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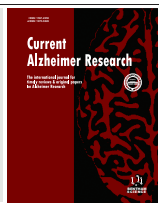
Probabilistic Cost-Effectiveness Analysis of Vaccination for Mild or Moderate Alzheimer's Disease



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Abstract: ***Background:*** Studies on the immunotherapy for Alzheimer's disease (AD) have increasingly gained attention since 1990s. However, there are pros (preventing of AD) and cons (incurred cost and side effects) regarding the administration of immunotherapy. Up to date, there has been lacking of economic evaluation for immunotherapy of AD. We aimed to assess the cost-effectiveness analysis of the vaccination for AD. ***Methods:*** A meta-analysis of randomized control trials after systemic review was conducted to evaluate the efficacy of the vaccine. A Markov decision model was constructed and applied to a 120,000-Taiwanese cohort aged ≥65 years. Person years and quality-adjusted life years (QALY) were computed between the vaccinated group and the the unvaccinated group. Economic evaluation was performed to calculate the incremental cost-effectiveness ratio (ICER) and cost-effectiveness acceptability curve (CEAC). ***Results:*** Vaccinated group gained an additional 0.84 life years and 0.56 QALYs over 10-years and an additional 0.35 life years and 0.282 QALYs over 5-years of follow-up. The vaccinated group dominated the unvaccinated group by ICER over 5-years of follow-up. The ICERs of 10-year follow-up for the vaccinated group against the unvaccinated group were $13,850 per QALY and $9,038 per life year gained. Given the threshold of $20,000 of willingness to pay (WTP), the CEAC showed the probability of being cost-effective for vaccination with QALY was 70.7% and 92% for life years gained after 10-years of follow-up. The corresponding figures were 87.3% for QALY and 93.5% for life years gained over 5-years follow-up. ***Conclusion:*** The vaccination for AD was cost-effective in gaining QALY and life years compared with no vaccination, under the condition of a reasonable threshold of WTP.

Keywords: Alzheimer's disease, cost-effectiveness analysis, immunotherapy, meta-analysis, vaccination.

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INTRODUCTION

In 2003, WHO health report estimated that in people over 60 years old, dementia contributed disability life years than cardiovascular disease, stroke and cancer. Among the elderly aged 60 years or older, the Delphi study also estimated that 42.3 million people worldwide, 60-80% of whom are at risk of having Alzheimer's disease (AD) [1] would suffer from dementia in 2020, The nature course of AD is progressive and evolves with age if no intervention and treatment are administered. Therefore, AD becomes the burden for aging population. Although pharmacological therapies for AD have been available since mid-1990s, there is still no cure for AD currently [2].

The mainstays of conventional pharmacotherapy for AD are acetylcholineterase inhibitors (AchEI, using donepezil, galantamine and rivastigmine) and the inhabitation of N-methyl-D-aspartate (NMDA) receptors (using memantine). However, the effects of these treatments are effective for only about half of individuals. Besides, the effects are temporarily limited to slow symptoms worsening 6 to 12 months [3-5]. The AchEIs for mild to moderate AD was cost-effective in several previous researches [6-11]. In addition, cost-effective results of memantine for moderate-to-severe AD were also noted [12-15]. Recently, the advances in basic research showed the abnormal metabolism of amyloid β peptides (Aβ) is related to AD [16, 17]. Therefore, Aβ becomes an important target for intervention in AD. Studies on the immunotherapy for AD have been conducted to exam the efficacy. Since then, more immunotherapies with various clinical trial designs entered the different stages. Although most of them are underway, there is strong evidence suggesting that the active Aβ immunotherapy has potential of modifying disease [17, 18]. However, economic evaluation of immunotherapy has been lacking.

Recently, U.S. Department of Health and Human Services initiated the second draft of National Alzheimer's Project Act. In addition to research of pathogenesis and development of effective treatment for AD, decision-making process is also important [19] because costs involved with administration of immunotherapy for AD is enormous. The balance between efficacy (pros) and cost (cons) needs to be considered. Therefore, the aim of this study was to assess whether the immunotherapy for AD in comparison with non-intervention is cost-effective.

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MATERIAL AND METHODS

Currently, there are active immunotherapy with synthetic Aβ, passive immunotherapy with antibiodies against Aβ and intravenous immunoglobulin. Because we aimed to evaluate the immunotherapy for AD, we searched the randomized controlled trials published in Pubmed. The key words "Alzheimer's" and "immunotherapy" were combined. The related citations were also used for searching relevant articles. Another filtering criteria were "in human" and written in English. Furthermore, only studies designed with experimental types were included.

In active immunotherapies, there were six studies of synthetic intact Aβ42 (AN1792) [20-25], one study of synthetic fragments of Aβ conjugated to carrier protein [26], and one study of peptides mimicking part of Aβ sequence [27]. In passive immunotherapies, there were two studies of bapineuzumab [28, 29] and one of solaneuzmab [30]. There were two studies of intravenous immunoglobulin [31, 32]. Although the studies of AN1792 was discontinued in phase II owing to the development of aseptic meningoencephalitis in 6% of the patients, these studies still revealed the most information of cognition, life function and longer follow-up. In comparison with studies of AN1792, other studies of immunotherapy were few, either in pilot study or phase I, and short period of follow-up. Therefore, we performed a meta-analysis for estimating the effects of immunotherapy for AD using the clinical trials of AN1792.

There were 6 relevant articles of AN1792 [20-25]. We excluded one study [21], because its clinical outcome of one study was the subgroup of the entire cohort [22]. All five studies used two cognitive scales: the AD assessment Scale-Cognitive subscale (ADAS-Cog) [33] and Mini-Mental State Examination (MMSE) [34]. ADAS-Cog scores range 0 to 70 and the higher scores indicate greater impairment. MMSE scores range 0 to 39 and the lower scores indicate greater impairment. Furthermore, all five studies used Disability Assessment for Dementia (DAD) [35] to assess the basic self-care and instrumental activity of daily living (IADL). DAD scores is the sum of 28 items expressed as a percentage of all items answered. DAD scores range from 0 to 100% and lower scores indicate greater impairment. Three studies used AD Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC) [36] as a global rating scale. ADCS-CGIS is a 7-point scale assessing the change from baseline and the lower scores indicate greater impairment. Because AD is a degenerative disease, the cognitive and activity of daily living would decline with time. Although the scores at baseline and post-treatment were shown, some studies only offered the final score at final visit. Moreover, the time of follow-up among studies was different. Therefore, we used the score change from the baseline and compared the mean differences between the experimental and control group (mean difference = the score change of the experimental group – that of the control group). To estimate the effect of AN1792 based on these five studies, we applied directed acyclic graphic (DAG) model to do the meta-analysis. In the DAG model, Baysian random-effect regression model was adopted for posterior mean difference and 95% credible interval [CI]. Whether the 95% CI covers 0 was used to judge whether it is statistically significant.

Study Cohort

We assumed a hypothetical cohort of 120,000 AD patients based on the dementia prevalence rate of 4.6% [37] derived from the population of people aged 65 years or older consisting of 2,528,249 in the year 2010 in Taiwan. According to the previous surveys in Taiwan, we assumed that the cohort consisted of 50% mild state and 50% moderate state. The intervention of active immunization was compared to the control group. There was no pharmacological treatment for the control group. In the intervention group, we assumed that the patients received the active immunization, whose efficacy was derived from the result of meta-analysis of AN1792.

Model Structure

We used a Markov model to construct the nature course of AD. The nature course commences from mild, moderate, severe and finally to death, which was proposed by Neumann *et al.* [11] (Fig. **1**). The AD state was defined according to Clinical Dementia Rating (CDR). The cycle length of each state was one year. The base case estimates of annual transition probability were derived from previous studies [6, 38-40], which were updated by using Bayesian conjugated beta prior distribution (Table **1**). According to the current survival studies of AD [41-43], we simulated the Markov Model for 5 years after the diagnosis of AD. Meanwhile, 10-year simulation was also performed for evaluating the long-term effects of active immunization. The clinical efficacy was estimated by relative risk after active immunization. The relative risk was applied to early status to late status in the vaccinated group. Although there was reversible transition from moderate to mild status, this might be due to the misclassification of clinical assessment [11]. Therefore, we assumed that the transition probability from moderate to mild status was not changed after active immunization. The duration of protection offered by vaccine was assumed to persist during 10 years.

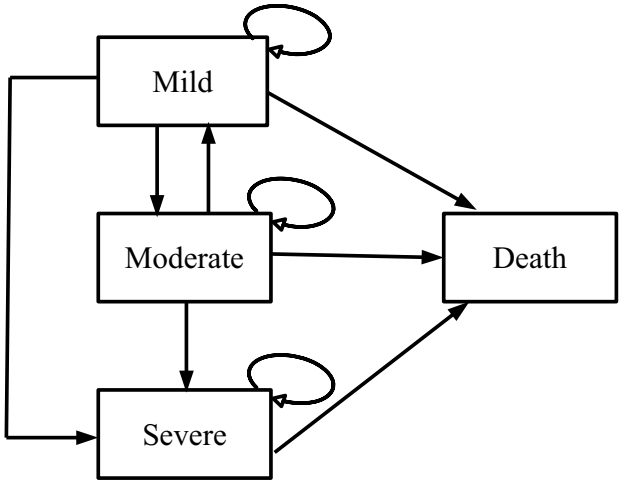

Fig. (1). Markov model for nature history of AD. The direction of arrows directs the disease progression from on state to another.

We estimated the direct and indirect costs in each AD state from the previous Taiwan study [6]. The direct costs included the medical expenses paid by National health insur-

ance and out-of-pocket payments. The indirect costs mainly included caregiver time, which was calculated by opportunity cost of time and replacement cost. The costs parameters were specified by the triangular distribution, including the minimum, a mode and a maximum. Because there was lacking of study on willingness-to-pay (WTP) for AD vaccine, we took the cost of the current most expensive vaccine, human papillomavirus vaccine as a reference [44]. All analyses were performed from a societal perspective. All costs and effectiveness were discounted at 3% annually.

The healthy outcome measure was quality-adjusted life year (QALY). There was no healthy utility survey in Taiwanese AD patient, we used the utility scores from Neumann's study, which measured QALY via the Health Utilities Index Mark II (HUI:2 [11]. Because the majority of AD patients were cared at home in Taiwan [45], we used the scores of the community aspect of the utility in Neumann's study.

Cost-Effectiveness Analysis

Considering the uncertainty of parameters, incremental cost-effectiveness ratios (ICERs) were simulated with probabilistic sensitivity analyses by using Monte Carlo simulation. A total of 5000 simulations were performed according to Briggs *et al.* [46]. A series of ICERs were plotted in the cost-effectiveness (C-E) plane and the probability of being cost-effective was also plotted with acceptability curve. The threshold of WTP was set $US 20,000 per QALY or per life year gained referring to the average Gross Domestic Product in Taiwan.

RESULTS

Meta-Analysis of Efficacy of AN1792

After extracting data from the five studies, we combined the results of MMSE, ADAS-Cog and DAD. In MMSE, the mean change of score from baseline was lower in the vaccinated group than unvaccinated group. However, the mean difference was not statistically significant between the two groups (-0.54, 95% CI [-1.591, 0.5329]). In ADAS-Cog, the score change from baseline was higher in the vaccinated group but the difference was not statistically significant. The mean difference was 0.3, 95% CI [-1.77, 2.41]. In regard of DAD, the score change from baseline was lower in vaccinated group and the mean difference between the two groups was statistically significant (-6.46, 95% CI [-10.62, -2.33]). Concerning the global rating of the ADCS-CGIC, the mean difference of score change between two groups was not statistically significant (-0.07, [-0.35, 0.22]). In previous cost effectiveness studies of donepezil, the risk reduction proportion from early to late status was estimated about 0.5 [6, 8, 10, 11]. Currently, the effects of immunotherapy for AD seemed to be limited for daily life function, not cognition function. We consulted the neurologist by showing the meta-analysis of our study and donezepil together [47]. Meanwhile, the treatment efficacy from previous cost-effectiveness analysis of AchEI was also considered [6-11]. According to the results of DAG model, the scale changes of AN1792 were not as large as those of donezepil. Therefore, the relative risk of AD progression for the vaccinated group compared with the unvaccinated group was estimated at 0.8 conservatively.

Cost-Effectiveness Analysis

The results of the cost-effectiveness analysis show that active immunization in the vaccinated group cost $7,756 more but gained additional 0.56 QALYs over 10 years (Table **2**). Meanwhile, active immunization also cost $7,565 more but gained additional 0.837 life years. It saved 67,200 QALYs and 100,440 life years in the AD cohort over 10 years. In terms of ICER, the vaccinated group traded an excess of $13,850 for one additional QALY gained and $9,038 for one additional life year gained. In the simulation of 5-year follow-up, the vaccinated group gained 0.282 QALYs and 0.352 life years. It saved 33,840 QALYs, 42,240 life years and $2.9 million in duration of 5 years. Concerning ICER, the vaccinated group dominated the unvaccinated group, whatever in terms of QALY or life years.

The result of Monte Carlo simulation on the C-E plane is shown in Figs. (**2-3**). In terms of QALY over 10 years, the probability of being cost-effective in the vaccinated group was 70.7% given the WTP threshold of $20,000 compared to the unvaccinated group (Fig. **2A**). However, only 5.7% of the simulated ICER points located at Win-Win area. Regarding the simulation of QALY for 5 years, the probability of being cost-effective was 87.3% given the WTP threshold of $20,000 and 45.4% of ICER points located at Win-Win Area (Fig. **2B**). In terms of life years over 10 years of follow-up, the probability of being cost-effective in the vaccinated group was 92% given the WTP threshold of $20,000 compared to the unvaccinated group (Fig. **3A**). Regarding the simulation of life years for 5 years of follow-up, the probability of being cost-effective in the vaccinated group was 93.5% given the WTP threshold of $20,000 compared to the unvaccinated group (Fig. **3B**).

The acceptability curve for QALY in (Fig. **4**) also shows the probability of being cost-effective under different values of WTP. In terms of the simulation of QALY for 10-year follow-up, the probability of being cost-effective under the threshold of $20,000 was 70.7%. The probability was 90% when WTP increased to $33,000 per QALY (Fig. **4A**). However, the probability of simulation for 5-year follow-up was 87.3% to 93% when WTP ranged from $20,000 to $33,000 per QALY. Fig. (**4B**) also shows the acceptability curve for life years under different values of WTP. In terms of life years for 10-year of follow-up, the probability of being cost-effective was 92% under the ceiling value of $20,000. Regarding to the simulation of 5-year follow-up, although the probability was 93.5% under the value of $20,000, it reached 90% when the WTP was $17,000 per person year.

DISCUSSION

Our study demonstrated that this active immunization could improve the AD patients' basic self-care and IADL significantly (difference of DAD decrement between the vaccinated and the unvaccinated group: -6.46, 95% CI [-10.62, -2.33]). However, the improvements for cognitive function were not promising.

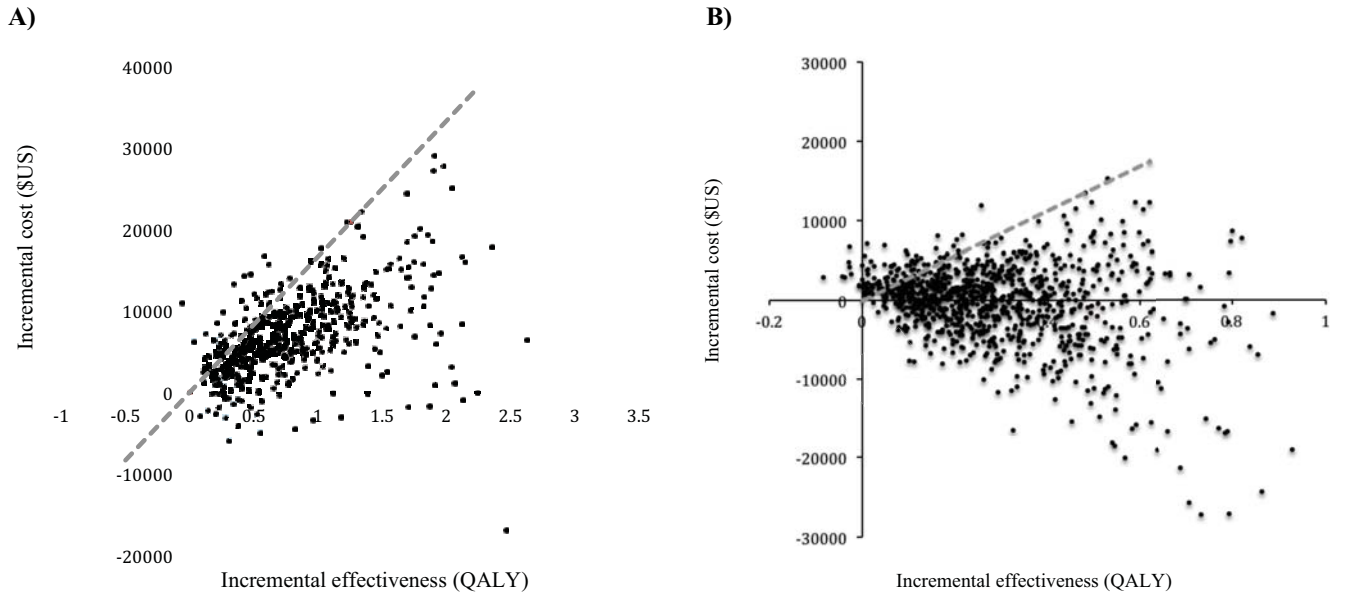

Fig. (2). Simulated results of the cost-effectiveness plane for quality-adjusted life year (QALY). Each point represents a simulated incremental cost-effectiveness ratio value. The dash line represents the threshold of willingness to pay of $US 20,000. (A) Simulation for 10 years. (B) Simulation for 5 years.

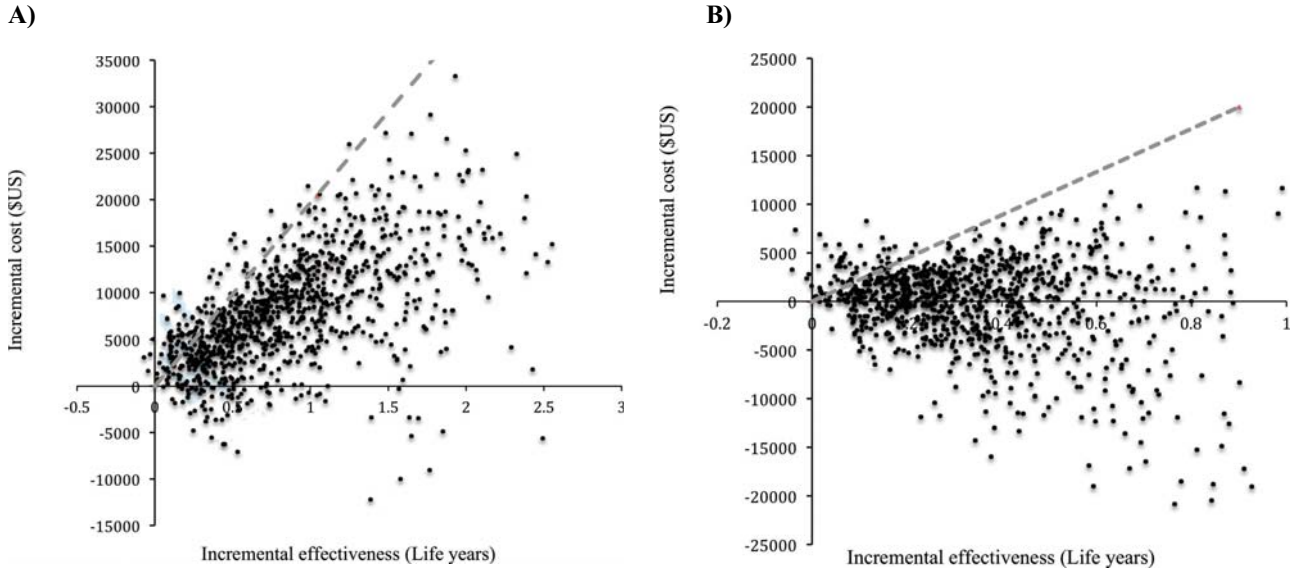

Fig. (3). Simulated results of the cost-effectiveness plane for survival time. Each point represents a simulated incremental cost-effectiveness ratio value. The dash line represents the threshold of willingness to pay of $US 20,000. (A) Simulation for 10 years. (B) Simulation for 5 years.

AD is a degenerative disease with progressive cognitive decline. The current pharmacotherapy for AD focuses on enhancing the levels of acetylcholine and enhancement of glutamate pathway. These offer primarily symptomatic treatment and provide delaying decline temporarily [48]. Recently, disease-modifying treatments (DMTs) are developing and have shown some results. Abnormal processing of Aβ is an important event in AD, which is supported by current available evidences [16]. Immunotherapy is one of these treatments and AN1792 was first-generation active immunization vaccine. The mechanism is to increase Aβ clearance and reduce Aβ deposits [17]. Therefore, it is worthwhile to evaluate whether immunotherapy would be cost-effective by modifying the AD course. Although these five studies have shown the efficacy of AN1792 on cognitive or functional tests, the results were not statistically significant [20, 22-25]. The possible reasons included small sample size or heterogeneity caused by different subgroups. This sort of immunotherapy for AD compared to traditional AchEI trials, faced more difficulties of problematic informed consent procedures and confidentiality limitations [49]. We conducted a meta-analysis using Baysian DAG to increase the statistical power. Although the cognitive function was not improved statistically significant, active immunization indeed was potential to improve the AD patients' daily life function. In a recent Sweden cost-effective analysis of DMT for AD, the

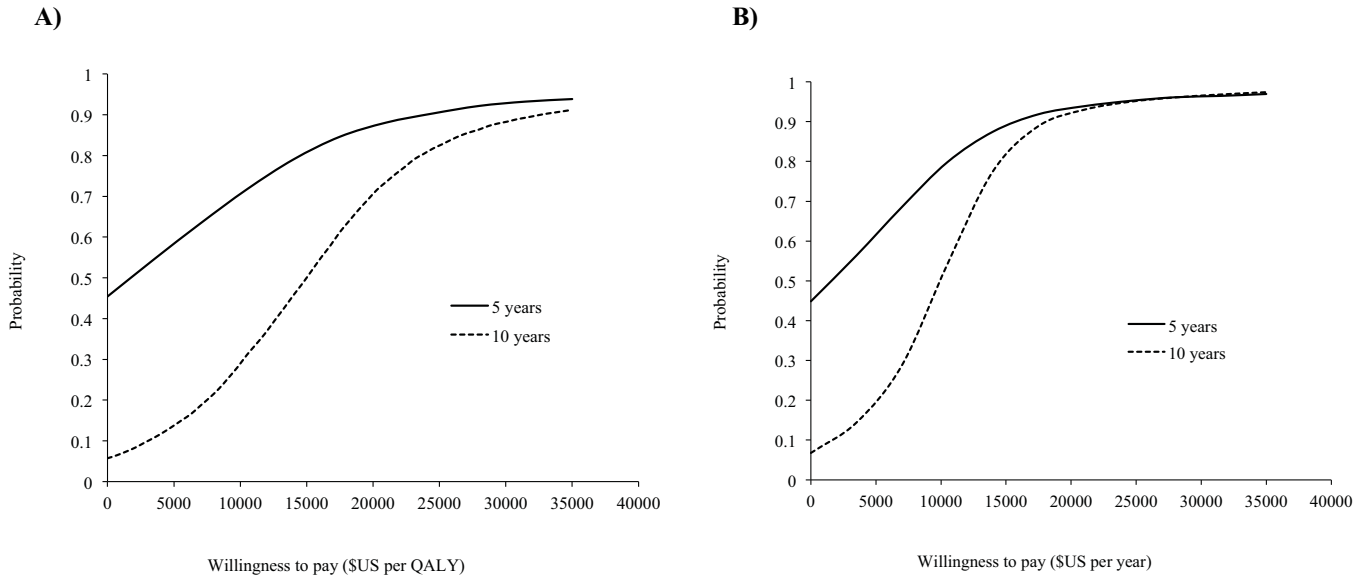

Fig. (4). Cost-effectiveness acceptability curve for 5 and 10 years. (A) Quality-adjusted life year (QALY) . (B) Life year.

Table 1. **Base-case estimate and distribution of parameters.**

Variable	Base case estimate	Distribution	References
Transition probability			
Mild to moderate	0.261	Beta (349.32, 986.54)	[38-40]
Mild to severe	0.019	Beta (127.96, 6746.1)	[38-40]
Mild to death	0.028	Beta (301.81, 10490.98)	[38-40]
Moderate to mild	0.11	Beta (27.03, 219.35)	[38, 40]
Moderate to severe	0.312	Beta (333.63, 739.26)	[38-40]
Moderate to death	0.094	Beta (119.3, 1156.1)	[38-40]
Severe to death	0.182	Beta (92.29, 414)	[38-40]
Costs			
Medical cost of mild	1,266	Triangular (633, 1266, 2533)	[37]
Care cost of mild	8,996	Triangular (4498, 8996, 17992)	[37]
Medical cost of moderate	1,298	Triangular (649, 1298, 2596)	[37]
Care cost of moderate	17,593	Triangular (8797, 17593, 35187)	[37]
Medical cost of severe	1,586	Triangular (793, 1586, 3173)	[37]
Care cost of severe	24,367	Triangular (12184, 24367, 87350)	[37]
QALY			
Mild	0.68	Beta (26.98, 12.69)	[11]
Moderate	0.54	Beta (24.45, 20.83)	[11]
Severe	0.37	Beta (8.84, 15.06)	[11]

Table 2. Cost-effectiveness analysis

	Cost ($US)	Effectiveness	C/E[b]	ICER[c]
10 years				
QALY[a]				
Experimental group	156542	3.469	45126	13850
Control group	148786	2.909	51147	
Survival				
Experimental group	156385	6.768	23107	9038
Control group	148820	5.931	25092	
5 years				
QALY[a]				
Experimental group	107995	2.534	42618	Dominant
Control group	108243	2.252	48065	
Survival				
Experimental group	108206	4.777	22651	Dominant
Control group	108427	4.425	24503	

[a] QALY: Quality adjusted life year.
[b] C/E: cost per QALY or life year.
[c] ICER: incremental cost-effectiveness ratio.

relative risk of progression was hypothetically assumed to be 0.5 in the DMT group without any empirical data [50]. Our study adopted the results of meta-analysis of AN1792 and compared our result to that of donezepil. Therefore, our basic assumption is more robust and specific than the previous cost-effectiveness analysis of DMT.

In terms of QALY, when we compared the results of 5-year simulation with that of 10-year simulation (87.3% vs. 70.6%), the probability of being cost-effective for the active immunization was higher in 5-year simulation given the threshold of $20,000 of WTP. In terms of life years, active immunization had similar probability of being cost-effective in 5-year and 10-year simulation (93.5% vs. 92%). However, the more ICER points (45.4%) were located in Win-Win Area of C-E plane in 5-year simulation than that in 10-year simulation (8.7%). Furthermore, ICER was dominant in active immunization during 5-year simulation in terms of QALY and life years. Even we assumed the efficacy of active immunization persists through 10 years, the marginal effects seemed to decline after 5 years. The possible reasons are several-fold. First, AD is a degenerative disease. Although active immunization delayed the progression, patients still entered the more severe stage when time passed. This was also supported by the fact that the costs in the vaccinated group were lower than that in the unvaccinated group in 5-year simulation. Because societal costs of AD are vary high, active immunization that are able to delay progression of disease has potential to save costs [51]. However, after 10-year simulation, the costs of vaccinated group became higher than that of the unvaccinated group. Secondly, we assumed that the efficacy of active immunization did not have effects for the transition probability of moderate to mild. In some economic analyses, the efficacy of donepezil was also applied to the rate of transition from moderate to mild stages among initially mild patients [6, 9, 11]. Compared with the previous studies, we used a conservative and defensible measure for the efficacy of active immunization.

Actually, the development of AN1792 was stopped at the phase 2a because aseptic meningoencephalitis occurred in 6% of the participants treated with AN1792 compared to 0 on placebo [52]. Some immunological mechanisms for meningoencephalitis and amendments for vaccine were proposed [30]. For the policymaker, the simulated results in this study show the active immunization was a possible choice in future. Currently, several second-generation vaccines, which improved the safety of AN1792 are in phase I-III clinical trials [53]. Meanwhile, there are rapid developments for passive immunotherapy and immunogrobulin (IVIG). Bapineuzumab and solanezumab, the monoclonal antibody, are the representatives of passive immunotherapy. Unfortunately, Phase III trial of bapineuzumab failed to show clinical efficacy [54]. Although solanezumab improved the adverse effects of bepineuzumab [28-30], the passive immunizations have to be injected regularly and repetitively to achieve the clinical effects. Moreover, IVIG is derived from human whole blood donor by plasmaphoresis. The direct cost of medical expenses and indirect costs of caregiver time in passive immunization might be higher than active vaccination. The primary outcomes of a multicenter double-blinded Phase III study of IVIG (400 or 200mg/kg vs. low dose albumin placebo every two weeks), Gammaglobulin Alzheimer's Partnership (GAP) study, were reported to be negative [55].

Therefore, compared with other possible immunotherapies, the results of active immunization in this study were more conservative in view of costs and more realistic for the utilization of immunotherapy.

The previous studies of AchEIs might underestimate the uncertainty because only the transition probabilities of single cohort were adopted. In this study, we conjugated the transition probabilities from different races and cohorts [38-40] to get better estimation. Furthermore, the Markov probabilistic approach had considered the parameters uncertainty by specific distributions and therefore the results were convincing. It also projected the possible efficacy of active immunization into future and was also helpful for policy makers. In order to validate the credibility of results, we compared the survival time of our hypothetical cohort with the previous studies. The estimated 5-year life years gained was 4.425 years, which was slightly lower than that in the previous survey in Taiwan (4.48 years) [42]. The mean survival time changed in different races and subgroups. It varied from 3.3 years in Canadian study to 7.6 years in Hispanics [41]. In a study of US population, the median survival was 4.2 years for men and 5.7 years for women with Alzheimer disease [56].

LIMITATIONS

This study illustrates the hypothetical projections of daily life in the valuation of long-term effects of active immunotherapy for progressive AD. The efficacy was estimated from the few stopped clinical trials of AN1792. However, the meta-analysis of Bayesian DAG method has aggregated the statistical power from five studies. The probabilistic cost-effective analysis with different distribution assignments further alleviates some uncertainties of hypothetical projections. Actually, the clinical trial of AN-1792 was halted when meningoencephalitis appeared in a small subset of participant. Its long-term effect was unable to be measured. Despite this disappointment, long-term follow-up of patients immunized with AN-1792 showed significant less functional decline in antibody responders [24] and lower Aβ peptides loads in brain [25]. These results can support the hypothesis that Aβ immunotherapy may have long-term functional benefits. The real long-term effect should be derived from the empirical data of the second-generation vaccine with shorter peptide sequences in future [55]. Therefore, the policy maker should consider it cautiously because of the assumption made for long-term efficacy of immunotherapy. Secondly, it was not intuitive to realize the efficacy of active immunization by using the difference of the score change from baseline between experimental and control groups [24, 25].

Thirdly, although the direct and indirect costs were included in our model, the care cost is a complicated issue. The direct cost, such as medical expenses was highly dependent on Taiwan's National Health Insurance system. For example, patients' co-payment is low. Therefore, it may influence the generalizability to different care systems. The subjects with AD might be cared in institution or informal care, such as retired family or caregivers of working ages. When the cost of care was calculated by replacement method, it is still hardly realistic to have exact ratio of professional care to informal care. Finally, the healthy outcome measure (QALY) was only from one study and there was no local data from Taiwan. However, the cost-effectiveness analysis for any newest and advanced clinical treatment would have such weakness. Fortunately, different health care systems do not impact on the progression of AD but affect the management of AD [57]. Therefore it is important to consider the resources utilization pattern in cost-effectiveness analysis of new treatment for AD [58].

In conclusion, the available data indicated that the use of vaccination for AD patient may be cost-effective. By considering the current evidences and developments of active immunization, we can update the current studies and re-evaluate the cost-effectiveness of vaccination for AD in future.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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Declared none.

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