Sleep Medicine 80 (2021) 315–321

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Original Article

Efficacy and safety of modafinil in patients with idiopathic hypersomnia without long sleep time: a multicenter, randomized, double-blind, placebo-controlled, parallel-group comparison study

Yuichi Inoue [a, b, *], Toshiyuki Tabata [c], Naoji Tsukimori [d]

[a] Japan Somnology Center, Institute of Neuropsychiatry, 5-10-10 Yoyogi, Shibuya-ku, Tokyo, 151-0053, Japan
[b] Department of Somnology, Tokyo Medical University, 6-7-1 Nishishinjuku, Shinjuku-ku, Tokyo, 160-0023, Japan
[c] Research and Development Headquarters, Alfresa Pharma Corporation, 2-2-9 Koku-machi, Chuo-ku, Osaka, 540-8575, Japan
[d] Medical Affairs Headquarters, Alfresa Pharma Corporation, 2-2-9 Koku-machi, Chuo-ku, Osaka, 540-8575, Japan

ARTICLE INFO

Article history:
Received 11 September 2020
Received in revised form
9 December 2020
Accepted 14 January 2021
Available online 20 January 2021

Keywords:
Modafinil
Idiopathic hypersomnia without long sleep time
Randomized controlled trial
Maintenance of Wakefulness Test
Japanese version of the Epworth Sleepiness Scale

ABSTRACT

Background: Few treatments are available for patients with idiopathic hypersomnia (IH). Modafinil, an established treatment for narcolepsy, was tested for efficacy and safety in Japanese patients with IH without long sleep time.

Methods: This multicenter, randomized, double-blind, placebo-controlled, parallel-group comparison study was conducted at 20 institutions in Japan. Patients who met the diagnostic criteria of IH in the International Classification of Sleep Disorders (second edition) were included. The study comprised a ≥17-day observation period and a 3-week treatment period during which modafinil (200 mg) or placebo was administered orally once daily (in the morning). The primary efficacy endpoint was change in mean sleep latency on the Maintenance of Wakefulness Test (MWT). Adverse events (AEs) were also recorded to evaluate safety.

Results: In total, 123 patients were screened and 71 were randomized to receive modafinil (N = 34) or placebo (N = 37). Patients treated with modafinil experienced a significantly prolonged mean sleep latency on the MWT at the end of the study compared with placebo (5.02 min, 95% confidence interval: 3.26–6.77 min; $p < 0.001$). AEs occurred in 58.8% (20/34) and 27.0% (10/37) of patients in the modafinil and placebo groups, respectively. Frequent AEs in the modafinil group were headache (n = 6), dry mouth (n = 3), and nausea (n = 3); no clinically significant AEs occurred.

Conclusion: Modafinil was shown to be an effective and safe treatment for excessive daytime sleepiness in patients with IH without long sleep time.

Clinical trial registration: JapicCTI; 142539.

1. Introduction

A syndrome characterized by excessive daytime sleepiness (EDS), prolonged sleep, and sleep drunkenness with the absence of cataplexy was named idiopathic hypersomnia (IH) in 1976 [1]. The disease characteristics of IH were put forward in the first edition of the International Classification of Sleep Disorders (ICSD; 1990) [2]. In 2005, the ICSD-2 further classified IH into “IH with long sleep time” and “IH without long sleep time” [3]. However, in 2014 the ICSD-3 unified IH into a single category, defining it as central hypersomnia without an increased propensity for rapid eye movement (REM) sleep and with no distinction of whether it is accompanied by long sleep [4].

IH manifests as EDS, and typical IH is characterized by long sleep and severe prolonged sleep inertia consisting of irritability, automatism, and confusion known as “sleep drunkenness” [4]. In central hypersomnias, including IH, a remarkable reduction in quality of life has been reported, owing to the psychosocial and environmental changes that occur along with the symptoms [5]. Detailed information about the prevalence of IH has not been obtained, but it has been reported that the typical IH is 10 times less frequent than narcolepsy [6].

* Corresponding author. Department of Somnology, Tokyo Medical University, 6-7-1 Nishishinjuku, Shinjuku-ku, Tokyo, 160-0023, Japan. Fax: +81 3 3460-3033.
E-mail address: inoue@somnology.com (Y. Inoue).

https://doi.org/10.1016/j.sleep.2021.01.018
1389-9457/

Abbreviations

AEs	Adverse events
ANCOVA	Analysis of covariance
CGI-C	Clinical Global Impression of Change
CI	Confidence interval
EDS	Excessive daytime sleepiness
ESS	Epworth Sleepiness Scale
FAS	Full analysis set
ICSD	International Classification of Sleep Disorders
IH	Idiopathic hypersomnia
JESS	Japanese version of the Epworth Sleepiness Scale
LS	Least squares
MSLT	Multiple Sleep Latency Test
MWT	Maintenance of Wakefulness Test
NPSG	Nocturnal polysomnography
REM	Rapid eye movement

So far, there has been no established treatment for IH; most patients have received off-label treatment with drugs approved for narcolepsy [7]. Modafinil [8,9] is a selective dopamine reuptake inhibitor that primarily works by promoting the function of the dopamine transporter, and has been frequently used as an off-label treatment for IH [7]. In the United States, although the American Society of Sleep Medicine guidelines mentioned the effectiveness of modafinil for the treatment of IH [10], it has not been approved by the United States Food and Drug Administration. In Europe, modafinil was initially approved by the European Medicines Agency for the treatment of IH, but the indication was removed in 2011 because there was a paucity of data from appropriately controlled clinical trials of modafinil for this use [11]. The studies demonstrating the efficacy of modafinil for IH, on which approval was based, were uncontrolled [12] or were reported retrospectively [13]. After 2011, a randomized controlled trial of modafinil for the treatment of IH was conducted with a relatively small number of patients; the trial did not report superiority in the reduction of mean sleep latency on the Maintenance of Wakefulness Test (MWT), the primary outcome measure, for modafinil versus placebo [14]. This result showed that appropriately powered clinical trials, with a similar number of patients as trials evaluating modafinil in patients with narcolepsy [15,16], are warranted to examine the effectiveness and safety of modafinil treatment for patients with IH.

Considering this, we conducted a multicenter, randomized, double-blind, placebo-controlled, parallel-group comparison study to evaluate the efficacy and safety of modafinil treatment in Japanese patients with IH without long sleep time, using previous clinical trials on narcolepsy as a reference for trial design [15,16]. To our knowledge, this was the first clinical trial to evaluate modafinil treatment for Asian patients with IH.

2. Patients and methods

We conducted a multicenter, randomized, double-blind, placebo-controlled, parallel-group comparison study between April 2014 and August 2015 at 20 institutions in Japan that specialized in sleep disorders. This study was conducted in compliance with the Declaration of Helsinki and Good Clinical Practice research guidelines. The institutional review board of each participating medical institution approved the study protocol prior to study initiation; the study was registered with the Japan Pharmaceutical Information Center – Clinical Trials Information (JapicCTI; 142539). All patients provided written informed consent prior to inclusion in the study.

2.1. Patients

Patients who were diagnosed as having IH (with or without long sleep time) according to the ICSD-2 [3], were aged 16–64 years, had a Japanese version of the Epworth Sleepiness Scale (JESS) total score of ≥11 [17], had a total sleep time of ≥6 h on nocturnal polysomnography (NPSG) [18], had an average sleep latency of <8 min and sleep onset REM periods of ≤1 time as measured using the Multiple Sleep Latency Test (MSLT) [19], were eligible for the study. Patients were excluded if they had ≥2 sleep onset REM periods on the MSLT, an apnea-hypopnea index >10/h on the NPSG, Periodic Limb Movement Index of >15/h on the NPSG; chronic sleep deprivation or significantly irregular bedtime, including shift- or night-shift workers, and patients who had less than 12 days with a sleep duration of ≥6 h in the 14 days prior to patient enrollment (based on sleep diary records); concomitant mental disorders such as depression or schizophrenia; concomitant brain organic disorders or epilepsy, cerebrovascular complications, or a history of cerebrovascular disorder; or had been previously treated with modafinil.

2.2. Study schedule

Prior to initiating the 3-week treatment period, there was an observation period of ≥17 days which included the screening period and recording of baseline characteristics. Patients were randomly assigned to receive two tablets of either modafinil (100 mg per tablet, 200 mg total) or placebo, which were to be taken orally once daily in the morning for 3 weeks. A 3-week treatment period of once daily modafinil was chosen based on two previous studies in patients with narcolepsy where 3 weeks was the shortest time point that significant improvements in efficacy measures were reported [15,16]. Confirmation of the masking (the placebo and modafinil tablets were made indistinguishable from one another) and assignment of placebo/modafinil were performed by a third party (Bell Medical Solutions Co., Ltd., Tokyo, Japan). The permuted block randomization method was used for drug assignment.

Assessments of sleep logs, JESS records, NPSG, MSLT, MWT, and Clinical Global Impression of Change (CGI-C) scale [20] were performed according to the study schedule. Concomitant use of the following drugs was prohibited from 15 days before NPSG administration (during the observation period) or 7 days before the start of sleep diary recording, whichever occurred first: central nervous system stimulants (methylphenidate, pemoline, methamphetamine, caffeine), antipsychotics, antidepressants, antiepileptics, anxiolytics, sedative-hypnotics, antihistamines, warfarin, vasopressors, monoamine oxidase inhibitors, migraine-specific drugs, and other investigational drugs.

2.3. Efficacy evaluation

2.3.1. Primary endpoint

The primary endpoint was change in mean sleep latency on the MWT, which is an index for EDS. The MWT, as an objective evaluation, was carried out both during the observation period (baseline) and in the third week of the treatment period. Four sessions of MWT were performed for 20 min every 2 h according to the method of Doghramji et al. [21], which was similar to previous studies evaluating modafinil in patients with narcolepsy [15,16]. The time to sleep in each session was used to calculate the mean

sleep latency. Determination of sleep onset for the MWT sessions was performed by a third-party sleep specialist.

2.3.2. Secondary endpoints

Evaluations for secondary endpoints were conducted as described as follows: the JESS was used for subjective evaluation of the severity of daytime sleepiness, and assessments were conducted during the observation period and after 1 and 3 weeks of treatment. Patients whose JESS total score was reduced from ≥11 during the observation to <11 in the third week of treatment were defined as "JESS Total Score Normalized"; the proportion of these patients was calculated for each group.

The number of daytime naps (per week) was calculated using the information self-recorded by patients in sleep diaries, which were maintained throughout the observation and treatment periods. CGI-C was evaluated by physicians, as a subjective evaluation, in the first and third weeks of the treatment period using the following seven levels (vs. baseline): "very much improved", "much improved", "minimally improved", "no change", "minimally worse", "much worse", and "very much worse" [20]. NPSG was performed during the observation period and in the third week of the treatment period. Sleep parameters such as sleep latency, total sleep time, and percentages of respective sleep stages were used to evaluate the effects of the study drug on nocturnal sleep.

2.4. Safety evaluation

To evaluate the safety of modafinil, the occurrence of adverse events (AEs) was determined by interviews during the observation period and after 1 and 3 weeks of treatment. Clinical laboratory tests (hematology, blood chemistry, and urinalysis) and body weight measurement were performed in the observation period and after 3 weeks of treatment. Vital signs (blood pressure and pulse rate) and 12-lead electrocardiogram data were collected in the observation period and after 1 and 3 weeks of treatment.

2.5. Statistical analysis

The sample size was determined using the data from two randomized clinical trials that evaluated the safety and efficacy of modafinil in patients with narcolepsy diagnosed according to the ICSD (1990) criteria [15,16]. From these studies, we extracted cases in which the diagnosis was assumed to be IH based on the ICSD-2 (2005) criteria. We estimated the difference between the placebo and modafinil groups in these trials and, along with original data provided from an affiliated company, we calculated the number of cases needed to verify the superiority of the active drug group compared with the placebo group. All patients who received at least one dose of the study drug and had at least one efficacy evaluation after the start of the investigational drug administration were included in the full analysis set (FAS), which was used for efficacy analysis.

The change from baseline to 3 weeks in the mean sleep latency on the MWT, the JESS score, and the number of daytime naps was compared between the modafinil and placebo groups using analysis of covariance (ANCOVA) with the baseline value as the covariate. Point estimates and 95% confidence intervals (CI) for the difference between the placebo and modafinil groups were computed using least squares (LS) mean change. Fisher's exact test was also used to compare modafinil with placebo for the percentage of JESS Total Score Normalized patients and the percentage of patients with "much improved" or better score in the CGI-C.

A two-sided significance level of 5% was used; a p value of <0.05 was considered significant. The CI was two-sided with a confidence coefficient of 95%. Statistical analyses were performed using SAS (version 9.4; SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Patients

Patient disposition is shown in Fig. 1. A total of 123 patients were screened and 52 were excluded. Nine of the 52 patients who were excluded withdrew consent and 43 met the exclusion criteria, including ≥2 sleep onset REM periods on the MSLT (n = 20), an apnea-hypopnea index >10/h on the NPSG (n = 10), mean sleep latency on the MSLT ≥8 min (n = 7), Periodic Limb Movement Index >15/h on the NPSG (n = 4), sleep duration of ≥6 h for less than 12 days in the 14 days prior to enrollment (based on sleep diary records; n = 3), and others (n = 7); some patients were excluded for multiple reasons. The remaining 71 patients were enrolled and randomized to receive modafinil (N = 34) or placebo (N = 37). Thirty-three patients in the modafinil group and 37 in the placebo group completed treatment. One patient in the modafinil group discontinued treatment due to difficulty initiating sleep, and fatigue or malaise, both of which newly appeared during the treatment period. No patients were excluded from the FAS.

Patient characteristics are shown in Table 1. There were no significant differences in sex, age, body mass index, or the length of self-reported IH morbidity between the modafinil and placebo groups. Patients in both groups mostly reported having IH without long sleep time, and a single patient in each group had IH with long sleep time. Six patients (17.6%) in the modafinil group and 12 (32.4%) in the placebo group had received pretreatment drugs such as pemoline. There were no notable differences in other characteristics between the two groups.

3.2. Efficacy

Efficacy results are summarized in Table 2.

3.2.1. Mean sleep latency on the Maintenance of Wakefulness Test

The changes in mean sleep latency on the MWT are shown in Fig. 2. Mean sleep latency on the MWT from baseline to 3 weeks increased from 8.05 to 11.32 min in the modafinil group and decreased from 7.91 to 6.46 min in the placebo group. Using the baseline value as a covariate, the LS mean changes from baseline to 3 weeks were 3.60 min in the modafinil group and −1.42 min in the placebo group. The difference between the groups was 5.02 min (95% CI: 3.26–6.77 min), which was significant (p < 0.001, ANCOVA).

3.2.2. Japanese version of the Epworth Sleepiness Scale total score

The results for the JESS total score are shown in Fig. 3. The JESS total score from baseline to 3 weeks decreased from 16.71 to 10.00 in the modafinil group and from 18.22 to 15.86 in the placebo group. Using the baseline value as a covariate, the LS mean changes from baseline to 3 weeks were −7.06 in the modafinil group and −2.05 in the placebo group. The difference between the groups was −5.01 (95% CI: −7.23 to −2.78), which was significant (p < 0.001, ANCOVA).

At 3 weeks, the percentage of JESS Total Score Normalized patients was 54.5% (18 of 33 patients) in the modafinil group and 8.1% (3 of 37 patients) in the placebo group, which was significant (p < 0.001, Fisher's exact test).

3.2.3. Number of self-reported daytime naps

Information obtained from sleep diary records showed that the number of daytime naps per week from baseline to 3 weeks

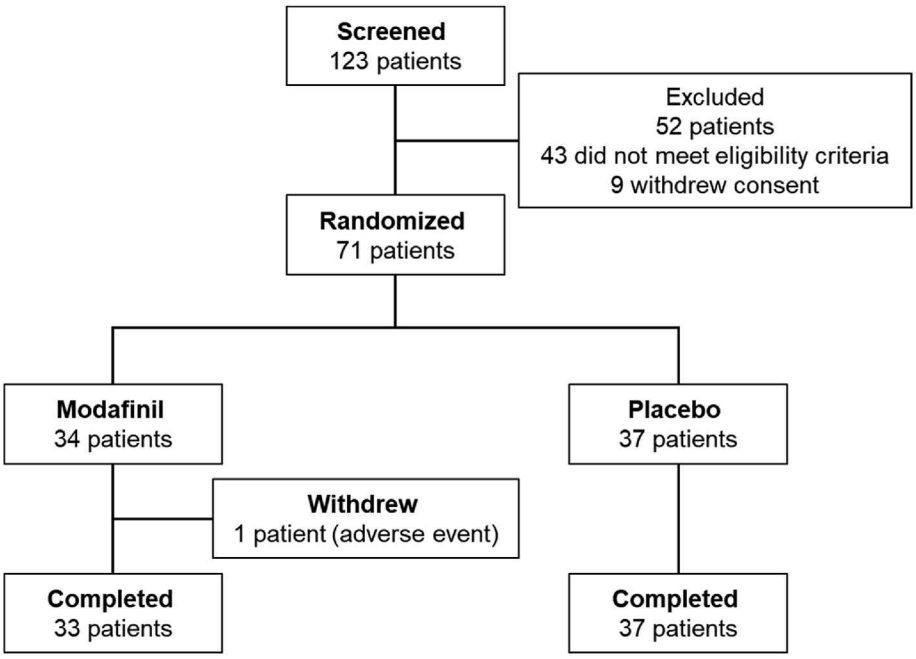

Fig. 1. Patient disposition.

Table 1
Patient characteristics.

Characteristics	Modafinil (N = 34)	Placebo (N = 37)
Sex		
Male	14 (41.2)	18 (48.6)
Female	20 (58.8)	19 (51.4)
Age, years		
Mean ± SD	30.6 ± 9.6	27.9 ± 9.7
Min–Max	19–53	16–61
Body mass index, kg/m^2		
Mean ± SD	22.37 ± 3.74	21.66 ± 2.79
Min–Max	17.5–31.6	16.9–29.6
Duration of disease, years		
Mean ± SD	11.7 ± 9.2	10.1 ± 9.5
Min–Max	1–40	0–45
Diagnosis		
IH with long sleep time	1 (2.9)	1 (2.7)
IH without long sleep time	33 (97.1)	36 (97.3)
Premedicated (stimulants)		
Yes	6 (17.6)	12 (32.4)
No	28 (82.4)	25 (67.6)
MSLT mean sleep latency, min		
Mean ± SD	3.93 ± 1.68	4.72 ± 2.00
Min–Max	1.2–7.4	1.4–7.8
JESS total score, points		
Mean ± SD	16.71 ± 3.15	18.22 ± 2.82
Min–Max	11.0–21.0	13.0–24.0
Number of daytime naps, per week		
Mean ± SD	9.53 ± 6.69	10.57 ± 7.81
Min–Max	0.0–26.0	0.0–40.0

Data are n (%) unless otherwise stated.
Abbreviations: IH, idiopathic hypersomnia; JESS, Japanese version of the Epworth Sleepiness Scale; MSLT, Multiple Sleep Latency Test; SD, standard deviation.

decreased from 9.53 to 4.73 in the modafinil group and from 10.57 to 8.76 in the placebo group. The LS mean change, calculated with the baseline value as the covariate, from baseline to 3 weeks was −4.99 in the modafinil group and −1.63 in the placebo group. The difference between the groups was −3.37 (95% CI: −5.25 to −1.48), which was significant ($p < 0.001$, ANCOVA).

3.2.4. Clinical Global Impression of Change

At 3 weeks, the percentage of patients with a CGI-C of “very much improved” or “much improved” was 54.5% (18 of 33 patients) in the modafinil group and 18.9% (7 of 37 patients) in the placebo group ($p = 0.002$, Fisher's exact test).

3.2.5. Effects on nocturnal sleep

Changes in the sleep parameters of NPSG at 3 weeks were inconsistent when compared with baseline in either group; there were no significant differences in these changes between the two groups.

3.3. Safety

AEs occurred in 20 of 34 patients (58.8%) in the modafinil group and 10 of 37 patients (27.0%) in the placebo group; the difference in the frequency of AEs between the groups was significant ($p = 0.008$, Fisher's exact test). AEs with an incidence of 5% or more are shown in Table 3. In the modafinil group, the following AEs were reported in 5% or more of patients: headache, six patients (17.6%); dry mouth and nausea, three patients (8.8%) each; and diarrhea, loss of appetite, and weight loss in two patients (5.9%) each. The only AE reported in the placebo group was headache, which occurred in three patients (8.1%). Most AEs were mild in severity; no deaths or serious AEs occurred. One patient in the modafinil group discontinued the study due to difficulty initiating sleep, and fatigue or malaise; the patient recovered 2 days after study discontinuation. No notable clinical changes were reported in either group with regard to clinical laboratory tests, physical examination, vital signs (including 12-lead electrocardiogram), or body weight.

4. Discussion

In this study, the primary outcome of prolonged mean sleep latency on the MWT was achieved. Mean sleep latency was

Table 2
Efficacy results.

Treatment group	Modafinil			Placebo			Difference in treatment effect		p value
	Baseline	Week 3	Change	Baseline	Week 3	Change			
N	34	33	33	37	37	37			
	Mean ± SD	Mean ± SD	LS mean ± SE	95% CI	Mean ± SD	Mean ± SD	LS mean ± SE	95% CI	
MWT mean sleep latency, min	8.05 ± 5.11	11.32 ± 4.71	3.60 ± 0.64	2.33, 4.88	7.91 ± 5.29	6.46 ± 5.35	−1.42 ± 0.60	−2.62, −0.21	5.02 ± 0.88	3.26, 6.77	<0.001[a]
JESS total score, points	16.71 ± 3.15	10.00 ± 5.23	−7.06 ± 0.80	−8.66, −5.47	18.22 ± 2.82	15.86 ± 4.39	−2.05 ± 0.75	−3.56, −0.55	−5.01 ± 1.12	−7.23, −2.78	<0.001[a]
Number of daytime naps, per week	9.53 ± 6.69	4.73 ± 5.38	−4.99 ± 0.69	−6.37, −3.62	10.57 ± 7.81	8.76 ± 6.62	−1.63 ± 0.65	−2.92, −0.33	−3.37 ± 0.95	−5.25, −1.48	<0.001[a]
JESS normalization, % (n/N)	54.5 (18/33)				8.1 (3/37)						<0.001[b]
CGI-C improvement, % (n/N)	54.5 (18/33)				18.9 (7/37)						0.002[b]

Abbreviations: ANCOVA, analysis of covariance; CGI-C, Clinical Global Impression of Change; CI, confidence interval; JESS, Japanese version of the Epworth Sleepiness Scale; LS, least squares; MWT, Maintenance of Wakefulness Test; SD, standard deviation; SE, standard error.
[a] ANCOVA with baseline values as covariates.
[b] Fisher's exact test.

Fig. 2. Mean sleep latency on the Maintenance of Wakefulness Test. Data are mean ± SD with the N for each group shown in parenthesis. *p < 0.001, ANCOVA. Abbreviations: ANCOVA, analysis of covariance; MWT, Maintenance of Wakefulness Test; SD, standard deviation.

Fig. 3. JESS total scores. Data are mean ± SD with the N for each group shown in parenthesis. *p < 0.001, ANCOVA. Abbreviations: ANCOVA, analysis of covariance; JESS, Japanese version of the Epworth Sleepiness Scale; SD, standard deviation.

Table 3
Adverse events occurring in ≥5% of patients.

Adverse events	Modafinil (N = 34)	Placebo (N = 37)
Adverse events, all	20 (58.8)	10 (27.0)
Headache	6 (17.6)	3 (8.1)
Dry mouth	3 (8.8)	–
Nausea	3 (8.8)	–
Diarrhea	2 (5.9)	–
Loss of appetite	2 (5.9)	–
Weight loss	2 (5.9)	–

Data are n (%).

significantly prolonged in the modafinil group (200 mg once daily for 3 weeks) compared with the placebo group, thus confirming the effectiveness of modafinil for treating objective daytime sleepiness in IH without long sleep time. Mean sleep latency was prolonged to 11.32 min in the modafinil group, which suggests that objective daytime sleepiness with treatment may approach a level that does not interfere with daily functioning; Doghramji et al. estimated 11 min as the cutoff value to determine a pathological level in the MWT standardization test [21]. Similarly, the JESS mean total score was lower than the pathological cutoff value of 11 points [22] after modafinil treatment, and the proportion of JESS Total Score Normalized patients in the modafinil group was significantly higher than in the placebo group. Together, these

results suggest an improvement in subjective daytime sleepiness after modafinil treatment. Furthermore, the CGI-C improvement rate (patients with "very much improved" or "much improved") at 3 weeks was significantly higher in the modafinil group than in the placebo group. Taking the above results together, the efficacy of modafinil for improvement of EDS in patients with IH was confirmed by both objective (primary endpoint) and subjective (secondary endpoints) evaluations.

The changes in sleep parameters on NPSG that were reported in the present study indicated that modafinil (200 mg, once daily in the morning) did not affect nocturnal sleep, which is similar to the results reported in previous clinical trials of the effects of modafinil on either narcolepsy [15,16] or residual sleepiness in patients with obstructive sleep apnea who were being treated with nasal continuous positive airway pressure therapy [23].

A placebo-controlled trial conducted by Mayer et al. in Germany [14] reported that modafinil significantly improved the Epworth Sleepiness Scale (ESS) total score and CGI over placebo, but there was no significant difference in the mean sleep latency on the MWT between the two groups. The reasons for the difference between their study and the current study, in which there was a significant difference in mean sleep latency on the MWT observed with modafinil vs. placebo, are yet to be elucidated. The total number of patients was much smaller in the study by Mayer et al. (N = 31) [14] compared with our study (N = 71), which may have had an effect on the results of statistical testing. As for respective demographic characteristics, most of the variables were comparable between the studies, with 16.71 vs. 15.00 for the JESS/ESS total scores and 8.05 vs. 12.50 min for the baseline sleep latency on the MWT [14]. This suggests that the IH severity was not lower in the present study than in the Mayer et al. study. Both their study and ours had a treatment duration of 3 weeks; however, the present study treated patients with 200 mg once daily (morning) while the aforementioned study treated patients with 100 mg twice daily (morning and noon) [14]. According to a review by McClellan et al. [24], the maximum concentration of modafinil in the blood is lower when 200 mg of modafinil is administered as two daily doses of 100 mg than when the 200 mg dose is given at one time; it is possible that this pharmacokinetic difference influenced the efficacy results of the two studies.

To the best of our knowledge, our study is the first randomized controlled trial to successfully report the superior efficacy of modafinil versus placebo for IH without long sleep time. The disease severity at baseline, measured as the mean sleep latency on the MWT, in our study was slightly longer (8.05 min; 200 mg modafinil group) compared with that of the two placebo-controlled double-blind trials of modafinil in patients with narcolepsy conducted in the US (6.1 and 5.8 min, respectively) [15,16]. The improvements in the mean sleep latency on the MWT and ESS total score with modafinil treatment (vs. placebo) were greater in the current study compared with the previous reports. Of note, patients with narcolepsy were administered up to 400 mg modafinil daily in the above mentioned US studies compared with 200 mg once daily modafinil for patients with IH in the current study. These findings are compatible with the results of our previous study, showing that patients with IH without long sleep time have a lower severity of hypersomnia and respond better to a treatment with lower dosages of psychostimulant drugs (methylphenidate equivalent) than patients with narcolepsy with cataplexy [25].

In the present study, no serious AEs were observed in the modafinil group. AEs occurring most frequently were headache, dry mouth, and nausea and almost all events were mild in severity; none were of clinical concern. Our safety results are aligned with the safety findings reported by Mayer et al. [14] who also reported that all AEs were mild to moderate.

This study has several limitations. First, the number of patients with IH with long sleep time, which represents the cardinal phenotype of IH [6], was small (only two patients, one per group) and this limits the generalizability of the efficacy findings of the present study to the wider patient population. In addition, we could not objectively confirm whether the patients had long sleep time or not. Second, we did not investigate sleep inertia in the present study. However, given that sleep inertia is a common symptom in patients with IH with long sleep time, and that nearly all of the patients in this study had IH without long sleep time, it can be assumed that few study patients had trouble with sleep inertia prior to administration of the study drug. Third, because IH diagnosis in our study was based on the ICSD-2, which did not consider the recently highlighted problems with obtaining a clear diagnosis between IH and other central hypersomnolence disorders [26], the number of patients who would have been diagnosed with idiopathic excessive sleepiness was not assessed in the present study. Fourth, inclusion of only Japanese patients in our study limits the generalizability to other ethnicities. Finally, as the treatment duration of our study was only 3 weeks, evaluation of long-term efficacy and safety of modafinil in patients with IH was beyond the scope of this study.

5. Conclusions

The safety and efficacy of modafinil treatment to improve EDS in Japanese patients with IH without long sleep time was objectively confirmed for the first time in this multicenter, randomized, double-blind, placebo-controlled, parallel-group comparison study using the change in mean sleep latency on the MWT as a primary outcome measure, and JESS, weekly number of daytime naps, and CGI-C as secondary outcome measures. Modafinil is expected to become a potential treatment for patients with IH, for whom few treatment options are available.

Data statement

Additional deidentified data are not available to protect patient confidentiality.

Funding

This work was funded by Alfresa Pharma Corporation. The sponsor contributed to the study design, data collection, data analysis, data interpretation, and writing of the clinical study report.

CRediT authorship contribution statement

Yuichi Inoue: Conceptualization, Methodology, Writing - review & editing. **Toshiyuki Tabata:** Conceptualization, Data curation, Formal analysis, Methodology, Software, Validation, Writing - review & editing. **Naoji Tsukimori:** Conceptualization, Investigation, Methodology, Project administration, Supervision, Validation, Writing - original draft.

Acknowledgements

We wish to thank the patients who participated in the present study. We thank the members of the Modafinil Idiopathic Hypersomnia Study Group in Japan for their help with this study. We also thank Sarah Bubeck, PhD, of Edanz Evidence Generation for providing medical writing support, which was funded by Alfresa Pharma Corporation through EMC K.K., in accordance with Good

Publication Practice (GPP3) guidelines (http://www.ismpp.org/gpp3).

Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2021.01.018.

References

[1] Roth B. Narcolepsy and hypersomnia: review and classification of 642 personally observed cases. Schweiz Arch Neurol Neurochir Psychiatr 1976;119:31–41.
[2] ICSD. International Classification of Sleep Disorders: diagnostic and coding manual. Diagnostic classification staging committee. Rochester, MN: American Sleep Disorders Association; 1990.
[3] International Classification of Sleep Disorders. Diagnostic and coding manual. 2nd ed. Westchester, IL: American Academy of Sleep Medicine; 2005.
[4] International Classification of Sleep Disorders. 3rd ed. Darien, IL: American Academy of Sleep Medicine; 2014.
[5] Ozaki A, Inoue Y, Hayashida K, et al. Quality of life in patients with narcolepsy with cataplexy, narcolepsy without cataplexy, and idiopathic hypersomnia without long sleep time: comparison between patients on psychostimulants, drug-naive patients and the general Japanese population. Sleep Med 2012;13:200–6.
[6] Billiard M, Sonka K. Idiopathic hypersomnia. Sleep Med Rev 2016;29:23–33.
[7] Dauvilliers Y, Bassetti C. Idiopathic hypersomnia. In: Kryger MH, Roth T, Dement WC, editors. Principles and practice of sleep medicine. 6th ed. Philadelphia: Elsevier; 2017. p. 883–91.
[8] Mignot E, Nishino S, Guilleminault C, et al. Modafinil binds to the dopamine uptake carrier site with low affinity. Sleep 1994;17:436–7.
[9] Madras BK, Xie Z, Lin Z, et al. Modafinil occupies dopamine and norepinephrine transporters in vivo and modulates the transporters and trace amine activity in vitro. J Pharmacol Exp Therapeut 2006;319:561–9.
[10] Morgenthaler TI, Kapur VK, Brown T, et al. Practice parameters for the treatment of narcolepsy and other hypersomnias of central origin. Sleep 2007;30:1705–11.
[11] Evangelista E, Lopez R, Dauvilliers Y. Update on treatment for idiopathic hypersomnia. Expert Opin Invest Drugs 2018;27:187–92.
[12] Bastuji H, Jouvet M. Successful treatment of idiopathic hypersomnia and narcolepsy with modafinil. Prog Neuro-Psychopharmacol Biol Psychiatry 1988;12:695–700.
[13] Lavault S, Dauvilliers Y, Drouot X, et al. Benefit and risk of modafinil in idiopathic hypersomnia vs. narcolepsy with cataplexy. Sleep Med 2011;12:550–6.
[14] Mayer G, Benes H, Young P, et al. Modafinil in the treatment of idiopathic hypersomnia without long sleep time–a randomized, double-blind, placebo-controlled study. J Sleep Res 2015;24:74–81.
[15] Randomized trial of modafinil as a treatment for the excessive daytime somnolence of narcolepsy: US Modafinil in Narcolepsy Multicenter Study Group. Neurology 2000;54:1166–75.
[16] Randomized trial of modafinil for the treatment of pathological somnolence in narcolepsy. US Modafinil in Narcolepsy Multicenter Study Group. Ann Neurol 1998;43:88–97.
[17] Takegami M, Suzukamo Y, Wakita T, et al. Development of a Japanese version of the Epworth Sleepiness Scale (JESS) based on item response theory. Sleep Med 2009;10:556–65.
[18] A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects. Los Angeles: BIS/BRI, UCLA; 1968.
[19] Carskadon MA, Dement WC, Mitler MM, et al. Guidelines for the multiple sleep latency test (MSLT): a standard measure of sleepiness. Sleep 1986;9:519–24.
[20] Guy W. ECDEU assessment manual for psychiatric review, US Department of Health, Education, and Welfare publication (ADM 76-338). Rockville, MD: National Institute of Mental Health; 1976.
[21] Doghramji K, Milter MM, Bart Sangal R, et al. A normative study of the maintenance of wakefulness test (MWT). Electroencephalogr Clin Neurophysiol 1997;103:554–62.
[22] Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991;14:540–5.
[23] Inoue Y, Takasaki Y, Yamashiro Y. Efficacy and safety of adjunctive modafinil treatment on residual excessive daytime sleepiness among nasal continuous positive airway pressure-treated Japanese patients with obstructive sleep apnea syndrome: a double-blind placebo-controlled study. J Clin Sleep Med 2013;9:751–7.
[24] McClellan KJ, Spencer CM. Modafinil: a review of its pharmacology and clinical efficacy in the management of narcolepsy. CNS Drugs 1998;9:311–24.
[25] Sasai T, Inoue Y, Komada Y, et al. Comparison of clinical characteristics among narcolepsy with and without cataplexy and idiopathic hypersomnia without long sleep time, focusing on HLA-DRB1(*)1501/DQB1(*)0602 finding. Sleep Med 2009;10:961–6.
[26] Lammers GJ, Bassetti CLA, Dolenc-Groselj L, et al. Diagnosis of central disorders of hypersomnolence: a reappraisal by European experts. Sleep Med Rev 2020;52:101306.