

---

# A Controlled Trial of Mitoxantrone in Multiple Sclerosis: Serial MRI Evaluation at One Year

*S. Bastianello, C. Pozzilli, F. D'Andrea, E. Millefiorini, M. Trojano, S. Morino, C. Gasperini, A. Bozzao, M. Gallucci, C. Andreula, L. Bozzao, D. Gambi and M. Prencipe*

---

**Abstract:** We present the results of a randomized double-blinded placebo controlled, multicenter trial, of low-dose mitoxantrone (MX), after one year, in 25 patients with relapsing-remitting multiple sclerosis, who had serial enhanced magnetic resonance imaging (MRI). Treatment groups were balanced for age, gender, duration of illness and neurological disability. Five of the 13 MX patients and 10 of the 12 placebo patients had exacerbations during treatment ( $p < 0.02$ ). The mean change in the extended disability status scale was not significantly different between the MX and placebo treatment groups. Serial Gadolinium-DTPA enhanced MRI detected no significant difference between the MX treated and placebo groups in the mean total number of new, enlarging, or Gadolinium-DTPA enhancing lesions; there was a trend toward a reduction of new, enlarging and Gadolinium-DTPA enhancing lesions in MX patients. Despite this ameliorating effect, the results indicate that serial Gadolinium-DTPA enhanced MRI, performed over one year in a limited number of patients, could not provide conclusive evidence for a role of MX therapy in relapsing-remitting multiple sclerosis.

**Résumé: Étude contrôlée du mitoxantrone dans la sclérose en plaques: évaluation sériée par RMN à un an.** Nous présentons les résultats à un an d'une étude multicentres, à double insu, contrôlée par placebo, du mitoxantrone (MX) à faible dose chez 25 patients, atteints de sclérose en plaques (SEP) évoluant par poussées et rémissions, qui ont subi une évaluation sériée par RMN rehaussé. Les groupes étaient équilibrés pour l'âge, le sexe, la durée de la maladie et l'atteinte neurologique. Cinq des 13 patients sous MX et 10 des 12 patients sous placebo ont eu des poussées sous traitement ( $p < 0.02$ ). Le changement moyen à l'échelle élargie d'évaluation de l'invalidité n'était pas significativement différent entre les groupes. Le RMN sérié rehaussé, au Gadolinium-DTPA, n'a pas détecté de différence significative entre le groupe traité au MX et le groupe placebo quant au nombre total moyen de lésions nouvelles, en expansion ou rehaussantes; il y avait une tendance à la diminution des lésions nouvelles, en expansion et rehaussantes chez les patients sous MX. En dépit de cette amélioration, les résultats indiquent que l'évaluation sériée, par RMN rehaussé, au Gadolinium-DTPA, faite sur une période d'un an chez un petit nombre de patients, n'a pu apporter de preuve concluante d'un rôle du traitement par le MX dans la SEP évoluant par poussées et rémissions.

Can. J. Neurol. Sci. 1994; 21: 266-270

---

Besides the well-established diagnostic value of magnetic resonance imaging (MRI) in multiple sclerosis (MS),<sup>1,2</sup> recent studies suggest that it reveals the presence of disease activity as measured by new abnormalities on T2 weighted images or by gadolinium enhancing lesions in patients who are clinically stable.<sup>3-11</sup> Thus, MRI may provide a suitable tool for assessing the effectiveness of clinical therapeutical trials.<sup>10-14</sup> The useful effect of treatment should be observed by MRI in a limited number of patients and after a shorter period of time than that required by clinical monitoring alone.<sup>13</sup> Some limited benefits of immunosuppressant and immunomodulatory drugs have been reported in the treatment of MS. One recent approach has been the use of mitoxantrone (MX) as a therapeutic agent.

Mitoxantrone is an antineoplastic agent which intercalates into DNA and exerts a potent suppressive influence upon the humoral immune response.<sup>15-17</sup>

---

From the Chair of Neuroradiology (S.B., L.B.) and Chair of Neurology (C.P., E.M., S.M., C.G.), Department of Neurosciences, University of Rome "La Sapienza"; Chair of Neurology (F.D., M.P.) and Chair of Radiology (A.B., M.G.), University of Aquila; Chair of Neurology (M.T.) and Chair of Neuroradiology (C.A.), University of Bari; Chair of Neurology (D.G.), University of Chieti.

RECEIVED JULY 15, 1993. ACCEPTED IN FINAL FORM JANUARY 25, 1994.

Reprint requests to: Stefano Bastianello, MD, PhD, Cattedra di Neuroradiologia, Dipartimento di Scienze Neurologiche, Università di Roma "La Sapienza", Viale dell'Università 30, 00185 Rome, Italy.

Preliminary open-label trials to assess the potential efficacy of treatment with MX have been performed only in progressive MS,<sup>18-20</sup> suggesting that MX did not completely suppress clinical and MRI evidence of ongoing disease.<sup>21</sup> Recent data, however, indicate that therapy may be more effective if used early when there is less neurological damage and when the demyelinating process is just beginning.<sup>22</sup> On the basis of these assumptions, we started a 2-year, randomised double-blinded, placebo controlled, multicenter trial of MX in relapsing-remitting MS patients to determine the clinical efficacy of this therapy. We now present the preliminary results after 1-year treatment in a subgroup of patients who underwent serial MRI evaluation.

## SUBJECTS AND METHODS

The 2-year randomized, double-blinded, placebo controlled multicenter trial was conducted at seven Italian centers: Universities of Bari, Catanzaro, Chieti, Napoli, Roma, Siena, and L'Aquila, the latter also being the coordinating center.

The subgroup of patients which underwent serial MRI evaluation was selected from four centers (Universities of Bari, Chieti Roma and L'Aquila) and referred to L'Aquila University in order to perform sequential scans.

The trial design was approved by Internal Review Boards and by the National Health Service.

### Patient enrolment and pre-trial observation

Inclusion criteria were: a definite diagnosis of MS;<sup>23</sup> a relapsing-remitting disease course, defined as two or more relapses occurring in the 24 months prior to study entry; age between 18 and 45 years; disease duration from 1 to 10 years; disability no less than 2 or more than 5 on the Kurtzke Expanded Disability Status Scale (EDSS).<sup>24</sup>

We excluded patients who were HIV-positive, with previous cardiovascular disease, with left ventricular ejection fraction of less than 50% as determined by echocardiography, subjects presenting renal, liver and/or respiratory dysfunctions, diabetes, malignancy, psychiatric illness, pregnancy and women not practicing contraception, as well as patients who had taken previous immunosuppressant medications (such as azathioprine, cyclophosphamide, plasmapheresis) or were taking steroids during the 3 months before entry. Finally, patients incapable of fulfilling the requirements of the study or signing the informed consent were also excluded.

### Study design and data collection

When a patient became eligible, the investigators notified the relevant center which validated the eligibility of the patient and assigned a randomisation code number.

For determination of sample size, it was assumed to be important to detect a 1 point difference in the mean change from baseline of the EDSS in 25% of the MX treated group relative to 50% of the placebo treated group at the time of scheduled efficacy analysis. According to this design and with an alpha error = 0.05 and beta error = 0.20, the required number of patients to achieve statistical significance was 45 patients per arm. Up to June 1993, 52 patients had been enrolled into the study.

After examining clinical and MRI data at 1-year, the code was broken by two not blinded investigators (BS and PC);

therefore the blindedness of the second year of the study was maintained.

Of the total patients who were randomised in the trial, 25 (screened between January 1991 and December 1992) were enrolled in the present 1-year serial MRI follow-up study.

The subjects (10 men and 15 women) were randomly assigned to a recipient group that either received MX (n. = 13) or a placebo (n. = 12). Randomisation for both groups was performed simultaneously.

### Treatment

Patients assigned to immunosuppressive treatment received a 30 minute infusion of MX intravenously (8 mg/m<sup>2</sup>) every month for 1 year; the intravenous bag and tubing were black to ensure patients blinding. Placebo group patients received a solution containing the vehicle alone.

Blood and urine samples and ECG were carried out upon entry to the trial and at each visit. Complete blood counts were obtained from each patient every two weeks. Echocardiography at 0, 6 and 12 months was performed in order to assess the potential cardiac toxicity.

Other drugs were allowed during the trial such as cholinergic and spasmolytic drugs or short courses of steroids (high dose intravenous methylprednisolone 1 g day for 6 days) for relapses.

### Evaluation of patients

All patients were examined by four blinded neurologists at each center. Neurological examination was undertaken by means of the EDSS prior to starting therapy and at 12-months. Primary clinical end-points were considered the change in EDSS and the number of exacerbations experienced during the follow-up.

We defined as clinical worsening an increase > 1 point on the EDSS.

Exacerbation was defined as the appearance of new symptom or worsening of an old one, attributable to MS and lasting at least 24 hours in absence of fever. Participating neurologists were trained in the application of the EDSS during a joint session which included repeated rating of patients with MS who have varying levels of disability.

### MRI assessment

MRI examinations, performed at 0, 2, 4, 6 and 12 months, were obtained with a 0.2 Tesla permanent unit, using T2 spin echo sequences on axial plane; the enhanced study performed after Gd-DTPA administration (0.1 mmol/kg) was undertaken using T1 weighted sequences on the same axial planes. Slices with 7.5 mm thickness without gap between sections were obtained for all the sequences. In order to obtain comparable examinations during the follow-up scans, a midline sagittal scout slice was always performed at the beginning of the study. In this way we oriented axial sections on the same horizontal plane along a line passing through the basis of the frontal lobe and the caudal portion of quadrigeminal plate.<sup>8</sup>

### Image evaluation

MRI data were analysed by two blinded neuroradiologists (BS, BA) and questionable lesions were reviewed by a third neuroradiologist as supervisor (BL). Prior to the study, the neuroradiologists were trained to minimize inter- and intra-observer

variability in establishing when lesions first appear, changes in size and enhancement. The inter- and intra-rater variability during serial examinations was less than 5%. Demyelinating areas, seen on T2 weighted images, and Gd-DTPA enhancement seen on T1 weighted images, were detected at the initial MRI study. Follow-up T2 and T1 weighted scans were sequentially analysed for the presence of new disease activity. Three types of "active" lesions were identified: 1) new lesions; 2) lesions which subsequently enlarge; a change exceeding more than 33% (1/3) should be required;<sup>25</sup> 3) enhancing lesions.

**Statistical analysis**

Differences between means and mean changes were tested using the Student's 2-sample t test, and differences between proportions were tested using the chi-squared test. The Spearman Rank correlation coefficient was used to compare changes in EDSS score and the total number of new, enlarging and enhancing MRI lesions at 1-year follow-up.

**RESULTS**

The clinical and MRI characteristics of the 25 patients included in the study are shown in Table 1; they were balanced for age, gender, duration of illness and neurological disability. All patients completed the entire treatment being able to tolerate the medication; adverse reactions were generally mild and readily treated. Seven patients reported nausea, 2 patients experienced amenorrhea which resolved rapidly with cessation of therapy and 1 patient had diarrhoea, vomiting and low grade fever. Side effects due to contrast media were not observed.

There was a statistically significant difference in the mean exacerbation rate and number of patients exacerbating during

the study favouring MX (Table 2). However, no statistical difference was observed in mean EDSS change at 1-year and in the proportion of patients with EDSS deterioration; a worsening in EDSS (1 point or more) was seen in 1 (8%) MX treated patient and in 2 (17%) cases of the placebo group (p = 0.49).

The number of patients showing new, enlarging and Gd-DTPA enhancing lesions during 1 year follow-up study are reported in Figure 1. New, enlarging and enhancing lesions were detected respectively in 11 (85%), 5 (38%) and 4 (31%) patients treated with MX and in 11 (92%), 8 (67%) and 7 (58%) patients of the placebo group.

Mean number of new, enlarging and Gd-DTPA enhancing lesions at 2, 4, 6 and 12 months for both treatment groups are shown in Table 3. There were no significant differences in the mean number of lesions/patient between the two groups at each serial examination. In the MX group, however, a trend was noted towards a total reduction of new (MX 2.30, placebo 3.91; p < 0.22), enlarging (MX 1, placebo 1.83; p < 0.42) and Gd-DTPA

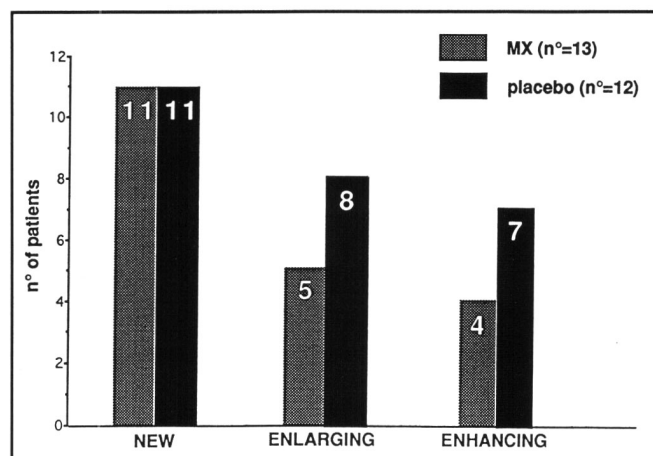


Figure 1. Number of patients showing new, enlarging and Gd-DTPA enhancing lesions during 1-year follow-up.

Table 1: Baseline clinical and MRI characteristics of patients entering treatment.

	MX	Placebo	Statistical test/p *
No. of patients (male/female)	13 (5/8)	12 (5/7)	Chi.sq/0.87
Age	29.9 (5.2) <sup>o</sup>	28.5 (6.5)	t test/0.55
Age at onset (yrs)	23.7 (5.6)	24.3 (5.3)	t test/0.81
Duration (yrs)	5.2 (2.4)	5 (2.7)	t test/0.86
Exacerbations in prior 2 years	2.8 (1.2)	3.3 (1.2)	t test/0.25
EDSS	3.7 (0.7)	3.5 (1.0)	t test/0.49
No. of lesions	25.5 (21.7)	28 (24.9)	t test/0.78
No. of enhancing lesions	0.3 (0.5)	0.5 (0.9)	t test/0.51

\* All t tests are two tailed

<sup>o</sup> Mean (SD)

MX Mitoxantrone

EDSS Expanded Disability Status Scale score

Table 2: Treatment groups after 1-year follow-up.

	MX (13)	Placebo (12)	Statistical test/p *
Mean exacerbation rate	0.54 (0.9) <sup>o</sup>	1.67 (1.2)	t test/0.014
No. of patients exacerbating	5 (38%)	10 (83%)	Chi.sq/0.02
Mean change in EDSS <sup>oo</sup>	-0.27 (0.7)	+0.08 (0.6)	t test/0.18
Proportion of patients with EDSS deterioration <sup>ooo</sup>	8%	17%	Chi.sq/0.49

\* All t tests are two tailed

<sup>o</sup> Mean (SD)

<sup>oo</sup> EDSS Expanded Disability Status Scale score (+ indicate a worsening at the end of treatment).

<sup>ooo</sup> A worsening >1 point on the EDSS.

**Table 3:** Mean number of new, enlarging and Gd-DTPA enhancing lesions/patient at serial MRI examinations for both treatment groups.

Months	MX			Placebo		
	New	Enlarging	Enhancing	New	Enlarging	Enhancing
0-2	0.61 (0.8) <sup>°</sup>	0.23 (0.6)	0.31 (0.6)	0.58 (0.8)	0.50 (0.8)	0.33 (0.5)
2-4	0.23 (0.6)	0.31 (0.8)	0	0.91 (1.7)	0.25 (0.6)	0.50 (1.4)
4-6	0.23 (0.6)	0.31 (0.9)	0.08 (0.3)	0.50 (1.0)	0.25 (0.6)	0.25 (0.5)
6-12	1.23 (1.7)	0.15 (0.4)	0.08 (0.3)	1.92 (2.5)	0.83 (2.0)	0.08 (0.3)
Total	2.30 (2.1) [ 2 ] <sup>°°</sup>	1 (1.8) [ 0 ]	0.46 (0.7) [ 0 ]	3.91 (4.1) [ 2.5 ]	1.83 (3.0) [ 1 ]	1.16 (1.5) [ 1 ]

<sup>°</sup> Mean (SD)  
<sup>°°</sup> Median

enhancing lesions (MX 0.46, placebo 1.16;  $p < 0.13$ ). This reduction was of 41%, 45% and 60% for new, enlarging and enhancing respectively.

Finally, there were no significant relationships between changes in the EDSS score and the total number of new, enlarging and Gd-DTPA enhancing MRI lesions at 1 year follow-up in both groups (data not shown).

## DISCUSSION

The rationale for immunosuppressive treatment lies in the suppression of the inflammatory reaction of the immune system in order to prevent or to arrest the process of demyelination. Drug treatments with immunosuppressive agents such as azathioprine, cyclophosphamide, cyclosporin or total lymphoid irradiation show only modest therapeutical benefit at safe doses in relapsing-remitting MS.<sup>26</sup>

Mitoxantrone is a well-known antineoplastic agent with recently detected immunomodulating properties, especially on B-lymphocyte function. Because the clinical tolerance of MX is better than that of other immunosuppressive drugs and long-term toxicity markedly lower, early pilot studies in progressive MS patients suggested that MX should be a candidate for controlled clinical trials.<sup>18-20</sup>

The primary purpose of this double-blinded, placebo-controlled trial was to determine whether monthly therapy with MX at a dose of 8 mg/m<sup>2</sup> every month for 1 year could alter disease progression in relapsing-remitting MS patients.

We found in this 1-year interim analysis a slowing of the clinical progression in MX treated patients compared with placebo as demonstrated by a reduction in the mean exacerbation rate and in the number of patients showing clinical exacerbations (see Table 2). Furthermore, a minor improvement in the mean EDSS score was detected in the MX group but not in the placebo group. However, it has been suggested that change in mean EDSS is clinically irrelevant and methodologically incorrect.<sup>27</sup> Differences in the proportion of patients changing by a given degree of disability represent the most feasible endpoint in the context of short-term clinical trials.<sup>28</sup> However, because of the small sample and the short-term follow-up period, we could observe a 1 point worsening in EDSS only in 2 (17%) patients receiving placebo and in 1 (8%) of the MX group.

Therefore, for a proper evaluation of the clinical results we must await the end of the multicenter study in the whole randomised sample.

Serial MRI examination has been recently proposed as an effective tool to evaluate the efficacy of short-term therapy.<sup>10,11,13-14</sup> When measuring therapeutic efficacy by MRI it is necessary to consider several different aspects such as the duration of the study, the number of patients and the frequency of scanning.<sup>13</sup> The enumeration of new, enlarging and Gd-DTPA enhancing lesions seems to be the most suitable measure of short-term outcome, while lesion/volume measurement is more appropriate for long-term studies.<sup>13,29</sup>

The marked variation in MRI activity, both between and within patients over time, implied the need to study a substantial number of patients. As recently suggested by McFarland et al.,<sup>11</sup> the sample size required to detect a significant reduction in lesion frequency in a therapeutical trial using a parallel group design, closely depends on the number of monthly MRI scans per subject. Monthly examinations for up to six months seems to be the most suitable interval using Gd-DTPA enhanced MRI.<sup>11,13</sup> With this frequency at least 90 subjects for each of the two groups (treated and placebo) would be required to make the trial design statistically acceptable.<sup>11</sup> On the basis of these assumptions the small sample (25 patients) and the frequency of scanning (2, 4, 6 and 12 months), appear to be the major limitations of the present study.

Considering our scan frequency, the likelihood of missing MRI activity appears more related to the detection of the enhanced lesions rather than new and enlarging ones. The duration of enhancement in relapsing-remitting patients is extremely variable ranging from less than 1 month to greater than 2 months;<sup>30</sup> generally, however the enhancing phase disappears within 4 weeks in about 2/3 of lesions.<sup>8,10</sup> In our placebo group, we detected a mean rate of 0.33 Gd-DTPA enhancing lesions/patient every two months, whereas the mean number of enhancing lesions/month observed in previous reports on untreated relapsing-remitting patients, ranges between 1.33 to 3.25.<sup>8,10,11</sup> Therefore, we might miss an enhancement in at least 50% of lesions with a bimonthly scan interval.

The effect of treatment evaluated by MRI and presented in both Figure 1 and Table 3 shows that no significant differences were observed between the MX and placebo treated patients when examined at 2, 4, 6 and 12 months.

Although not statistically significant, however, the yearly rate reduction observed in MX patients was of 41%, 45% and 60% for new, enlarging and Gd-DTPA enhancing lesions respectively. These findings are consistent with the significant trend towards a clinical improvement identified in the MX group and need to be confirmed by the end of the multicenter study before a potential benefit of MX can be claimed.

Another interesting point to be discussed is the lack of a significant relationship between change in EDSS score and MRI findings found in both placebo and MX patients. This is far from surprising since clinical and MRI methods measure different aspects of disease activity. Serial MRI studies of relapsing-remitting MS have shown that new abnormalities on the MRI occurred seven times more frequently than clinical events.<sup>7,10,30</sup> Our results confirm these findings showing a relative stable clinical course demonstrated by low variation of EDSS score after 1 year when compared with MRI activity.

#### ACKNOWLEDGEMENTS

We would like to thank Prof. Cesare Fieschi for his editorial criticisms and suggestions.

#### REFERENCES

- Young IR, Hall AS, Pallis CA, et al. Nuclear magnetic resonance imaging of the brain in multiple sclerosis. *Lancet* 1981; 2: 1063-1066.
- Lukes SA, Crooks LE, Aminoff MJ, et al. Nuclear magnetic resonance imaging in multiple sclerosis. *Ann Neurol* 1983; 13: 592-601.
- Gonzales-Scarano F, Grossman RI, Galletta S, Atlas SW, Silberberg DH. Multiple sclerosis disease activity correlates with gadolinium-enhanced magnetic resonance imaging. *Ann Neurol* 1987; 21: 300-306.
- Grossman RI, Braffman BH, Bronson JR, et al. Multiple sclerosis: serial study of gadolinium-enhanced MR imaging. *Radiology* 1988; 169: 117-122.
- Isaac C, Li DKB, Genton M, et al. Multiple sclerosis: a serial study using MRI in relapsing patients. *Neurology* 1988; 38: 1511-1515.
- Miller DH, Rudge P, Johnson G, et al. Serial gadolinium-enhanced magnetic resonance imaging in multiple sclerosis. *Brain* 1988; 111: 927-939.
- Willoughby EW, Grochowski E, Li DKB, et al. Serial magnetic resonance scanning in multiple sclerosis: a second prospective study in relapsing patients. *Ann Neurol* 1989; 25: 43-49.
- Bastianello S, Pozzilli C, Bernardi S, et al. Serial study of gadolinium-DTPA MRI enhancement in multiple sclerosis. *Neurology* 1990; 40: 591-595.
- Kermode AG, Tofts PS, Thompson AJ, et al. Heterogeneity of blood-brain barrier changes in multiple sclerosis: an MRI study with gadolinium-DTPA enhancement. *Neurology* 1990; 40: 229-235.
- Harris JO, Frank JA, Patronas N, McFarlin DE, McFarlan HF. Serial gadolinium-enhanced magnetic resonance imaging scans in patients with early, relapsing-remitting multiple sclerosis: implications for clinical trials and natural history. *Ann Neurol* 1991; 29: 548-555.
- McFarland HF, Frank JA, Albert PS, et al. Using gadolinium-enhanced magnetic resonance imaging lesions to monitor disease activity in multiple sclerosis. *Ann Neurol* 1992; 32: 758-766.
- Kappos L, Stadt D, Ratzka M, et al. Magnetic resonance imaging in the evaluation of treatment in multiple sclerosis. *Neuroradiology* 1988; 30: 299-302.
- Miller DH, Barkhof F, Berry I, et al. Magnetic resonance imaging in monitoring the treatment of multiple sclerosis: concerned action guidelines. *J Neurol Neurosurg Psychiatry* 1991; 54: 683-688.
- Miller DH, Thompson AJ, Morrissey SP, et al. High dose steroids in acute relapses of multiple sclerosis: MRI evidence for a possible mechanism of therapeutic effect. *J Neurol Neurosurg Psychiatry* 1992; 55: 450-453.
- Fidler JM, Quinn De Joj S, Smith III FR, Gibbons JJ. Selective immunomodulation by the antineoplastic agent mitoxantrone. Non-specific adherent suppressor cell derived from mitoxantrone treated mice. *J Immunol* 1986; 136: 2747-2754.
- Fidler JM, Quinn De Joj S, Gibbons JJ. Selective immunomodulation by the antineoplastic agent mitoxantrone. Suppression of B lymphocyte function. *J Immunol* 1986; 137: 727-732.
- Levine S, Saltzman A. Regional suppression, therapy after onset and prevention of relapses in experimental allergic encephalomyelitis by mitoxantrone. *J Neuroimmunol* 1986; 13: 175-181.
- Gonsette RE, Demonty L. Immunosuppression with mitoxantrone in multiple sclerosis: a pilot study for 2 years in 22 patients. *Neurology* 1990; 40 (Suppl 1): 261.
- Kappos L, Gold R, Kunstler E, et al. Mitoxantrone (MX) in the treatment of rapidly progressive multiple sclerosis: a pilot study with serial gadolinium (GD)-enhanced MRI. *Neurology* 1990; 40 (Suppl 1): 261.
- Noseworthy JH, Lee D, Penman M, et al. A phase II evaluation of mitoxantrone HCl in the treatment of progressive multiple sclerosis. *Neurology* 1991; 41 (Suppl 1): 146.
- Noseworthy JH, Hopkins MB, Vandervoort MK, et al. An open-trial evaluation of mitoxantrone in the treatment of progressive MS. *Neurology* 1993; 43: 1401-1406.
- Paty D, Willoughby E, Whithaker J. Assessing the outcome of experimental therapies in multiple sclerosis patients. *In: "Treatment of Multiple Sclerosis. Trial Design, Results and Future Perspectives."* Rudick RA, Goodkin DE, eds. Springer-Verlag, Germany 1992: 47-90.
- Poser CM, Paty DW, Scheinberg L, et al. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. *Ann Neurol* 1983; 13: 227-231.
- Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology* 1983; 33: 1442-1452.
- Goodkin DE, Ross JS, Vanderbrug Medendorp S, Konecni J, Rudick RA. Magnetic resonance imaging lesion enlargement in multiple sclerosis. Disease-related activity, chance occurrence, or measurement artefact? *Arch Neurol* 1992; 49: 261-263.
- McDonald WI. The dynamics of multiple sclerosis. *J Neurol* 1993; 240: 28-36.
- Kurtzke JF. Neuroepidemiology. Part II: assessment of therapeutic trials. *Ann Neurol* 1986; 19: 311-319.
- Weinshenker BG, Rice GPA, Noseworthy JH, et al. The natural history of multiple sclerosis: a geographically based study. 4. Applications to planning and interpretation of clinical therapeutic trials. *Brain* 1991; 114: 1057-1067.
- Matthews WB, Matthews WC, eds. *McAlpine's Multiple Sclerosis*, 2nd ed. Edinburgh, Churchill Livingstone, 1991.
- Thompson AJ, Kermode AG, Wicks D, et al. Major differences in the dynamics of primary and secondary progressive multiple sclerosis. *Ann Neurol* 1991; 29: 53-62.