A 6-months, multicenter, randomized, controlled study to evaluate the effect of an internet-based physical training (e-training) on fatigue in patients with relapsing-remitting multiple sclerosis treated with Fingolimod – first results of the PACE study

IP 012

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Conclusion

- **No difference in levels of fatigue between the e-training versus waiting group could be observed**
- **Significant effects could be observed in an untrained (low VO_2 max) patient cohort**
- **No added safety concerns in both treatment arms have been documented, therefore exercise and Fingolimod treatment are not mutually exclusive**

Background

MS is a neuro-immunological disease which frequently occurs in young adults and severely reduces quality of life. Progress, severity and the individual symptoms like muscle weakness, depression, cognitive impairment and fatigue cannot be predicted. Especially fatigue is one of the most common and disabling symptoms of multiple sclerosis and it is reported by up to 80 % of all MS patients.

Recent studies have highlighted the positive influence of physical activity and exercise on quality of life and fatigue.

The aim of the study is to evaluate the effect of individualized internet-based exercise (e-training) on MS-related fatigue versus no additional training. Patients eligible for inclusion had to fulfill fatigue score assessed by mFIS of equal or greater than 14 at screening. Health related QoL, functional performance, muscular strength and aerobic capacity are secondary outcome parameters of the study.

To carefully dissect the effect of exercise on fatigue outcomes in RRMS patients, disease modifying therapy has to be restricted to the least confounding factor. In the present study, only patients were included who received stable and efficient immunomodulatory treatment with Fingolimod.

Study objectives

To evaluate the effect of structured physical e-Training vs. no training on:

1) Fatigue in Fingolimod-treated RRMS patients after 6 months; assessed by the mFIS fatigue scale.

2) Isometric and dynamic muscular strength measured by Isomed 2000 isometric measurement device (knee flexion / tension, trunk flexion / extension)

3) Aerobic capacity measured by a graded exercise test on a treadmill using spiroergometry

Demographics

Table 1 | Demographic summary by treatment groups (safety set)

Parameter		e-training; N = 94	Waiting; N = 84	Total; N = 178
Age (years)	Mean ± SD	40.9 ± 10.4	39.4 ± 8.7	40.2 ± 9.6
	Median	42.0	39.5	41.0
Height (cm)	Mean ± SD	171.6 ± 8.5	171.5 ± 8.8	171.5 ± 8.6
	Median	170.0	171.0	170.0
Weight (kg)	n, Mean ± SD	93, 76.3 ± 19.4	84, 76.6 ± 18.6	177, 76.5 ± 19.0
	Median	73.0	73.0	73.0
BMI (kg / m²)	n, Mean ± SD	93, 25.8 ± 5.9	84, 26.0 ± 5.6	177, 25.9 ± 5.7
	Median	24.2	25.0	24.7
Gender, n (%)	Male	29 (30.9)	27 (32.1)	56 (31.5)
	Female	65 (69.1)	57 (67.9)	122 (68.5)

BMI = body mass index, SD = standard deviation

Methods

A prospective, 6-months, randomized, controlled, parallel-group study in RRMS patients treated with Fingolimod plus structured e-Training versus no training (waiting list control group).

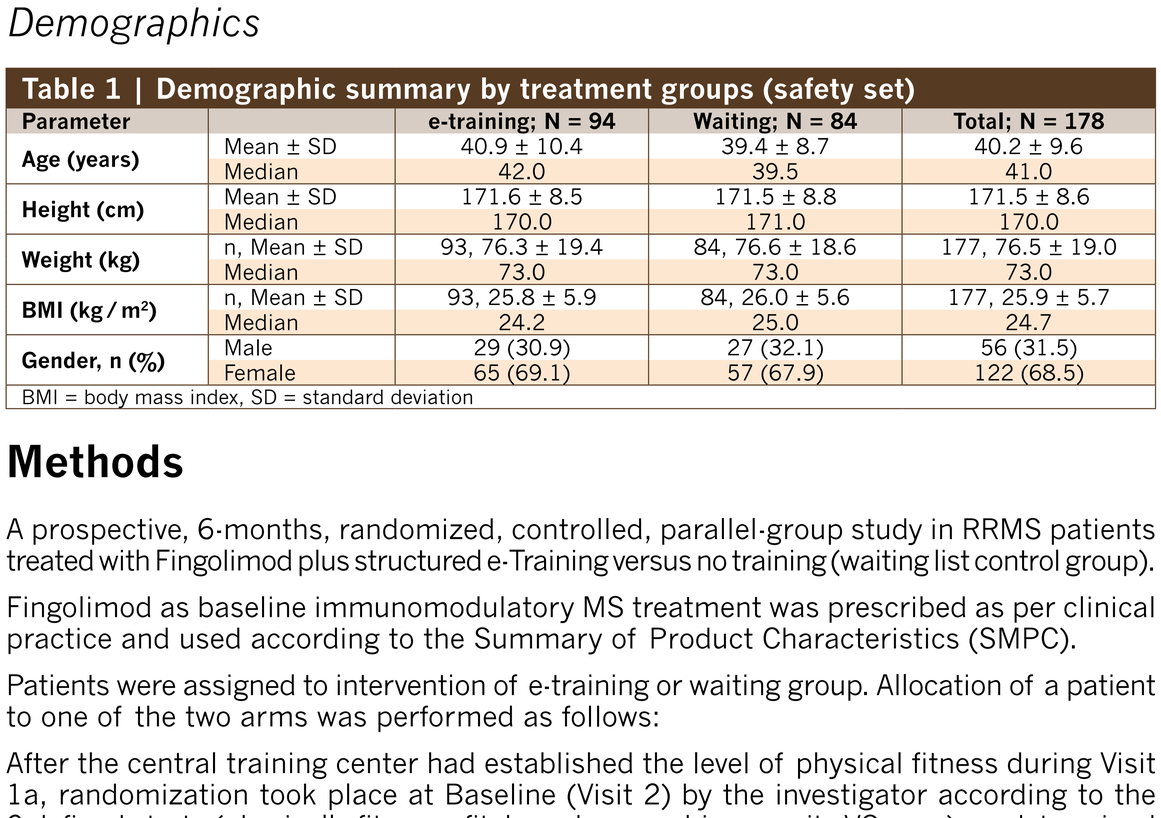
Fingolimod as baseline immunomodulatory MS treatment was prescribed as per clinical practice and used according to the Summary of Product Characteristics (SMPC).

Patients were assigned to intervention of e-training or waiting group. Allocation of a patient to one of the two arms was performed as follows:

After the central training center had established the level of physical fitness during Visit 1a, randomization took place at Baseline (Visit 2) by the investigator according to the 2 defined strata (physically fit vs. unfit, based on aerobic capacity VO_2max), as determined by the central training center. Assessors at the central training center were blinded as to the intervention.

Results

1) Patientflow



2) Primary outcome mFIS

The primary endpoint was defined as change (decrease) in mFIS at the end of Visit 6 compared to baseline (Visit 2), i. e. the difference mFIS Visit 6 – mFIS Visit 2.

At Visit 6, slight improvements of –3.5 ± 11.7 in the e-training group and of –2.0 ± 12.1 in the waiting group were observed in the FAS (full analysis set) population. The difference for the change in fatigue from baseline to Visit 6 of –2.40 with a 95 % CI of [–5.71; 0.92] was, however, not statistically significant (p = 0.1554). (ANCOVA adjusted for the covariates)

Table 2 | Course of fatigue and mean differences to baseline by (raw mean) mFIS (FAS)

	e-training; N = 93		Waiting; N = 84	
Visit	mean ± SD	difference	mean ± SD	difference
Visit 2 (Baseline)	30.6 ± 14.9		34.4 ± 13.8	
Visit 4	27.4 ± 15.9	–3.2 ± 10.9	33.4 ± 13.8	–1.1 ± 11.4
Visit 6	27.1 ± 14.8	–3.5 ± 11.7	32.4 ± 16.2	–2.0 ± 12.1

mFIS = modified fatigue impact scale, FAS = full analysis set, SD = standard deviation;
mFIS ranged from 0 (not tired) to 84 (tired)

3) Subgroup analysis (low VO_2 max Baseline)

In a subgroup of physically unfit patients (defined as VO_2max < 27 at baseline) a significant difference between patients receiving e-training and patients in the waiting group at month 6 could be observed (p = 0.0065).

Table 3 | ANCOVA model for change in fatigue assessed by last mFIS until V6 compared to baseline; Subgroup: low V02-Baseline (ie., lower than 27); FAS/locf

Effect	Group Contrast / LS Mean	ANCOVA			Not-adjusted		
		Estimate	95 % CI of Est.	P | Diff = 0	N	Raw Mean	Raw SD
EDSS baseline		1.08	[–2.38; 4.54]	0.5341			
mFIS baseline		–0.43	[–0.65; –0.21]	0.0003			
Sex	Male – Female	–2.00	[–9.46; 5.47]	0.5939			
Intervention	G1 – G2	–9.07	[–15.5; –2.65]	0.0065			
	e-training (1)	–8.00	[–12.4; –3.63]		31	–7.65	14.56
	waiting (2)	1.07	[–4.18; 6.32]		26	–0.38	11.05

P-values are calculated using Type III SS, locf = last observation carried forward

4) AE / SAE

The overall incidence of adverse events over the 6-months core study phase was 58.5 % in the exercise group and 60.7 % in the waiting group (safety analysis set). In both intervention groups, about 90 % of patients experienced no relapse during the core study period (e-training group: 89.4 %, waiting group: 95.2 %).

Discussion

The objective of this study was to evaluate the effect of structured physical e-training versus no training (waiting) on fatigue in Fingolimod-treated RRMS patients after 6 months, assessed by the modified fatigue impact scale (mFIS). The results of the primary efficacy parameter could not show a difference in fatigue between patients of the e-training group and those of the waiting group. The difference of –2.40 with a 95 % CI of [–5.71; 0.92] was statistically not significant (p = 0.1554) and lower than that assumed by the sample size estimation.

Regarding the subgroup of patients with low aerobic capacity (untrained patients); effects double as high as in the comparative study group were seen.

With respect to safety, the combination of Fingolimod and training did not confer any added risk. Especially no hints for cardiac diseases or risks were observed.

The failure to show an effect on mFIS by e-training implies, that the study design was probably biased and underpowered, likely due to missing initial recruitment targets and low compliance.

References

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Disclosures

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