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Efficacy and safety of NAD+ ADP-ribosyltransferase 1 agonist versus Donepezil in elderly Chinese patients with Alzheimer disease: A novel target for effective therapy

Jianhong Wang[1#], Shu Yang[1#], Zicheng Hu[2], Haimei Yang[2], Dong Wei[3], Duozi Wang[1] and Fuqiang Guo[1]*

[1]Department of Neurology, Sichuan Provincial People's Hospital, University of Electronic Science and Technology of China, Chengdu, China
[2]Department of Neurology, Daping Hospital, Third Military Medical University, Chongqing, China
[3]Department of Neurology, The People's Hospital of Lezhi, Ziyang, Sichuan, China

Abstract: This pilot study designed to evaluate the efficacy and safety of NAD+ ADP-ribosyl transferase 1 (NART) agonist in comparison with Donepezil (DNP) in elderly Chinese patients with Alzheimer disease (AD). In the present clinical trial, Chinese elderly patients aged ≥65 years with a confirmed diagnosis of AD were enrolled. The patients received NART agonist (test, DAG-structured PKC blockers (GF109203X)) or DNP 10mg daily (reference) for 6 months. The efficacy and safety data were collected from 120 patients (60 patients in each group) every 3 weeks until 6 months. The primary endpoints were to assess the change in cognitive score from baseline in both the treatment group. The result of the present study showed that the patients treated with DNP and NART agonist have similar efficacy and safety profile. Considering the clinical benefit, improvement in sign and symptoms of was numerically greater in DNP-treated patients as compared to NART agonist. However, a statistical difference in terms of clinical benefit was similar between both the treatment groups. Overall, both the study drugs were found comparable in relieving the symptoms of AD. This indicates that NART is a potential target for the treatment of AD in China. The results of the present study may help to design a large clinical trial to evaluate the efficacy and safety of NART agonist in comparison with DNP in AD patients.

Keywords: NAD+ ADP-ribosyltransferase agonist, donepezil, Alzheimer disease, Chinese elderly

INTRODUCTION

Alzheimer disease (AD) is a progressive degenerative disease related to advanced cognitive deterioration and dementia. Cognitive capability becomes gradually compromised in patients with progressive AD. Currently approved treatments for AD are mainly symptomatic and neither slows the progression of the disease nor prevents neurological degeneration (World Alzheimer Report 2015, Ministry of Health, Labour and Welfare, Service Guide (English) 2015). It is estimated that currently more than 46 million people worldwide live with dementia and by the year 2050 the number of people with dementia will reach 131.5 million. With the rapidly increasing number of elderly people with dementia in China, it is very important to know the root cause of developing AD in healthy subjects (Guzior 2015, Cummings 2017). Currently, there are several approved treatment modalities are available for managing AD worldwide, such as AChEIs that includes donepezil, galantamine, rivastigmine, and NMDA receptor blockers, which have reported to improve the symptoms of AD, however no curative treatment available (Harvey 2018, Reddy 2019, Cui 2019, O'Brien 2017).

Donepezil HCL (DNP) is a specific, short-acting AChEI and has the ability to improve cholinergic transmission in the central nervous system (Harvey 2018, Reddy 2019, Cui 2019, O'Brien 2017). The approved daily dose for Donepezil HCL was 10 mg and was related with up to 30% inhibition of AChE activity in CNS. A Japanese study showed that DNP in a dose of 5-10 mg per day after 6 months of treatment was associated with significant improvement in memory (Nozawa 2009). NAD+ ADP-ribosyl transferase 1 (NART) is an enzyme mainly involved in DNA healing and transcription. Role of NAD+ ADP-ribosyl transferase 1 enzyme in the signaling of the cholinergic receptor is well studied (Ttrosznajder 2005, Adamczyk 2005, Shaw 2002). It has been reported that activation of cholinergic receptor improves the signaling pathways of NART in cortical regions and hippocampus region of rat's brain (Trosznajder 2005, Adamczyk 2005, Shaw 2002). The results of pre-clinical studies show activation of NART in the central nervous system, especially in the hippocampus and cortical region, which lead to increased signaling transmission of cholinergic receptors, which may results in increased level acetylcholine in hippocampus and cortical region.

**Corresponding author:* e-mail: gracehuynhjlc@yahoo.com #Equally contributed

Decreased transmission of cholinergic receptors and acetylcholine was found in AD, which is well known pathological characteristic of AD (Cohen-Armon 2004, Hernández 2009, Goldberg 2009, Zeng 2016, Rivas-Ramírez 2015). Also, NMDA receptor blockers improve cognitive functions by increasing the signaling transmission of NART in cortical regions and the hippocampus region (Kumar 2019, Graham 2013, Marwick 2019, Yamada 2017, Warming 2019). This indicates the increasing signaling transmission of NART in brain regions would be helpful in improving the cognitive functions in AD. This could be a novel treatment option for effective therapy in patients with AD.

The functional role of NART in patients with AD was not evaluated in Chinese individuals. There is no clinical trial which evaluates the efficacy of and safety NART agonist in patients with AD in comparison with the standard therapy such AChEI (such as DNP). This is a first clinical trial which compares the efficacy and safety of NART agonist with DNP in patients with AD. We, therefore, designed this pilot study to evaluate the efficacy and safety of NART agonist in comparison with DNP in elderly Chinese patients with AD. Our study may help to design a large clinical trial to evaluate the efficacy and safety of NART agonist in comparison with DNP in AD patients of other countries. We hypothesize that NART agonist would improve the transmission of cholinergic receptor and thereby improve the cognitive function among the AD patients. We, thus, designed this pilot study to evaluate the efficacy and safety of NART agonist in comparison with DNP in elderly Chinese patients with AD.

MATERIALS AND METHODS

In the present clinical trial, Chinese elderly patients with aged ≥65 years with a confirmed diagnosis of AD was explained the study protocol and methodology and then enrolled at Department of Neurology, Sichuan Provincial People's Hospital, China after getting their written informed consent form. Study design and inform consent form and other study-related documents including protocol were submitted in an ethical committee for review and approval. The study was conducted after getting written approval from the ethics committee. All the enrolled subjects underwent laboratory examination to authorize their suitability for this study.

Patients with any other neurodegenerative disorder were excluded from the trial. Also, patients with hypersensitivity to any of the study products will be excluded. Hypersensitivity of study product was ruled out using patients past history during the screening visit. Also, the patients with dementia due to cerebrovascular or Huntington's disease was excluded from the trial. Also, patients with any other pathology, which investigator feels may harm or confound the results of the study will be excluded. Also, the patients taking concomitant medicines were recorded. The patient who can't discontinue the concomitant medication which may affect the efficacy and safety of study drugs were excluded.

The enrolled patients who satisfied all the eligibility criteria were equally randomized in two groups in the allocation ratio of 1:1. The patients in the test group were received NART agonist and the subjects who were in the active comparator group received DNP 10 mg daily for 6 months. In the NART agonist group, subjects received DAG-structured PKC blockers (GF109203X) for 6 months. After treatment, the efficacy and safety data were collected at every 3 weeks to 6 months. The primary endpoints were to assess the change in cognitive score from baseline in both the treatment group using the SIB scale. Also, each enrolled patients was interviewed to assess the functional status using the CIBIC scale.

SIB scale is forty item scales, with score ranged from 0 (severely affected) to 100 (least affected) was subjected to each patient. The CIBIC scale recorded data from the patients and their caregiver on a seven-point scale (low score denotes improvements, where a high score indicates low improvements leading to worsening of symptoms). The CIBIC scale has used a baseline score of patients and caregiver as a reference and change from baseline at each follow-up visit was calculated. Also, the ADCS-ADL scale was used to evaluate daily living score to assess whether there was any notable benefit among the patients after treatment or not. Also, the cognitive function of each subject was tested using the MMSE scale, which ranges from 0 to 54, where 0 indicates that severely impaired or severely affected and 54 indicates least affected/impaired. All the scales were subjected by trained staff and were the blind observer. Safety data were also assessed.

Since the present study was intended as a pilot trial study to evaluate the efficacy and safety of NART agonist in comparison with DNP in elderly Chinese patients with AD. Thus, no formal sample size calculation was accomplished. The present pilot trial planned to enroll at least 50 AD patients in each treatment group.

Our study may help to design a large clinical trial to evaluate the efficacy and safety of NART agonist in comparison with DNP in AD patients of other countries. Numerical data were analyzed using Mann Whitney or unpaired t-test after subjecting data into normality analysis. Based on the result of normality, appropriate test either unpaired or Mann Whitney test was applied to find p-value between both the treatments. Numerical data were presented using Mean (SD). Categorical data were analyzed using Fisher exact test or chi-square test based on the number of data in each row/column and data were presented using an absolute number or % of patients. A p-value of less than 0.05 was considered a statistically significant difference between both the study drugs.

Table 1: Demography and baseline characteristic

Variable	DNP group N=60	NART agonist N=60
Age	67.32 (2.1)	66.12 (3.2)
Gender		
Male	73	70
Female	27	30
BMI	25.6	26.3
CIBIS+ score	4.23 (1.2)	3.98 (2.3)
Living status		
Living with friend	23	29
Living with caregiver	27	29
Living with relative or friend	50	52
Mental illness status		
Mild	21	19
Moderate	29	11
Severe	50	80
Baseline scores		
SIB	71.3	64.3
AD severity	62.1	68.1
CIBIS+/CIBIC	67.3	62.4
ADCS-ADL	73.7	74.3
MMSE	78.4	71.1

Table 2: Effectiveness of donepezil or NART agonist in patients with moderate to severe Alzheimer's disease

Variable	DNP group N=60	NART agonist* N=60
SIB		
Baseline	71.3	64.3
At follow visit	62.1	54.1
At endpoint	9.3	10.1
AD severity		
Baseline	62.1	68.1
At follow visit	52.3	54.1
At endpoint	11.2	14.2
CIBIS+/CIBIC		
Baseline	67.3	62.4
At follow visit	52.3	53.4
At endpoint	15.3	9.4
ADCS-ADL		
Baseline	73.7	74.3
At follow visit	62.3	64.3
At endpoint	11.3	10.2
MMSE		
Baseline	78.4	71.1
At follow visit	64.4	59.1
At endpoint	14.3	12.2

*Non-significant difference between both the groups.

Table 3: Summary of AEs in patients treated with donepezil or NART agonist in patients with Alzheimer's disease

Variable	DNP group N=60	NART agonist* N=60
Nausea	3	2
Vomiting	6	8
UTI infection	8	11
Agitation	2	3
Asleep	1	2
Bradycardia	7	8
Contusion	2	2
Headache	8	1
Anorexia	11	3
Hypotension	3	6
Dizziness	2	8
Diarrhea	7	3
Pneumonia	4	3
Confusional arousals	6	4

*Non-significant difference between both the groups.

The current hypothesis was that NART agonist is non-inferior to DNP in AD patients. Graph Pad Prism latest version was used statistical analysis of data.

RESULTS

A total of 150 patients were screened for the present study, of those 120 AD patients who met eligibility criteria were recruited at the Department of Neurology, Sichuan Provincial People's Hospital, China. All 120 patients who were recruited have completed the study period of 6 months. Data were analyzed, and results pertaining to demography and baseline characteristics were compared and found that there was no significant difference between both the treatment groups. Demography and baseline characteristic was found similar between both the treatment groups (table 1).

After treatment at each visit, SIB score at baseline was similar in AD patients of both the groups. Change in SIB score from baseline was statistically similar in both the treatment group; however, the SIB score was numerically greater in patients who received standard therapy (DNP) as compared to NART agonist. The severity of AD signs and symptoms were similar at the baseline visit, however, the difference was not statistically significant between both the treatment groups and however, DNP-treated patients had numerically greater relief in signs and symptoms of AD as compared to the patients treated with NART agonist. A similar trend of results was found for CIBIC scale results. The severity of functional status was similar at the baseline visit, however, the difference was not statistically significant between both the treatment groups and however, DNP-treated patients had numerically greater relief in signs and symptoms of AD as compared to the patients treated with NART agonist (table 2). Also, the ADCS-ADL scale which was used to evaluate daily living score showed a similar trend of results, favoring both the study treatments. However, improvement in daily living scores was numerically greater in patients treated with DNP as compared to NART agonist. However, the difference in daily living scores after both the treatment at every visit till 6 months, showed no statistically significant difference between both the treatments. However, numerically trend of data showed that patient treated with DNP had numerically greater improvement in daily living scores as compared to the patients treated with NART agonist. A similar trend of results for the cognitive function was noted and showed that difference between both the treatment groups was not statistically significant; however, DNP-treated patients had numerically greater relief in signs and symptoms of AD as compared to the patients treated with NART agonist (table 2).

Additional subgroup analysis was also performed to assess the impact of disease severity on treatment. Both the study drugs were tested in AD patients with mild to moderate severity. Sub-group analysis results analysis showed significantly greater improvement of AD score in patients with moderate severity of AD after treatment of both the study drug; however, the improvement was significantly higher in patients treated with DNP compared to NART agonist. In respect to the tolerability of both the study drugs, both the study drugs were found to have acceptable tolerability profile and no case of fatal adverse event was found in either treatment group (table 3).

The most common adverse events in both the treatment group were GI disturbance, dizziness, vomiting, and diarrhea. The incidence of AEs was comparable in both

the group, however, numerically; it was greater among patients treated with DNP as compared to the incidence rate of NART agonist (table 3).

DISCUSSION

This was the first study designed to evaluate the efficacy and safety of NART agonist in comparison with DNP in elderly Chinese patients with AD. The result of the present study showed that the patients treated with DNP and NART agonist have similar efficacy and safety profile. Although, considering the clinical benefit, improvement in sign and symptoms of was numerically greater in DNP-treated patients as compared to NART agonist. However, a statistical difference in terms of clinical benefit was not present between both the treatment groups. Thus, overall, both the study drugs were found comparable in relieving the symptoms of AD. Our study results pertaining to DNP was consistent with other reported published studies (Harvey, 2018; Reddy, 2019; Cui, 2019; O'Brien, 2017). The results of the present study may help to design a large clinical trial to evaluate the efficacy and safety of NART agonist in comparison with DNP in AD patients of other countries.

This was the first study to suggest the role of NART agonist in Chinese patients with AD (Strosznajder 2005, Adamczyk 2005, Shaw 2002). The present results showed attractive results for NART agonist in the management of AD. The present study suggests targeting to NAD+ ADP-ribosyl transferase 1 pathway to find better treatment modalities for the management of AD. Our finding in the present study supports the finding of previously published studies that the activation of cholinergic receptor improves the signaling pathways of NART in cortical regions and the hippocampus region of the rat's brain. This could be the reason for the positive results of NART agonist in Chinese patients with AD. Moreover, the results of pre-clinical studies show activation of NART in the central nervous system, especially in the hippocampus and cortical region, which lead to increased signaling transmission of cholinergic receptors, which may results in increased level acetylcholine in hippocampus and cortical region (Strosznajder 2005, Adamczyk 2005, Shaw 2002, Cohen-Armon 2004, Hernandez 2009, Goldberg 2009, Zeng 2016, Rivas-Ramirez 2015). Decreased transmission of cholinergic receptors and acetylcholine was found in AD, which is well known pathological characteristic of AD. This indicates that NART is a potential target for the treatment of AD in China. Also, our study results are consistent with the previous reports suggesting NMADA receptor blockers improve cognitive functions by increasing the signaling transmission of NART in cortical regions and the hippocampus region. This indicates the increasing signaling transmission of NART in brain regions would be helpful in improving the cognitive functions in AD. This could be a novel treatment option for effective therapy in patients with AD. The present study results showed that NART agonist would improve the transmission of cholinergic receptor and thereby improve the cognitive function among the AD patients. Our study may help to design a large clinical trial to evaluate the efficacy and safety of NART agonist in comparison with DNP in AD patients of other countries. We encourage to conduct multi-centric studies in China and globally to generalize this finding.

CONCLUSION

This was the first study to suggest that the patients treated with DNP and NART agonist have similar efficacy and safety profile. Although, considering the clinical benefit, improvement in sign and symptoms of was numerically greater in DNP-treated patients as compared to NART agonist. However, both the study drugs were found comparable in relieving the symptoms of AD. This indicates that NART is a potential target for the treatment of AD in China. The results of the present study may help to design a large clinical trial to evaluate the efficacy and safety of NART agonist in comparison with DNP in AD patients of other countries.

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