

Evaluation of the Efficacy and Safety of Terguride in Patients With Fibromyalgia Syndrome

Results of a Twelve-Week, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study

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Objective. To assess the efficacy and safety of terguride, a partial dopamine agonist, in patients with fibromyalgia syndrome (FMS).

Methods. In a 12-week, multicenter, double-blind, placebo-controlled, parallel-group study, 99 patients were randomized at a ratio of 2 to 1 to receive terguride or placebo. Over 21 days, the dosage was titrated to a

maximum daily dose of 3 mg of terguride or placebo, and this fixed dosage was continued over 9 weeks. The primary efficacy variable was the intensity of pain (100-mm visual analog scale). Secondary efficacy variables included the Fibromyalgia Impact Questionnaire (FIQ) score, the tender point score (TPS), and the Hamilton Depression Scale (HDS) score. During the study, patients were evaluated for the presence of cervical spine stenosis by magnetic resonance imaging (MRI).

Results. No significant differences in the change in pain intensity, FIQ score, TPS, or HDS score between baseline and 12 weeks were observed in the terguride group as compared with the placebo group. Cervical spine stenosis was detected in 22% of the patients. Only patients with cervical spine stenosis responded to terguride treatment. FIQ scores improved significantly (per-protocol analysis), and pain intensity, the TPS score, and the HDS score showed a trend toward improvement in the terguride group as compared with the placebo group. Terguride treatment was safe. Only those adverse events already known to be side effects of terguride were observed. Premature termination of the study in patients receiving terguride (26%) occurred predominantly during up-titration and in the absence of comedication for treatment of nausea.

Conclusion. Terguride treatment did not improve pain, the FIQ score, the TPS, or the HDS score in the total study population. However, a subgroup of patients with cervical spine stenosis seemed to benefit from terguride treatment.

Fibromyalgia syndrome (FMS) is a common, yet poorly understood, syndrome characterized by chronic

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widespread pain and tenderness to digital palpation of at least 11 of 18 defined tender points (1). Studies (2,3) have demonstrated that FMS patients experience pain differently from the general population and that dysfunctional pain processing plays a role. Central sensitization (3–5), dysfunction of inhibitory pathways (6,7), and altered neurotransmitter concentrations in the brain and the spinal cord (8–10) have been discussed as pathogenic mechanisms and as targets for therapeutic intervention.

A central role of dopaminergic neurotransmission in modulating pain perception (10–13) has also been proposed. Dopaminergic neurons have been implicated in the control of the perception of pain intensity (14), the anticipation and emotional response to pain (15), the stress response (11), as well as in the spinal modulation of nociceptive input (16).

The effects of the dopamine agonists pramipexole, ropinirole, and rotigotine in FMS have been, or are being, studied in prospective randomized clinical trials (17–19). In a 12-week trial in FMS patients receiving uncontrolled doses of concomitant medications that could affect FMS symptoms (17), dosage titration of pramipexole resulted in significant improvements in pain, in the Fibromyalgia Impact Questionnaire (FIQ) score, and in distinct subscales of the Multidimensional Health Assessment Questionnaire. Based on these results, the European League Against Rheumatism evidence-based recommendations for the management of FMS list pramipexole as “should be considered for treatment of FMS” (20), but emphasize the need for monotherapy trials without concomitant FMS medications for conclusive assessment of the effects.

We report here the results of a randomized, double-blind, placebo-controlled study of tergeride in patients with primary fibromyalgia without relevant concomitant medical conditions who were not receiving concurrent FMS-targeted therapy. Tergeride is a partial dopamine agonist. It has been approved in Japan (Teluron; Nihon Schering, Osaka, Japan) for the treatment of hyperprolactinemia (21,22). Since FMS patients who had comorbid cervical pain or compression were excluded from the randomized controlled trial of pramipexole (17), we also assessed patients in this study for cervical spine stenosis by magnetic resonance imaging (MRI), and possible differences in the response to tergeride were explored.

PATIENTS AND METHODS

Entry criteria. Patients were screened for eligibility ~6.6 days (range 2–28 days) prior to the start of treatment.

Eligible male or female patients met the following criteria: a diagnosis of FMS according to the American College of Rheumatology (ACR) 1990 criteria (1), a pain score ≥ 50 mm on the patient-reported visual analog scale (VAS; 100 mm) (23), a tender point score (TPS) ≥ 11 (24), age between 18 and 60 years, and a body mass index (BMI; kg/m^2) between 18.9 and 30.0.

Patients meeting the following criteria were excluded from the study: known sensitivity to tergeride, relevant liver, kidney, cardiovascular, or pulmonary disease, peptic ulcers, Raynaud's phenomenon, psychosis, encephalomyelitis disseminata, chronic inflammatory diseases, a diagnosis of pituitary tumor representing extrasellar expansion, uncontrolled systolic blood pressure ≥ 140 mm Hg and a diastolic pressure ≥ 90 mm Hg, a history of drug or alcohol abuse, or mental impairment. Female patients who had not used reliable contraception in the cycle before the study, were pregnant, or were lactating were excluded.

Patients receiving concurrent FMS-targeted therapy (i.e., antidepressants, selective serotonin reuptake inhibitors [SSRIs], antiepileptics, anxiolytics, muscle relaxants, or hypnotics) were excluded if they did not discontinue therapy at least 6 weeks prior to enrollment, or in the case of antiepileptics, anxiolytics, muscle relaxants, or hypnotics, if they had not discontinued these medications for ≥ 10 elimination half-lives prior to enrollment. Constant treatment with nonsteroidal antiinflammatory drugs (NSAIDs) was allowed.

Study design. The study was performed as a controlled trial at 1, 2, and 7 centers in Switzerland, the Czech Republic, and Germany, respectively. The study protocol, amendments, and consent forms were approved by the local ethics committees and health authorities. Written informed consent was obtained from all patients at the time of enrollment. The study was performed in compliance with the Declaration of Helsinki.

The trial was designed as a proof-of-concept study of the treatment of FMS, with study medication administered over a period of 12 weeks. Active drug (0.5 mg tergeride) and placebo were supplied as identical tablets with a subdividing break mark. A randomized, double-blind, placebo-controlled, parallel-group design was used, with a ratio of tergeride to placebo of 2 to 1. The study consisted of a screening visit, a 3-week period during which the study medication was titrated up to 6 tablets per day, a 9-week fixed-dose treatment phase, and a subsequent 5-day down-titration period. Study medication was administered orally in the morning and in the evening.

Treatment was initiated (visit 0 [V_0]) with a half tablet in the evening. After 3 days at a constant dosage, this was increased by an additional half tablet in the morning. Thereafter, the daily dose was increased by 1-tablet increments every 3 days up to a maximum of 6 tablets after 21 days (V_3). In cases of insufficient tolerability, the dosage increase could be modified. After day 12, a dosage increase could be postponed by 3 days in cases of suspected drug-related adverse events (AEs). In cases of reoccurrence of the AE, the dosage increase was cancelled, and the patient was maintained on a constant dosage of ≥ 3 tablets throughout the study period. Any patient who did not tolerate 3 tablets per day was withdrawn from the study. From day 22 until day 84 (V_{12}), the study medication remained at a constant dosage. Thereafter, the dosage was titrated down over a period of 5 days (V_{13}). Dosages of comedications remained constant from 4 weeks prior to V_0 and throughout the study.

The primary efficacy variable was pain intensity as reported by the patient on a 100-mm VAS (23). A standard deviation value of 24 for the VAS score and a clinically relevant difference of -17 mm in the mean change from baseline to V_{12} in the terguride group as compared with the placebo group were derived from Rao and Bennett (7). Assuming a 1-sided significance level of 0.025 and a power of 80% at a 2:1 randomization ratio in favor of active treatment, a sample size of 72 patients (intent-to-treat [ITT] analysis) was obtained. Secondary efficacy variables were the differences in the FIQ score (25), the TPS (24) and the 17-point Hamilton Depression Scale (HDS) (26) score between treatment groups.

Safety assessments consisted of monitoring all AEs and serious AEs. These included measurement of blood pressure and pulse rate, the performance of physical examinations, including electrocardiography (EKG) and echocardiography, monitoring of hematologic parameters, blood chemistry profile, and urinalysis. Prolactin levels were quantified using routine assays.

Oral administration of proton pump inhibitors (esomeprazole ≤ 40 mg/day, omeprazole ≤ 40 mg/day, or pantoprazole ≤ 40 mg/day) or up to 20 mg of domperidone (a peripherally acting dopamine antagonist) 3 times per day was allowed on demand for the treatment of nausea and were used by 17 and 16 patients, respectively. In cases of unbearable pain, the patient was allowed ≤ 2 gm/day of acetaminophen as rescue medication.

MRI assessment. A standardized protocol for neuro-radiologic assessment (including T1-weighted and T2-weighted sagittal and axial images) of the cervical spine with a 1.5T MRI scanner was followed by all centers. Imaging was allowed at any time during the study. Midline sagittal views of the cervical spine canal with the neck in neutral alignment were obtained. Centralized readings were performed by a neuroradiologist who was blinded with regard to the treatment group (MB). Sagittal diameters of the spinal canal and the spinal cord were quantitated, and spinal canal stenosis was graded according to modified criteria described by Muhle et al (27).

Statistical analysis. Statistical analyses were based on a safety analysis set, an ITT analysis set, and a per-protocol (PP) analysis set. The safety analysis set included all randomized patients who received at least 1 dose of study medication. The ITT analysis set included all randomized patients who received at least 1 dose of study medication and who had a valid assessment of the primary variable at baseline and at least 1 assessment postbaseline. The PP analysis set excluded patients with major protocol deviations and those who did not complete the assessment at V_{12} for reasons that were definitely not related to the study medication.

Continuous variables were summarized according to the numbers of observations, for which the arithmetic mean, the standard deviation, the standard error of the mean, and the 95% confidence interval (95% CI) were calculated. Categorical data were described using absolute and relative frequencies. Efficacy was evaluated by comparing the absolute changes on the pain VAS score in the ITT analysis in the 2 treatment groups. The primary efficacy variable was evaluated by analysis of covariance using the baseline value as the covariate. Analysis of secondary efficacy variables included descriptive summary statistics for the FIQ score and the TPS at each time point. Categorical data were compared using Fisher's exact test.

For the subgroup analysis, patients with no or only partial obliteration of the anterior or posterior subarachnoid space of the cervical spine were allocated to one subgroup. Patients with spinal cord hyperintensity or cervical cord compression or displacement were allocated to a second subgroup. The latter subgroup also included patients with complete obliteration of the subarachnoid space (grade 2 on the Muhle scale for spinal canal stenosis) in the neutral position, which implies an increased probability of functionally relevant stenosis or worsening thereof during flexion or extension (27) and can significantly impair the function of the spinal cord.

All efficacy analyses were performed in these 2 subgroups for exploratory purposes. *P* values less than 0.05 were considered significant.

The safety evaluations were based on the safety set assessment by treatment group and included analyses of AEs, laboratory assessments of safety, physical examinations, blood pressure and pulse rate assessments, EKGs, and echocardiograms. Safety data were evaluated by Fisher's exact test.

RESULTS

Characteristics of the study patients. Between February 12, 2007 and February 1, 2008, a total of 118 patients were screened for participation in the study. Of these, 99 patients were eligible for the study. These patients were enrolled and were randomized to treatment with terguride ($n = 65$) or placebo ($n = 34$). All patients were of Caucasian race, and 88 (88.9%) of the patients were women. A total of 77 of the study patients (77.8%) were between the ages of 41 and 55 years. No significant differences in sex, age, height, weight, BMI, smoking status, and alcohol consumption between the treatment groups were observed (Table 1). No significant differences in the baseline characteristics of the efficacy parameters between the terguride group and the placebo group were noted.

The comorbidities most frequently observed between the treatment groups were comparable. Ten patients had previously taken either opioids (5 patients), anxiolytics (5 patients), or both (1 patient). In 6 patients (4 receiving terguride and 2 receiving placebo), this was given for treatment of FMS. A single patient in the terguride group had a diagnosis of restless legs syndrome. The most frequently taken concomitant medications did not differ between treatment groups. Patients reported taking NSAIDs/antirheumatic drugs (27 [41.5%] in the terguride group and 14 [41.2%] in the placebo group) or other analgesics and antipyretics (21 [32.3%] in the terguride group and 11 [32.4%] in the placebo group) for pain. Opioids were used "on demand" less than once a week or only during 1 treatment week in the midst of the treatment period by 2 patients (1 in each treatment group). Furthermore, 2 patients received opioids for only a single day during the treat-

Table 1. Demographic characteristics of the FMS study population and efficacy parameters at baseline*

	All patients (n = 99)	Terguride group (n = 65)	Placebo group (n = 34)
Demographic characteristics			
Ethnic group, no. (%)			
Caucasian	99 (100)	65 (100)	34 (100)
Sex, no. (%)			
Female	88 (88.9)	58 (89.2)	30 (88.2)
Male	11 (11.1)	7 (10.8)	4 (11.8)
Age			
Total population, mean \pm SD	48.7 \pm 6.4	48.5 \pm 6.1	49.0 \pm 7.0
Age group, no. (%)			
26–30 years	1 (1.0)	–	1 (2.9)
31–35 years	4 (4.0)	3 (4.6)	1 (2.9)
36–40 years	5 (5.1)	4 (6.2)	1 (2.9)
41–45 years	21 (21.2)	13 (20.0)	8 (23.5)
46–50 years	26 (26.3)	20 (30.8)	6 (17.6)
51–55 years	30 (30.3)	17 (26.2)	13 (38.2)
56–60 years	12 (12.1)	8 (12.3)	4 (11.8)
Height, mean \pm SD cm	165.8 \pm 7.5	165.4 \pm 7.6	166.5 \pm 7.3
Weight, mean \pm SD kg	70.3 \pm 10.3	70.9 \pm 11.1	69.2 \pm 8.7
BMI, mean \pm SD kg/m ²	25.6 \pm 3.2	25.9 \pm 3.3	25.0 \pm 3.0
Smoking status, no. (%)			
Nonsmoker	55 (55.6)	36 (55.4)	19 (55.9)
Former smoker	16 (16.2)	9 (13.8)	7 (20.6)
Current smoker	28 (28.3)	20 (30.8)	8 (23.5)
Alcohol consumption, no. (%)			
Almost abstinent	67 (67.7)	45 (69.2)	22 (64.7)
Moderate†	32 (32.3)	20 (30.8)	12 (35.3)
Efficacy parameters at baseline			
Pain, mean \pm SD mm on 100-mm VAS	71.3 \pm 15.6	70.8 \pm 16.7	72.2 \pm 13.5
Men (n = 11)	70.2 \pm 15.1	70.1 \pm 15.3	70.3 \pm 17.0
Women (n = 86)	71.4 \pm 15.8	70.9 \pm 17.0	72.4 \pm 13.3
FIQ score	59.2 \pm 16.4	59.3 \pm 16.7	59.1 \pm 16.0
Tender point score	38.2 \pm 10.1	38.3 \pm 10.6	38.2 \pm 9.4
No. of tender points	16.4 \pm 1.7	16.4 \pm 1.7	16.5 \pm 1.7
HDS 17-item score‡	14.2 \pm 7.3	14.2 \pm 7.0	14.1 \pm 8.1

* *P* values for differences between groups were not significant, as determined by analysis of variance using treatment group as a factor. FMS = fibromyalgia syndrome; BMI = body mass index; VAS = visual analog scale; FIQ = Fibromyalgia Impact Questionnaire.

† Moderate alcohol consumption was defined as \leq 16 gm of alcohol/day in women and \leq 24 gm of alcohol/day in men.

‡ The 17-item Hamilton Depression Scale (HDS) score was determined in 70 patients (46 taking terguride and 24 taking placebo).

ment period (1 in each treatment group). A total of 7 patients were excluded from the ITT and PP data analyses because of ongoing daily intake of opioids (3 patients in each group) or because of pramipexole treatment for restless legs syndrome (1 patient) during the up-titration phase. Six patients received concomitant treatment with bromazepam 1.5 mg/day (5 [7.7%] in the terguride group and 1 [2.9%] in the placebo group) and 5 received lormetazepam 1 mg/day (4 [6.2%] in the terguride group and 1 [2.9%] in the placebo group) for the treatment of insomnia.

An MRI was performed in a total of 78 patients (51 [78.5%] receiving terguride and 27 [79.4%] receiving placebo); 21 patients did not consent to MRI. One patient was excluded due to a lack of technical compli-

ance with the MRI protocol, which resulted in insufficient quality of the data to allow a complete evaluation. When the patients who took pramipexole and the patients who underwent continuous treatment with opioids were excluded from the analysis, we found no (grade 0) or only partial (grade 1) obliteration of the anterior or posterior subarachnoid space in 24 patients (13 receiving terguride and 11 receiving placebo) and in 33 patients (25 receiving terguride and 8 receiving placebo), respectively (Table 2).

Complete obliteration of the anterior or posterior subarachnoid space (grade 2), cervical compression or displacement of the spinal cord (grade 3), or spinal cord hyperintensity (grade 4) was observed in 4 patients (3 receiving terguride and 1 receiving placebo), 11

Table 2. Mean sagittal diameter of the spinal canal and spinal cord, and frequency distribution of spinal stenosis grades by cervical segment*

	Spinal canal diameter, mean (95% CI) mm	Spinal cord diameter, mean (95% CI) mm	No. (%) with spinal canal diameter <10 mm	Cervical spine stenosis grade				
				0	1	2	3	4
Cervical spine segment								
C1–C2	14.4 (14.1–14.7)	7.9 (7.8–8.1)	0 (0)	73	–	–	–	–
C2–C3	12.7 (12.4–13.0)	7.7 (7.6–7.8)	3 (4.1)	73	–	–	–	–
C3–C4	11.6 (11.2–12.0)	7.5 (7.4–7.6)	10 (13.7)	65	6	–	2	–
C4–C5	11.1 (10.7–11.5)	7.3 (7.2–7.4)	12 (16.4)	57	13	1	2	–
C5–C6	10.3 (9.8–10.8)	7.0 (6.9–7.1)	27 (37.0)	36	26	3	7	1
C6–C7	10.7 (10.3–11.2)	6.8 (6.7–6.9)	23 (31.5)	44	19	7	3	–
C7–T1	12.0 (11.7–12.3)	6.7 (6.6–6.8)	3 (4.1)	73	–	–	–	–
Spinal stenosis grading								
All patients (n = 73)†	–	–	–	24	33	4	11	1
Terguride group (n = 46)	–	–	–	13	25	3	5	–
Placebo group (n = 27)	–	–	–	11	8	1	6	1
<i>P</i> ‡						0.164		

* Patients who took pramipexole (n = 1 with grade 1 cervical spine stenosis) or received continuous treatment with opioids (n = 3 with grade 0 cervical spine stenosis) were excluded from this analysis. Data from the magnetic resonance imaging of 1 patient were not used since there was a lack of technical compliance with the protocol.

† Grading for cervical spine stenosis was not performed in 20 patients (13 receiving terguride and 7 receiving placebo).

‡ Difference between treatment groups was calculated by chi-square test.

patients (5 receiving terguride and 6 receiving placebo), and 1 patient (0 receiving terguride and 1 receiving placebo), respectively. Only a single patient in the terguride group who had grade 2 cervical spine stenosis received transient therapy with bromazepam during weeks 3–8 for insomnia.

No significant differences between treatment groups were observed. A spinal canal measuring <10 mm in diameter at the C3–C4, C4–C5, C5–C6, C6–C7, and C7–T1 level of the cervical spine was observed in 13.7%, 16.4%, 37.0%, 31.5%, and 4.1% of the patients, respectively. No statistically significant differences in baseline efficacy parameters in the patient subgroups with and without cervical spine stenosis were observed.

A total of 47 patients (72.3%) in the terguride group and 32 patients (94.1%) in the placebo group completed the study. The mean \pm SEM daily intake of study medication was 4.7 ± 0.20 tablets and 5.5 ± 0.19 tablets in the terguride and placebo groups, respectively. The study was prematurely terminated by 17 patients in the terguride group (26.2%) and 1 patient in the placebo group (2.9%) because of AEs. Treatment of 1 patient in each study group was terminated because of protocol violations.

Efficacy. In the total study population, pain intensity as the primary end point showed a mean change from baseline to V_{12} (last observation carried forward [LOCF]) of -9 mm. This decrease in pain intensity (mean -9 mm [95% CI -14 , -4] for terguride and -9 mm [95% CI -18 , -1] for placebo) was not different between treatment groups over the course of the study ($P =$

0.971). The mean decrease in the FIQ score from baseline to V_{12} (LOCF) was 8.2 in the study cohort. The mean decrease was more pronounced in the terguride group (8.8 [95% CI 4.2, 13.4]) than in the placebo group (6.6 [95% CI 1.3, 12.0]), but was not significantly different between groups ($P = 0.221$). The TPS and the number of positive tender points decreased from baseline to V_{12} (LOCF) by 3.5 and 0.8, respectively. The mean decrease in the TPS was slightly less pronounced in the terguride group (3.3 [95% CI 1.4, 5.2]) than in the placebo group (4.4 [95% CI 0.6, 8.2]). The mean decrease in the TPS ($P = 0.703$) or the total number of positive tender points ($P = 0.377$) was not significantly different between treatment groups.

Furthermore, when patients were grouped according to their response to therapy (Table 3), no significant between-group differences in the pain VAS score, the FIQ score, and the TPS were observed. No treatment-related changes in the HDS score were observed during the course of the study between the terguride and placebo treatment groups ($P = 0.937$).

Results of the subgroup analysis. In 57 patients with no or only partial obliteration of the subarachnoid space of the cervical spine, no significant differences in the pain VAS score (mean -1 mm [95% CI -12 , 9]; $P = 0.795$), the FIQ score (-2.6 [95% CI -11.6 , 6.5]; $P = 0.572$), and the TPS (0.8 [95% CI -2.3 , 0.3]; $P = 0.659$) from baseline to V_{12} (LOCF) between the terguride treatment group (n = 38) and the placebo treatment group (n = 19) were observed. In contrast, a differential response to terguride was observed in patients with

Table 3. Response of the efficacy variables of pain by VAS, FIQ, and TPS to study medication from baseline to day 84*

	No. (%) receiving terguride (n = 59)	No. (%) receiving placebo (n = 31)
Pain, by VAS		
≥50% improvement	10 (16.9)	6 (19.4)
≥20% and <50% improvement	10 (16.9)	3 (9.7)
Change within ±20%	30 (50.8)	17 (54.8)
≥20% worsening	9 (15.3)	5 (16.1)
FIQ score		
≥50% improvement	9 (15.3)	3 (9.7)
≥20% and <50% improvement	11 (18.6)	3 (9.7)
Change within ±20%	33 (55.9)	22 (71.0)
≥20% worsening	6 (10.2)	3 (9.7)
TPS		
≥50% improvement	4 (6.8)	0 (0)
≥20% and <50% improvement	9 (15.3)	6 (19.4)
Change within ±20%	44 (74.6)	23 (74.2)
≥20% worsening	1 (1.7)	2 (6.5)
Not quantifiable†	1 (1.7)	0 (0.0)

* Patients who took pramipexole or received continuous treatment with opioids were excluded from analysis. Values are the mean change from baseline to day 84, using the last observation carried forward method. *P* values for differences between groups were not significant, as determined by chi-square test. VAS = visual analog scale; FIQ = Fibromyalgia Impact Questionnaire; TPS = tender point score.

† Excluded from statistical analysis.

cervical spine stenosis (8 receiving terguride and 8 receiving placebo). The pain VAS score, the FIQ score, and the TPS decreased more strongly with terguride than with placebo.

In the ITT analysis, the differences in the mean decrease in pain intensity (−10 mm [95% CI −42, 2]; *P* = 0.578), in the FIQ score (−16.7 [95% CI −30.1, 1.7]; *P* = 0.093), and in the TPS (−10.9 [95% CI −23.8, 2.0]; *P* = 0.087) from baseline to V₁₂ (LOCF) between the terguride group and the placebo group were more pronounced in comparison to the respective patient groups without cervical spine stenosis. In the PP analysis, effects of terguride treatment on the FIQ score in patients with cervical spine stenosis (mean −18.54 [95% CI −36.6, −0.45]; *P* = 0.046) reached statistical significance (Figure 1). The pronounced effect of terguride versus placebo treatment on the FIQ score in the subgroup of patients with grade 2–4 cervical spine stenosis was attributed predominantly to mean decreases in the physical impairment (−2.18; *P* = 0.0328), do work (−1.88; *P* = 0.0917), fatigue (−1.57; *P* = 0.2359), rested (−1.48; *P* = 0.3382), stiffness (−1.67; *P* = 0.1288), anxiety (−3.66; *P* = 0.0411), and depression (−2.33; *P* = 0.132) subscales (Figure 2).

Safety. A total of 61 patients (93.8%) in the terguride group and 27 patients (79.4%) in the placebo

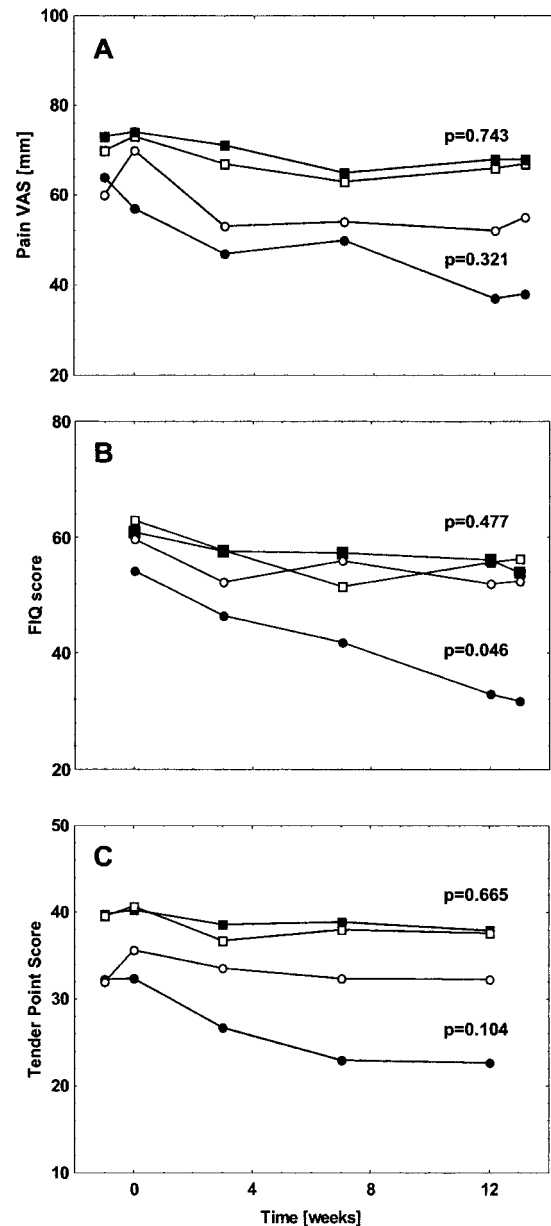


Figure 1. Time course of changes in the mean values for pain intensity by visual analog scale (VAS; 100 mm), the Fibromyalgia Impact Questionnaire (FIQ) score, and the tender point score in terguride-treated (solid symbols) and placebo-treated (open symbols) patients (per-protocol analysis). Squares represent patients with grades 0–1 cervical spine stenosis (n = 57; 38 receiving terguride and 19 receiving placebo). Circles represent patients with grades 2–4 cervical spine stenosis (n = 16; 8 receiving terguride and 8 receiving placebo). Values are the mean. *P* values represent the difference between terguride versus placebo treatment.

group experienced at least 1 AE. AEs were predominantly of mild or moderate intensity. No patient experienced a serious AE.

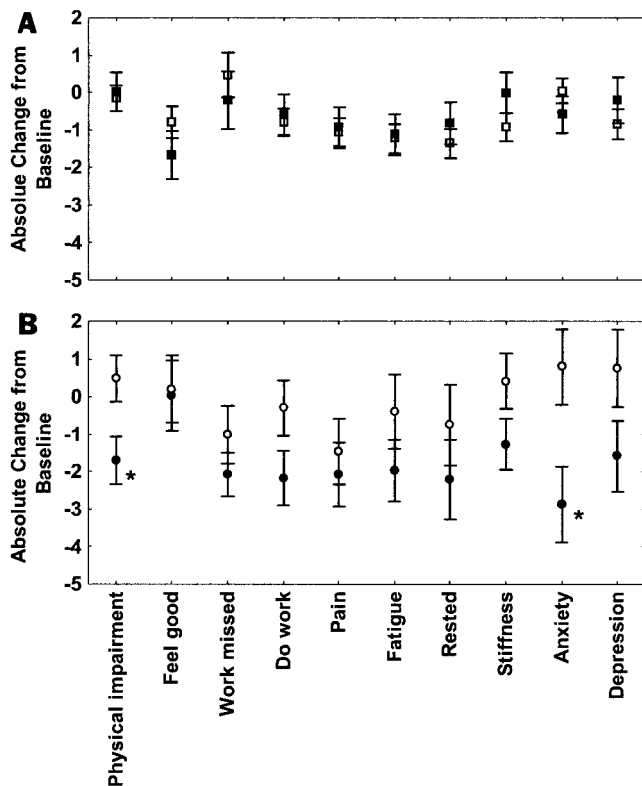


Figure 2. Absolute change from baseline in the subscales of the Fibromyalgia Impact Questionnaire (FIQ) in terguride-treated (solid symbols) and placebo-treated (open symbols) patients. Squares represent patients with grades 0–1 cervical spine stenosis (n = 57; 38 receiving terguride and 18 receiving placebo). Circles represent patients with grades 2–4 cervical spine stenosis (n = 16; 8 receiving terguride and 8 receiving placebo). Values are the mean ± SEM. * = *P* < 0.05 versus placebo.

Patients reported nausea (24 [36.9%] with terguride and 4 [11.8%] with placebo), headache (14 [21.5%] with terguride and 9 [26.5%] with placebo), and insomnia (14 [21.5%] with terguride and 3 [8.8%] with placebo) as the most frequent AEs (Figure 3). Nausea was noted at significantly higher frequency in the terguride group than in the placebo group (*P* < 0.05). Other AEs, including upper abdominal pain, malaise, dyspepsia, vomiting, vertigo, abdominal pain, and headache were not significantly different between treatment groups.

A total of 21 patients in the terguride group (32.3%) and 6 in the placebo group (17.6%) experienced an AE that resulted in a dosage reduction or prevented a further dosage increase. Seventeen patients in the terguride group (26.2%) and 1 in the placebo group (2.9%) terminated the study prematurely because of nausea (8 [12.3%] receiving terguride and 1 [2.9%]

receiving placebo), vomiting (4 [6.2%] receiving terguride and 0 receiving placebo), dizziness (3 [4.6%] receiving terguride and 0 receiving placebo), and constipation (2 [3.1%] receiving terguride and 0 receiving placebo). Premature termination occurred predominantly during up-titration of the dosage.

Vital signs and findings on EKG, physical examination, and echocardiography did not indicate a significant effect of terguride on individual patients. There was no relevant change in laboratory safety parameters in the treatment groups. Consistent with its pharmacologic mode of action, terguride treatment resulted in a lowering of serum prolactin levels (mean -3.1 μg/liter [95% CI -5.4, -0.8]), indicating that pharmacologically relevant concentrations of terguride had been achieved. No relevant change in serum prolactin levels was observed in the placebo group (mean 0.5 μg/liter [95% CI -1.2, 2.2]).

DISCUSSION

Based on the dopaminergic hypothesis of FMS (28), we studied the therapeutic effects of terguride in FMS patients who were not concurrently receiving other FMS-targeted drug therapy. Terguride was administered at or above the dosage levels demonstrated for dopamine-agonistic actions in Parkinson’s disease (29) and restless legs syndrome (30). No significant differences in the primary end point, which was a reduction in pain intensity as assessed on a VAS, between those taking terguride and those taking placebo were ob-

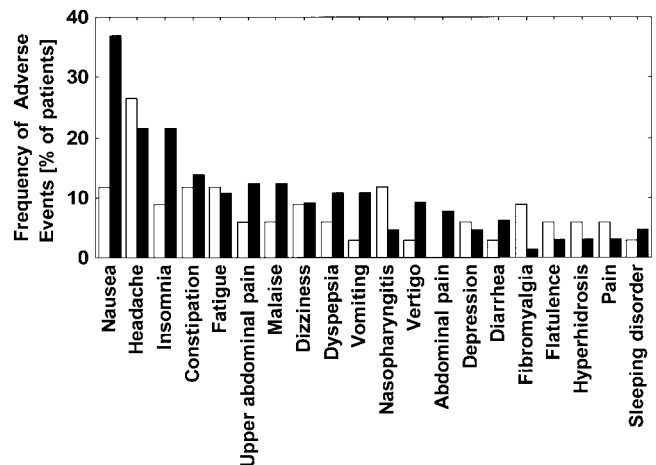


Figure 3. Frequencies of treatment-emergent adverse events in terguride-treated (solid bars) and placebo-treated (open bars) patients. Frequencies represent the percentages of patients with at least 1 treatment-emergent adverse event. Nausea occurred significantly more frequently in the terguride group than in the placebo group (*P* < 0.05).

served. Similarly, the secondary efficacy end points, which were the FIQ score, the TPS, and the HDS score, were not significantly different between the terguride and placebo groups.

Our findings are similar to the results of the study on safety and efficacy of the dopamine agonist ropinirole CR in FMS patients. While that study is unpublished, the results are available from public repositories (19). No improvement in the primary or secondary clinical end points was observed following ropinirole treatment as compared with placebo. Similarly, according to a recent press release on a phase II study of the dopamine agonist rotigotine in FMS (NCT00464737), the primary end point of a reduction in pain during rotigotine treatment did not reach statistical significance as compared with a control group receiving placebo (31). In contrast, Holman and Myers (17) reported a significant therapeutic effect of the dopamine agonist pramipexole in FMS patients receiving concomitant medication.

The apparent discrepancy between the findings of this latter study and the findings of our study may be due to differences in the study populations, trial designs, and pharmacologic profiles of the drugs evaluated. First, patients in the pramipexole trial received multiple medications, including narcotics, antiepileptics, antidepressants, SSRIs, anxiolytics, muscle relaxants, or hypnotics, making it difficult to accurately discern the therapeutic effect of the study drug. This may reflect differences in the patient populations or in practice patterns of the clinicians in terms of the number or types of medications they provide to patients, or it may reflect geographic difference in FMS treatment algorithms with off-label uses for drugs.

Second, although there was no significant difference for individual drug classes, the treatment groups in the pramipexole study differed with respect to the subgroups that received multiple FMS-targeted medications. Patients receiving dual drug therapy were more frequently allocated to the pramipexole group, and a larger number of patients receiving quadruple drug therapy were in the placebo group. This may have favored an overall improved response in the pramipexole group.

Third, drug interactions that potentiate analgesic effects, such as interactions between opioids and dopamine agonists (32,33), may have contributed to an enhanced response to pramipexole as compared with placebo.

Finally, differences in the pharmacologic profile of terguride and pramipexole must be considered. In

contrast to pramipexole, which has an ~20-fold specificity for dopamine D₃ receptors over dopamine D₂ receptors, terguride binds to dopamine D₂ and D₃ receptors with comparable affinity (34). Therefore, terguride may act on a different subset of dopaminergic neurons as compared with pramipexole. Furthermore, terguride acts as a partial dopamine agonist, which implies that rather than resulting in dopaminergic overstimulation, it preferably normalizes a deficit in dopamine receptor signaling. In contrast, pramipexole acts as a full agonist, and involvement of supraphysiologic dopaminergic stimulation by pramipexole at high dosages in FMS patients may be considered.

Patients in our study were recruited predominantly from rheumatology referral centers. They are regarded as a representative cross-section of FMS patients. The neurologic status of our study patients was not evaluated. However, no apparent neurologic findings were reported in the examinations conducted at study entry or noted in the patients' medical history records. In 22% of our patients, complete obliteration of the subarachnoid space, cervical cord compression or displacement, or spinal cord hyperintensity was detected with the neck in a neutral position. Heffez et al (35) reported cervical spine stenosis in 23% of a nonrandomly selected FMS population when the neck was positioned in extension, and Holman (36) reported an abutment or compression of the cervical spine canal in 71% of the FMS study population on cervical extension, but only in 29% when the neck was in the neutral position.

These studies emphasize that despite an apparently normal appearance of the cervical central spinal canal in neutral view, significant stenosis and intermittent functional impairment does occur with motion of the cervical spine. Clauw et al (37) reported a 50% prevalence of cervical spine stenosis in an FMS cohort but no difference in the prevalence of cervical spine stenosis in FMS patients and sex-matched subjects without a diagnosis of FMS and asymptomatic for cervical spine stenosis. Therefore, a direct causal relationship between cervical spine stenosis and FMS remains unlikely. Nevertheless, irritation at the spinal level (38) or altered spinal nociceptive processing (39) may exaggerate the symptoms of FMS. Patients meeting the ACR diagnostic criteria for FMS and having concomitant cervical spine stenosis may represent a form of secondary FMS with possibly differential symptoms (40) and a differential response to therapy.

When analyzing the results of this study, it should be taken into account that only 16 patients were identi-

fied by MRI to have grades 2–4 cervical spine stenosis and that the assessment of therapeutic effects was based on small group sizes. Nevertheless and despite the large variability in patient-oriented scores, a significant decrease in the FIQ score was observed, including effects on the physical impairment, do work, rested, stiffness, anxiety, and depression subscales.

The pathophysiology of spinal stenosis is still a topic under discussion. Besides static factors that lead to canal encroachment, including a congenitally narrowed canal, disk bulging, and spondylitic osteophytes, alterations in the spinal vasculature appear to play a role (41). Thus far, drug treatment of spinal stenosis is predominantly of a symptomatic nature, but therapeutic effects of prostaglandin E₁ treatment in patients with lumbar spine stenosis (42) were recently reported. Furthermore, promising effects of the 5-hydroxytryptamine receptor 2A (5-HT_{2A}) antagonist sarpogrelate have been observed in patients (43) and in animal models of disc herniation or experimentally induced spinal stenosis (44,45). Terguride, in addition to being a dopamine agonist, also acts as a high-affinity antagonist of 5-HT₂ receptors as well as an α_2 -adrenolytic agent in functional bioassays (46). Thus, 5-HT₂ antagonism might provide a potential explanation for the therapeutic effects of terguride in patients with cervical spine stenosis.

In the present study, only AEs that were already known to be side effects of terguride were observed. These occurred predominantly and transiently during up-titration of the terguride dosage. As known from previous clinical experience and as expected for this drug class, nausea was noted as the most frequent terguride-related AE. Premature study withdrawal of patients receiving terguride treatment was observed, with nausea, vomiting, and dizziness being named as the most frequent causes. The dropout rate in the terguride group was 26% as compared with 3% in the placebo group. A rather rapid dosage escalation, a lack of comedication for control of gastrointestinal side effects in 10 of 17 dropouts, and a generally increased sensitivity of FMS patients to AEs of medications may have contributed to these findings. In clinical use, peripherally acting dopamine antagonists (47,48) are highly effective in improving the tolerability of dopamine agonists without interfering with the therapeutic effects. Indeed, most patients who received either domperidone or proton pump inhibitors as comedication for nausea completed the study on schedule.

We observed an increased frequency of insomnia and of the use of bromazepam or lormetazepam for the

treatment of insomnia in the terguride treatment group, although these features did not differ significantly between the treatment groups. The profile of terguride differs in this respect from other dopamine agonists, for which an increased prevalence of sleep attacks in patients with Parkinson's disease (49) has been noted and which remains a matter of concern in the use of dopamine agonists.

In summary, terguride treatment did not improve pain, FMS intensity, or the HDS score in the total study population. However, a subgroup of patients with cervical spine stenosis seems to have benefitted from terguride therapy, and this warrants further studies.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Müller-Ladner had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Distler, Eich, Dokoupilova, Dvorak, Gaubitz, Hechler, Jansen, Pache, Reiter, Müller-Ladner.

Acquisition of data. Distler, Eich, Dokoupilova, Dvorak, Fleck, Gaubitz, Hechler, Jansen, Krause, Bendszus, Pache, Müller-Ladner.

Analysis and interpretation of data. Distler, Eich, Dokoupilova, Dvorak, Gaubitz, Hechler, Bendszus, Pache, Reiter, Müller-Ladner.

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