Clinical benefits of antioxidative supplement Twendee X for mild cognitive impairment : a multicenter, randomized, double-blind, and placebo-controlled prospective interventional study

軽度認知障害に対する抗酸化サプリメント Twendee X の臨床的利点 : 多施設二重盲検プラセボ対照前向き介入試験

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Running title: Placebo-controlled trial of Twendee X in MCI

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ABSTRACT

Oxidative stress involves in a whole pathological process of the development of Alzheimer's disease (AD) including mild cognitive impairment (MCI) stage. Twendee X (TwX) is a strong antioxidative mix supplement containing 8 antioxidants, which showed a clinical and pathological benefit in AD model mice. Here we conducted a multicenter, randomized, double-blind, and placebo-controlled prospective interventional study to evaluate the efficacy of TwX on MCI subjects. The primary outcomes were the differences of the mini-mental state examination (MMSE) and Hasegawa dementia scale-revised (HDS-R) score changes from baseline at 6 month between placebo and TwX groups. 78 MCI subjects underwent randomization for 37 to placebo and 41 to TwX. TwX showed a significant difference of MMSE at 6M compared with placebo (p = 0.018), and also a significant improvement of HDS-R score from baseline at 6 M (p = 0.025). TwX showed no effect on affective and ADL scores at 6 M. The present study revealed the clinical benefits of strong antioxidative supplement TwX for cognitive functions of MCI subjects.

【要約】

酸化ストレスは、軽度認知障害（MCI）を含めたアルツハイマー病発達の全病理的過程に関与している。Twendee X（TwX）は 8 つの抗酸化物質を含む強力な抗酸化混合サプリメントであり、AD モデルマウスでは病理的改善が見られた。本研究で我々は MCI 被験者における TwX の効能を評価するため多施設二重盲検プラセボ対照前向き介入試験を実施した。主要評価項目はミニメタルステート検査（MMSE）の差と、プラセボ‐TwX グループ間の長谷川式認知症スケール（HDS-R）スコアの 6 か月におけるベースラインからの変化である。TwX は 6 Mにおいてプラセボと比較して MMSE で有意な差を見せた(p = 0.018)。また 6M における HDS-R スコアのベースラインからの変化に有意な改善をみせた(p = 0.025)。TwX は 6 M において情緒および ADL スコアに効果がみられなかった。本研究では強力な抗酸化サプリメント TwX が MCI 被験者の認知機能に臨床的改善がみられることを明らかにした。

Key words: Dementia, dietary supplement, mild cognitive impairment, oxidative stress, randomized controlled trial,

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INTRODUCTION

Dementia is a serious growing problem all over the world, and Alzheimer's disease (AD) is the most common cause of dementia. Although there is a great demand for effective interventions to prevent dementia, any drugs or supplement therapies have not been established.

Oxidative stress contributes to the development of AD through mitochondrial dysfunction[1], neuroinflammation[2], lipid peroxidation[3], and other mechanisms[4, 5] from prodromal stage, namely mild cognitive impairment (MCI)[6]. Therefore, antioxidant therapy is a potential intervention for preventing AD.

Twendee X (TwX) is a patented supplement containing 8 antioxidants. We have reported the clinical and pathological benefits of TwX in animal models of AD and ischemic stroke through strong antioxidant effects[7, 8]. Here, we carried out a clinical trial to evaluate the efficacy of TwX for cognitive functions of MCI subjects.

【序文】

認知症は世界中で拡大を続ける深刻な問題であり、アルツハイマー病（AD）は最も一般的な認知症の要因である。認知症を予防する効果的な介入が大いに求められていたものの、これまでいかなる薬剤もサプリメントも確立されていなかった。

酸化ストレスは、ミトコンドリアの機能不全、神経炎症、脂質の過酸化、その他のメカニズムを通して、前駆期、すなわち軽度認知障害（MCI）のときから AD の進行に関与している。そのため、抗酸化治療は AD 予防において効果的介入となりうる。

Twendee X（TwX）は 8 つの抗酸化剤を含む特許取得済みのサプリメントである。我々は TwX の強力な抗酸化効果によりマウスの AD および虚血性脳卒中モデルにおいて臨床的・病理的改善が得られたことを報告した。本研究では MCI 被験者の認知機能に対する TwX の効能を評価するため臨床治験を実施した。

MATERIALS AND METHODS

Participants

The present study included native Japanese participants with cognitive impairment (mini-mental state examination (MMSE) score ≥ 24 and clinical dementia rating (CDR) score[9] = 0.5), aged from 65 to 85. Patients with neurodegenerative diseases such as Parkinson's disease, dementia with Lewy bodies (DLB), fronto-temporal lobar degeneration (FTLD), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and multiple system atrophy (MSA), cognitive declines due to hypothyroidism, vitamin deficiency, idiopathic normal pressure hydrocephalus (iNPH), head trauma, epilepsy, encephalitis, and meningitis, past history of psychiatric disorders including schizophrenia, depression, alcoholism, and drug addiction, and stroke within 3 months (M), diabetes mellitus with HbA1c ≥ 8.0, and metabolic syndrome diagnosed by the Japanese criteria[10] were excluded. Subjects taking anti-dementia drugs or any supplements were excluded. All participants gave written informed consent.

【参加者】

本研究では認知障害（ミニメンタルステート検査(MMSE)スコア 24 以上、かつ Clinical dementia rating(CDR)スコアが 0.5）を持つ６５－８５歳のネイティブ日本人が参加した。パ

ーキンソン病、レビー小体型認知症（DLB）、頭側頭葉変性症（FTLB）、進行性核上性麻痺（PSP）、大脳皮質基底核変性症（CBD）、そして多系統萎縮症（MSA）といった神経変性疾患を持つ患者、甲状腺機能低下症、ビタミン欠乏症、特発性正常圧水頭症（iNPH）、頭部外傷、てんかん、脳炎、髄膜炎に起因する認知機能低下、精神分裂病、鬱、アルコール・薬物依存症、過去 3 か月以内の脳卒中といった精神疾患の既往歴を持つ者、HbA1c8.0 以上の糖尿病、そして日本の基準におけるメタボリックシンドロームと診断された者は除外された。認知症治療薬やあらゆるサプリメントを服用している被験者は除外された。すべての参加者は書面にてインフォームドコンセントを取得した。

Study supplement

TIMA Japan Corporation (Osaka, Japan) provided the study supplement, TwX; a tablet containing coenzyme Q10 (10 mg), niacin amid (2 mg), L-cystine (50 mg), ascorbic acid (94 mg), succinic acid (10 mg), fumaric acid (10 mg), L-glutamine (85 mg), and riboflavin (4 mg). Participants orally took placebo or TwX once a day more than 20 min before breakfast every day. Daily tablet dose was determined depending on the body weight (BW) of the subjects; 2 tablets for BW less than 40 kg, 3 tablets for BW between 40 and 60 kg, and 4 tablets for BW more than 60 kg.

【被検サプリメント】

Tima Japan 株式会社（大阪、日本）が被検サプリメントである TwX を提供した：これは coenzyme Q10 (10 mg), ナイアシンアミド(2 mg), L-シスチン (50 mg), アスコルビン酸 (94 mg), コハク酸(10 mg), フマル酸 (10 mg), L-グルタミン(85 mg), そしてリボフラビン (4 mg)を含有する錠剤である。被験者は毎日朝食から 20 分以上前に 1 回、プラセボまたは TwX を経口にて服用した。1 日の錠剤服用量は被験者の体重をもとに決定した：体重 40kg 未満は 2 錠、40~60 kgは 3 錠、60 kg以上は 4 錠。

Study design

The present study was a multicenter, randomized, double-blind, and placebo-controlled prospective interventional study. 17 medical institutions in Japan were registered in the study, and the study duration was originally planned from June 2017 to March 2024. An institutional review board at each institution or the representative institution approved the study protocol. The study was registered in the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR) with a registration number UMIN000026268.

The study period was originally designed for 12 M. After checking eligibility, participants were randomized to placebo or TwX group with a stratification by age and sex. Subjects visited hospital once in 3 M, and received medical examination including cognitive and blood tests to monitor adverse events.

【実験デザイン】
本研究は多施設二重盲検プラセボ対照前向き介入試験である。日本の 17 の医療施設が本研究に登録され、研究期間は当初 2017 年 7 月から 2024 年 3 月までとした。各機関または代表期間の倫理委員会は本研究プロトコールを承認した。本研究は大学病院医療情報ネットワーク臨床試験登録に、登録番号 UMIN000026268 にて登録された。

本研究期間は当初 12 か月として計画された。被験者は試験に適格か確認ののち、プラセボまたは TwX グループにランダム化され、年齢と性別によって階層化された。被験者は 3 か月に一度病院を訪れ、有害事象を監視するため認知・血液検査を含めた健診を受けた。

Study outcomes

The primary outcomes were the differences of the mini-mental state examination (MMSE)[11] and Hasegawa dementia scale-revised (HDS-R)[12] score changes from baseline at 6 and 12 M between placebo and TwX groups, indicating the differences of cognitive functional changes.

The secondary outcomes were the differences of geriatric depression scale (GDS)[13], apathy scale (AS)[14], Abe's behavioral and psychological symptoms of dementia (BPSD) score (ABS)[15], and Alzheimer's disease cooperative study-activities of daily living inventory (ADCS–ADL)[16] score changes from baseline at 6 and 12 M between placebo and TwX groups, indicating the differences of affective functional and activity of daily living changes.

【研究成果】

主要評価項目は、プラセボ群と TwX 群間におけるミニメンタルステート検査（MMSE）および長谷川式認知症スケール（HDS-R）スコアのベースラインと比較した 6 か月及び 12 か月地点での変化であり、これにより認知機能変化の差を示した。

副次評価項目はプラセボ群と TwX 群間における老年期うつ病評価尺度（GDS）、やる気スコア（AS）、Abe's behavioral and psychological symptoms of dementia (BPSD) score (ABS)、そして Alzheimer's disease cooperative study-activities of daily living inventory (ADCS–ADL) のベースラインから 6 か月及び 12 か月の変化であり、これにより情緒昨日と日常生活変化の活動を示した。

Statistical analysis

According to our previous report[17], we estimated MMSE score at 12 M of 26.5 in placebo group and 28.0 in TwX group with standard deviation of 4.0. Then, we originally calculated that 200 participants for each group would be needed to provide 80 % statistical power.

The analyses for primary and secondary outcomes were based on per-protocol population after excluding discontinuation and trial termination (Fig. 1). Analysis of covariance (ANCOVA) was performed to evaluate the difference of score changes between placebo and TwX groups, with the

baseline MMSE score as covariate. Friedman test and Wilcoxon signed rank test were performed to assess the score changes from baseline. Baseline characteristics of each group was evaluated by using Student's t-test for continuous and normally distributed data, Mann-Whitney U test for continuous and not normally distributed data, and Pearson's chi square test for categorical data. A two-sided level of significance of 5 % was chosen for interpretation.

All of the statistical analyses were performed using a statistical software (SPSS 22.0.0.0; IBM, Armonk, New York, USA).

【統計解析】

我々の以前の報告によると、12 か月における MMSE スコアをプラセボで 26.5、TwX で 28.0 で標準偏差 4.0 と推定した。そして当初我々は 80%の統計的検出力を得るためには各群につき 200 の被験者が必要と見積もった。

主要・副次評価項目の解析は試験中止・終了を除いたのち、Per-protocol population に基づいた。プラセボ群と TwX 群間のスコア変化の相違を評価するため共分散分析（ANCOVA）を実施し、ベースラインの MMSE スコアを共変量とした。ベースラインからのスコア変化を評価するためフリードマン検定とウィルコクソンの符号順位検定を実施した。各群の背景因子については、連続的かつ正規分布に従うデータは Student's t-test、連続的かつ正規分布に従わないデータは Mann-Whitney U test、カテゴリーデータには Pearson's chi square test を用いて評価した。両側検定で 5%有意水準が採用された。

すべての統計解析は統計ソフトウェアを用いて実施された(SPSS 22.0.0.0; IBM, Armonk, New York, USA).

RESULTS

Subject characteristics

78 MCI subjects underwent randomization for 37 to placebo and 41 to TwX (Fig. 1). The number was smaller than that of original plan owing to the premature trial termination caused by the Governmental Clinical Trials Act enforced in Japan on April 2018 requiring unacceptable modification of the study. At the time of trial termination (March 2019), 59 subjects (27 in placebo and 32 in TwX groups) reached the evaluation at 6 M (Fig. 1). In each group, 7 subjects discontinued for reasons other than study termination by 6 M. Because of the above legal change, outcomes were analyzed only at 6 M.

Baseline characteristics of subjects who reached the evaluation at 6 M were summarized in Table 1. Between both groups, there was no significant difference in demographic characteristics (sex and age), baseline cognitive (MMSE and HDS-R), affective (GDS, AS and ABS) and ADCS-ADL scores. Although GDS (3.4 ± 2.8 in placebo and 4.4 ± 4.0 in TwX group) and AS (11.3 ± 5.9 in placebo and 10.3 ± 6.9 in TwX group) were slightly elevated in both groups, those scores

did not reach the criteria for depressive nor apathic states (GDS > 5[13], AS ≥ 14[14]). In the complications of present subjects, hypertension was the most frequent (48.1 % in placebo and 25.0 % in TwX groups), followed by dyslipidemia, and diabetes mellitus (3.7 % in placebo and 18.8 % in TwX groups), but ischemic heart disease was rare (Table 1). There was no significant difference in the prevalence of hypertension, diabetes mellitus, and ischemic heart disease, except for dyslipidemia in placebo (40.1 %) than TwX group (Table 1, 15.6 %, *$p < 0.05$).

【結果】

【被験者の特性】

78 の MCI 被験者がランダム化され、37 がプラセボ、41 が TwX となった（Fig.1）。2018 年 4 月に日本で施行された臨床研究法で研究に受け入れがたい変化を要求されたため、当初の計画よりも被験者数は少なくなった。試験終了時（2019 年 3 月）には、59 の被験者（プラセボ群 27、TwX 群 32）が 6 か月地点おける評価に達した。各グループにつき、7 の被験者が 6 か月までに試験終了以外の事由により試験を中止した。上記の法改正のため、6 か月地点のみでの評価項目を分析した。

6 か月の評価まで試験が続いた被験者の背景因子を Table 1 に要約した。両グループ間で、性別・年齢の構成、ベースラインの認知機能（MMSE 及び HDS-R）、情緒（GDS、AS、ABS）そして ADCS-ALD スコアに有意差はなかった。GDS(プラセボ：3.4 ± 2.8 、TwX: 4.4 ± 4.0) および AS (プラセボ：11.3 ± 5.9、TwX：10.3 ± 6.9)は両群でわずかに増加したものの、いずれのスコアも鬱や無関心状態の基準には達しなかった(GDS > 5[13], AS ≥ 14[14])。現在の被験者の合併症のなかで、高血圧が最も多く(プラセボ：48.1 %、TwX：25.0 %)、それに脂質異常、そして糖尿病が続いた(プラセボ：3.7 %、TwX：18.8 %)が、虚血性心疾患はまれであった。高血圧、糖尿病、虚血性心疾患の有病率に有意差はなかったが、プラセボ(40.1 %)における脂質異常のみ TwX より有意に有病率が高かった(Table 1, 15.6 %, *$p < 0.05$).

Endpoints

The results of primary and secondary endpoints at 6 M were summarized in Table 2. The MMSE score change from baseline at 6M was -0.85 ± 2.48 in placebo and 0.66 ± 2.60 in TwX groups, and the difference of MMSE score changes between both groups was significant (Table 2, Fig. 2, ANCOVA: *$p = 0.018$, placebo vs TwX). The change of MMSE score from baseline to 6 M in each group was not significant (Table 2, Wilcoxon signed rank test: $p = 0.092$ in placebo, $p = 0.181$ in TwX).

The difference of HDS-R change from baseline at 6M between both groups was not significant (Table 2, 0.74 ± 2.19 in placebo and 1.09 ± 2.62 in TwX group), but only TwX group showed a significant improvement of HDS-R from baseline to 6 M (Table 2, Fig. 2, Wilcoxon signed rank test: #$p = 0.025$).

The changes of GDS, AS, ABS and ADCS-ADL scores from baseline to 6 M in each group were not significant (Table 2). The differences between both groups were not significant in GSD, AS, ABS, and ADCS-ADL from baseline at 6 M (Table 2, ANCOVA: p = 0.315, 0.356, 0.252, and 0.284, respectively).

【エンドポイント】

主要・副次評価項目の 6 か月におけるエンドポイントの結果を Table 2 に要約した。6 か月でのベースラインからの MMSE スコア変化はプラセボが-0.85 ± 2.48、TwX が 0.66 ± 2.60 であり、両群の MMES スコア変化の違いに有意差があった(Table 2, Fig. 2, ANCOVA: *p = 0.018, placebo vs TwX)。各群のベースラインから 6 か月への MMSE スコア変化に有意差はなかった(Table 2, Wilcoxon signed rank test:プラセボ： p = 0.092 , TwX: p = 0.181 in).

6 か月における両群間の HDS-R 変化の差に有意差はなかった(Table 2, 0.74 ± 2.19 in placebo and 1.09 ± 2.62 in TwX group)が、TwX 群のみベースラインから 6 M への HDS-R の有意な改善を見せた(Table 2, Fig. 2, Wilcoxon signed rank test: #p = 0.025).

ベースラインから 6 か月への各群における GDS、AS、ABS、ADCS-ADL スコア変化に有意差はなかった（Table 2)。6 か月におけるベースラインで GSD、AS、ABS、ADCS-ADL スコアに両群間の有意差はなかった(Table 2, ANCOVA: それぞれ p = 0.315, 0.356, 0.252, 0.284).

DISCUSSION

Oxidative stress plays an important role in the pathology of MCI and early stage of AD[5, 6]. TwX is a strong antioxidative supplement containing 8 antioxidants, showing a significant amelioration of cognitive decline, amyloid-β pathology, neuronal loss, oxidative stress, and neuroinflammation in the AD model mice with chronic cerebral hypoperfusion and ischemic stroke model mice[7, 8]. Thus, we first conducted the present clinical trial to examine the efficacy for preventing cognitive declines of MCI subjects. In the present study, TwX significantly improved MMSE score change of the MCI subjects at 6 M compared with placebo (Fig. 2, Table 2), and HDS-R score from baseline to 6 M (Fig. 2, Table 2). On the other hand, TwX showed no effect on affective (GDS, AS, ABS) and ADL scores (Table 2).

【考察】

酸化ストレスは MCI 及び早期 AD の病理において重要な役割をもつ。TwX は 8 つの抗酸化剤を含む強力な抗酸化サプリメントであり、慢性脳低潅流及び虚血性脳卒中による AD モデルマウスにおいて認知機能低下、アミロイド-β 病態、神経喪失、酸化ストレス、そして神経炎症の有意な緩和を見せている。そのため我々は、MCI 被験者の認知機能低下を予防する効果を検証するため本臨床治験を初めて実施した。本研究では、TwX はプラセボと比較して、6 か月地点における MCI 患者の MMSE スコア変化及びベースラインから 6 か月

への HDS-R スコアを有意に改善した。一方で、TwX は情緒（GDS、AS、ABS）や ADL スコアに何の影響も与えなかった（Table 2）

Dietary supplements have been expected to reduce the risk of dementia[18, 19]. However, systematic reviews concluded that a single supplement such as vitamin B[20-22], vitamin C[20, 22], vitamin D[22], vitamin E[20-22], polyunsaturated fatty acid (PUFA)[21, 22], and their mixtures[20, 21, 23], lacks the evidence of effects on ameliorating cognitive declines, showing no or small benefit [24-27]. Other promising supplements including curcumin[28-30], ferulic acid[31, 32] and rosmarinic acid[33, 34] have yet to establish clear clinical effectiveness for preventing dementia. To our knowledge, TwX is the first supplement that clearly improved MMSE score change of MCI subjects in randomized placebo-controlled prospective multicenter interventional trial. Although antioxidant vitamins C or E did not show therapeutic benefit for dementia[20-22], combined 8 different antioxidants of TwX showed stronger antioxidant and anti-inflammatory effects than single antioxidant vitamins, which clearly improved cognitive functions of MCI subjects (Fig. 2). Stronger antioxidant effects of TwX than vitamin C was also demonstrated in irradiated mice model[35]. On the other hand, TwX showed no effect on affective (GDS, AS, ABS) and ADL scores (Table 2), although oxidative stress is also associated with pathologies of affective disorders[36, 37]. One possible reason might be that deteriorations of affective and ADL baseline scores was too mild to show significant differences after treatments.

栄養補助食品は認知症リスクを低下させると期待されてきた。しかしながら、システマティックレビューはビタミン B[20-22], ビタミン C[20, 22], ビタミン D[22], ビタミン E[20-22], 多価不飽和脂肪酸 (PUFA)[21, 22], そしてその混合剤[20, 21, 23]といったサプリメントでは効果が一切またはほとんどないとして、認知機能低下の予防効果の証拠が十分なものはなかったと結論付けている。クルクミン、フェルラ酸、ロスマリン酸といった他の有望なサプリメントも、認知症予防において明確な臨床効果がいまだ確立されていない。我々の知る限り、TwX はランダム化プラセボ対照前向き多施設介入試験の MCI 被験者の MMSE スコア変化を明確に改善した初めてのサプリメントである。抗酸化剤であるビタミン C や E は認知症に対する臨床的効果を示さなかったが、TwX に含まれる 8 つの異なる抗酸化剤は単独の抗酸化ビタミンよりも強力な抗酸化および抗炎症効果を見せ、MCI 被験者の認知機能を明確に改善した（Fig.2）。ビタミン C よりも強い TwxX の抗酸化効果はマウス被ばくモデルでも実証されている。一方で、酸化ストレスは情緒障害の病態にも関与しているが、TwX は情緒（GDS、AS、ABS）および ADL スコアに何の影響も見せなかった（Table 2）。その理由の一つとして、情緒及び ADL のベースラインスコアの悪化は治療後の違いに有意差を見せるには軽度すぎた可能性が考えられる。

The present study has some limitations. First, the premature trial termination due to

Government Clinical Trials Act of Japan shortened the study period from 12 into 6 M. To evaluate longer term effects of TwX, a further study with longer period is required. Next, only per-protocol analysis was originally designed in this study to evaluate the treatment effect of TwX. Most of the data of the subjects after discontinuation was missed, thus an intention-to-treat analysis was not performed. Finally, there are some concerns about the cognitive evaluations using MMSE and HDS-R that are not fully sensitive to detect the cognitive decline of MCIs[38, 39]. However, MMSE and HDS-R are commonly used in both clinical settings and trials [24, 40]. Furthermore, a recent study demonstrated that MMSE could detect the efficacy of treatment in MCI subjects, which was more sensitive compared to ADAS-Cog [41]. Therefore, we designed to use MMSE and HDS-R as primary endpoints in the present clinical trial for MCI subjects

In conclusion, the present study revealed the clinical benefits of TwX for cognitive functions of MCI subjects, suggesting that the strong antioxidative therapy may be useful for MCI subject to convert into AD.

本研究にはいくつかの制限が伴っている。まず、日本の臨床治験法により試験終了が早まったことで試験期間が 12 か月から 6 か月となった。より長期間における TwX の効果を検証するためには、さらに長い期間に及ぶ治験が必要である。次に、本試験では TwX の治療効果を検証するのに per-protocol analysis のみが実施される想定であった。試験中断後の被験者データのほとんどは失われ、そのため intention-to-treat analysis は実施されなかった。最後に、MCI の認知機能低下を必ずしも十分な感度で検出できない MMSE や HDS-R を使用した認知機能評価には憂慮すべき点もある。しかしながら、MMSE と HDS-R は臨床現場や試験で普遍的に使用されている。さらに、最近の研究では MCI 被験者の治療効果を検出しうることが実証されており、これは ADAS-Cog と比較して　より感度があることになる。そのため我々は本臨床治験の MCI 被験者の主要エンドポイントとして MMSE と HDS-R を採用した。

まとめると、本研究では MCI 被験者の認知機能に対する TwX の臨床効果を明らかにし、これにより強力な抗酸化治療がアルツハイマー病に変化しやすい MCI を防ぐのに役立つ可能性が示唆された。

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CONFLICTS OF INTEREST

TIMA e.s. has patents on Twendee X. Haruhiko Inufusa and Fukka You belong to antioxidant laboratory of Gifu University, sponsored by TIMA e.s.. Toshikazu Yoshikawa is an adviser of TIMA e.s.. Markus Matuschka von Greiffenclau is a chairman of TIMA e.s..

TIMA 財団は Twendee X の特許を所持している。Haruihi Inufusa と Fukka You は TIMA 財団が後援する岐阜大学抗酸化研究部門に所属する。Toshikazu Yoshikawa は TIMA 財団のアドバイザーである。Markus Matuschka von Greiffenclau は TIMA 財団の代表である。

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Table 1. Characteristics of the subjects who reached evaluation at 6 month
6 か月後検査まで到達した被験者の特徴

	placebo	**Twendee X**	
	(n = 27)	**(n = 32)**	**p value**
Demographic characteristics **人口統計的特性**			

Female　女性	44.4 %	56.2 %	0.366
Age (y)　年齢（年）	76.3 ± 5.0	75.2 ± 4.4	0.383
Complications　合併症			
Hypertension 高血圧	48.1 %	25.0 %	0.064
Diabetes mellitus 糖尿病	3.7 %	18.8 %	0.075
Dyslipidemia 脂質異常	40.1 %	15.6 %	0.031*
Ischemic heart disease 虚血性心疾患	3.7 %	0.0 %	0.272
Baseline scores ベースラインスコア			
MMSE (/30)	27.2 ± 2.0	27.2 ± 2.2	0.945
HDS-R (/30)	25.6 ± 3.3	26.5 ± 2.6	0.305
GDS (/15)	3.4 ± 2.8	4.4 ± 4.0	0.616
AS (/42)	11.3 ± 5.9	10.3 ± 6.9	0.493
ABS (/44)	2.1 ± 3.4	1.1 ± 1.7	0.408
ADCS-ADL (/30)	26.1 ± 3.4	27.6 ± 3.0	0.119

MMSE, Mini-mental state examination; HDS-R, Hasegawa dementia scale - revised;
GDS, geriatric depression scale; AS, Apathy scale; ABS, Abe's BPSD score; ADCS-ADL,
Alzheimer's disease cooperative study - activities of daily living inventory.
MMSE：ミニメンタルステート検査、HDS-R：長谷川式認知症スケール、GDS:老年期うつ病評価尺度、AS：やる気スコア、ABS, Abe's BPSD score; ADCS-ADL, Alzheimer's disease cooperative study - activities of daily living inventory.
* $p < 0.05$ (vs placebo)

Table 2. Cognitive and affective score changes in primary and secondary outcomes from baseline at 6 month

6 か月地点におけるベースラインからの主要・副次評価項目における認知・情緒スコア変動

	placebo (p value for change from baseline) ベースラインからの変化の p 値	**Twendee X** (p value for change from baseline) ベースラインからの変化の p 値	**p value** placebo vs Twendee X
Primary outcomes **主要評価項目**			
MMSE	-0.85 ± 2.48 (0.092)	0.66 ± 2.60 (0.181)	0.018*
HDS-R	0.74 ± 2.19 (0.112)	1.09 ± 2.62 (0.025#)	0.593
Secondary outcomes **副次評価項目**			
GDS	0.08 ± 2.10 (0.829)	-0.43 ± 3.19 (0.554)	0.315
AS	-0.38 ± 5.05 (0.615)	0.93 ± 5.96 (0.684)	0.356
ABS	-0.38 ± 1.44 (0.228)	-0.26 ± 1.10 (0.294)	0.252
ADCS-ADL	0.59 ± 1.96 (0.210)	-1.11 ± 3.61 (0.379)	0.284

MMSE, Mini-mental state examination; HDS-R, Hasegawa dementia scale - revised; GDS, geriatric depression scale; AS, Apathy scale; ABS, Abe's BPSD score; ADCS-ADL, Alzheimer's disease cooperative study - activities of daily living inventory.

MMSE：ミニメンタルステート検査、HDS-R：長谷川式認知症スケール、GDS:老年期うつ病評価尺度、AS：やる気スコア、ABS, Abe's BPSD score; ADCS-ADL, Alzheimer's disease cooperative study - activities of daily living inventory.

* $p < 0.05$ (vs placebo), # $p < 0.05$ (vs baseline)

Fig. 1 Randomization, assignment and follow-up

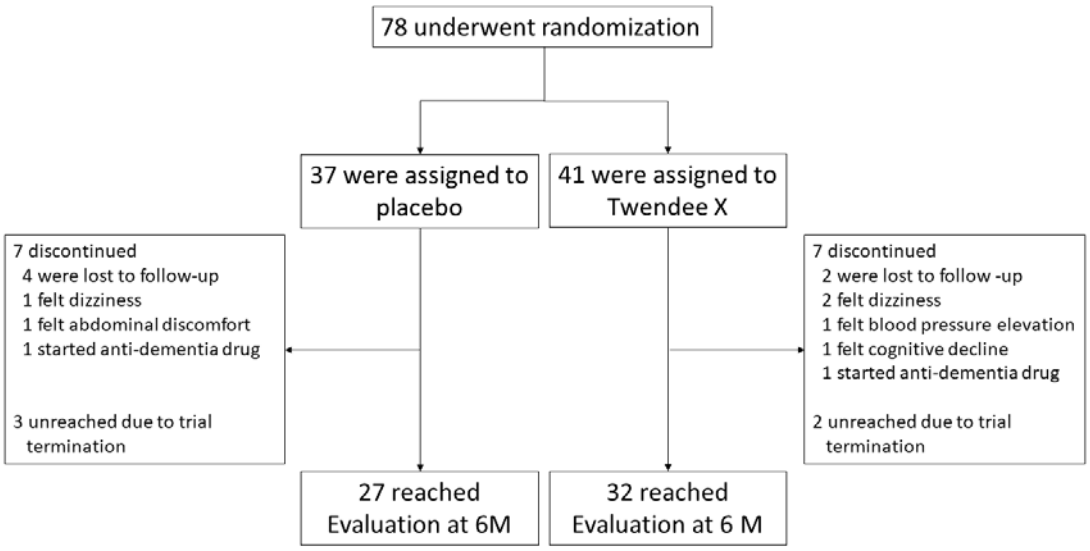

Fig1、ランダム化、割り当て及び経過観察
78 名がランダム化

37 名をプラセボ群に配置

41 名を TwX 群に配置

7 名が試験中止
4 名が追跡不能
1 名がめまい
1 名が腹部に不快感
1 名が抗認知症薬を開始
3 名が試験終了により到達不可

7 名が試験中止
2 名が追跡不能
2 名がめまい
1 名が血圧上昇
1 名が認知機能低下
1 名が抗認知症役を開始
2 名が試験終了により到達不可

27 名が 6M の評価に到達

32 名が 6M の評価に到達

Fig. 2 MMSE and HDS-R change

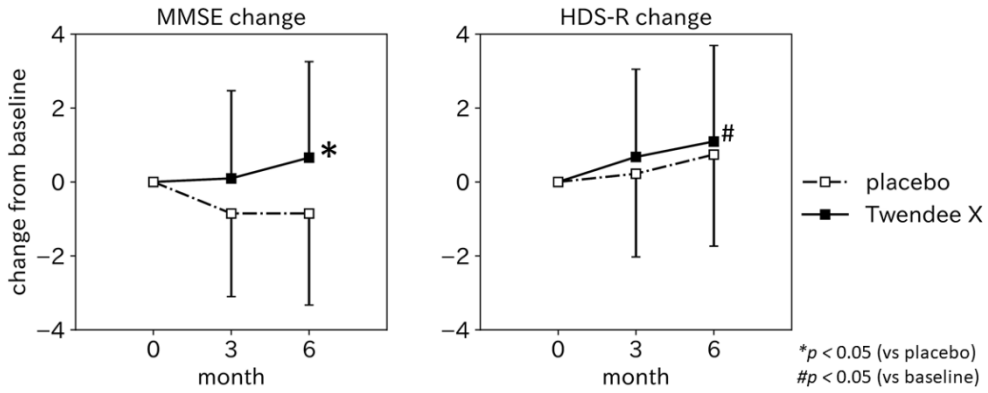

Fig.2 MMSE 及び HDS-R の変化

FIGURE LEGENDS

Fig. 1) Randomization, assignment and follow-up of the present trial.

Fig.1)本試験のランダム化、割り当て及び経過観察

Fig. 2) MMSE and HDS-R change in 6 M. Note the significant difference of MMSE score between Twendee X and placebo at 6 M (*$p < 0.05$, left panel), and a significant improvement of HDS-R from baseline to 6 M only in TwX group (#$p < 0.05$, right panel).

Fig.2）6M における MMSE 及び HDS-R の変化。6M において Twendee X とプラセボの MMSE スコアに有意差があること、そして TwX 群のみ 6M でベースラインと比較し HDS-R に有意な改善がみられる。