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ORIGINAL RESEARCH

COCHRANE CAM REVIEW: SUMMARY OF FINDINGS

Long-term effects of BEMER magnetic field therapy on the level of fatigue in patients with multiple sclerosis: an open label follow-up study.

Running head: Long-term magnetic field therapy for MS fatigue

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Abstract

Background: Electromagnetic field therapy has reportedly beneficial effects in multiple sclerosis patients (MS) with significant fatigue.

Primary Study Objectives: To evaluate the long-term effects of Bio-Electro-Magnetic-Energy-Regulation (BEMER) therapy on MS-related fatigue we designed a crossover control of a previously performed randomized controlled trial and a long-term open label follow-up trial.

Design & Setting: Monocenter, crossover and open label follow-up trial at a neurological outpatient centre.

Participants: Thirty-seven relapsing-remitting patients with MS presenting with significant fatigue.

Intervention: After previous random exposure to low-frequency pulsed magnetic fields for eight minutes twice daily or to placebo treatment for 12 weeks a crossover from control to verum for another 12 weeks and a three years' open label follow-up were applied.

Primary Outcome Measures: The primary outcome criteria were changes in the Modified Fatigue Impact Scale (MFIS) and Fatigue Severity Scale (FSS) between the end of the initial double-blind study and the follow-up as well as the end of the crossover trial (12 weeks). The secondary outcome criteria were changes in a general depression scale (ADS-L), the Multiple Sclerosis Functional Scale (MSFC), and the Expanded Disability Status Scale (EDSS).

Results: MFIS and FSS scores were significantly lower in the open label group than in the controls after follow-up (MFIS: 16.78 versus 42.54; p= 0.00; FSS: 2.35 versus 5.16; p= 0.00). Participation in the open label treatment was the strongest predictor of low fatigue outcome after follow-up (ANCOVA $MFIS_{3years}$: p= 0.00; η^2= 0.597). Patients previously on placebo experienced significant reductions in fatigue after crossing over to treatment (MFIS: 33.23 to 22.42, p= 0.006; FSS: 4.13 to 3.04, p= 0.005). BEMER therapy was well tolerated.

Conclusions: In this long-term open label study, we were able to demonstrate a beneficial effect of chronic BEMER therapy on MS fatigue. Electromagnetic field therapy may be a useful therapeutic addition in MS patients with severe fatigue.

Introduction

Fatigue is among the most common symptoms of multiple sclerosis (MS) affecting more than 75% of patients.[1] For the majority of patients it constitutes one of the worst and most distressing features.[2] Fatigue is reported in all clinical phenotypes of MS and affects patients of all ages.[3] This symptom is an integral part of the disease process that is usually present at the time of diagnosis and in some cases represents one of the reasons for which patients originally consult a neurologist.

Fatigue is not closely related to physical signs of disability or with magnetic resonance imaging markers of disease activity, although it seems to increase when the patient experiences a relapse.[2,4] The aetiology and pathophysiology of MS-related fatigue remain unknown. Studies were not able to demonstrate an association between MS-related fatigue and the level of disability, clinical disease subtype, or gender.[5]

Management strategies include medications, exercise, and behavioural therapy.[6] There have been reports on positive effects of immunomodulatory drugs on fatigue.[7] However, the efficacy of treatment remains disappointing.[6]

The potential benefits of nonpharmacological magnetic field therapy as reported in a recent meta-analysis[8] warranted further investigation, even when the mechanism of modulating MS-related fatigue is far from being resolved.[8] Therefore, we previously performed a randomized, double-blind controlled trial[9] (RCT) on the effect of Bio-Electro-Magnetic-Energy-Regulation (BEMER, Innomed International AG, Lichtenstein) therapy, which uses broadband, extremely weak, low-frequency pulsed electromagnetic fields,[10] on patients with relapsing-remitting MS with significant fatigue in a typical outpatient setting. Our findings indicated that the level of fatigue as measured by different fatigue scales was significantly lower in the verum than in the placebo group after 12 weeks of treatment (t3).[9]

To follow these results up we extended the study protocol by a single crossover control and a long-term open label follow-up.

We hypothesized that regular BEMER therapy over a period of three years will improve fatigue in MS patients compared to patients not using this device. In addition, we anticipated

that patients switching from placebo to BEMER treatment in the crossover period will experience progressive fatigue reduction compared to their level at the end of the placebo trial.

Materials and Methods

The present study was a monocenter, open label and crossover follow-up trial conducted in a neurological outpatient centre in Dresden. The crossover trial lasted 12 weeks (from t3 to t5) and was performed between 2006 and 2007. The long-term open label trial was conducted three years after the end of crossover in 2009. The study protocol was approved by the international ethical committee Freiburg, Germany. It was designed according to the Declaration of Helsinki (Hong Kong Amendment) and to pertinent national legal and regulatory requirements. Prior to study entry, each patient provided written informed consent and was free to withdraw from the study at any time for any reason without consequences on the care provided.

The design of the initial study has been described in detail elsewhere.[9] In short, thirty-seven (37) ambulatory patients between 18 and 65 years with clinically definite, relapsing-remitting MS were evaluated over 3 months (from t1 to t3) being randomly assigned to treatment with Bio-Electro-Magnetic-Energy-Regulation (BEMER, Innomed International AG, Lichtenstein) or to sham therapy. Patients and physicians/statisticians were blinded to the treatment. The patients were unblinded after the end of the initial study.

The BEMER therapy induced an extremely weak, low-frequency pulsed electromagnetic field (mean field intensity of 14 µT) by flexible, flat electric coils. A detailed description has been published previously.[9] As in the initial study, MS patients were asked to lie down on the mattress for 8 minutes twice daily at their private home. Compliance of the patient was controlled by a special diary documenting the correct application of the BEMER device.

Out of 18 patients in the placebo group 13 enrolled in the following crossover trial. One patient had to be excluded from the evaluation because of deviant time intervals of data

acquisition. Crossover patients were evaluated at inclusion (t3) and after 6 (t4) and 12 weeks (t5) of treatment at the same time of the day (10 am) (Fig. 1).

After crossover trial all 37 patients were asked to participate in a long-term open label follow-up trial continuing BEMER treatment by their own choice. Out of all 9 patients agreed to continue treatment (open label group). All patients were reassessed after three years (t6) (Fig. 1).

At each visit (from t1 to t6), patients underwent a full neurologic assessment. Any relapses occurring between visits were documented and disability was assessed with the Expanded Disability Status Scale (EDSS).[11] Multiple Sclerosis Functional Composite (MSFC) was also performed at each occasion. Fatigue was assessed using the Fatigue Severity Scale (FSS) and the validated German version of the Modified Fatigue Impact Scale (MFIS).[12] The FSS scored from 0 (no fatigue) to 7 (maximal possible fatigue). The 21 items comprising MFIS yielded a total score ranging from 0 (no impact of fatigue) to 84 points (maximal impact of fatigue). Depression was evaluated by the long German version of the Center for Epidemiologic Studies Depression Scale (CES-D) and the General Depression Scale–Long Version (ADS-L).[13]

Group differences in MFIS, FSS, MSFC, EDSS, and ADS-L scores between open label and control group at different time points were evaluated by Student's t-test for independent samples. Changes in fatigue scores over time were assessed by paired t-tests for the open label and the control group, respectively, and by Wilcoxon signed-rank test for crossover trial analysis. Differences in gender group composition were assessed with a χ^2 test. Treatment effects on fatigue at the end of the open label trial were evaluated by analysis of covariance (ANCOVA) using the two treatments as factor variables and initial scores assessed at t1 and t3 as adjustments. All comparisons were two-tailed and a p value of <0.05 was taken as being statistically significant. SPSS package version 17.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical computations.

Results

Study population and baseline characteristics

Demographic baseline characteristics (t1) for verum (N=19) and placebo group (N=18) did not differ with respect to age, gender group composition and test score as described previously.[9] Comparing baseline characteristics (t1) of the open label (N=9) and the non open label control group (N=28) no differences were found for age, gender group composition, EDSS score (Student's test: t_{t1}=0.48; n.s.), MSFC score (Student's test: t_{t3}= -0.36; n.s.) or ADS-L score (Student's test: t_{t1}=0.98; n.s.). Fatigue scores (MFIS, FSS) tended to be higher in the control group compared to the open label group, but this effect did not reach statistical significance (Student's test: MFIS t_{t1}= 1.70; n.s.; FSS t_{t1}= 1.40; n.s.) (Tab. 1).

Primary open label outcome endpoint: MFIS & FSS scores after RCT (t3) and follow-up (t6)

The MFIS and FSS scores were significantly lower in the open label group than in the control group after three years' of follow up (t6) (MFIS 16.78 versus 42.54; Student's t-test for independent samples: $MFIS_{3years(t6)}$ t= 6.31; p= 0.00; FSS_{t6} t= 5.85; p= 0.00). At the beginning of the open label trial (t3) MFIS scores did not differ between the groups (MFIS 25.11 versus 33.71; Student's t-test for independent samples: $MFIS_{t3}$ t= 1.72; n.s.). Although to a smaller extent, FSS scores were significantly different between the groups at the beginning of the open label phase (t3) (Student's t-test for independent samples: FSS_{t3} t= 2.82; p= 0.008) (Tab. 1).

Evaluating changes in fatigue over time, a non-significant trend towards a lower FSS Score was measured in the open label group after three years (paired t-test: FSS_{t3t5} t= 1.10; n.s.) while fatigue increased in the control group (paired t-test: FSS_{t3t6} t= -4.32; p= 0.00). Similarly, MFIS scores decreased in the open label group (paired t-test: $MFIS_{t3t6}$ t= 2.67; p= 0.028) but increased in controls (paired t-test: FSS_{t3t6} t= -5.06; p= 0.00) (Tab. 1) (Fig. 2).

To distinguish the effect of the open label treatment from that of the initial RCT intervention[9] we applied ANCOVAs on the final MFIS and FSS scores (t6) (ANCOVA $MFIS_{t6}$: η^2= 0.804; FSS_{t6} η^2= 0.812). Attendance to open label group was the best predictor for a low fatigue

level after the follow-up (ANCOVA $MFIS_{t6}$: F= 45.927; p= 0.00; η^2= 0.597; Power= 1.00; ANCOVA FSS_{t6}: F= 31.901; p= 0.00; η^2= 0.507; Power= 1.00). Assignment to verum or placebo group in the initial intervention study did not impact significantly on the fatigue scores at the end of follow-up (ANCOVA $MFIS_{t6}$: F= 1.047; p= 0.31; η^2= 0.033; Power= 0.171; ANCOVA FSS_{t6}: F= 3.774; p= 0.061; η^2= 0.109; Power= 0.469). Differences between adjusted means of $MFIS_{open\ label\ vs.\ control}$ (20.60 versus 41.23; ANCOVA: $MFIS_{t6}$ p= 0.00) and $FSS_{open\ label\ vs.\ control}$ (2.90 versus 4.96; ANCOVA: FSS_{t6} p= 0.00) at t6 underlined the open label group benefits. No interaction effects between the open label and the RCT period (ANCOVA: $MFIS_{t6}$ F= 0.006; n.s.; FSS_{t6} F= 0.231; n.s.) were reported. Accordingly, the differences in fatigue scores between verum and placebo group ascertained at t3[9] disappeared after three years of follow-up (t6) ($MFIS_{t6}$ 33.58 versus 39.11; Student's t-test for independent samples: $MFIS_{t6}$ t= -1.099; n.s.; FSS 4.27 versus 4.70; Student's t-test for independent samples: FSS_{t6} t= 0.743.; n.s) (Fig. 3).

Secondary open label outcome endpoint: RCT (t3) versus follow-up (t6)

Self-rated depressive symptoms on the CES-D did not differ between groups at the end of follow-up (t6) (Student's t-test for independent samples: $ADS\text{-}L_{t6}$ t= 1.38; n.s.) (Fig. 2). There was a trend towards a higher MSFC score in the open label group (Student's t-test for independent samples: $MSFC_{t6}$ t=1.85; n.s.) No changes in MS-related disability assessed by EDSS were detected (Tab. 1).

Primary outcome of crossover study: MFIS & FSS scores after RCT (t3) and crossover trial (t5)

During crossover trial (from t3 to t5) MFIS and FSS scores decreased significantly from 33.23 to 22.42 (Wilcoxon $MFIS_{t3t5}$: Z= -2.764; p= 0.006) and from 4.13 to 3.04 (Wilcoxon FSS_{t3t5}: Z= -2.803; p= 0.005), respectively (Tab. 2) (Fig. 3).

Secondary outcome of crossover study: RCT (t3) versus crossover trial (t5)

MSFC score increased during crossover treatment (from 0.26 to 0.54, Wilcoxon MSFC $_{t315}$: Z= -2.936; p= 0.003), while there was a steady improvement in depression score as already observed during RCT[9] (ADS-L: from 11.42 to 7.25, Wilcoxon ADS-L $_{t315}$: Z= -2.255; p= 0.024) (Tab. 2) (Fig. 3).

Discussion

Our current study aimed to determine long-term effects of pulsed low-frequency electromagnetic fields on MS fatigue. The patients were evaluated by a panel of different questionnaires and tests (MFIS, FSS, ADS-L, MSFC, EDSS) assessing fatigue, disease severity, disability, and depression. Using an open label protocol, we were able to demonstrate a reduction of MS-related fatigue after long-term exposure to pulsed low-frequency electromagnetic fields (open label treatment group) while disease severity remained constant. Our results substantiate the positive effects of pulsed low-frequency electromagnetic fields on MS fatigue demonstrated in the initial RCT[9].

There is growing evidence of a beneficial effect of magnetic field therapy on different MS symptoms such as fatigue, bladder control, spasticity, and quality of life. Nielsen and Sinkjaer demonstrated a reduction of spasticity by local magnetic stimulation of the thoracic myelon[14]. Furthermore, Sandyk reported cases of faster recovery from physical activity-induced fatigue during treatment with electromagnetic fields.[15,16] A meta-analysis summarized beneficial effects of electromagnetic field therapy on MS fatigue, but evidence from long-term studies is lacking.[8] In another study, Lappin et al. demonstrated a 20 % reduction of MS-related fatigue after continuous exposure of the brachial plexus with pulsed electromagnetic fields for 4 weeks.[17] However, the fatigue of the placebo group also decreased by 14% in that study. The same investigators provided evidence for improvement of bladder control, cognitive function, fatigue level, mobility, spasticity, and vision on a combined performance scale rating in 30 MS patients using portable pulsed electromagnetic devices 24 hours per day over a 2-month period.[18] Although another study used a similar device (magnetic cell regeneration system by Santerra) than the BEMER system the investigators were not able to demonstrate

improvements of fatigue during pulsed electromagnetic field therapy (twice daily for 16 minutes, respectively) as part of a multimodal neurologic rehabilitation program.[19] Unlike our study, their patients had a higher fatigue score (FSS: 5.5) and the level of fatigue was directly assessed after the application of electromagnetic field therapy. Additionally, our patients were not enrolled in a specific rehabilitation program which may have masked additional positive effects on MS fatigue. In agreement, Mostert and Kesselring had previously described that a special rehabilitation program with short-time exercise treatment was able to reduce MS fatigue.[20] Comparison of results is further complicated by use of different scales of fatigue assessment and different duration of electromagnetic field application at a time. Since the visual analogue scale used by Mostert and Kesselring yielded strongly diverging results, we decided to focus our evaluation of MS fatigue on FSS and MFIS scales.

There are statistical limitations that warrant consideration. The participants in the open label trial as well as in the crossover trial enrolled in a non restricted, non randomized manner which may have introduced selection bias. The small sample size of the open label group (N=9) may have limited the power for detecting treatment effects although other studies reporting beneficial effects investigated a comparable number of patients.[18,19] Trials on a larger number of patients are certainly needed in order to confirm the findings of this study. A further disadvantage was that a full crossover was not realized.

Conclusions

In this long-term study, we were able to demonstrate a beneficial effect of regular BEMER therapy on MS-related fatigue which sustained for up to three years. To our experience, magnetic field therapy seems an appropriate therapy for MS fatigue. Due to high acquisition costs we recommend individual efficacy analyses over several weeks in order to detect non responders.

Disclosure Statement

No competing financial interests exist.

References

1. Freal JE, Kraft GH, Coryell JK. Symptomatic fatigue in multiple sclerosis. Arch Phys Med Rehabil 1984;65:135–138.

2. Fisk JD, Pontefract A, Ritvo PG, et al. The impact of fatigue on patients with multiple sclerosis. Can J Neurol Sci 1994;21:9–14.

3. Ziemssen T. Multiple sclerosis beyond EDSS: Fatigue and depression. J Neurol Sci 2008;273:S32–S35.

4. Vercoulen JH, et al. The measurement of fatigue in patients with multiple sclerosis: A multidimensional comparison with patients with chronic fatigue syndrome and healthy subjects. Arch Neurol 1996;53:642–649.

5. Bakshi R. Fatigue associated with multiple sclerosis: Diagnosis, impact and management. Multiple Sclerosis 2003;9:219–227.

6. Lee D, Newell R, Ziegler L, Topping A. Treatment of fatigue in multiple sclerosis: A systematic review of the literature. Int J Nurs Pract 2008;14:81–93.

7. Ziemssen T, Hoffmann J, Apfel R, Kern S. Effects of glatiramer acetate on fatigue and days of absence from work in first-time treated relapsing-remitting multiple sclerosis. Health Quality Life Outcomes 2008;6:67.

8. Neill J, Belan I, Ried K. Effectiveness of non-pharmacological interventions for fatigue in adults with multiple sclerosis, rheumatoid arthritis, or systemic lupus erythematosus: A systematic review. J Adv Nurs 2006;56:617–635.

9. Piatkowski J, Kern S, Ziemssen T. Effect of BEMER Magnetic Field Therapy on the Level of Fatigue in Patients with Multiple Sclerosis: A Randomized, Double-Blind Controlled Trial. J Altern Complement Med. 2009 May;15(5):507-11.

10. Walther M, Mayer F, Kafka W, Schutze N. Effects of weak, low-frequency pulsed electromagnetic fields (BEMER type) on gene expression of human mesenchymal stem cells and chondrocytes: An in vitro study. Electromagnetic Biol Med 2007;26:179–190.

11. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: An expanded disability status scale (EDSS). Neurology 1983;33:1444–1452.

12. Multiple Sclerosis Council for Clinical Practice Guidelines. Fatigue and Multiple Sclerosis: Evidence-Based Management Strategies for Fatigue in Multiple Sclerosis. Washington, DC: Paralyzed Veterans of America, 1998:1–33.

13. Hautzinger M. Die CES-D Skala: A depression scale for evaluation of general populations [in German]. Diagnostika 1988;34:167–173.

14. Nielsen JF, Sinkjaer T. Long-lasting depression of soleus motoneurons excitability following repetitive magnetic stimuli of the spinal cord in multiple sclerosis patients. Multiple Sclerosis 1997;3:18–30.

15. Sandyk R. Immediate recovery of cognitive functions and resolution of fatigue by treatment with weak electromagnetic fields in a patient with multiple sclerosis. Int J Neurosci 1997;90:59–74.

16. Sandyk R. Resolution of sleep paralysis by weak electromagnetic fields in a patient with multiple sclerosis. Int J Neurosci 1997;90:145–157.

17. Lappin MS, Lawrie FW, Richards TL, Kramer ED. Effects of a pulsed electromagnetic therapy on multiple sclerosis fatigue and quality of life: A double-blind, placebo controlled trial. Altern Ther Health Med 2003;9:38–48.

18. Richards TL, et al. Double-blind study of pulsing magnetic field effects on multiple sclerosis. J Altern Complement Med 1997;3:21–29.

19. Mostert S, Kesselring J. Effect of pulsed magnetic field therapy on the level of fatigue in patients with multiple sclerosis: A randomized controlled trial. Multiple Sclerosis 2005;11: 302–305.

20. Mostert S, Kesselring J. Effects of a short-term exercise training program on aerobic fitness, fatigue, health perception and activity level of subjects with multiple sclerosis. Multiple Sclerosis 2002;8:161–168.

Figure 1. Combined study design of the initial RCT[9] and the study extension.
RCT, Randomized Controlled Trial.

Figure 2. Fatigue in MS patients by long-term open label BEMER treatment versus controls
Data are means and 95% confidence intervals (CI). MFIS, Modified Fatigue Impact Scale; FSS, Fatigue Severity Scale; RCT, Randomized Controlled Trial.

Figure 3. Fatigue and depressivity in MS patients assigned to verum and placebo group during RCT, single crossover and follow-up
Data are means and 95% confidence intervals (CI). MFIS, Modified Fatigue Impact Scale; FSS, Fatigue Severity Scale; ADS-L, general depression scale–long version; RCT, Randomized Controlled Trial.

Table 1. Changes of fatigue, disability and depression scores in the open label group (N=9) and the control group (N=28) at baseline, after RCT and follow-up

	Baseline (t1)				*End of RCT (t3)*				*Open label follow-up (t15)*			
	Open Label		Control		Open Label		Control		Open Label		Control	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
MFIS	28.00	13.88	36.82	13.45	25.11	11.83	33.71	13.44	16.78*	8.76	42.54*	11.15
FSS	4.23	1.34	4.93	1.29	2.91*	1.45	4.44*	1.46	2.35*	1.13	5.16*	1.29
MSFC	-0.38	2.09	-0.58	1.13	-0.11	2.03	-0.20	1.18	0.45	0.85	-0.21	.096
EDSS	3.17	2.15	3.50	1.69	3.17	2.15	3.50	1.69	3.22	2.12	4.07	1.76
ADSL	13.00	6.50	15.93	8.20	8.22	6.26	14.43	8.63	12.56	9.07	17.11	8.48

Data are presented as mean±standard deviation (SD). * $p < 0.01$

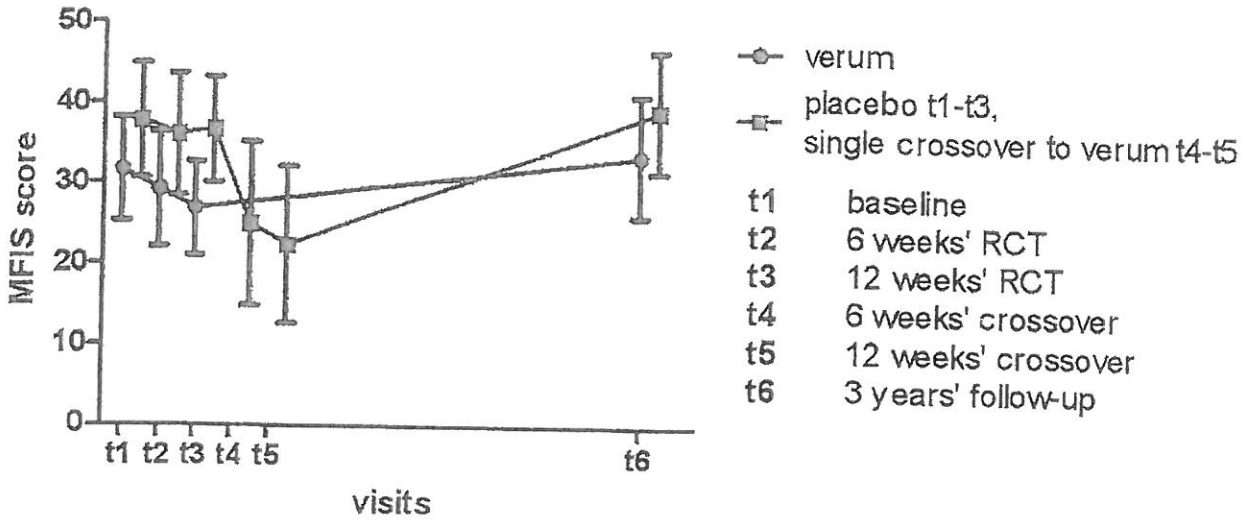
MFIS, Modified Fatigue Impact Scale; FSS, Fatigue Severity Scale; MSFC, Multiple Sclerosis Functional Scale; EDSS, Expanded Disability Status Scale; ADS-L, general depression scale–long version.

Table 2. Changes of MSFC, EDSS, MFIS, FSS, and ADS-L in crossover group (N=13) after RCT, after 6 weeks' crossover and after 12 weeks' crossover

	End of RCT (t3)		*6 weeks crossover (t4)*		*12 weeks crossover (t5)*	
	Mean	SD	Mean	SD	Mean	SD
MFIS	32.33**	12.54	25.00	15.95	22.42**	15.35
FSS	4.13**	1.61	3.26	1.71	3.04**	1.75
MSFC	0.26**	0.58	0.44	0.59	0.54**	0.54
EDSS	2.87	1.30	2.83	1.34	2.83	1.34
ADSL	11.42*	7.15	10.33	7.87	7.25*	4.29

Data are presented as mean±standard deviation (SD). ** $p< 0.01$; * $p< 0.05$.

MFIS, Modified Fatigue Impact Scale; FSS, Fatigue Severity Scale; MSFC, Multiple Sclerosis Functional Scale; EDSS, Expanded Disability Status Scale; ADS-L, general depression scale–long version; RCT, Randomized Controlled Trial.


MFIS score
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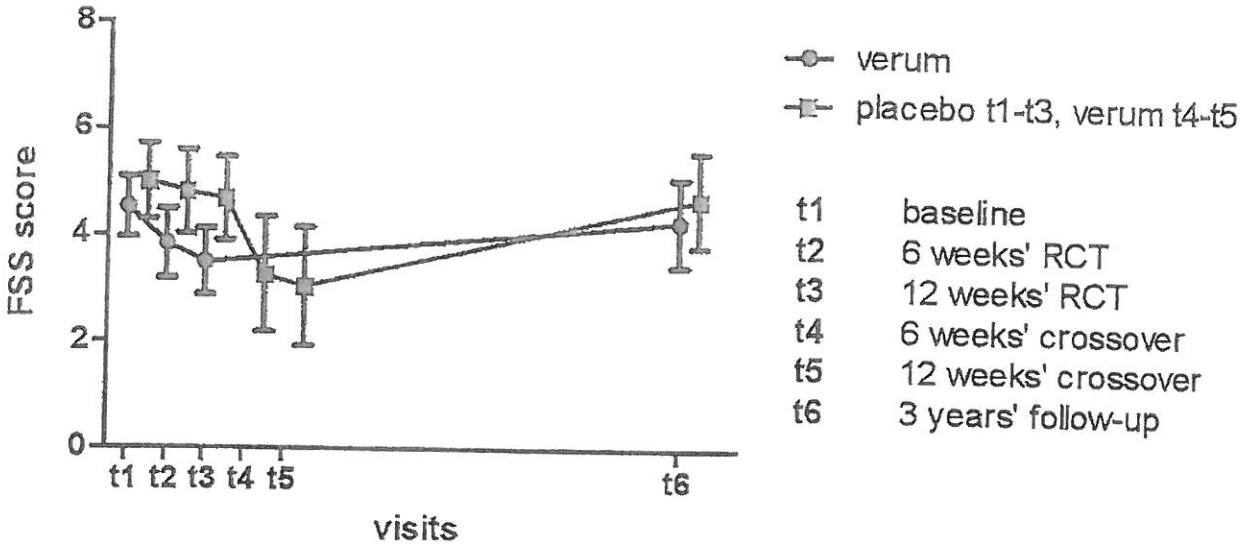
t4 6 weeks' crossover
t5 12 weeks' crossover
t6 3 years' follow-up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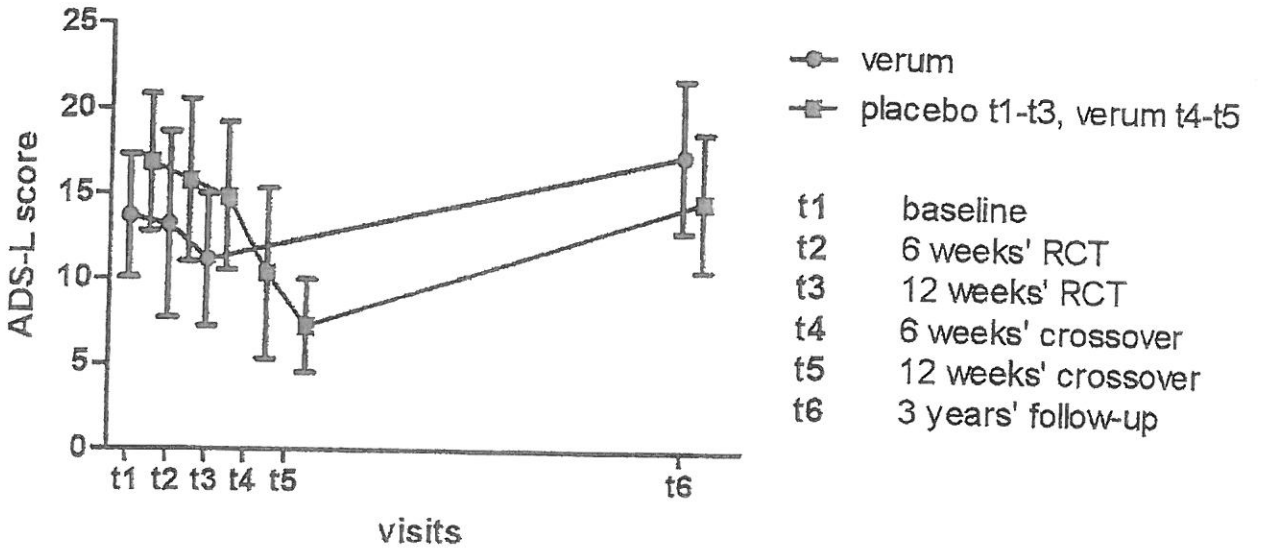
t5 12 weeks' crossover
t6 3 years' follow-up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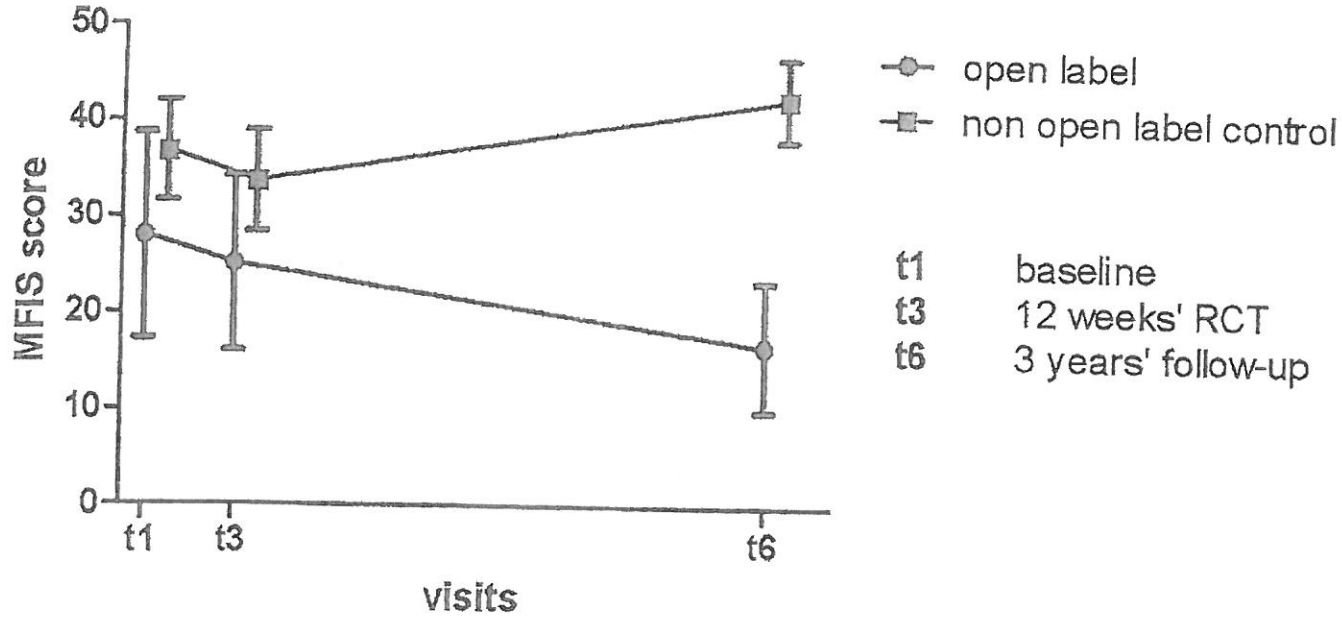
t5 12 weeks' crossover
t6 3 years' follow-up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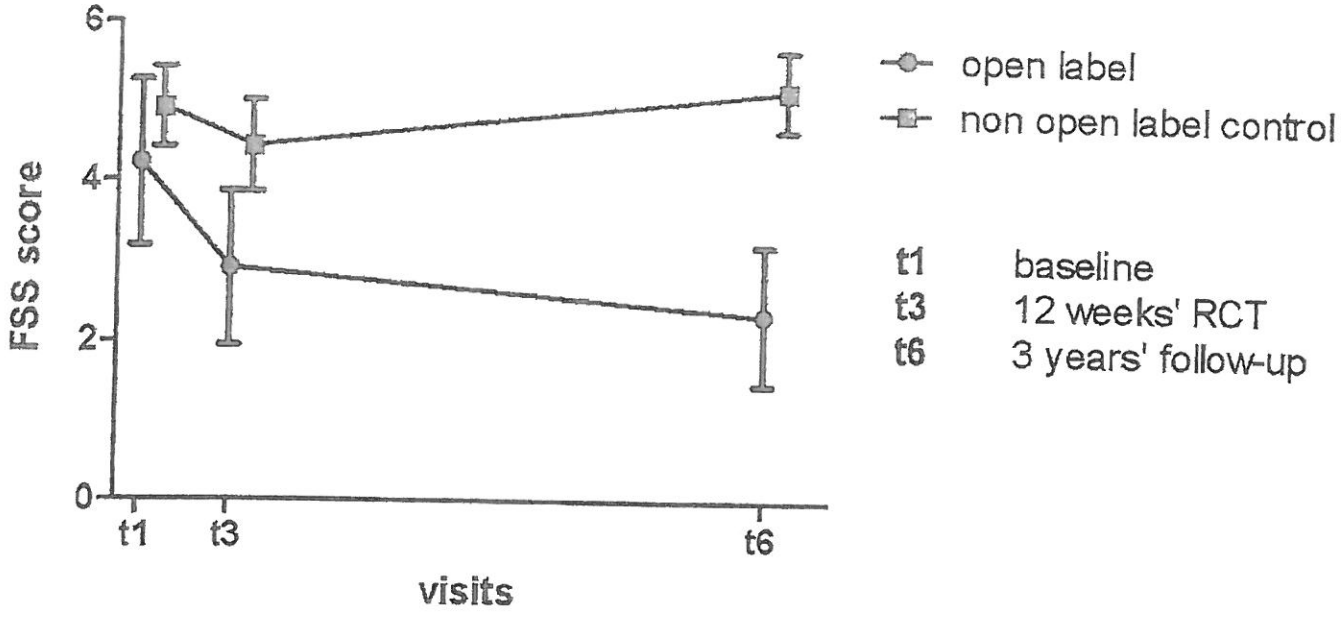
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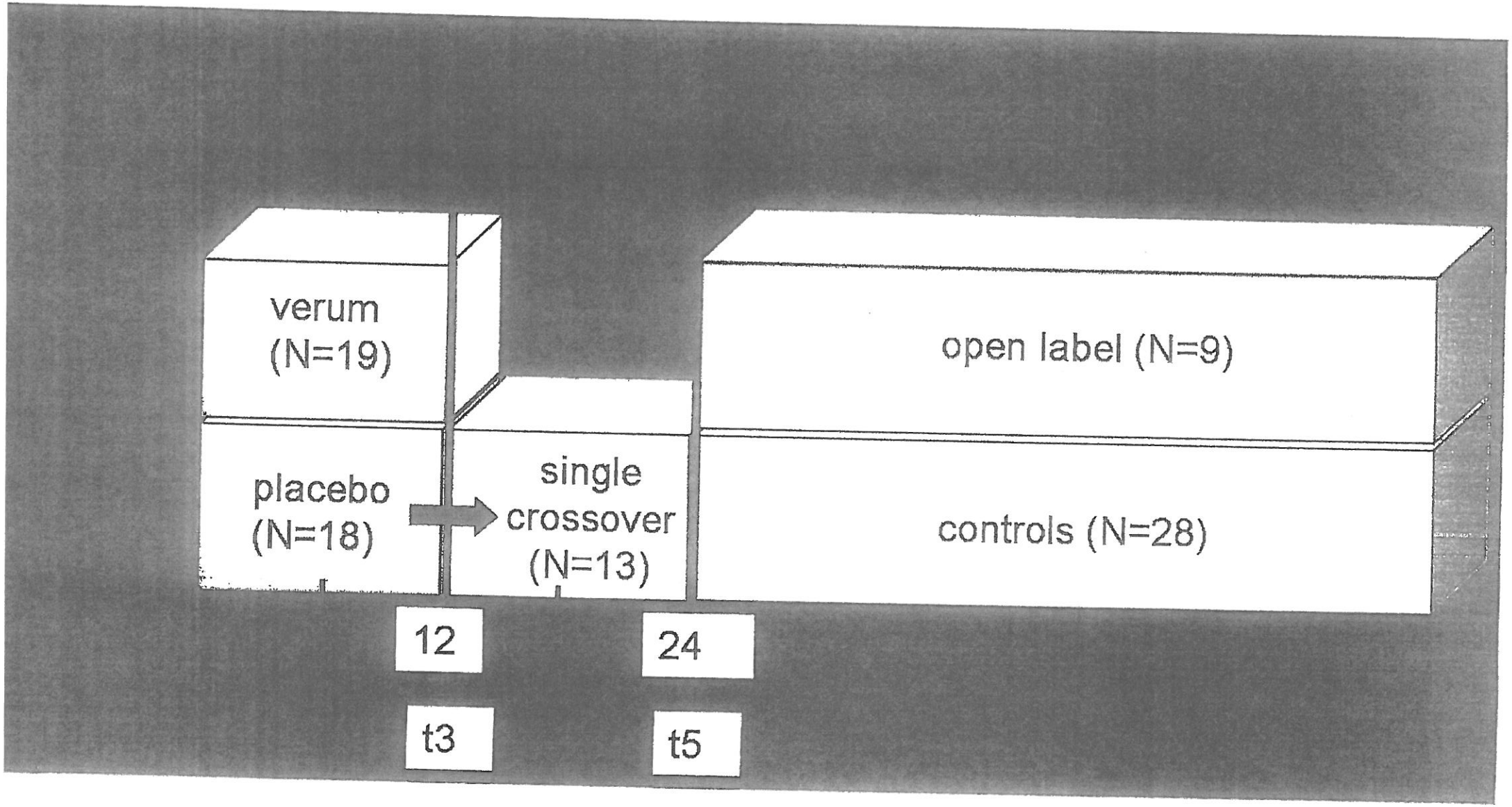
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