表3　EssenCES-JPN因子分析結果

項目番号	下位項目	factor1	factor2	factor3
7		*0.809*	−0.018	0.172
10		*0.668*	0.042	0.099
13	TH	*0.613*	0.102	0.074
4		*0.584*	−0.056	0.171
16		*0.472*	−0.062	0.083
15		−0.170	*0.714*	0.088
6		−0.056	*0.699*	0.173
3	ES	−0.065	*0.601*	−0.082
12		0.052	*0.532*	−0.179
9		0.141	0.354	−0.007
14		0.094	−0.067	*0.657*
11		0.137	0.043	*0.620*
5	PC	0.385	−0.087	*0.530*
2		0.219	−0.090	*0.412*
8		0.001	0.020	0.125
因子負荷量		3.38	2.35	1.56
因子寄与率		22.5%	15.7%	10.4%

斜体太字の数字は負荷量が0.4以上のもの
EssenCES-JPN；エッセン精神科病棟風土 評価スキーマ 日本語版 Essen Climate Evaluation Schema-Japanese version
PC；患者間の仲間意識・相互サポート Patients' cohesion and mutual support
ES；安全性への実感 Experienced safety
TH；治療的な関心 Therapeutic hold

性の検討において，有意差をもって第1因子と中等度の相関が，第3因子とは弱い相関が認められた。第2因子との相関は認められなかった。

考察

1. EssenCES信頼性・妥当性

第1因子「治療的な関心」として抽出された5項目については，因子としてのまとまりもよく，GMIとの相関も得られた。ここの質問文には，患者がスタッフに率直に話しができ，スタッフは時間をかけて親身に対応し，患者理解を深めているという内容が含まれる。精神科入院医療の中で，スタッフ患者間の治療的関係を評価する既存の尺度がないことから，EssenCESの「治療的な関心」の下位項目は有用なものとなっていくと思われる。

第2因子「安全性への実感」および第3因子「患者間の仲間意識・相互サポート」については，負荷量が少ない項目(8番，9番)が含まれていること，第3因子のα係数はやや低く，また第2因子はGMIとの相関がなかったことから，課題を残している。8番の質問項目については，イギリスの報告においても「患者間の仲間意識・相互サポート」の因子への負荷が認められなかった。このことからEssenCESの原著者は8番が反転項目であることが原因ではないかと考え，2010年10月の改訂版では「患者は，患者仲間の問題を気にかけている」へと変更している。9番の質問内容は患者の内面をたずねているものである。EssenCESはスタッフと患者の両者に行うものであり，患者自身の回答が得られれば，十分な負荷量が得られる余地があるといえる。

今回の結果からは，EssenCESの精神科急性期治療を担っている病棟スタッフへの適応は，第1

因子「治療的な関心」に限られるという結果であった。

2. EssenCES 今後の発展

今回の調査では，スタッフを対象とした調査であり，入院患者への調査は次のステップと位置づけている。病棟風土，病棟環境を論じる場合は，患者の認識を知ることは必須である。WASの一連の研究ではスタッフと患者の回答に乖離を示す領域があることが指摘されており，患者の認識を把握することによって，スタッフの認識との乖離を知ることができ，病棟環境の改善につながると考えられる。

次に，原著のドイツ，引き続き報告されたイギリスの調査は，いずれも触法病棟を対象としている。ドイツの触法病棟(シュトラウビンク司法精神科病院)の平均入院期間が2年2か月，イギリスの触法病棟のうち最大の保安度のもと治療するHigh secure hospital(ブロードモア病院)の平均入院期間が8年と記述されている[7]。今回の調査対象となった精神科救急入院料病棟および急性期治療病棟は，診療報酬上3か月の入院を目標にしている。入院期間の短い病棟においては，第3因子「患者間の仲間意識・相互サポート」については，成熟しにくい環境にあるのではないかと考えられる。一方，日本の医療観察法病棟は1年6か月とされており[4]，病棟内でのさまざまな治療プログラムを通して患者間の相互関係が生まれていると思われる。したがって，EssenCES-JPNを医療観察法病棟にも適応を広げることによって第3因子への信頼性・妥当性が得られる可能性がある。

3. 本研究の限界

EssenCES-JPNの併存妥当性の評価に用いたGMIは，構成概念が妥当であると判断され，本調査にて内的一貫性が十分あり，また先行研究にてWASとの相関が得られているものである[13]。ただし本邦においてGMIの使用経験はなく，今後は，患者に対しては日本語版Client Satisfaction Questionnaire 8項目版[17]，スタッフに対しては職務満足感[18]を併用するなどして，GMIのさらなる検証が必要である。

まとめ

EssenCESは17項目からなり簡便に使用できる病棟環境の評価尺度である。今後，病棟へのなんらかの介入を試みる際には，従来の標準的尺度であったWASにとって変わる可能性がある。実際，オリジナルのドイツ語をはじめすでに6か国版が作成されており[20]，この種の調査票がないわが国において，今後の利用が期待できる。今回の研究で，EssenCESの第1因子「治療的な関心」については，その信頼性・妥当性が確認できた。該当質問項目は，すでに他の調査での試用が始まっている[8]。十分な結果が得られなかった第2因子「安全性への実感」と第3因子「患者間の仲間意識・相互サポート」についてはさらなる検討が必要であり，患者を対象者に含めての調査，あるいは新たになった質問文(8番)を用いての調査が望まれる。

本研究は平成20年度厚生労働省 精神・神経疾患研究委託費(課題番号：20委—8，課題名：「地域中心の精神保健医療福祉」を推進するための精神科救急及び急性期医療のあり方に関する研究，主任研究者：伊藤順一郎)の支援を受け実施した。なお，本調査は日本フィンランド隔離・身体拘束調査研究プロジェクト(SAKURAプロジェクト)の一環として行われた。本調査にご協力くださいました精神科病院の医師，看護師ならびにスタッフの皆様に心よりお礼申し上げます。

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Summary

Psychometric Properties of the Japanese Version of the Essen Climate Evaluation Schema (Essen CES)

Noda Toshie[1], *Sugiyama Naoya*[2]
Matsumoto Keiko[3], *Tsujiwaki Kunihiko*[4]
Hasegawa Toshio[5], *Ito Hiroto*[1]

The Japanese version of the "Essen Climate Evaluation Schema (EssenCES)", originally developed by Schalast, was develoved (EssenCES-JPN) and applied to working staff at emergency and acute psychiatric wards from four Japanese hospitals to examine its usability. The Japanese version analytically extracted three factors："Therapeutic hold," "Experienced safety," and "Patient cohesion and mutual support"；this was consistent with the findings of previous studies. A sufficient Cronbach's α value was obtained for the factor "Therapeutic hold," which also demonstrated a sufficient correlation with the Good Milieu Index, a scale designed to measure general satisfaction at ward milieu used as the standard in previous studies.

1) Department of Social Psychiatry, National Institute of Mental Health, National Center of Neurology and Psychiatry, Kodaira, Japan
2) Fukkokai Foundation, Numazu Chuo Hospital
3) Japanese Red Cross College of Nursing
4) Midorikai Healthcare Group, Narimasu Kosei Hospital
5) Faculty of Health Science, Kyorin University

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MONOGRAPH

ZONISAMIDE: A NEW DRUG FOR PARKINSON'S DISEASE

M. Murata

Department of Neurology, National Center Hospital, National Center of Neurology and Psychiatry, Tokyo, Japan

CONTENTS

SUMMARY

Zonisamide, a benzisoxazole derivative, is an antiepileptic drug with a long half-life. Three nationwide, double-blind, placebo-controlled studies carried out in Japan prompted the approval of zonisamide as an antiparkinsonian agent in early 2009. The addition of zonisamide at 25-50 mg/day to currently used antiparkinsonian drugs significantly improved cardinal symptoms in patients with advanced Parkinson's disease. The effects were maintained over more than 1 year even in patients with advanced disease. Zonisamide has multiple modes of action, and its effects on Parkinson's disease include activation of dopamine synthesis, inhibition of monoamine oxidase, inhibition of T-type calcium channels and inhibition of an indirect pathway in the basal ganglia through the δ opioid receptor. Furthermore, zonisamide exhibits neuroprotective effects in animal models of Parkinson's disease. It strongly inhibits quinoprotein formation and markedly increases glutathione S-transferase levels in the striatum by enhancing the astroglial cysteine transport system and/or astroglial proliferation via S100β production and secretion.

Correspondence: Miho Murata, MD, PhD, Department of Neurology, National Center Hospital, National Center of Neurology and Psychiatry, 4-1-1 Ogawa-higashi, Kodaira, Tokyo, Japan, 187-8551. E-mail: mihom@ncnp.go.jp.

INTRODUCTION

Zonisamide, a benzisoxazole derivative (1) (Fig. 1), has been used for 20 years in Japan to treat intractable epilepsy and is currently used worldwide for that pur-

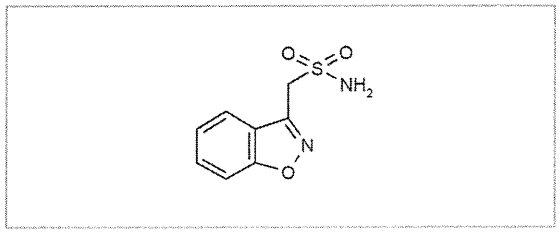

Figure 1. Chemical structure of zonisamide.

pose. In 2000, we serendipitously found that zonisamide had beneficial effects in Parkinson's disease. A 58-year-old man with a 10-year history of Parkinson's disease incidentally experienced convulsion attacks and was administered zonisamide for the treatment of epileptic attacks. Not only were the convulsions controlled, but he also showed marked improvement in parkinsonian symptoms. Subsequently, we conducted a small open trial of zonisamide in patients with advanced Parkinson's disease (2). We demonstrated that 50-200 mg of zonisamide once or twice daily, in addition to their antiparkinsonian drugs, significantly improved the cardinal symptoms of Parkinson's disease. Based on these findings, we conducted three nationwide clinical trials, and zonisamide was subsequently approved in January 2009 as an antiparkinsonian drug in Japan.

MECHANISM OF ACTION

The antiparkinsonian effects of zonisamide appear to be mediated through various mechanisms. Firstly, zonisamide activates dopamine (DA) synthesis (3, 4) and release (5). Although it is a moderate monoamine oxidase (MAO) inhibitor (3), the lack of change in the efficacy of zonisamide when coadministered with selegiline (a MAO type B inhibitor) suggests that MAO inhibition is not the main mechanism of its antiparkinsonian effects (6, 7). In addition to the DA system, zonisamide may exert its antiparkinsonian effects through T-type calcium channels (4) and the δ opioid receptor (8). These mechanisms, in addition to its effects on the DA system, may explain how it improves motor symptoms in Parkinson's disease, with less hallucinations and dyskinesia than L-DOPA or DA agonists.

Zonisamide has multiple modes of action, including effects on ion channels and neurotransmitter systems (4). Specifically, zonisamide blocks Na^+ channels, binding preferentially to inactive channels, producing use- and voltage-dependent blockade and slowing the rate of recovery (9). It also reduces the low-threshold T-type Ca^{2+} channel current, thereby suppressing inward Ca^{2+} currents, and thus reducing cellular bursting (10, 11). Zonisamide also modulates various neurotransmitters, including γ-aminobutyric acid (GABA) and serotonin (5-HT) (6). Zonisamide is a weak inhibitor of carbonic anhydrase and is considered to be 100-200 times less potent than acetazolamide (12).

Effects of zonisamide on dopaminergic system

Okada et al. reported that single and repeated (14 days, q.d.) administration of zonisamide (20 or 50 mg/kg) increased intracellular and extracellular DA levels, and increased DA turnover in the rat striatum (3). However, a higher dose (100 mg/kg) of zonisamide decreased DA levels. Thus, it is conceivable that zonisamide has a biphasic effect on DA, depending on the dose used. The authors suggested that zonisamide increases DA synthesis, since it increases intracellular and extracellular DOPA levels even after administration of NSD-1015, a central aromatic amino acid decarboxylase inhibitor. We also showed that long-term administration of zonisamide (20 and 50 mg/kg for 14 days) increased the activity and protein levels of tyrosine hydroxylase (TH; a limiting enzyme in DA synthesis) in the rat striatum. The levels of TH mRNA also increased prior to the increase in TH protein levels in SH-SY5Y cells. These data suggest that zonisamide activates DA synthesis by increasing TH mRNA. Zonisamide had no effect on the protein levels of DOPA decarboxylase, or the levels of biopterin or neopterin (coenzymes of TH) (4).

Zonisamide showed a weak inhibitory effect on MAO activity. The IC_{50} value using liver microsomal fractions was rather high (600 μM), whereas that using striatal membrane fractions was 28 μM in rats and 10 μM in monkeys (3, 4). Zonisamide had no effect on the activity of catechol-O-methyltransferase (4). It has been reported that zonisamide increases DA release indirectly (5, 13). Moreover, zonisamide showed no affinity for any of the DA receptor subtypes: D_1, D_2, D_3, D_4 or D_5 (4).

Effects of zonisamide on indirect pathways of basal ganglia through the δ opioid receptor

Yamamura et al. reported that striatal perfusion with 100 μM zonisamide, which did not affect striatal extracellular DA levels, decreased and increased extracellular GABA levels in the globus pallidus (GP) and subthalamic nucleus (STN), respectively, and decreased extracellular glutamate levels in the substantia nigra pars reticulata (SNr) (8). Furthermore, striatal perfusion of TAN-67,

a δ opioid receptor agonist, also increased extracellular GABA levels in the STN, and decreased extracellular GABA levels in the GP and glutamate levels in the SNr, similar to the effects of zonisamide. The inhibitory effect of zonisamide on neurotransmitters in the indirect striatopallidal pathway was inhibited by the δ receptor antagonist 7-benzylidenenaltrexone (BNTX) but not by naltriben (NTB). Based on these results, the authors concluded that the antiparkinsonian effect of zonisamide is attributed to the suppression of neurotransmission in the indirect striatopallidal pathway mediated through the δ opioid receptor.

Effects of zonisamide on T-type Ca^{2+} channels

Inhibition of the T-type Ca^{2+} channel increases the burst firing of dopaminergic neurons in the striatum (14). T-type Ca^{2+} currents are translated into small-conductance Ca^{2+}-activated potassium currents by their functional coupling in the substantia nigra (SN) DA neurons. The $K_{ca}2.3$ channel (apamin-sensitive) controls pacemaker frequency and precision in SN dopamine neurons, but not in a subpopulation of DA neurons in the ventral tegmental area (15). $NiCl_2$ (T-type Ca^{2+} channel blocker) and apamin increase the levels of TH mRNA and TH protein in a similar time course to zonisamide (16). Therefore, zonisamide may increase DA synthesis through the T-type Ca^{2+} channel (4).

Effect and mechanism of action of zonisamide on tremor

Zonisamide improved not only resting tremor of Parkinson's disease but also course essential tremor (17-21). It also significantly suppressed both harmaline- and oxotremorine-induced tremors in a dose-dependent manner (22). In addition, zonisamide considerably suppressed tacrine-induced tremulous jaw movements and this effect was not lost under conditions of monoamine depletion or dopaminergic blockade (22). These results suggest that the antitremor action of zonisamide is mediated by a nondopaminergic mechanism. A new selective T-type Ca^{2+} channel inhibitor showed a dose-dependent decrease in harmaline-induced tremor, in a manner similar to zonisamide, suggesting that the antitremor effect of zonisamide may also be mediated through inhibition of the T-type Ca^{2+} channel (23).

PHARMACOKINETICS, DISTRIBUTION AND METABOLISM OF ZONISAMIDE

Zonisamide is rapidly absorbed following oral administration (time to peak plasma concentration [t_{max}] = 2-6 h) and has high bioavailability (95%), which is unaffected by food. It has hepatic (70%) and renal (30%) elimination, and a long half-life ($t_{1/2}$) (24). Zonisamide shows low to moderate plasma protein binding (40%). The reported plasma $t_{1/2}$ of zonisamide (200-800 mg) as an antiepileptic agent is 50-63 h, and is rather long for 25 mg in normal adults (n = 12) (94.0 ± 26.3 h; prescribing information, Dainippon Sumitomo Pharma). In parkinsonian patients, the steady-state concentration at 50 mg of zonisamide was 3.5 ± 1.4 μg/mL (prescribing information, Dainippon Sumitomo Pharma).

Zonisamide is evenly distributed throughout the entire body. The concentrations in various organs, as investigated using [^{14}C]-zonisamide, are similar to the plasma concentrations, except for the liver, kidney and adrenal glands, in which the tissue concentrations are approximately twice the plasma concentrations. Furthermore, a distribution study of zonisamide in a rat brain model showed high concentrations in the cerebral cortex and midbrain (26).

The main metabolites of zonisamide in humans are the glucuronide of the open-ring metabolite 2-(sulfamoylacetyl)phenol glucuronide and *N*-acetylzonisamide. Experimental evidence indicates that zonisamide kinetics are unaffected by renal insufficiency, age or gender (4).

CLINICAL TRIALS

Nationwide double-blind clinical trials

Based on the results of our open study, we carried out three nationwide, double-blind, randomized, placebo-controlled clinical trials of zonisamide. All studies were conducted in patients with advanced Parkinson's disease who showed insufficient response, such as motor fluctuation, to standard medications. At the time of each study, all participating patients were being treated with L-DOPA, more than 90% were treated with DA agonists and about 50% were on selegiline. Zonisamide was added to these antiparkinsonian drugs.

The first study was conducted in 2001 and included 136 patients with advanced Parkinson's disease. The patients were divided into four groups: placebo, 50, 100 and 200 mg/day of zonisamide. The mean duration of disease was 10 years, mean age was 62.9 years and mean Yahr staging was 2.5 (on) and 3.6 (off). The results showed that zonisamide at 50 and 100 mg/day significantly improved values of Unified Parkinson's Disease Rating Scale (UPDRS) Part III, and at 50 mg/day in Part II (off).

The frequencies of adverse effects in patients treated with 50 and 100 mg/day were almost similar as in the placebo group, but those of the 200-mg group were significantly higher and included sleepiness, hallucinations and loss of appetite (27).

Since the first study showed a high placebo effect, we adopted a new strategy in the second and third clinical trials, with a single-blind and double-blind design. All patients were given placebo during the first 2 weeks (single-blind phase) and then switched to zonisamide for 12 weeks (double-blind phase). In the second study conducted in 2004, 347 patients were divided into four groups: placebo, 25, 50 and 100 mg zonisamide. The mean duration of disease was 8.6 years, mean age was 64.4 years and mean Yahr staging was 2.5 (on) and 3.5 (off). The primary endpoint was a change from baseline in the total score of the UPDRS Part III at final assessment. The study showed significant improvement in UPDRS Part III total score in the 25-mg (−6.3 ± 0.8, mean ± SD) and 50-mg (−5.8 ± 0.8) groups compared with placebo (−2.0 ± 0.8) (Fig. 2). The duration of 'off' time according to the patient's diary was significantly reduced in the 50-mg (−1.30 h) and 100-mg (−1.63 h) groups vs. placebo. Dyskinesia was not increased in the zonisamide groups and the incidence of adverse effects was similar among all four groups. In the 100-mg group, the frequency of sleepiness was somewhat higher than in the placebo group. The proportion of responders, defined as patients with a ≥ 30% reduction in the UPDRS Part III total score at the final assessment relative to baseline was: placebo, 22.0%; 25 mg, 35.1% (P = 0.067, χ^2 test vs. placebo); 50 mg, 38.8% (P = 0.018, χ^2 test vs. placebo); and 100 mg, 31.7% (P = 0.158, χ^2 test vs. placebo group) (Fig. 3) (7).

In the third clinical trial conducted in 2007, 185 patients were divided into three groups (0, 25 and 50 mg zonisamide). The mean duration of disease was 7.5 years, mean age was 64.8 years and mean Yahr staging was 2.7 (on) and 3.5 (off). The protocol and primary endpoints were similar to the second clinical trial, but the duration of 'off' time was not assessed because of the time limitation for approval. The changes in the UPDRS Part III were as follows: intention to treat, placebo group, −2.9 ± 0.9; 25 mg, −5.9 ± 0.9 (P = 0.029, Dunnet test vs. placebo); 50 mg, −5.5 ± 0.9 (P = 0.073, Dunnet test vs. placebo) (Fig. 4). The proportion of responders (UPDRS Part III) was: placebo, 27.0%; 25 mg, 41.0% (P = 0.038, χ^2 test vs. placebo); and 50 mg, 45.8% (P = 0.049, χ^2 test vs. placebo). The mean value of the UPDRS Part II (off) improved significantly in the 25-mg group

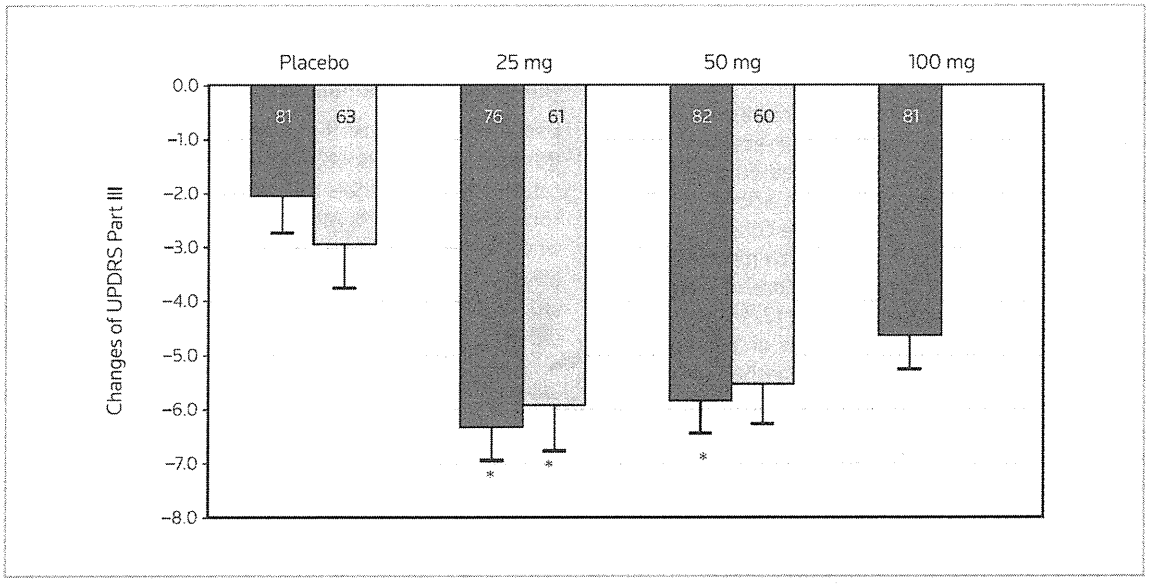

Figure 2. Effects of zonisamide on total score of Unified Parkinson's Disease Rating Scale (UPDRS) Part III. Dark bars, second clinical trial; light bars, third clinical trial. Data are mean ± SD. Numbers indicate patient numbers. *P < 0.05 compared with the placebo group (Dunnet test).

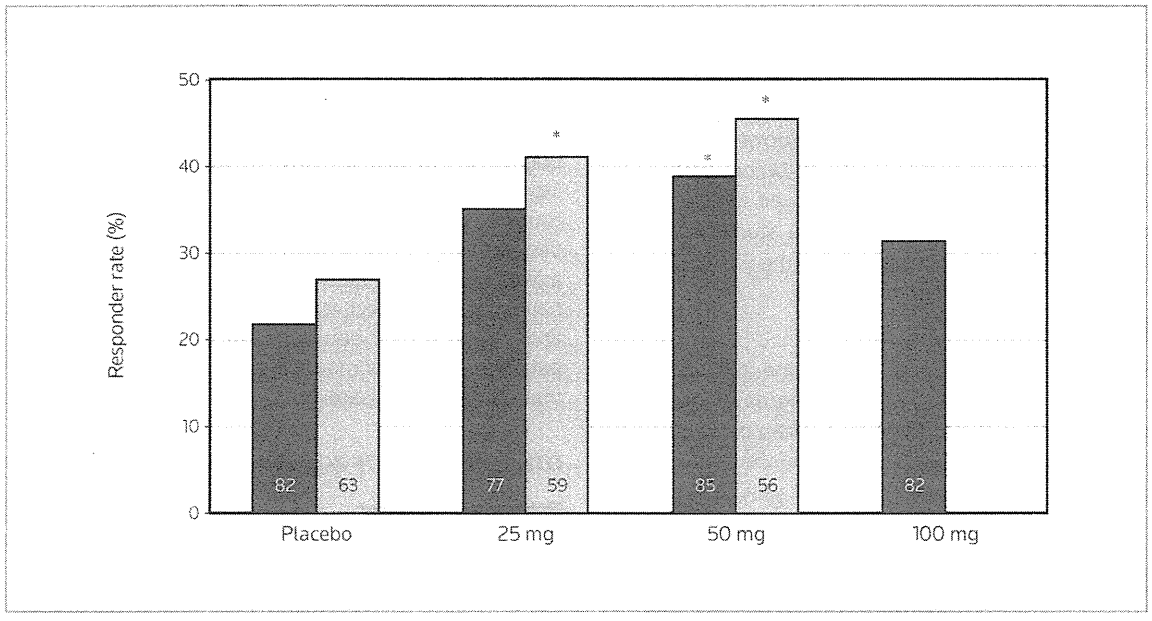

Figure 3. The response rate determined by changes in the UPDRS Part III, in patients treated with different doses of zonisamide. Dark bars, second clinical trial; light bars, third clinical trial. Data are mean ± SD. Numbers indicate patient numbers. *$P < 0.05$ compared with the placebo group (χ^2 test).

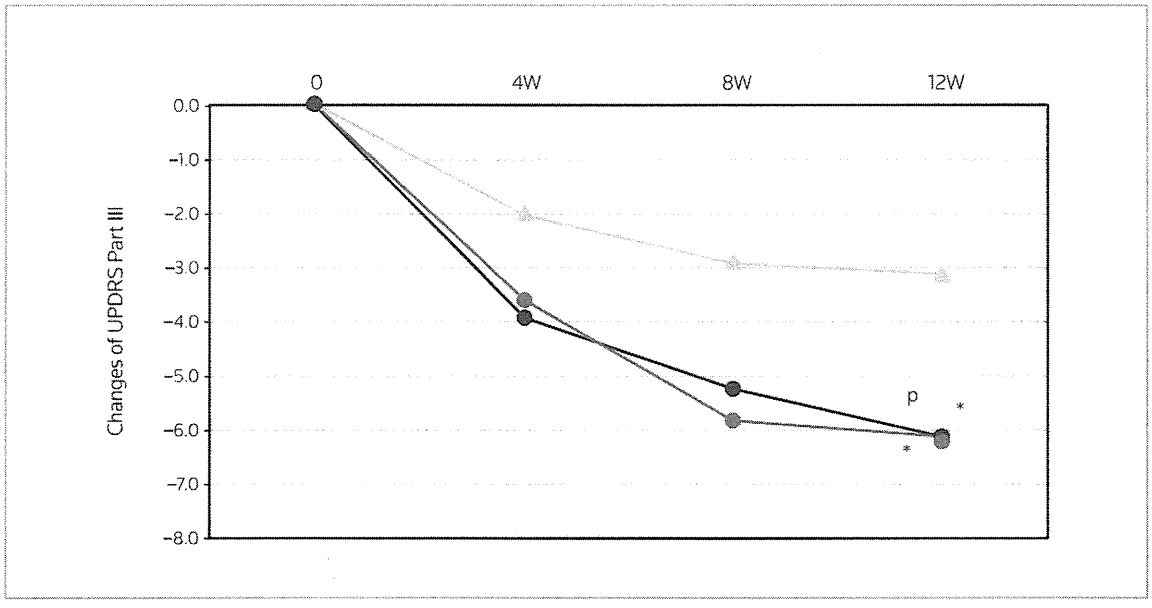

Figure 4. Serial changes in total score of the UPDRS Part III induced by zonisamide treatment from baseline (only completed cases)of the ITT group. Data from the third clinical trial. *$P < 0.05$ compared with the placebo group (Dunnet test). W, week. Δ, placebo; ●, 25 mg; ●, 50 mg.

(−2.5, $P = 0.039$, Dunnet test vs. placebo). The incidence of adverse effects was similar among all three groups (28).

According to these three studies, patients treated with 25 and 50 mg of zonisamide showed significant improvement in the UPDRS Part III. Unfortunately, only zonisamide 25 mg has been approved for Parkinson's disease in Japan because the final study showed no advantage for the 50-mg relative to the 25-mg dose.

Long-term effects

Another study designed to examine the long-term effects of zonisamide at 25-100 mg/day included 92 patients with Parkinson's disease (mean duration of disease was 10 years) (29). The results of the study showed persistent improvement for up to 1 year. In the group receiving a maximum dose of 25 mg/day (n = 28), the score was improved at 28 weeks and maintained up to 56 weeks. However, in other groups with a maximum dose of 50-100 mg/day (n = 62), the scores improved up to 56 weeks.

Side effects

Although many adverse events, such as somnolence (21.8%), dizziness (20.5%), anorexia (16.7%), tiredness (15.1%), nausea (13.2%), headache (12.0%) and confusion (12.0%), are reported in patients with epilepsy treated with zonisamide (30), the incidence of adverse events in patients with Parkinson's disease is very low, probably due to the low dose used in the treatment of such patients. The main adverse events with an incidence > 5% in Parkinson's disease were somnolence (10.4%), anorexia (8.6%), nausea (6.2%), apathy (5.2%) and hallucinations (5.2%) (25-200 mg/day zonisamide, n = 613). It should be noted, however, that this frequency of adverse effects in the 25-50-mg group was similar to the placebo group (7, 27), although it was much higher in the 200-mg group (sleepiness and hallucination).

Interestingly, the frequency of dyskinesia was not increased in the zonisamide group compared with the placebo group. Furthermore, the frequency of disabling dyskinesia was decreased in the zonisamide group (7). Why zonisamide improved parkinsonian symptoms without worsening dyskinesia and hallucinations is not clear. Effects of zonisamide on T-type Ca^{2+} channels and the δ opioid receptor may account for these effects.

Effects of zonisamide on clinical features of Parkinson's disease

Adding a small dose of zonisamide once a day (25-50 mg/day with food), improves cardinal motor symptoms of Parkinson's disease and motor fluctuations. The frequency of dyskinesia and hallucinations was not increased by zonisamide. Therefore, one can use zonisamide to treat motor fluctuations even in patients with dyskinesia. The infrequent occurrence of dyskinesia is advantageous, especially in young patients. On the other hand, due to its effectiveness against intractable tremor and the infrequent occurrence of hallucinations, aged patients with tremor may also be suitable candidates for treatment with zonisamide.

OTHER EFFECTS OF ZONISAMIDE

Pain and depression

Zonisamide has multimodal effects, including relief of chronic pain, depression and anxiety (31, 33-35). Thus, these actions of zonisamide may relieve unpleasant symptoms at the 'off' state in Parkinson's disease. The δ receptor agonist effect of zonisamide may be responsible for these effects.

Neuroprotective effects

Experimental evidence suggests that zonisamide could provide neuroprotection in cerebral ischemia and epilepsy. In addition to the effects described above, zonisamide is also a scavenger of hydroxyl radicals (OH•) and nitric oxide (NO) (36, 37). It inhibits lipid peroxidation in iron-induced epileptic foci in rats (38), nitric oxide synthase (NOS) activity (39), and the formation of 8-hydroxy-2'-deoxyguanosine (8-OHDG) (40), a marker of oxidative DNA damage. These effects suggest that zonisamide may protect neurons from oxidative stress. The neurotoxicity of DA quinones as dopaminergic neuron-specific oxidative stress is considered to play a role in the pathogenesis and/or progression of Parkinson's disease. Zonisamide significantly inhibits quinoprotein formation and also prevents DA quinone formation induced by excess amount of cytosolic DA outside the synaptic vesicles (41).

Zonisamide also protects dopaminergic neurons lesioned by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (or MPP+, the active toxin metabolite of MPTP) and 6-hydroxydopamine (6-OHDA), both in vitro and in vivo (42-45). We showed that reduction of nigrostriatal DA neurons in the lesioned side of hemiparkin-

sonian mice was significantly abrogated by repeated injection of zonisamide starting 3 weeks after 6-OHDA lesioning. Moreover, we also showed that zonisamide markedly increased glutathione levels in the striatum by enhancing the astroglial cystine transport system and/or astroglial proliferation via S100β production or secretion (45). Yano et al. reported that zonisamide provides neuroprotection in the MPTP model in mice and suggested that these effects may be mediated by increased TH activity in the dopaminergic system (44).

The above experimental data were obtained using zonisamide at concentrations close to those used for Parkinson's disease in clinical studies, taking into consideration the shorter half-life of zonisamide in rodents ($t_{1/2}$ = 8 h) compared to humans ($t_{1/2}$ = 62-90 h). Therefore, the clinically used dose of zonisamide may also provide neuroprotection in Parkinson's disease. Further studies are needed to elucidate the actual pathophysiological mechanism underlying the antiparkinsonian effects of zonisamide and to verify its neuroprotective effects in patients with Parkinson's disease.

CONCLUSIONS

A small dose of zonisamide coadministratered with L-DOPA improves parkinsonian symptoms with infrequent side effects including dyskinesia and hallucinations, even in patients with progressed disease. Zonisamide has multimodal activity, including effects on DA synthesis and neuroprotection. The exact mechanism of zonisamide as an antiparkinsonian drug is not completely understood. Further investigations are needed to clarify the mechanism of action of zonisamide in Parkinson's disease.

DISCLOSURES

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ORIGINAL ARTICLE

Effects of enzyme replacement therapy on five patients with advanced late-onset glycogen storage disease type II: a 2-year follow-up study

Yoshihiko Furusawa · Madoka Mori-Yoshimura · Toshiyuki Yamamoto · Chikako Sakamoto · Mizuki Wakita · Yoko Kobayashi · Yutaka Fukumoto · Yasushi Oya · Tokiko Fukuda · Hideo Sugie · Yukiko K. Hayashi · Ichizo Nishino · Ikuya Nonaka · Miho Murata

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Abstract We examined the efficacy of 2-year enzyme replacement therapy (ERT) using recombinant human α-glucosidase (GAA; Myozyme®) in five long-term ventilator-dependent adults and aged patients with advanced, late-onset glycogen storage disease type II (GSDII, also known as Pompe disease). Although all patients had advanced respiratory failure and were ventilator-dependent for more than 6 years, four showed obvious improvements in muscle strength, pulmonary function, and activities of daily living after ERT. Improvement in each parameter was more prominent in the first year than in the second year. Values in the second year were still significantly better than those at study entry and indicate stabilization in the clinical status of all patients. These results suggest that ERT continues to be effective in the second year of treatment even in patients suffering from advanced late-onset GSDII disease with severe respiratory failure.

Introduction

Glycogen storage disease type II (GSDII), or Pompe disease, is an autosomal recessive lysosomal glycogen storage disease

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Y. Furusawa · M. Mori-Yoshimura (✉) · T. Yamamoto · Y. Oya · M. Murata
Department of Neurology, National Center Hospital, National Center of Neurology and Psychiatry, 4-1-1 Ogawahigashi-cho, Kodaira, Tokyo, Japan 187-8551
e-mail: yoshimur@ncnp.go.jp

C. Sakamoto · M. Wakita · Y. Kobayashi
Department of Rehabilitation, National Center Hospital, National Center of Neurology and Psychiatry, 4-1-1 Ogawahigashi-cho, Kodaira, Tokyo 187-8551, Japan

Y. Fukumoto
Dental Branch, National Center Hospital, National Center of Neurology and Psychiatry, 4-1-1 Ogawahigashi-cho, Kodaira, Tokyo 187-8551, Japan

I. Nonaka
Department of Pediatrics, National Center Hospital, National Center of Neurology and Psychiatry, Tokyo, Japan

T. Fukuda · H. Sugie
Department of Pediatrics, Jichi Medical School, 3311-1, Yakushiji, Shimotsuke-city, Tochigi 329-0498, Japan

Y. K. Hayashi · I. Nishino
Department of Neuromuscular Research, National Institute of Neuroscience, National Center of Neurology and Psychiatry, 4-1-1 Ogawahigashi-cho, Kodaira, Tokyo 187-8551, Japan

resulting from a deficiency in α-glucosidase (GAA) activity (OMIM #232300). The different clinical phenotypes of GSDII include classic infantile-onset; non-classic infantile-onset; childhood, juvenile, and adult forms of GSDII; and late-onset GSDII. However, GSDII presents as a broad spectrum with varying degrees of severity and rates of progression. The classic infantile-onset form is characterized by hypertrophic cardiomyopathy and generalized muscle weakness, which appear in the first few months of life (Hirshhorn and Reuser 2001; Engel et al. 2004). Late-onset GSDII is characterized by progressive skeletal muscle weakness and loss of respiratory function.

Enzyme replacement therapy (ERT) using recombinant human GAA (rhGAA) derived from transfected Chinese hamster ovary cells resulted in marked improvement in the survival rate of 18 patients with infantile-onset GSDII (Kishnani et al. 2008). Nicolino and colleagues also reported that rhGAA reduced the risk of death and invasive ventilation by 79 and 58%, respectively, in infants and children with advanced Pompe disease (Nicolino et al. 2009). The use of ERT with Myozyme® (α-glucosidase) was approved by the U.S. Food and Drug Administration (FDA) in 2006 and by the Japan Ministry of Health, Labor and Welfare (MHLW) in 2007.

Previous studies confirmed the efficacy of ERT in late-onset GSDII patients with acute respiratory failure or relatively mild respiratory dysfunction (Winkel et al. 2004; Pascual-Pascual et al. 2006; Merk et al. 2007, 2009; Case et al. 2008; Yamamoto et al. 2008; Rossi et al. 2007; van Capelle et al. 2008; Strothotte et al. 2010; van der Ploeg et al. 2010). On the other hand, ERT efficacy in advanced patients seemed to be lower than that in milder patients (Orlikowski et al. 2011). It is not clear whether ERT is continuously effective in ventilator-dependent patients with advanced disease and long-term respiratory failure. Because ERT is relatively expensive, it is important to determine whether continuous administration is effective, or whether therapy is only effective for a short duration. In the present study, we evaluated the efficacy of ERT in five patients with advanced late-onset GSDII for 2 years and analyzed factors related to its efficacy.

Patients and methods

Patients

Patients with late-onset Pompe disease diagnosed based on both muscle biopsies and fibroblast/muscle residual GAA activity, and who had undergone ERT at the National Center Hospital (National Center of Neurology and Psychiatry), were included in this study. Written informed consent was obtained before enrollment. The study protocol was approved by the National Center Hospital Ethics Committee. Patients 4 and 5 have been reported previously (Sasaki et al. 1992; Yamazaki et al. 1992). Table 1 lists the characteristics of all five patients (two men and three women).

Genomic DNA was extracted from blood or muscle biopsy samples according to standard protocols. All exons and flanking intronic regions of GAA were amplified and sequenced using an automated 3100 DNA sequencer (Applied Biosystems, Foster, CA). Primer sequences are available upon request. All patients had previously reported mutations (Tsujino et al. 2000; Tsunoda et al. 1996; Lam et al. 2003; Pipo et al. 2003; Hermans et al. 2004). The average (SD) age at ERT initiation was 47 (13.6) years (range 32–66 years), and the average duration of disease was 26 (4.5) years (range 20–31 years). The average duration of mechanical ventilatory support before ERT was 8.0 (1.9) years (range 6–11 years). Patients 1, 2, 4, and 5 had been treated with noninvasive ventilation (NIV), and patient 3 had been treated with invasive ventilation. All patients were wheelchair-bound for a mean of 7.0 (5.1) years (range 2–14 years). Only patient 4 was able stand for a few minutes or walk a few steps with assistance. Others were completely wheelchair-bound.

Methods

ERT (Myozyme®) was administered at 20 mg/kg body weight biweekly at a dose of 1 mg/kg/h for the first 30 min, 3 mg/kg/h for the second 30 min, and then increased to 5 mg/kg/h, and finally 7 mg/kg/h every 30 min. Patients were carefully monitored for infusion-related reactions during and after ERT administration. Clinical condition was assessed every 6 months, including physical examination, manual muscle test (MMT), ECG, Holter ECG, ultrasound cardiography (UCG), and pulmonary function tests [% vital capacity (%VC), % force vital capacity (% FVC), forced expiratory volume in the first second (FEV1.0), peak expiratory flow rate (PEF), peak cough flow (PCF; Bach 2004)], and lean body mass (Discovery Bone Densitometer, Hologic, Bedford, MA). Muscle strength, including grip power (Dynamometer®, TTM, Japan, for patient 1; Grip Strength Dynamometer®, Takei, Japan, for patients 2–5) and pinch power (PinchTrack™, Jtech, Japan), was assessed every 2 weeks. The Barthel index and gross motor function measure manual (GMFM) were assessed every 6 months from the second year (Hosoda and Yanagisawa 2000; Kondo and Fukuda 2000). Occlusal force in the right and left first molar was measured using the Occlusal Force Meter GM10® (Nagano Keiki, Japan) every 6 months. In this test, which was repeated three times, patients were asked to bite on a block as hard as possible. All patients rested for more than 2 h before each muscle strength test. Normal values for grip power

Table 1 Baseline patient characteristics and conditions

Patient no.	1	2	3	4	5
Sex	Male	Male	Female	Female	Female
Age at inclusion (years)	66	55	44	38	32
Age at onset (years)	35	35	25	8	7
Observation period (weeks)	104	104	104	104	104
Symptom at onset (weakness)	Lower extremities	Lower extremities	Lower extremities	Neck	Lower extremities
Ventilator since (age in years)	58	49	36	32	21
Duration of ventilator use (years)	8	7	8	6	11
Wheelchair-bound	Complete	Complete	Complete	Complete	Partial
Ventilator use (h/day)	24	10 (at night)	24	22	10 (at night)
Tracheotomy (age in years)	None	48	36	None	None
Wheelchair since (age in years)	51	48	36	36	29
Genotype	c.1585–1586TC > GT(p.S529V) homozygote	c.546 G > T(p.T182T) homozygote	c.307 T > C(p.C103R)/ c.546 G > A(p.T182T)	c.1309 C > T(p.R437C)/ c. 1857 C > G(p.S619R)	c.546 G > T(p.T182T)/ c.1798 C > T(p.R600C)
Enzyme activity[a]	1.2 (M)	0.6 (M)	1.88 (M)	0.46 (F)	3.8 (M)
Complications	Diabetes mellitus	Atrial fibrillation	Interstitial pneumonia pneumothorax	Pneumothorax subcutaneous/ mediastinal emphysema	—
Pathology	Myopathic changes	Myopathic changes	Myopathic changes	Myopathic changes	Myopathic changes
AcP- and PAS-positive vacuoles	Few	Scattered	Scattered	Stained for acid phosphatase	Many

[a] *(M)* Muscle (nmols 4MU/mg/h) (14.6±4.4), *(F)* fibroblast (mmol/pg protein) (161±32.4)

and occlusal force were provided by the manufacturer, and three healthy volunteers were tested as controls for pinch power [see Table in Electronic Supplementary Material (ESM)]. Blood cell counts and blood chemistry tests were conducted regularly. We interviewed patients and their families about activities of daily living (ADL). IgG antibodies to rhGAA were measured regularly by enzyme-linked immunosorbent assay (ELISA) (Kishnani et al. 2006).

Annual changes in quantitative parameters (pulmonary function tests, grip power, pinch power, and occlusal force) were calculated for the first and second years by subtracting old data from new data. Changes were analyzed with the Mann-Whitney *U* test. Statistical analyses were performed with SPSS for Macintosh (version 18, SPSS, Chicago, IL).

Results

Case presentation

Patient 1 suffered from limb muscle atrophy at age 35. He could not climb stairs and visited us at age 44. Muscle biopsy and acid maltase activity revealed Pompe disease. He lost ambulation at age 51. He experienced dyspnea, and %VC was 22.4 at age 58. Nocturnal NIV was initiated; he required continuous NIV from age 63 and was able to remove the NIV mask for <1 min before ERT. ERT was initiated at age 66. After 6 months of ERT, the patient was able to stop NIV for 9 min, allowing for a much easier transfer of the patient from car to wheelchair by the caregiver. This also provided the caregiver more than 5 min for shaving and/or cleaning the patient's face, compared to the 1-min limit before ERT.

Patient 2 had difficulty climbing stairs from age 36. He experienced dyspnea in the supine position at age 47 and visited a physician due to morning headache and severe dyspnea. He presented with pneumonia and CO_2 narcosis; nocturnal oxygen therapy was initiated after recovery. A muscle biopsy led to the diagnosis of Pompe disease. The patient lost ambulation during hospitalization. He visited us at age 50 and nocturnal NIV was initiated. The patient had difficulty lying down in the supine position without NIV before ERT. After ERT was initiated at age 55, he was able to lie down for 10 min at 24 weeks of ERT and for 60 min at 48 weeks without respiratory support. He was also less fatigued in the afternoons and able to drive alone for 2 h after 40 weeks.

Patient 3 noticed gait disturbance at age 22, visited a neurologist at age 26, and was diagnosed with limb-girdle

muscular dystrophy. At age 36, she complained of morning headache and drowsiness; she was intubated and tracheostomy was performed due to CO_2 narcosis and pneumonia. The patient lost ambulation during hospitalization and had recurrent pneumothorax and pneumonia. She visited us at age 39 and was diagnosed with Pompe disease by muscle biopsy and GAA activity. Recurrent pneumonia due to *Pseudomonas aeruginosa* required hospitalization with intravenous antibiotics once every 2 months before ERT. After ERT was initiated at age 44, she developed a mild fever of <38°C twice at 12 and 36 weeks after ERT, and recovered without antibiotics. She was able to open a plastic bottle unaided after 24 weeks of treatment, a task that could not be completed for 8 years prior to treatment. She was able to easily move from bed to wheelchair after 44 weeks. She also noticed less fatigue during meals, was able to pull up both legs unaided after 2 years of ERT, and could put on socks while sitting in the wheelchair.

Patient 4 had proximal weakness at age 15. She was referred to a neurologist and found to have high creatine kinase levels (1,256 U/L) and mild respiratory dysfunction (%VC: 77) at age 21. She was diagnosed with late-onset Pompe disease by muscle biopsy and fibroblast acid maltase activity. At age 32, she experienced dyspnea and initiated NIV during the night. At age 35, her %VC decreased to 18.9 and she required NIV all day. She began to use a wheelchair due to exertional dyspnea. At age 36, she presented with a right-sided pneumothorax, and %VC decreased to 15.8. She was able to turn off NIV only for 5 min to take a bath and could not comb her hair by herself before ERT. At 24 weeks after ERT initiation, pinch power increased from 48.4 N to 55.2 N, and she was able to stand with less effort. At 64 weeks of treatment, she was able to switch off NIV for 15 min while taking a bath and combing her hair. However, she experienced severe dyspnea and recurrent pneumothorax after 64 weeks of ERT and became fully dependent on NIV thereafter. She developed pneumothorax and emphysema at 80 weeks of ERT again and was completely bedridden and required cuirass ventilation in addition to NIV. She was also treated with parenteral hyperalimentation, including standard calorie and protein, for approximately 1 month due to inability to eat caused by dyspnea. After recovery from severe emphysema, she remained bedridden and consequently lost ambulation. Occlusal force was also lower after parenteral hyperalimentation.

Patient 5 could not stand without hand support and visited a pediatrician at age 13 and visited us and muscle biopsy and acid maltase activity. She initiated NIV at age 21 and required a wheelchair at age 29. After ERT was initiated at age 31, she found it easier to expectorate sputum through coughing than before ERT and could move her hip from floor to chair unaided after 44 weeks, which had been impossible for several years. She also noticed alleviation of lumbago, and after three doses of ERT, she was able to discontinue non-steroidal anti-inflammatory drugs (NSAIDS) used for back pain. The patient suffered from emaciation before ERT and was advised that this could not be resolved, but she gained 3 kg of body weight after ERT. At present, she can drive 2.5 h to go to the hospital every 2 weeks, which was impossible before ERT due to fatigue and back pain.

ERT-induced changes

Table 2 lists the results of clinical and laboratory tests before and after ERT. The mean duration of follow-up was 104 weeks. Grip power (Fig. 1a) and pinch power (Fig. 1b) showed gradual improvement in all patients. In patient 4, both grip and pinch powers continued to improve until 60 weeks after ERT initiation, but deteriorated thereafter. Occlusal force improved markedly in patients 1 and 3 (Fig. 1c), but deteriorated in patient 4. No changes in MMT were noted in any of the patients. GMFM improved slightly in patients with a score of >25, while it remained unchanged in those with a score of <5. After initiation of ERT, all patients, except patient 4 who had severe emphysema and pneumothorax, showed improvement in %VC (Fig. 2a), PEF (Fig. 2b), PCF (Fig. 2c), %FVC (Fig. 2d), and/or FEV1.0 (Fig.2e).

Creatine kinase (CK) levels decreased during treatment in patients 2, 4, and 5, and particularly in patient 4 (Table 2). CK levels were normal in patients 1 and 3 at the commencement of treatment and did not show marked changes during and after treatment. Body weight [44.4 (17.0) to 43.6 (16.1) kg, $p=0.93$)] and lean body mass [25.8 (7.9) to 25.8 (10.2) kg, $p=0.99$] did not change.

Changes in the first year were greater than in the second year (Table 3). Most data were not available for patient 4 at the first year evaluation because bed rest was required for pneumothorax therapy. Changes in %VC, %FVC, PEF, PCF, pinch power, and occlusal force were greater in the first year than in the second year ($p<0.05$). While %VC, %FVC, PEF, PCF, pinch power, and occlusal force significantly changed in the first year after ERT, changes in these parameters were not significant in the second year.

IgG antibody against Myozyme® was measured in patients 1, 3, 4, and 5 (see figure in ESM). All patients were IgG antibody positive at around weeks 12 to 16, but patients 4 and 5 became negative thereafter. Furthermore, IgG antibody titers increased to a peak level in patient 3, and increased in patient 1 to 25,600. The antibody titer of patient 2, measured once at 108 weeks after ERT, was negative. Only patient 3 developed a skin rash immediately after Myozyme® infusion at 12 weeks, but the rash disappeared completely after treatment with an antihistamine. Other patients did not experience any infusion-related reactions.

Table 2 Results of clinical and laboratory tests before and after ERT

		Patient 1			Patient 2			Patient 3			Patient 4			Patient 5		
		Pre	1 year	2 year	Pre	1 year	2 year	Pre	1 year	2 year	Pre	1 year	2 year	Pre	1 year	2 year
MMT	Neck flexion	1	1	1	2	2	2	2	2	2	2	2	2	2	2	2
	Shoulder flexion	1	1	1	2	2	2	2	2	2	2	2	2	2	2	2
	Shoulder abduction	1	1	1	2	2	2	2	2	2	2	2	2	2	2	2
	Elbow flexion	1	1	1	3	3	4	3	3	3	4	4	4	3	4	4
	Elbow extension	1	1	1	4	4	4	4	4	4	4	4	4	3	3	3
	Wrist flexion	4	4	4	5	5	5	5	5	5	4	4	4	5	5	5
	Hip flexion	1	1	1	2	2	2	2	2	2	2	2	2	2	2	2
	Knee flexion	1	1	1	2	2	2	2	2	2	3	3	3	2	2	2
	Knee extension	1	1	1	2	2	2	2	2	2	3	3	3	2	2	2
	Ankle flexion	1	1	1	5	5	5	2	2	2	4	4	4	5	5	5
Body weight (kg)		44	43	43	73.0	70	69	42	40	42	33	31	31	30	31	33
Lean body mass (kg)		23.9	22.6	22.6	39.8	39.8	39.8	23.0	24.4	24.4	21.1	NT	19.9	21.4	22.2	22.2
Pulmonary function	%VC	4.9	10.7	9.6	45.6	62.0	67.2	12.1	15.4	17.3	17.6	NT	9.2	13.1	19.5	21.4
	%FVC	0.0	26.8	7.7	46.3	51.2	66.1	9.3	12.5	16.1	14.2	NT	7.0	10.3	17.7	20.4
	FEV1.0	0.00	0.62	0.21	1.52	1.78	1.99	0.24	0.49	0.41	0.32	NT	0.14	0.29	0.50	0.55
	PEF (L/s)	0.38	0.93	0.50	3.72	6.40	5.49	0.46	0.63	0.70	0.58	NT	0.25	1.24	1.63	1.70
	PCF (L/s)	0.34	0.74	0.69	4.87	7.26	7.16	0.60	0.82	0.85	1.52	NT	0.86	1.19	1.96	2.17
Grip power (kg)		3.4	4.1	4.4	39.6	42.7	44.1	14.2	17.4	16.5	17.0	18.0	17.7	17.5	23.9	25.0
Pinch power (N)		14.7	21.1	15.5	81.9	96.1	98.8	23.6	42.4	42.5	48.3	56.3	53.0	44.3	48.5	47.3
Occlusal force (kgf)		6.4	15	15.9	NT	50.0	55.2	24.1	42.8	46.3	16.4	NT	8.4	NT	65.8	64.0
GMFM		NT	3	3	NT	25	31	NT	5	5	NT	56	59	NT	32	35
CK (IU/l)		47	36	50	238.0	132	10	166	132	100	621	NT	154	241	161	166
Barthel index		20	20	20	75.0	75	75	55	55	55	80	80	70	80	80	80

%VC Percent vital capacity, *%FVC* percent force vital capacity, *FEV1.0* forced expiratory volume in the first second, *PEF* peak expiratory flow, *PCF* peak cough flow, *GMFM* gross motor function measure, *CK* creatine kinase, *NT* not tested

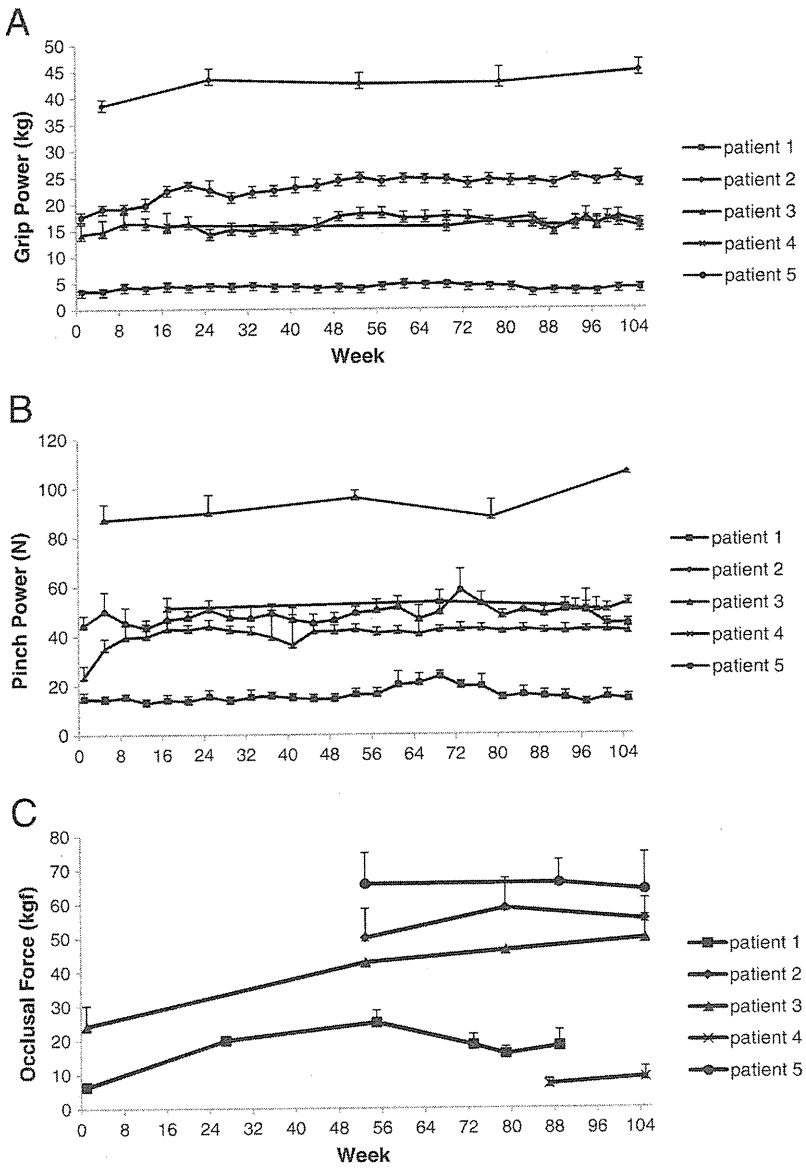


Fig. 1 Effects of ERT on grip power (**a**), pinch power (**b**), and occlusal force (**c**). Each data point represents the average of three bilateral measurements. ERT improved all of these parameters in four of five patients (with the exception of patient 4). Data are presented as mean ± SEM

Discussion

ERT is often difficult to initiate in the early stages of subclinical GSDII or in early-stage GSDII because the disease is difficult to diagnose due to heterogeneity in clinical presentation and overlapping symptoms with other neuromuscular diseases. Accordingly, it is important to gain an understanding of ERT efficacy in patients with advanced GSDII. Our study demonstrated that ERT is effective for 2 years without severe complications in adult patients who have advanced GSDII and are dependent on ventilator and wheelchair support. During the 2 years of ERT, all patients showed some improvements in muscle and pulmonary function and ADL.

All parameters improved during the first year of treatment. While the results of various tests in the second year were lower than those recorded at the end of the first year, they were still better than before ERT initiation. Although the rate of improvement differed widely among patients, our results indicate that ERT is more effective in the first year and it maintains its efficacy for 2 years. At present, there is no explanation for the better outcome in the first year compared to the second year. Taking into consideration the muscle pathology associated with GSDII, intracellular accumulation of large amounts of glycogen may cause displacement, replacement, or compression of normal cellular organelles. Thus, ERT may normalize cell function by reducing such accumulation in surviving

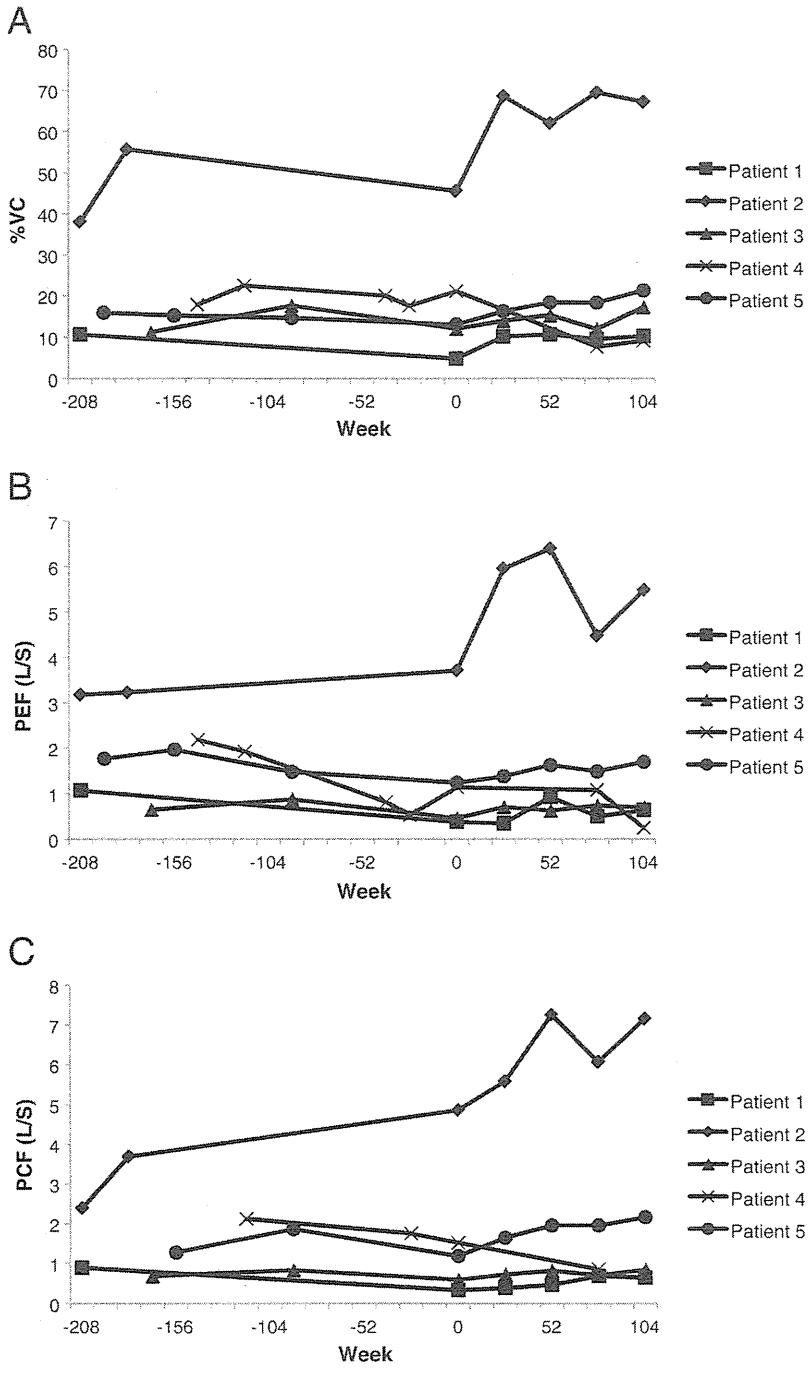
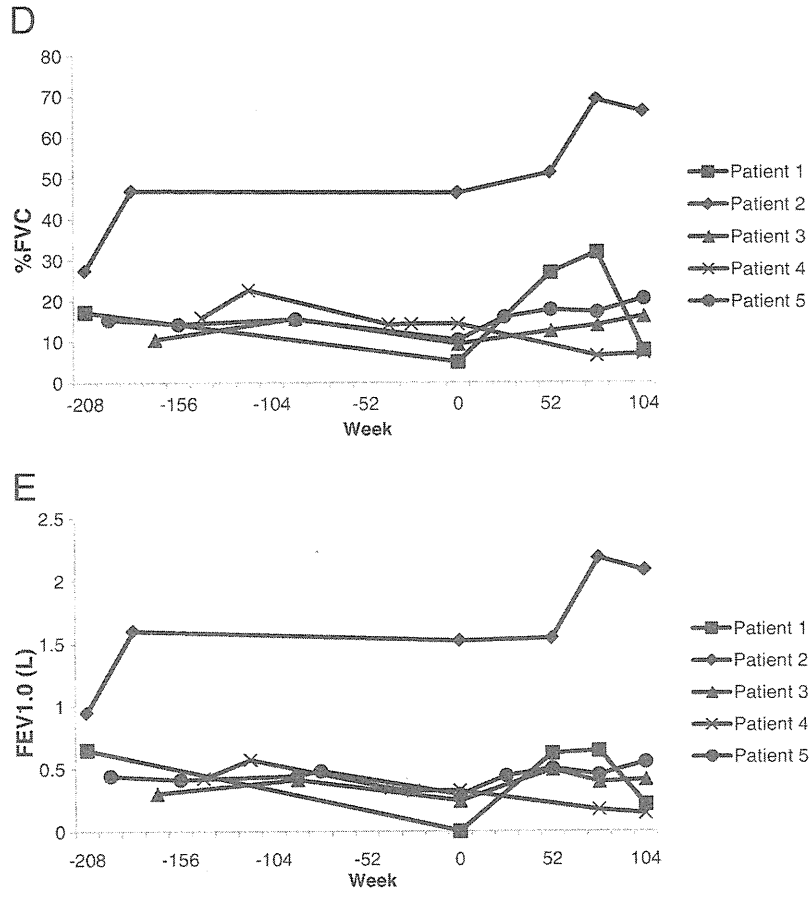


Fig. 2a–d Effects of ERT on respiratory function. Percent vital capacity (**a**), peak expiratory flow (**b**), peak cough flow (**c**), percent force vital capacity (**d**), and forced expiratory volume in the first second (**e**). Note the low values of all parameters prior to ERT and their improvement after ERT. The improvement is more pronounced in patients with spared baseline functions

myotubes, followed by a gradual regeneration of myofibers. The observed effects of ERT may represent its acute effect on intracellular glycogen accumulation.

Younger or milder cases, including those presented in a randomized controlled study of ERT, showed a greater improvement over advanced cases (Winkel et al. 2004; Pascual-Pascual et al. 2006; van der Ploeg et al. 2010). Van der Ploeg and colleagues reported on ambulant patients whose %VC was greater than 30 (van der Ploeg et al. 2010). In this clinical study, ERT elicited significant improvements in walking distance and stabilization of pulmonary function. On the other hand, efficacy of ERT in patients with advanced GSDII seemed to be milder or partial. A case report of a 67-year-old wheelchair-bound woman described alleviation of muscle symptoms following ERT, although pulmonary function tests showed no improve-

Fig. 2a–d (continued)



ment, suggesting cases with no respiratory recovery (Merk et al. 2007). Furthermore, one open-label observational study of ERT in 44 late-onset GSDII patients showed that both motor function tests and CK levels improved, and pulmonary function stabilized (Strothotte et al. 2010). Orlikowski et al. reported a 52-week follow-up of five patients (Orlikowski et al. 2011) with respiratory dysfunction as severe as in our patients, and respiratory and motor functions in all patients improved somewhat. Our data further these findings by suggesting that the improvements continue through the second year of ERT and that ERT is beneficial even for patients with advanced-stage Pompe disease.

Only patient 4 failed to show a clear recovery at the end of the follow-up period. However, grip and pinch powers increased in this patient at 60 weeks of ERT. Immobility and suspension of oral feeding resulted in reduction of muscle power, particularly in the masseter muscles. Pneumothorax also influenced the improvement in pulmonary function. Thus, we speculate that the small improvement was offset by the negative influence of pneumothorax. Because patients in similar condition at the beginning of the study responded to treatment (patients 3 and 5), one can rule out any effects of age, body weight, lean body mass, and lung dysfunction on the prognosis. Variability in the response to treatment may reflect individual differences in disease severity at treatment initiation and rate of disease progression.

The benefits conferred by ERT may not be adequate when considering ERT costs, as none of the patients exhibited an improvement in Barthel index; however, observation before ERT indicated gradual deterioration before the therapeutic intervention was initiated (Table 2). In one study, dramatic changes did not occur at the advanced stage, although certain benefits were evident (Orlikowski et al. 2011). However, we speculate that patient conditions will deteriorate if ERT is terminated after the first year, a period showing the greatest improvements. Serial pulmonary function tests indicated that the respiratory function of our patients will sequentially deteriorate (Fig. 2).

Based on our assumption that therapeutic effects of ERT cannot be measured by MMT or morbidity function in 6-min walk tests, we attempted to measure muscle power in relatively spared functions. Occlusal force is known to decrease in parallel with disease progression in Duchenne muscular dystrophy (DMD) (Ueki et al. 2007). Occlusal,

Table 3 Annual changes in parameters

	%VC						%FVC						FEV (L)						PEF (L)					
Years	1	2	1 + 2	*P*: 1 vs 2	*P*: 1 vs 1 + 2	*P*: 2 vs 1 + 2	1	2	1 + 2	*P*: 1 vs 2	*P*: 1 vs 1 + 2	*P*: 2 vs 1 + 2	1	2	1 + 2	*P*: 1 vs 2	*P*: 1 vs 1 + 2	*P*: 2 vs 1 + 2	1	2	1 + 2	*P*: 1 vs 2	*P*: 1 vs 1 + 2	*P*: 2 vs 1 + 2
Patient 1	5.8	−1.1	4.7				21.9	−19.1	2.8				0.6	−0.4	0.21				0.55	−0.43	0.1			
Patient 2	16.4	5.2	21.6				4.9	14.9	19.8				0.3	0.2	0.47				2.68	−0.91	1.8			
Patient 3	3.3	1.9	5.2	0.043	0.773	0.057	3.2	3.6	6.8	0.248	1.000	0.248	0.3	−0.1	0.17	0.200	0.306	0.043	0.17	0.07	0.24	0.020	0.468	0.430
Patient 4[a]	Not tested						Not tested						Not tested						Not tested					
Patient 5	5.4	2.9	8.3				7.4	2.7	10.1				0.21	0.05	0.26				0.39	0.07	0.46			

	PCF (L)						Grip power (kg)						Pinch power (N)						Occlusal force (kgf)					
	1	2	1 + 2	*P*: 1 vs 2	*P*: 1 vs 1 + 2	*P*: 2 vs 1 + 2	1	2	1 + 2	*P*: 1 vs 2	*P*: 1 vs 1 + 2	*P*: 2 vs 1 + 2	1	2	1 + 2	*P*: 1 vs 2	*P*: 1 vs 1 + 2	*P*: 2 vs 1 + 2	1	2	1 + 2	*P*: 1 vs 2	*P*: 1 vs 1 + 2	*P*: 2 vs 1 + 2
	0.4	−0.05	0.35				0.7	0.3	1.0				6.4	−5.6	0.8				8.6	0.9	9.5			
	2.39	−0.1	2.29				3.1	1.4	4.5				14.2	2.7	16.9				50	5.2	55.2			
	0.22	0.03	0.25	0.028	0.885	0.020	3.2	−0.9	2.3	0.083	0.905	0.142	18.8	0.1	18.9	0.009	0.69	0.016	18.7	3.5	22.2	0.021	0.886	0.021
	Not tested						Not tested		0.7				8	−3.3	4.7				Not tested					
	0.77	0.21	0.98				6.4	1.1	7.5				4.2	−1.2	3				65.8	−1.8	64			

%VC Percent vital capacity, *%FVC* percent force vital capacity, *FEV1.0* forced expiratory volume in the first second, *PEF* peak expiratory flow, *PCF* peak cough flow

[a] Patient 4 could not be evaluated at 1 year after ERT initiation due to severe pneumothorax

grip, and pinch powers were relatively spared in all patients, except patient 1. Four of five patients could write, use utensils, fasten a button, or bite foods as efficiently as healthy people, although their data revealed some decrements compared to normal controls. Cranial muscle involvement is thought to be rare, but we found that occlusal force was mildly reduced in patients with advanced Pompe disease. This suggests that occlusal force is a sensitive parameter for assessing the response to ERT.

Conclusions

The present study showed that ERT improved respiratory function and muscle power for 2 years even in adult patients with advanced GSDII. Improved muscle strength resulted in better ADL and quality of life during the long follow-up period. Taking our results into consideration, we recommend the initiation of ERT in GSDII patients, irrespective of age and disease severity.

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