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Meta-Analysis

Amyloid beta directed antibody for Alzheimer's disease, an evidence based meta-analysis

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Abstract: In several preclinical researches, antibody of Aacting directly in the central nervous system showed a great efficacy on the clearance of plaques. However, the other researches were opposite. We performed a meta-analysis to evaluate the amyloid-beta-directed antibody treatment of Alzheimer's disease. We searched Pubmed, Web of science, Embase and Cochrane library. Pooled data was calculated by standard mean difference. The heterogeneity and publication bias were evaluated by I^2 and funnel plot. Totally, 5 RCTs (randomized clinical trials) with high qualities were included. There weas no difference of mean change form baseline between therapy and placebo group based on Mini-Mental State Examination (MMSE, SMD = 0.00, p = 0.97, 95% CI = -0.23 0.22) and Clinical Dementia Rating–Sum of Boxes (CDR-SB, SMD = 0.22, p = 0.39, 95% CI = -0.28 0.71), but a significant decrease according to Alzheimer's Disease Assessment Scale (ADAS-cog, SMD = 0.07, p = 0.01, 95% CI = -0.02 0.13). In conclusion, Antibody was not benefit for AD based on MMSE and CDR-SB but had a little effect according to ADAS-cog.

Key words: Antibody, amyloid beta, Alzheimer's disease, therapy, meta analysis, systematic review.

Introduction

Alzheimer's disease (AD), characterized by cognitive deterioration, behavioral disturbances and even declining activities, is a progressive neurodegenerative disease. AD may be identified as the global public health issue in the following seasons, with more than 20 million individuals affected all over the world and expected 135 million patients by 2050 (1). Oxidative stress, Amyloid beta (Aβ) plaques and neurofibrillary tangles are thought to play an important role in the AD pathology (2, 3). In several preclinical researches, antibody of Aβ acting directly in the central nervous system showed a great efficacy on the clearance of plaques (4-7). Though Aβ-directed immunization strategy showed favorable effect in AD transgenic mouse models, the safety and efficacy of immunization therapy for humans was still unknown. Recently, a few of new therapeutic approaches currently are under investigation, involving active and passive immunization targeting Aβ (8). In some previous studies, several researches reported Aß-directed antibody did not improve the clinical outcomes in AD patients according to Alzheimer's Disease Assessment Scale (ADAS-cog), Mini-Mental State Examination (MMSE), Clinical Dementia Rating–Sum of Boxes (CDR-SB) and other scales (9-13). However, Chrispoth (14) reported antibody against β-amyloid was effective in slowing progression of Alzheimer's disease. Meanwhile, the effect of Aß-directed antibody treatments is not affirmatory perfectly lacking powered evidence as small samples data and no multi central clinical trials. As a consequence, we performed a systematic review and meta-analysis of available clinical trials to review the quantity and quality of research evidence as well as to evaluate the Aß-directed antibody treatment of AD.

Materials and Methods

Inclusion criteria for considering studies for this review

Types of studies

For this systematic review and meta-analysis, all studies based on humans, characterized as double-blind randomized clinical trials, in which treatment of Aß-directed antibody for AD in a group compared with placebo were included.

Types of participants

Patients met the criteria for probable Alzheimer's disease as follows: the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (15); Additional inclusion criteria was a score of MMSE from 15 to 26 (16).

Types of interventions

This systematic review considered researches comparing treatment of Aß-directed antibody without any route of administration, dose and duration limitations with a placebo.

Primary outcomes

The changes from baseline over time in scores on the MMSE, ADAS-cog and CDR-SB in patients with

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AD were tested.

Search methods for identification of studies

We searched the electronic database of PUBMED, EMBASE, WEB OF SCIENCE, and Cochrane Library of Clinical Trials. The search terms used were: antibody AND amyloid AND Alzheimer AND scale AND randomized.

The database searches were performed in the sources listed above and the latest searching time which date of inception was 5th August 5, 2015. The search strategies used can be found in Appendix 1. At the same time, we restricted our search to English language publications indexed in international databases due to resource constraints and the above mentioned concerns raised in the scientific literature.

Data collection and analysis

Selection of studies

Two reviewers (Qiaoya Ma, Songsheng Chen) accessed the initial studies retrieved by the search strategy independently and inclusion criteria would be applied to this processing. The third author Chen Li determined the studies eligible for review if there was controversy. All the searching processing followed the principle of PRISMA (17).

Quality assessment

Review authors evaluated the bias risk independently according to criteria described in the Cochrane Collaboration Handbook (18).

Data extraction

We extracted data from all included eligible studies. For every clinical outcome, the statistical value, including the mean change from the baseline, the standard deviation (SD) of the mean change and the number of participants at each scale assessment for each treatment group, were required and extracted. We also collected the mean, standard deviation and the number of participants at baseline and endpoint time, if the changes from baseline were not available.

Data analysis

When changes from baseline were not available, we then calculated the summary statistics required for the meta-analysis based on the standard error (SE) and 95% confidence interval (the conversion equations were from 1 to 3). Meanwhile, the data of two groups defined as subgroups would be merged into one group data according to the equations from 4 to 6. For continuous outcome, the pooled data of the difference between the placebo and intervention group was calculated as standard mean difference (SMD). Heterogeneity was evaluated using I^2 (I^2>50% indicating a heavy heterogeneity). The fixed-effect model would be used to calculate the SMD if the heterogeneity exists rather than fix-effect model. Publication bias was assessed by the funnel plots. Revman software was used to calculate the related pooled data in this meta-analysis.

$$SD = SE \times \sqrt{N} \quad 0.1$$

$$SD = \sqrt{N} \times (upper\ \lim it - lower\ \lim it) / 3.92 \text{ (if N>100)} \quad 0.2$$

$$SD = \sqrt{N} \times (upper\ \lim it - lower\ \lim it) / 4.128 \text{ (if N<100)} \quad 0.3$$

$$N = N_1 + N_2 \quad 0.4$$

$$M = \frac{N_1 M_1 + N_2 M_2}{N_1 + N_2} \quad 0.5$$

$$SD = \sqrt{\frac{(N_1 - 1)SD_1^2 + (N_2 - 1)SD_2^2 + \frac{N_1 N_2}{N_1 + N_2}(M_1^2 + M_2^2 - 2M_1 M_2)}{N_1 + N_2 - 1}} \quad 0.6$$

Results

Searching results

A total of 37 results were retrieved by the time of 7th August 2015. After the initial assessment and duplicates checking, according to the authors, publication year and title, 19 researches were left. Of these articles mentioned above, initial assessment of the research content was given based on the full text. At last, 5 studies were included in this systematic review and meta-analysis (9-12, 19)(shown in figure1).

Characteristics of included studies

From 5 clinical trials, we took 4800, 5052, 5025 research participants' research data, including interventions and type of antibody. Among them, two drugs were active immunization and three were passive immunization. Participants were mild to moderate AD mostly. Baseline characteristics of participants are described in Table 1.

Bias risk assessment

Risk of bias assessment suggested that in terms of random sequence generation, allocation concealment, binding of participants and personnel, binding of outcome assessment and incomplete outcome data, Chris-

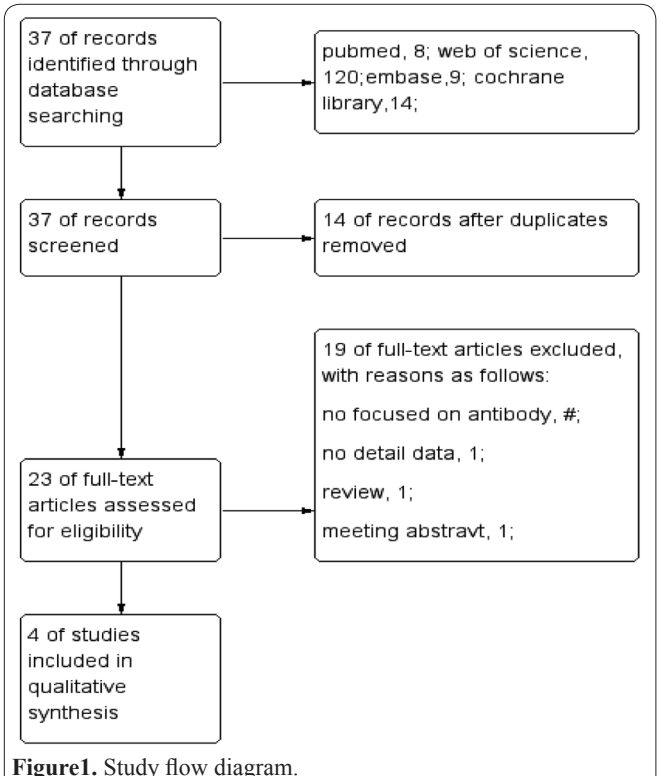

Figure1. Study flow diagram.

Table 1. Characteristics of included 5 studies

Author	Year	Participants	Drug	Type	Intervention
Christoph	2003	mild to moderate	QS-21	Active	-
Gilman	2005	-	AN1792	Active	0.5ml injection at months 1, 3, 6, 9, 12
Rachelle	2013	mild to moderate	Semagacestat	Passive	100mg daily for 76 weeks
Rachelle	2013	mild to moderate	Solanezumab	Passive	400mg every 4 weeks for 18 months
Stephen	2014	mild to moderate	Bapineuzumab	Passive	0.5mg/kg for 78weeks

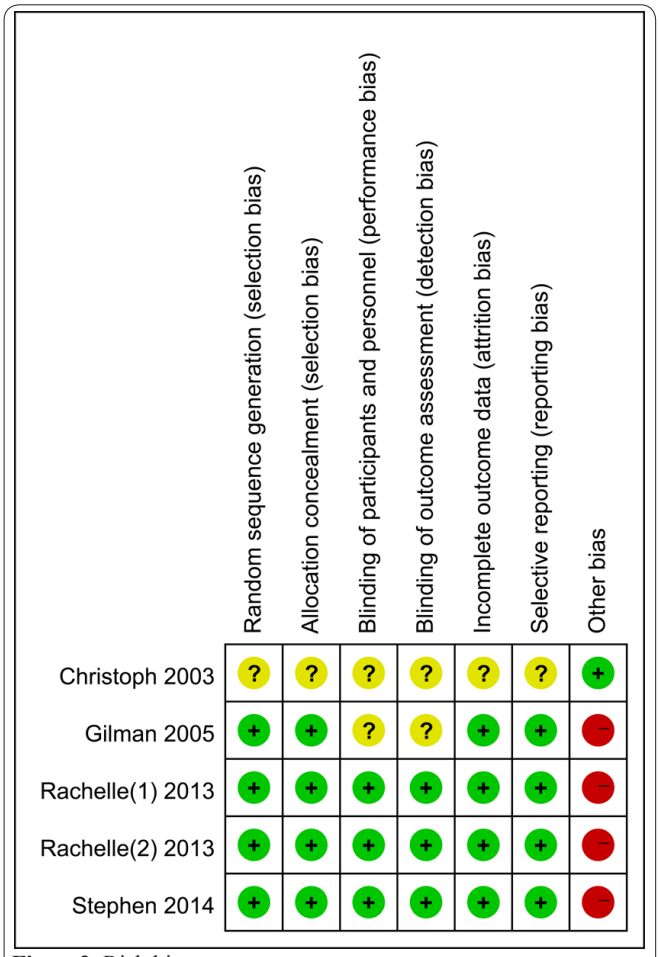

Figure2. Risk bias summary.

toph's study had an unclear risk (shown in figure 2). Meanwhile, Gilman's report also had an unclear risk of binding of participants and personnel and binding of outcome assessment. In addition, we believe that there is potential interest relationship between researchers and drug manufacturers, and hence whether manufactures were informed consent for other similar researches is an important source of bias. The evaluation results indicated that the studies of Rachelle and Stephen had high risks as the studies were supported by related drug manufacturers. However, as a whole, we believed the involved 5 studies generally are not at a high risk of bias.

Aß-directed antibody for AD (MMSE)

As compared with placebo group, pooled data showed that Aß-directed antibody therapy had an effect on the AD based on MMSE (SMD = 0.00, Z = 0.04, p = 0.97, 95% CI = -0.23 0.22, shown in figure3A). There was a heavy heterogeneity among included 4 studies (I^2=90%). The funnel plot suggested that there was a little publication bias (shown in figure4A).

Aß-directed antibody for AD (ADAS-cog)

Compared with control therapy, overall meta-analysis indicated that the use of antibody was associated with a significant decrease in the score of ADAS-cog (SMD = 0.07, Z = 2.58, p = 0.01, 95% CI = -0.02 0.13, shown in figure3B). The fixed model was used to pool the data as there was no significant heterogeneity among all articles (I^2=0%). The funnel plot indicated no publi-

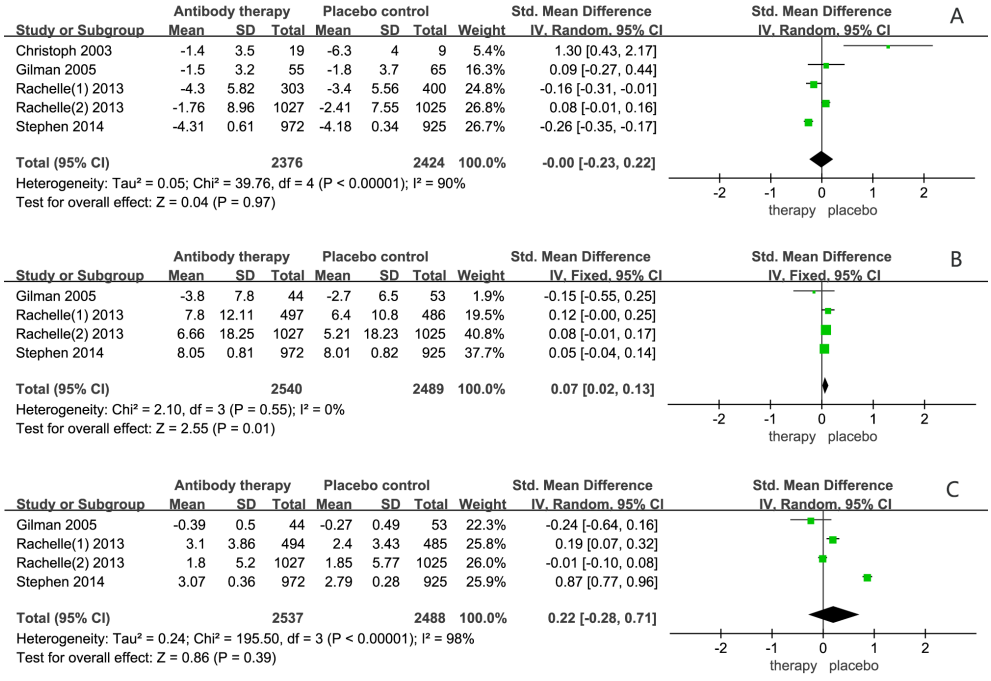

Figure 3. Forest plot (based on MMSE, ADAS-cog and CDR-SB respectively).

NOTE, Squares are study-specific SMD. Diamonds are summary SMD. Horizontal lines represent 95% confidence intervals (CIs).

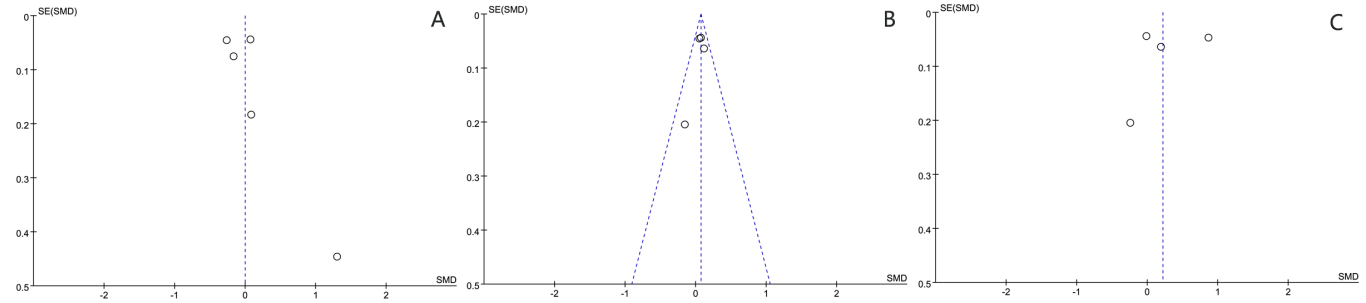

Figure 4. Funnel plot (based on MMSE, ADAS-cog and CDR-SB respectively).
NOTE, Circles mean studies. All circles are involved in the inverted funnel indicating low publication bias.

cation bias (shown in figure4B).

Aß-directed antibody for AD (CDR-SB)

Compared with placebo therapy, test for overall effect suggested the antibody against Aß did not improved the score of CDR-SB (SMD = 0.22, Z = 0.86, p = 0.39, 95% CI = -0.28 0.71, shown in figure3C). There was no significant heterogeneity among all articles (I^2=98%). Thus, a random model was performed to calculate the effect size. The funnel plot indicated there was a little publication bias (shown in figure4C).

Discussion

In this systematic review and meta-analysis, we outlined the effect of antibody targeting Aß in AD patients. We identified 5 RCTs of Aß-directed-antibody. Of these 5 reports, 3 were supported by Pharmaceuticals Company and may have bias risk sine the potential conflict of interest. However, bias risk assessment indicated there was low bias risk of studies in the mass.

The pooled data showed antibody targeting Aß may have no effect on clinical outcome of AD patients based on MMSE and CDR-SB. Meanwhile, high heterogeneity and little publication bias occurred in these two evaluation sections. In terms of ADAS-cog, it is significantly different between antibody therapy and placebo group and there was no heterogeneity and publication bias. Nevertheless, the value of difference effect size SMD was very small.

It has been reported that the therapy against Aß instituted early in the disease will be better as possibly in foreboding stages (20). In this review, most participants were mild to moderate AD and this may explain the invalid antibody acting on Aß. With regard to ADAS-cog, the score difference of mean change from baseline was only 0.07 suggesting antibody used in preventing AD or treating patients diagnosed in early stage may be better.

Furthermore, this study still has some limitations. First, few studies included in this review and meta-analysis resulting in the subgroup analysis not being performed. Second, little baseline information of individuals and few studies were the conjunction of factors of the fact that we could not find the resource of heterogeneity through meta-regression analysis.

In conclusion, available evidence suggests no consistent differences between the use amyloid beta plaques (Aß) in AD patients except a significant decrease according to Alzheimer's Disease Assessment Scale. Results in favor of the use of antibody targeting amyloid beta plaques (Aß) in AD patients are limited by low quality bodies of evidence.

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Appendix 1

Pubmed

((((alzheimer) AND amyloid AND randomized) AND antibody) AND (MMSE OR ADAS OR scale)

Web of science

TS=(alzheimer AND amyloid AND randomized AND antibody AND (MMSE OR ADAS OR scale))

Embase

alzheimer AND ('amyloid'/exp OR amyloid) AND randomized AND antibody AND ('mmse'/exp OR mmse OR adas OR scale) AND [animals]/lim

Cochrane

alzheimer in Title, Abstract, Keywords and amyloid in Title, Abstract, Keywords and antibody in Title, Abstract, Keywords and randomized in Title, Abstract, Keywords and scale in Title, Abstract, Keywords in Cochrane