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Evaluating the Role of Corticosteroid Pulse Therapy in Patients With Secondary Progressive Multiple Sclerosis Receiving Mitoxantrone: A Double Blind Randomized Controlled Clinical Trial

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Abstract

Background: Multiple sclerosis (MS) is a central nervous system disorder with periods of recurrence and recovery. Mitoxantrone has been approved for secondary progressive MS (SPMS) treatment but data lacks the role of corticosteroid pulse therapy in SPMS.

Objectives: To evaluate the role of corticosteroid pulse therapy in patients with SPMS receiving mitoxantrone.

Patients and Methods: A double blind randomized controlled clinical trial was performed on 71 patients with SPMS referred to Shahid Sadoughi Hospital (Yazd, Iran) for receiving mitoxantrone in two groups. The first group (35 patients) received 20 mg mitoxantrone plus 500 mg methylprednisolone monthly for six months. The second group (36 patients) received the same dosage of mitoxantrone plus 100 CC of 5% dextrose water monthly for six months. Expanded disability status scale (EDSS), MRI plaques in both groups before and after the treatment completion and six months after the end of trial were compared together.

Results: 28 men and 43 women enrolled in the study. MRI plaques number reduced in groups significantly (2.29 vs. 2.17) without significant difference between the groups (P = 0.782). Six months after trial completion, plaques number increased in groups without significantly difference (0.72 vs. 0.77, P = 0.611). The mean value of EDSS showed significant reduction at the end of treatment in groups (0.79 and 0.53) without significant difference between the groups (P = 0.953). Six months after trial completion, EDSS increased in groups without significant difference (0.35 vs. 0.43, P = 0.624).

Conclusions: Corticosteroid pulse therapy in SPMS was effective in inflammatory process, but could not postpone or decline the neurodegenerative process and besides the imposing side effects could not result in significant improvement in EDSS and MRI plaques number in long term.

Keywords: Methylprednisolone, Mitoxantrone, Secondary Progressive Multiple Sclerosis, MS therapy

1. Background

Multiple sclerosis (MS) is a central nervous system disorder recognized by frequent attacks to optic nerve, spinal cord and brain with periods of recurrence and recovery which could result in disability mainly in youth (1). Clinical features are hemiparesis or paraparesis, paresthesia, blurred vision, diplopia, nistagmus, dysarthria, imbalance, deep sensation disturbance and bladder dysfunction (2). MS is divided into four types:

1- Relapse and remitting (RR): periods of relapse with complete recovery or some sequels.

2- Primary progressive (PP): progression from the beginning with phases of Plato or mild improvement.

3- Secondary progressive (SP): relapsing and remitting from the beginning and then progression.

4- Progressive relapsing (PR): progression from the beginning with acute relapses without significant improvement (3).

Most patients with a relapsing-remitting course finally enter a chronic progressive condition (SPMS) with accumulating disability. Progression would continue with or without relapses with minor remissions between relapses (4). Sometimes it progresses constantly from the beginning (PPMS), usually occurs in cases with MS after the fourth decade. In progressive relapsing MS, the disease progresses from onset, with clear acute relapses and with or without full recovery (2). On the other hand, personal activities and social partnership of the individual are affected by disease (5). During the long period, inflammatory infiltrations decline (6), while neurodegenerative processes become a more prominent feature (7). Recent investigations revealed that inflammatory process in the brain occurs in RRMS and presents in the progressive course. Furthermore, in SPMS, inflammatory process in the meninges could be found. Interestingly, the extent of inflammatory process in the meninges correlates with the amount of neurodegeneration.

Therefore, inflammatory process appears to drive tissue degeneration in some patients (8). In summary, the inflammatory process is less important during the course of SPMS, while neurodegeneration is the substrate that drives the accumulating neurological disability (9). Based on the role of inflammatory and neurodegenerative processes in pathophysiology of SPMS, many drugs have been tested to treat these processes. Box 1 shows approved, not approved but common use and under examination drugs for SPMS therapy (9).

Mitoxantrone (drug for breast cancer chemotherapy) has been approved for SPMS treatment since 2002 (10). Mild adverse effects are transient leukopenia, liver enzymes elevation, nausea, vomiting, transient alopecia, urine color change and urinary tract infection (11). Moreover, mitoxantrone has serious but uncommon adverse effects such as bone marrow suppression, acute leukemia, infertility (12) and cardio toxicity with cumulative dose of 140 mg/m^2 (13). It could be prescribed 5 - 12 mg/m^2 intravenously monthly or every three months (14). The probable effects of mitoxantrone are relapse reduction, expanded disability status scale (EDSS) improvement and slowing the disability progression (15). On the other hand, methylprednisolone has been used for progressive MS. Standard therapy for acute relapse of MS is pulse therapy with high dose of methylprednisolone 500 - 1000 mg/daily for 3 to 5 days (16). New evidences show that severity of clinical signs and symptoms reduce by this protocol (17). As treatment protocols in SPMS are still limited, corticosteroids are used in SPMS. Although its efficacy in SPMS is not proven, the role of corticosteroids in treatment of progressive MS is still obscured. Different studies showed that corticosteroids may improve inflammation, but at later stages degeneration can hardly be influenced (17-20). First dose of intravenous methylprednisolone is usually administered in hospital for safety reasons. Potentially severe adverse effects are epileptic seizures, psychotic reactions, cognitive decline, venous thrombosis, anaphylactic reactions and cardiac arrhythmias (21-25). Furthermore, one study suggested that co-administration of mitoxantrone and methylprednisolone may reduce the progression of disability in patients with PP-MS and SP-MS (26).

Box 1. Therapies for Secondary Progressive Multiple Sclerosis (SPMS)

Approved
Interferon Beta 1b
Interferon Beta 1a
Mitoxantrone
Not approved but common
Intravenous Immunoglobulin
Corticosteroids
Azathioprine
Cyclophosphamide
Mycophenolate
Under examination
Daclizumab
Rituximab
Hematopoietic stem cell transplantation
Masitinib
Fingolimod

2. Objectives

The purpose of the present study was to evaluate the role corticosteroid pulse therapy in patients with SPMS referred to Shahid Sadoughi Hospital (Yazd, Iran) for receiving mitoxantrone.

3. Patients and Methods

Our study was a double blind randomized clinical trial performed in Shahid Sadoughi Hospital (Referral, Specialized, Governmental, 576 beds and 22 sections) of Yazd, Iran on 82 patients (aged 20 to 50 years) with SPMS referred for receiving mitoxantrone [(trial code: IRCT201107145943N3), IRCT: Iran registry of clinical trials]. The sample size formula was:

(1). $$x = \left(z_{1-\frac{\alpha}{2}} + z_{1-\beta}\right)^2 \times \frac{2S^2}{d^2}$$

(S = 4 and d = 2.5).

The expected power was 80%. Normal assumption and repeated measurement assumption were checked precisely. Simple randomized sampling procedure was performed based on the study criteria using the "Random Allocation Software" program (Figure 1). Eleven patients withdrew the trial due to refractory vomiting (4 patients), urinary tract or gastrointestinal infection (3 patients) and unreliability to the treatment results (4 patients). Inclusion criteria were any patient with SPMS between 20 - 50 years old, progressive deterioration period of at least 6 months and less than 4 years, EDSS between 4.0 and 7. Exclusion criteria were immune deficiency, cancer, pregnancy, breast feeding, renal or heart failure, diabetes mellitus and tuberculosis. Patients with leukopenia during the injection (neutrophils less than 1500/mL) and those who had received corticosteroids within 6 months before the trial were excluded from the trial. Finally, 71 patients enrolled in the study and randomly assigned into two groups. The first group (35 patients) received 20 mg mitoxantrone plus 500 mg methylprednisolone intravenously and the other group (36 patients) received the same dose of mitoxantrone and 100 CC of 5% dextrose water monthly for consecutive six months. All patients were evaluated by neurological exam, especially expanded disability status scale (EDSS), MRI of the brain and spinal cord (1.5 Tesla, without contrast, T2 phase), cell

blood count, hepatic tests and echocardiography before the treatment establishment. At the end of drug administration completion (sixth month), they were evaluated again by EDSS, MRI, blood cell count, hepatic tests and echocardiography. At the twelfth month they were evaluated repeatedly by EDSS and MRI plaque number. The patients, nurses administering the drugs and those registering the signs and symptoms of the patients were blinded to the study design. Neurologic examinations before and after the treatment were performed by one neurologist who was unaware of the treatment methods. Furthermore, by MRI study (1.5 Tesla, without contrast), the number of plaques in the brain and spinal cord were measured by a radiologist unaware of the type of treatments. At the sixth month, the above mentioned checkups were performed (by the same neurologist) and the number of plaques were measured (by the same radiologist) and compared to those before the trial establishment. Six months after the study completion, EDSS and MRI plaques were measured again. An informed consent was obtained from all patients. The ethics committee of Yazd University of Medical Sciences approved the study. Finally, gathered data was analyzed using statistical tests of t-test, chi-square, paired sample t-test and repeated measure ANOVA by SPSS version 11.5 software.

4. Results

Of 71 patients who completed the study, 28 patients were males (39.4%) and 43 females (60.6%). Age, sex and disease duration were not different significantly between the groups ($P > 0.05$). Demographic features are shown in Table 1. The main index evaluated in this study was the number of plaques in MRI of patients in the both groups before and after the treatment (sixth month and twelfth month). The mean number of MRI plaques showed significant reduction in the both groups after the treatment (P value < 0.05), but difference between the groups was not significant (P value = 0.782). Although the number of plaques increased in the both groups during 6 months after trial completion, the difference was not significant between the groups (P value = 0.611) (Table 2). EDSS reduced

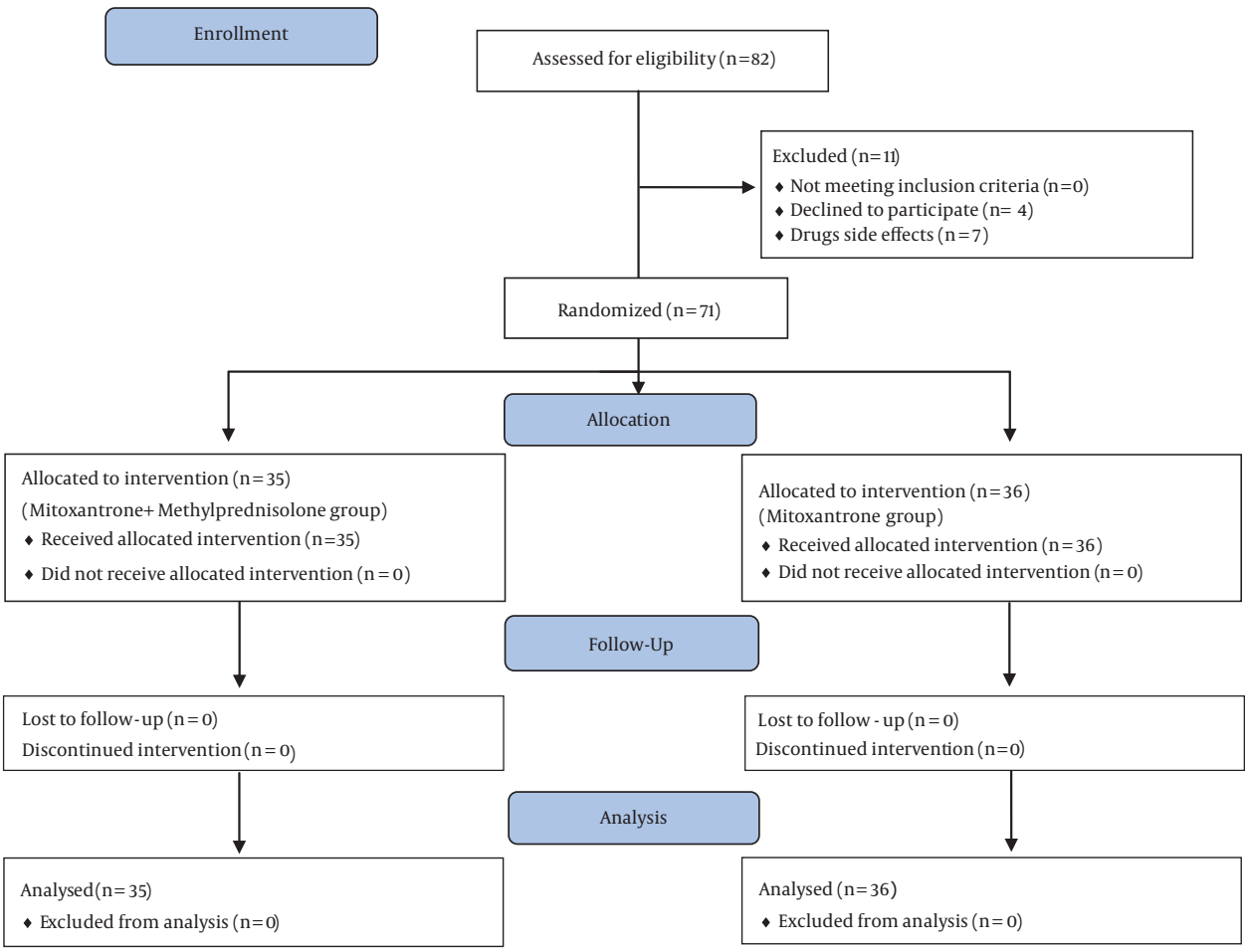

Figure 1. CONSORT Flow Diagram

significantly in the both groups at the end of treatment completion (P value < 0.05), but the difference between the groups was not significant (P value = 0.953). During six months after treatment completion, EDSS increased in the both groups, but the difference was not significant (P value = 0.624) (Table 3).

Table 1. Demographic Features of the Groups

Variations	Groups		P Value
	Mitoxantrone + MP	Mitoxantrone	
Age [a]	36.5 ± 9.2	35.7 ± 10.6	0.735
Male/Female	3/4	4/5	1
Disease duration, mo [a]	69.1 ± 45.6	74.8 ± 42.2	0.587

[a]Values are presented as mean± SD.

Table 2. Comparing MRI Plaques Between the Groups[a,b]

Groups	MRI Plaques Number [c]		
	Before the Treatment	End of the Treatment	6 Months After Treatment Completion
Mitoxantrone + MP	10.6 ± 4.37	8.31 ± 4.06	9.03 ± 3.56
Mitoxantrone	10.8 ± 4.56	8.63 ± 3.95	9.4 ± 4.33

[a]P value between before and the end of treatment was 0.782.
[b]P value between before the treatment and six months after the treatment completion was 0.611.
[c]values are presented as mean ± SD.

Table 3. EDSS of Groups During the Study[a,b]

Groups	EDSS [c]		
	Before the Treatment	End of the Treatment	6 Months After the Treatment Completion
Mitoxantrone + MP	5.40 ± 1.46	4.61 ± 1.87	4.96 ± 1.63
Mitoxantrone	5.17 ± 2.10	4.64 ± 2.16	5.07 ± 1.92

[a]P value comparing EDSS changes before the treatment and end of the treatment between the groups was 0.953.
[b]P value comparing EDSS changes before the treatment and end of the treatment between the groups was 0.624.
[c]values are presented as mean ± SD.

5. Discussion

In our trial, age, sex and duration of disease were not different statistically between the groups (P > 0.05). Today, the use of MRI makes it easier to evaluate patients with MS, in a way that it is possible to assess the activity of disease without clinical symptoms; furthermore, it can be used as a measurement criterion (27, 28). However due to limited facilities of our trial, the use of gadolinium contrast and obtaining MRI serially were not possible. Previous studies showed that mitoxantrone decreased the number of plaques in secondary progressive MS from 52% to 89% compared to placebo or methylprednisolone (15, 29-31). Our study showed that MS plaques decreased in both groups significantly (P < 0.05), but there was no difference between the groups (P > 0.05), so adding methylprednisolone to mitoxantrone had no significant influence on the number of plaques reduction. The number of plaques increased in both groups during six months after trial completion, but the difference between groups was not significant. It means that adding methylprednisolone to mitoxantrone had no influence on MRI plaques significantly. Numerous studies implicated the efficacy of mitoxantrone on declining EDSS or slowing disability progression (15, 30, 32). Also studies comparing the efficacy of mitoxantrone plus methylprednisolone to methylprednisolone alone (29) or mitoxantrone compared to methylprednisolone (33) show advantage of mitoxantrone use in reducing disability of secondary progressive MS.

Our study showed that the mean EDSS in the group treated with mitoxantrone decreased from 5.17 to 4.64 after the treatment and in the group treated with mitoxantrone and methylprednisolone, this decrement was from 5.4 to 4.6. Both these decrements were significant (P < 0.05), but the difference between the groups was not significant (P > 0.05). EDSS increased in both groups during six months after drug administration completion, but the difference was not significant. Although its efficacy in SPMS is not proven, the importance of glucocorticosteroids in treatment of progressive MS is still undisputed. The results of different trials suggest that glucocorticosteroids may improve inflammation, but at later stages degeneration can hardly be influenced (9). Table 4 shows paradoxes in efficacy of glucocorticosteroids therapy in MS. The strong points of our study were highly cooperative patients, study design and low missing values. The weak points were lack of MRI with contrast (due to high cost) and follow-up duration.

Table 4. Studies Regarding Corticosteroids Therapy in Multiple Sclerosis

Study	Type of MS	Root of Treatment	Result
Bergamaschi et al. (1993) (18)	PMS	1000 mg IVMP daily for 6 days	1- Delay in progression in progressive MS in 18 patients, whereas a worsening was present in 13 patients. 2- Disability was not affected by repeated IVMP
Frequin et al. (1994) (19)	RRMS and RPMS	1000 mg IVMP for 10 days, the application was repeated depending on sustaining deterioration on repeated clinical examinations	Reduction in the relapse rate
Goodkin et al. (1998) (20)	SPMS	500 mg IVMP bimonthly over 2 years	Delay of onset on ongoing disease progression
Zivadinov et al. (2001) (34)	RRMS	1000 mg IVMP was given every 4 months for 3 years and then every 6 months for the subsequent 2 years.	Slows development of T1 black holes, prevents or delays whole-brain atrophy and disability progression.
Pirko et al. (2004) (35)	PPMS or SPMS	Pulses of IVMP every month	1- Improvement in fatigue, spasticity and motor strength. 2- Acute exacerbations were occurred in 9 of 10 patients.
Zingler et al. (2005) (26)	PPMS and SPMS	10 cycles of combined mitox and MP. The intervals between the individual cycles were systematically prolonged from 3 months initially to 12 months	Mitox. combined with MP beneficially reduces the progression of disability in patients with PP-MS and SP-MS.
Araujo et al. (2008) (36)	PPMS	Periodic use of IVMP (30 mg/kg)	Decreased EDSS and postponed clinical worsening
Cohen et al. (2009) (11)	RRMS	Adding low-dose oral methotrexate(20 mg weekly) or every other month IVMP (1000 mg/day for 3 days) to interferon beta-1a	No benefit (The primary endpoint was new or enlarged T2 lesion number at month 12 vs. baseline)
Sorensen et al. (2009) (37)	RRMS	Oral MP given in pulses every 4 weeks as an add-on therapy to subcutaneous interferon beta-1a	Reduction in relapse rate
Ravnborg et al. (2010) (38)	RRMS	Monthly pulses of IVMP in combination with interferon beta-1a	No effect on disability progression

This study concluded that there were no significant differences in the clinical and radiologic results and long-term prognosis of patients with SPMS treated with mitoxantrone plus methylprednisolone versus mitoxantrone alone. Corticosteroid pulse therapy in SPMS was effective in inflammatory process, but could not postpone or decline the neurodegenerative process and besides the imposing adverse effects could not result in significant improvement in EDSS and MRI plaques number in long term. More studies should be performed for drawing certain conclusions.

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Footnotes

Authors' Contributions: Abolghasem Rahimdel, Ahmad Zeinal and Ali Mellat participated in the study design, data analysis, literature review, preparation and editing the manuscript.

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References

1. Whetten-Goldstein K, Sloan FA, Goldstein LB, Kulas ED. A comprehensive assessment of the cost of multiple sclerosis in the United States. *Mult Scler.* 1998;**4**(5):419–25. [PubMed: 9839302]
2. Brex PA, Ciccarelli O, O'Riordan JI, Sailer M, Thompson AJ, Miller DH. A longitudinal study of abnormalities on MRI and disability from multiple sclerosis. *N Engl J Med.* 2002;**346**(3):158–64. doi:10.1056/NEJMoa011341. [PubMed: 11796849]
3. Lublin FD, Reingold SC. Defining the clinical course of multiple sclerosis: results of an international survey. National Multiple Sclerosis Society (USA) Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis. *Neurology.* 1996;**46**(4):907–11. [PubMed: 8780061]
4. Weinshenker BG. The natural history of multiple sclerosis: update 1998. *Semin Neurol.* 1998;**18**(3):301–7. doi: 10.1055/s-2008-1040881. [PubMed: 9817534]
5. Kesselring J. Forum: Rehabilitation in MS Is Effective. *Int MS J.* 2001;**8**(2):68–71.
6. Frischer JM, Bramow S, Dal-Bianco A, Lucchinetti CF, Rauschka H, Schmidbauer M, et al. The relation between inflammation and neurodegeneration in multiple sclerosis brains. *Brain.* 2009;**132**(Pt 5):1175–89. doi: 10.1093/brain/awp070. [PubMed:

19339255]
7. Luessi F, Siffrin V, Zipp F. Neurodegeneration in multiple sclerosis: novel treatment strategies. *Expert Rev Neurother.* 2012;**12**(9):1061–76. doi: 10.1586/ern.12.59. [PubMed: 23039386]
8. Lassmann H. Cortical lesions in multiple sclerosis: inflammation versus neurodegeneration. *Brain.* 2012;**135**(Pt 10):2904–5. doi: 10.1093/brain/aws260. [PubMed: 23065786]
9. Rommer PS, Stuve O. Management of secondary progressive multiple sclerosis: prophylactic treatment-past, present, and future aspects. *Curr Treat Options Neurol.* 2013;**15**(3):241–58. doi: 10.1007/s11940-013-0233-x. [PubMed: 23609781]
10. Rieckmann P, Toyka KV. Escalating immunotherapy of multiple sclerosis.Austrian-German- Swiss Multiple Sclerosis Therapy Consensus Group [MSTCG]. *Eur Neurol.* 1999;**42**(3):121–7. doi: 10.1159/000008084. [PubMed: 10529535]
11. Cohen BA, Mikol DD. Mitoxantrone treatment of multiple sclerosis: safety considerations. *Neurology.* 2004;**63**(12 Suppl 6):S28–32. [PubMed: 15623667]
12. Vicari AM, Ciceri F, Folli F, Lanzi R, Colombo B, Comi G, et al. Acute promyelocytic leukemia following mitoxantrone as single agent for the treatment of multiple sclerosis. *Leukemia.* 1998;**12**(3):441–2. [PubMed: 9529141]
13. Posner LE, Dukart G, Goldberg J, Bernstein T, Cartwright K. Mitoxantrone: an overview of safety and toxicity. *Invest New Drugs.* 1985;**3**(2):123–32. [PubMed: 3894276]
14. Scott LJ, Figgitt DP. Mitoxantrone: a review of its use in multiple sclerosis. *CNS Drugs.* 2004;**18**(6):379–96. [PubMed: 15089110]
15. Hartung HP, Gonsette R, Konig N, Kwiecinski H, Guseo A, Morrissey SP, et al. Mitoxantrone in progressive multiple sclerosis: a placebo-controlled, double-blind, randomised, multicentre trial. *Lancet.* 2002;**360**(9350):2018–25. doi: 10.1016/S0140-6736(02)12023-X. [PubMed: 12504397]
16. Noseworthy JH, Lucchinetti C, Rodriguez M, Weinshenker BG. Multiple sclerosis. *N Engl J Med.* 2000;**343**(13):938–52. doi: 10.1056/NEJM200009283431307. [PubMed: 11006371]
17. McDonald WI, Compston A, Edan G, Goodkin D, Hartung HP, Lublin FD, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. *Ann Neurol.* 2001;**50**(1):121–7. [PubMed: 11456302]
18. Bergamaschi R, Versino M, Raiola E, Citterio A, Cosi V. High-dose methylprednisolone infusions in relapsing and in chronic progressive multiple sclerosis patients. One year follow-up. *Acta Neurol (Napoli).* 1993;**15**(1):33–43. [PubMed: 8456594]
19. Frequin ST, Lamers KJ, Barkhof F, Borm GF, Hommes OR. Follow-up study of MS patients treated with high-dose intravenous methylprednisolone. *Acta Neurol Scand.* 1994;**90**(2):105–10. [PubMed: 7801735]
20. Goodkin DE, Kinkel RP, Weinstock-Guttman B, VanderBrug-Medendorp S, Secic M, Gogol D, et al. A phase II study of i.v. methylprednisolone in secondary-progressive multiple sclerosis. *Neurology.* 1998;**51**(1):239–45. [PubMed: 9674809]
21. Chau SY, Mok CC. Factors predictive of corticosteroid psychosis in patients with systemic lupus erythematosus. *Neurology.* 2003;**61**(1):104–7. [PubMed: 12847167]
22. Stadler C, Vuadens P, Dewarrat A, Janzer R, Uske A, Bogousslavsky J. [Cerebral venous thrombosis after lumbar puncture and intravenous steroids in two patients with multiple sclerosis]. *Rev Neurol (Paris).* 2000;**156**(2):155–9. [PubMed: 10743014]
23. Stolz E, Klotzsch C, Schlachetzki F, Rahimi A. High-dose corticosteroid treatment is associated with an increased risk of developing cerebral venous thrombosis. *Eur Neurol.* 2003;**49**(4):247–8. doi: 10.1159/000070197. [PubMed: 12736545]
24. Brusaferri F, Candelise L. Steroids for multiple sclerosis and optic neuritis: a meta-analysis of randomized controlled clinical trials. *J Neurol.* 2000;**247**(6):435–42. [PubMed: 10929272]
25. Filippini G, Brusaferri F, Sibley WA, Citterio A, Ciucci G, Midgard R, et al. Corticosteroids or ACTH for acute exacerbations in multiple sclerosis. *Cochrane Database Syst Rev.* 2000;(4):CD001331. doi: 10.1002/14651858.CD001331. [PubMed: 11034713]
26. Zingler VC, Strupp M, Jahn K, Gross A, Hohlfeld R, Brandt T. [The effect of combined mitoxantrone and methylprednisolone therapy in primary and secondary progressive multiple sclerosis. An applied study in 65 patients]. *Nervenarzt.* 2005;**76**(6):740–7. doi: 10.1007/s00115-005-1885-x. [PubMed: 15803287]
27. McFarland HF, Frank JA, Albert PS, Smith ME, Martin R, Harris JO, et al. Using gadolinium-enhanced magnetic resonance imaging lesions to monitor disease activity in multiple sclerosis. *Ann Neurol.* 1992;**32**(6):758–66. doi: 10.1002/ana.410320609. [PubMed: 1471866]
28. Miller DH, Barkhof F, Berry I, Kappos L, Scotti G, Thompson AJ. Magnetic resonance imaging in monitoring the treatment of multiple sclerosis: concerted action guidelines. *J Neurol Neurosurg Psychiatry.* 1991;**54**(8):683–8. [PubMed: 1940938]
29. Edan G, Miller D, Clanet M, Confavreux C, Lyon-Caen O, Lubetzki C, et al. Therapeutic effect of mitoxantrone combined with methylprednisolone in multiple sclerosis: a randomised multicentre study of active disease using MRI and clinical criteria. *J Neurol Neurosurg Psychiatry.* 1997;**62**(2):112–8. [PubMed: 9048709]
30. Le Page E, Leray E, Edan G, French Mitoxantrone Safety G. Long-term safety profile of mitoxantrone in a French cohort of 802 multiple sclerosis patients: a 5-year prospective study. *Mult Scler.* 2011;**17**(7):867–75. doi: 10.1177/1352458511398371. [PubMed: 21325016]
31. Le Page E, Leray E, Taurin G, Coustans M, Chaperon J, Edan G. [Mitoxantrone as induction therapy in aggressive relapsing remitting multiple sclerosis: a descriptive analysis of 100 consecutive patients]. *Rev Neurol (Paris).* 2006;**162**(2):185–94. [PubMed: 16518258]
32. Hamzehloo A, Etemadifar M. Mitoxantrone reduced disability in Iranian patients with multiple sclerosis. *Arch Iran Med.* 2007;**10**(1):59–64. [PubMed: 17198456]
33. van de Wyngaert FA, Beguin C, D'Hooghe MB, Dooms G, Lissoir F, Carton H, et al. A double-blind clinical trial of mitoxantrone versus methylprednisolone in relapsing, secondary progressive multiple sclerosis. *Acta Neurol Belg.* 2001;**101**(4):210–6. [PubMed: 11851027]
34. Zivadinov R, Rudick RA, De Masi R, Nasuelli D, Ukmar M, Pozzi-Mucelli RS, et al. Effects of IV methylprednisolone on brain atrophy in relapsing-remitting MS. *Neurology.* 2001;**57**(7):1239–47. [PubMed: 11591843]
35. Pirko I, Rodriguez M. Pulsed intravenous methylprednisolone therapy in progressive multiple sclerosis: need for a controlled trial. *Arch Neurol.* 2004;**61**(7):1148–9. doi: 10.1001/archneur.61.7.1148. [PubMed: 15262754]
36. Araujo EA, Freitas MR. Benefit with methylprednisolone in continuous pulsetherapy in progressive primary form of multiple sclerosis: study of 11 cases in 11 years. *Arq Neuropsiquiatr.* 2008;**66**(2B):350–3. [PubMed: 18641870]
37. Sorensen PS, Mellgren SI, Svenningsson A, Elovaara I, Frederiksen JL, Beiske AG, et al. NORdic trial of oral Methylprednisolone as add-on therapy to Interferon beta-1a for treatment of relapsing-remitting Multiple Sclerosis (NORMIMS study): a randomised, placebo-controlled trial. *Lancet Neurol.* 2009;**8**(6):519–29. doi: 10.1016/s1474-4422(09)70085-7. [PubMed: 19409854]
38. Ravnborg M, Sørensen PS, Andersson M, Celius EG, Jongen PJ, Elovaara I, et al. Methylprednisolone in combination with interferon beta-1a for relapsing-remitting multiple sclerosis (MECOMBIN study): a multicentre, double-blind, randomised, placebo-controlled, parallel-group trial. *Lancet Neurol.* 2010;**9**(7):672–80. doi: 10.1016/s1474-4422(10)70132-0. [PubMed: 20542736]