. IvIg has several effects on the immune system that could have a beneficial influence on disease processes in multiple sclerosis (MS). Significant changes in serum levels of circulating cytokines after infusions of ivIg have been observed. As Interleukin-6 (IL-6) and Interleukin-10 (IL-10) play important role as pro- and anti-inflammatory factors, *in vivo* modulation of these cytokines may account for immunomodulatory and anti-inflammatory effect of intravenous Ig therapy. In order to better understand mechanism of action of low-dose ivIg cyclic therapy we have investigated serum levels of IL-6 and IL-10 before and a day after ivIg infusion in patients with multiple sclerosis. ***Methods:*** Serum levels of IL-6 and IL-10 were assayed in 20 patients with MS before and 24 hours after infusion of 5g (n = 11) and 2.5g (n = 9) ivIg. ***Results:*** We have not observed significant changes of pro-inflamatory IL-6 nor anti-inflammatory IL-10 serum levels after infusions of ivIg in both doses of 2,5g and 5g. ***Conclusion:*** Hereby presented data suggest that potential therapeutic effect of low-dose ivIg treatment in MS is not mediated by changes of pro-inflammatory IL-6 nor anti-inflammatory IL-10. As the modulating influence of ivIg on cytokines seems to be dose-dependent observation of serum levels of cytokines after ivIg might give important indications in determining ideal dosage of ivIg in treatment of MS.

P639

Immunglobulin treatment of relapsing-remitting multiple sclerosis - a retrospective data analysis

M. Bauer, S. Kremer, M. Freidel, Octapharma GmbH, FA Neurologie/Psychiatrie (Langenfeld, Kaltenkirchen, D)

The efficacy of immunoglobulin (IVIG) in the treatment of patients with multiple sclerosis (MS) is still under discussion. Though it has been used for many years the results presented in clinical trials are not yet accepted as sufficient to license this drug for MS treatment. Thus retrospective observation studies might further support the available results. In this retrospective observation study neurologists treating in medical offices or outdoor-patient departments in hospitals had been asked to report about IVIG treatment and its efficacy by number of relapses and by expanded disability status score (EDSS) for patients who fulfil certain inclusion criteria. Finally data of 54 patients reported by 21 study sites could be analysed. About 70 % of the patients had stopped a pretreatment and started with intravenous immunoglobulin (IVIG) for reason of adverse drug reaction, treatment failure or other contraindication. The mean annual relapse rate decreased by 62 % from 1.55 ± 0.72 (median: 1,5) during the 2 years before start of IVIG therapy to 0.59 ± 0.57 (median: 0,5) within the first two years after start of IVIG therapy ($p < 0.0001$). The annual relapse rate (ARR) improved in 81 % of the patients and remained constant in further 11 %. Disability improved in 18 % of patients by at least 1 EDSS point. Mean EDSS slightly but insignificantly increased. In conclusion the results confirm what has been reported from clinical trials that IVIG is efficient to reduce relapse rate and to stabilize disease progression of relapsing remitting multiple sclerosis. They thus add value to justify the use of IVIG at least in cases where licensed therapies are contraindicated.

P640

The effect of IVIG treatment on visual outcome after acute optic neuritis

H.G. Roed, A. Langkilde, F. Sellebjerg, M. Lautitzen, P. Bang, A. Moerup, J.L. Frederiksen, University Hospital of Copenhagen, Statens Serum Institute (Glostrup, Hvidovre, Copenhagen, DK)

Objective: The aim of the study was to investigate if intravenous immunoglobulin (IVIG) treatment initiated within 30 days after onset of optic neuritis (ON) could improve visual outcome after six months. ***Background:*** ON is a well characterized model of an MS relapse, and may occur as part of MS or as a clinically isolated syndrome. IVIG treatment decreases relapse rate and the accumulation of clinical disability and reduces the number of new lesions on MRI om patients with MS. IVIG treatment does not appear to have major effects on stable clinical deficits. No previous controlled trials have investigated the efficacy of IVIG treatment in ON. ***Design/Methods:*** The study was a double-blind, randomized, placebo-controlled study of 68 patients with acute ON. Treatment was initiated within 30 days after symptom onset. Patients were treated with 0.4 g/kg bodyweight of IVIG or placebo at day 1, 2, 3, 30, and 60. Visual acuity, color vision, and contrast sensitivity were assessed at baseline and at days, 7, 30, and 180. Visual evoked potential (VEP) and Gadolinium-enhanced magnetic resonance imaging (MRI) studies were performed prior to treatment and at days 30 and 180. New relapses were recorded throughout the study period. The primary outcome measure was contrast sensitivity after 6 months. Secondary outcome measures were: contrast sensitivity at other time points, and visual acuity, colour vision, VEP, new or enhancing lesions on MRI, and new relapses. ***Results:*** 68 patients were randomized. A total of 64 patients completed 6 months of clinical follow-up. Four patients discontinued medication because of adverse events. The randomization code was broken for one patient due to a serious adverse advent. Our results showed no difference at baseline or at follow-up visits in visual outcome, measured by contrast sensitivity, visual acuity and color vision or number of relapses in the study period between patients treated with IVIG and patients treated with placebo. Patients in the IVIG group had significantly more lesions at baseline at day 30 and 180 no difference between groups was found. ***Conclusions:*** Our study showed no improvement in visual outcome at any time-point in patients treated with IVIG compared to placebo. Treatment with IVIG does not appear to influence the duration or outcome of ON.

P641

Intravenous immunglobulins before, during and after pregnancy - a therapeutic option in multiple sclerosis?

I. Ringel, S. Adler, U. Zettl, University of Rostock (Rostock, D)

Background: Two thirds of multiple sclerosis (MS) patients are women, and the average age of onset overlaps the childbearing years. The PRIMS study (Confavreux *et al.*, 1998) showed that the relapse rate decreases significantly during pregnancy in MS patients, while it increases after delivery. Haas (2000) treated 43 MS patients with high dose intravenous immunglobulins (IVIG) after delivery and found a lower increase of exacerbation rates as compared with the untreated patients of the PRIMS study. The current therapeutic recommendations for most immuntherapies include an early start after onset of MS but also the discontinuation before pregnancy. We performed a study to evaluate the benefit of IVIG during the phase before and in the first months of pregnancy when the patients had to stop other immunmodulatory therapies. ***Methods:*** We studied 18 patients; 11 women had a wish of pregnancy. Another seven women became pregnant while they were on an interferon treatment. Six patients received no treatment before pregnancy while five patients were treated with IVIG. After onset of pregnancy nine patients received IVIG and nine patients had no treatment. After delivery all patients but one received IVIG. ***Results:*** We found a decrease of the relapse rate in the IVIG treated patients already before pregnancy from 2.4 to 0.8 relapses per year, but after onset of pregnancy there was no further reduction of exacerbations. The untreated patients showed a reduction of relapses only when pregnancy started from 1,3 to 0.4 relapses per year, but during pregnancy the rate of relapses was comparable with the rate in the treated patient group. After delivery there was no increase of post partum exacerbation in the 17 IVIG treated patients. ***Conclusion:*** It seems that treatment with IVIG before onset of pregnancy may reduce the rate of exacerbations compared with untreated patients. We did not see a benefit of IVIG therapy during pregnancy beyond the "natural protection". The positive effect of postpartum IVIG treatment confirms previous reports in the literature.

Fumerate

P642

A prospective, open-label, phase II study of oral fumarate therapy for the treatment of relapsing-remitting multiple sclerosis

S. Schimrigk, N. Brune, K. Hellwig, M. Rieks, V. Hoffmann, D. Pöhlau, H. Przuntek, St. Josef Hospital, Ruhr University (Bochum, D)

Background: Oral fumarate is an effective and safe therapy for the treatment of psoriasis. Similar to psoriasis, the inflammatory process in

multiple sclerosis (MS) is thought to be mediated by a T helper 1 (TH1)-type cytokine reaction due to global immune suppression or a TH2-mediated bystander suppression. ***Objective:*** To evaluate the safety and efficacy of oral fumarate therapy (Fumaderm) in patients with relapsing-remitting MS (RRMS). ***Methods:*** An exploratory, prospective, open-label study of oral fumarate therapy was conducted in patients with RRMS. The study consisted of four phases, a 6-week baseline, an 18-week treatment, a 4-week wash-out, and a second 70-week treatment phase. All patients were treated with oral fumarate therapy, with the dosage slowly titrated up to a maximum of 6 tablets per day (720 mg daily) in the first treatment period and up to 3 tablets per day (360 mg daily) in the second treatment period. Safety was assessed by physical and neurologic exams, blood chemistry/hematology, electrocardiogram, and urinalysis. The primary outcomes were the number and volume of gadolinium-enhancing (Gd+) lesions on serial T1-weighted magnetic resonance imaging (MRI) scans. Clinical outcomes included Expanded Disability Status Scale (EDSS) score, ambulation index (AI), and nine-hole peg test (9-HPT). ***Results:*** Ten patients with RRMS were enrolled in the study; 3 patients discontinued the study during the first 3 weeks of treatment. Mild to moderate gastrointestinal discomfort was initially experienced by 6 of 7 patients, but decreased gradually during the first 6 weeks of treatment in all patients. All other side effects were generally mild and transient. Significant reductions from baseline in the number of Gd+ lesions were observed starting after week 12 of treatment with fumarate ($p < 0.05$). In addition, there were significant reductions from baseline in Gd+ lesion volume starting after week 12 ($p < 0.01$). EDSS scores, AI, and 9-HPT remained stable or slightly improved from baseline in all patients; however, these effects were not statistically significant. ***Conclusions:*** Oral fumarate therapy significantly reduced the number and volume of Gd+ lesions over 70 weeks of treatment. All patients were clinically stable throughout the study and there were no serious adverse events. These findings indicate that oral fumarates may be a promising new treatment for RRMS.

P643

Oral fumarate therapy alters cytokine production in patients with relapsing-remitting multiple sclerosis

N. Brüne, S. Schimrigk, D. Meier, M. Rieks, M. Krane, V. Hoffmann, K. Hellwig, D. Pöhlau, H. Przuntek, St. Josef Hospital, Ruhr University (Bochum, D)

Background: The pathophysiology of multiple sclerosis (MS) is thought to be mediated, in part, by a shift from a T-helper (TH)2-type cytokine profile (interleukin [IL]-4, IL-10, tumor growth factor [TGF]-β) to a TH1-type cytokine profile (IL-2, tumor necrosis factor [TNF]-α, IFN-γ). TH2-type cytokines influence T-cell apoptosis and down regulate soluble adhesion molecule (sICAM-1)-mediated inflammatory processes. Oral fumarate therapy has been shown to reduce disease activity in psoriasis through stimulation of a TH2-type cytokines. ***Objectives:*** To investigate the effects of oral fumarate therapy (Fumaderm) on cytokine profiles, T-cell apoptosis, and sICAM-1 in patients with relapsing-remitting MS (RRMS). ***Methods:*** This was a prospective, 28-week, open-label study in patients with RRMS. Enrolled patients had at least 1 relapse in the year prior to enrollment, at least 1 active lesion on magnetic resonance imaging (MRI) scans, and an Expanded Disability Status Scale (EDSS) score of 2.0 to 6.0. The study consisted of three phases: pre-treatment baseline (6 weeks), treatment (18 weeks), and post-study (4 weeks). During treatment, all patients received oral fumarate therapy; dose was titrated to 720 mg daily (6 tablets). Intracellular production of TH1- and TH2-type cytokines by peripheral blood mononuclear cells (PBMCs) and T-cell apoptosis were measured by flow cytometry during baseline, after 6, 12, and 18 weeks of treatment, and at post study. Serum levels of sICAM-1 were measured using enzyme-linked immunosorbent assay. ***Results:*** Seven of 10 enrolled patients completed the study. A significant increase (126%) in CD4+ cells producing IL-10 was observed over 18 weeks of treatment compared with baseline and the post-study period. A corresponding 50% increase in the rate of apoptosis in TH cells was observed after 6 weeks of treatment and declined to baseline levels after an addition 6 weeks of treatment. There were no significant changes in IL-4, TGF-β, or TH1-type cytokine production. The total number of PBMCs and serum levels of sICAM-1 remained stable. ***Conclusions:*** Oral fumarate appears to increase TH-cell apoptosis, which may lead to increased IL-10 production and immune deviation toward a predominantly TH2-type cytokine profile. Further study of oral fumarate therapy for the treatment of RRMS appears warranted.

Laquinimod

P644

Pharmacokinetic evaluation in a double blind, randomised, phase II study of oral laquinimod versus placebo in patients with relapsing multiple sclerosis

O. Nordle, B. Sparre, A. Linde, T. Nederman, P.O. Gunnarsson, Active Biotech AB (Lund, S)

Objective: The objective was to study the pharmacokinetics (PK) of laquinimod and its relationship to the effect on development of active lesions. ***Background:*** In the clinical evaluation of the present phase II study, laquinimod at 0.3 mg/day showed evidence of biological activity on development of active lesions in relapsing multiple sclerosis (R-MS) patients. The present evaluation presents the PK of laquinimod during 24 weeks of daily oral treatment. The PK properties of laquinimod have previously been evaluated in single and repeat dose safety and tolerance studies in healthy volunteers as well as in secondary progressive MS patients. No dependencies in the PK due to sex or time were observed. The PK up to 0.6 mg/day was linear, but there was a slight decrease in the clearance at higher dose levels (1.2–2.4 mg/day). Furthermore, the clearance in MS patients was slightly lower than in healthy volunteers. ***Methods:*** Patients with R-MS ($n = 209$) were randomised to placebo, 0.1 or 0.3 mg/day. The PK evaluation was based on a population PK approach as sparse blood samples were collected from the patients. A one-compartment model was fitted to laquinimod plasma concentration data and the significance of various covariates was tested. The model was used to calculate the individual systemic exposure, and the relationship between the systemic exposure and the development of active lesions was evaluated. ***Results:*** Daily treatment for 24 weeks did not affect the PK of laquinimod. Furthermore, linear PK was indicated. The clearance value in the females was 17% lower than in the males. The clearance decreased with increasing EDSS score with about 7% per EDSS unit. There was a significant relationship between the systemic exposure and response, both for the cumulative number of active lesions in patients with more than two active lesions at baseline and for the cumulative volume of gadolinium enhanced T1 lesions in patients with a baseline volume above the median. These results suggest that a higher dose than 0.3 mg/day may further increase the effect on development of active lesions. ***Conclusions:*** The analysis of the systemic exposure in relation to the development of active lesions revealed that the best effect was found in the patients with the highest exposure.

Minocycline

P645

Minocycline treatment increases IL-12 p40 and s-VCAM in RRMS

R. Zabad, L. Metz, W. Yong, University of Calgary (Calgary, CAN)

Background: The ability of minocycline to alleviate many neurological diseases is being increasingly recognized. Minocycline has multiple activities, including the inhibition of microglia activation, T cell proliferation and modulation of levels of several inflammatory cytokines. It is also a direct inhibitor of MMP enzymatic activity. Because of these multiple immunomodulatory properties and efficacy in a murine model of MS minocycline was tested in 10 patients with relapsing-remitting multiple sclerosis (RRMS). ***Material and Methods:*** Eight women and 2 men with active RRMS received oral minocycline100mg twice daily for