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A Cross-sectional Comparison of mAB Drugs for Alzheimer's Disease

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Abstract:

Alzheimer's disease (AD), as a serious chronic neurological disease, has brought tremendous pressure to global health.This devastating disease primarily impairs cognitive abilities and causes most people with dementia. Current treatments, including acetylcholinesterase inhibitors (AChEI) and anti-amyloid monoclonal antibodies (mAbs), offer limited effectiveness. In later a long time, monoclonal antibodies have risen as treatments for Ad, with encouraging results in reducing amyloid accumulation and alleviating clinical manifestations. This article reviews the latest development of mAb-based AD drugs, with emphasis on aducanumab, lecanemab and donanemab. A comparative investigation of clinical trials assessed the viability and security of these monoclonal antibodies in cognitive decay, utilitarian capacity, and generally quality of life. mAbs targeting Aβ deposition such as aducanumab and lecanemab developed for Aβ deposition are designed to clear or reduce these deposits in the brain to potentially slow the rate of AD progression. The instrument of activity of mAb in Ad treatment, such as crossing the blood-brain obstruction, official to the AÎ² target and advancing its clearance, is additionally talked about. This article proposes the potential of monoclonal forebear within the administration of Ad, but recognizes the require for thorough advantage and hazard evaluation of important security prove.

Keywords: Alzheimer's disease, mAb drugs, cross-sectional compare.

1. Introduction

Alzheimer's disease(AD), is a dynamic neurodegenerative malady [1]. It is one of the leading diseases that impairs cognition and leads to dementia and accounts for three-quarters of all dementias [2, 3]. Approximately 40 million individuals worldwide are currently affected by AD, and projections indicate that this number could exceed 100 million by the year 2050 [4]. In order to face this disease is a huge risk for the elderly. The disease has been the subject of ongoing research around the world for decades.

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The main drugs that can be used at present are Acetylcholinesterase inhibitor (AChEI), anti-beta-amyloid mAb, etc [2].

At present, numerous ponders have appeared that monoclonal antibodies (mAbs) have a great execution within the treatment of Ad. For example, Chowdhury's experiment demonstrated the role of Lecanemab in coping with AD, and there was a positive effect between the reduction of amyloid protein and the clinical manifestations of patients [5]. In addition, a variety of drugs using mAbs to treat AD are under development and progress [4]. In Sims JR's trial, Donanemab has been shown to bring symptoms under control in the early stages of AD [6]. However, this experiment has certain limitations, and due to some problems with the dose data used, some people have more serious side effects in the subsequent experiment, but this cannot deny the role of mAbs in the treatment of AD [7]. It is enough to illustrate the importance of mAbs for the remission and treatment of AD. Therefore, this article will summarize these drugs related to mAbs and compare these drugs in a horizontal manner.

Cross-sectional comparisons of these drugs can evaluate the efficacy of these drugs and understand the clinical relief effect. These comparisons often involve a meticulous examination of the results from multiple clinical trials, where the drugs are tested against a placebo or another active comparator. Key performance indicators such as the rate of cognitive decline, functional abilities, and overall quality of life are assessed over time. By comparing the information from different tests, analysts can decide which drugs can more altogether moderate the design and heading of the advancement of Alzheimer's malady. Moreover, analyzing the safety profiles of these drugs is paramount [8]. As mentioned, some mAbs, like Donanemab, have shown promising efficacy but have also been associated with severe side effects, including brain swelling and bleeding. Cross-sectional comparisons allow for a systematic review of the frequency, severity, and predictability of such adverse events across different drug candidates. This information is invaluable for doctors and patients alike, as it informs decisions about risk-benefit ratios and helps to identify potential subpopulations that may be more susceptible to adverse reactions. This will provide doctors and patients with more comprehensive treatment basis and clear research direction.

2. Mechanism

There are two main hypothesis of the cause of AD, some scientists think that the damage of cholinergic function is a key reason AD happens, at the same time there are other voices that think alterations in amyloid beta production and processing are the main initiating factors [8, 9]. These two are just the main factors, in addition to age, lifestyle, or head injury can all contribute to the development of AD.

2.1 Cholinergic Hypothesis

ACh is the primary neurotransmitter to be recognized. ACh is a neurotransmitter used by all cholinergic neurons and features a very vital part within the fringe anxious framework and the central apprehensive framework. Cholinergic neurons are broadly disseminated within the central anxious framework. So it makes sense that he's in charge of regulating important nerve functions [10]. AD itself is also a neurological disease, so there is reason to suspect that the occurrence of AD is related to cholinergic neurons. So in the 1970s, Research results show that the decline of neocortical and presynaptic cholinergic function is closely related to choline acetyltransferase (ChAT), which is a key enzyme in the synthesis of acetylcholine [9]. Therefore, researchers proposed the cholinergic disease hypothesis of adenoids cystic sclerosis based on this.

This theory recommends that the cholinergic framework is closely included in memory arrangement and capacity. In patients with Ad, harm of basal forebrain cholinergic neurons and related cholinergic neurotransmission disability in cortex and hippocampus may be an important cause of memory and cognitive impairment.

2.2 Amyloid Hypothesis

In later decades, it has been recognized that irregular statement of beta-sheets within the central apprehensive framework encompasses a clear relationship with dementia, and in this way the concept of amyloid theory has been proposed. Be that as it may, with the deepening of research, it is steadily found that amyloid plaque (AP) is additionally kept within the typical and sound brain with the increment of age, which is opposite to the speculation that the testimony of AP will lead to the event of Ad, so people have also questioned this hypothesis, that the accumulation of AP is not 100% associated with the occurrence of AD. This has led to different hypotheses being proposed for non-hereditary AD (NIAD) in recent years, and despite a variety of voices, overall the amyloid-β hypothesis is widely considered to be the pathological basis of hereditary Alzheimer's disease (familial clustering) [9].

The amyloid speculation recommends that overproduction or deferred clearance of AÎ²42 or other AÎ² polypeptide parts leads to the statement of dissolvable AÎ² oligomers and insoluble amyloid proteins within the brain, shaping amyloid plaques. Intuitive of these plaques with microglia, astrocytes, blood vessels, and neurons trigger numer-

ous destructive cellular reactions that eventually lead to neuronal brokenness and passing.

The amyloid hypothesis and cholinergic hypothesis are two important theoretical frameworks in the current study of the pathogenesis of AD, which explain the underlying causes of this complex neurodegenerative disease from different perspectives. Cholinergic hypothesis explains the pathological mechanism of AD from the perspective of neurotransmitter dysfunction. Defects in the cholinergic system that affect ACh synthesis eventually lead to cognitive impairment.The amyloid hypothesis is a theoretical model that explains the pathological process of AD by studying the abnormal deposition of proteins. Amyloid plaques that accumulate in the brain trigger a series of pathological reactions that affect cognition.

Although there is no single hypothesis that can fully explain the cause of AD, the complementary and continuous improvement of these theoretical frameworks will help us to understand this disease more deeply and provide new ideas and directions for its treatment.

3. Drugs Based on the A-β and Cholinergic Hypothesis

3.1 mABs

Based on the amyloid theory, researchers have created A arrangement of monoclonal drugs that target AÎ², pointing to moderate or halt the movement of Ad by clearing or lessening AÎ² stores within the brain.These mAbs include aducanumab already on the market, lecanemab, and donanemab in the pipeline. Data from clinical trials of these drugs show that they can reduce Aβ levels in the brain to some extent and may delay cognitive decline.

4.1.1 Aducanumab

Aducanumab is a fully human IgG1 monoclonal antibody with high affinity that specifically targets the Aβ conformational epitope and can selectively bind to amyloid deposits in the brains of AD patients. This drug has the ability to clear such substances and activate the immune system [11].

Treatment with anti-AÎ² mAbs in creature models of Advertisement has been exceptionally viable, moving forward cognitive work and diminishing brain injuries by invigorating microglia and anticipating AÎ² conglomeration [12]. Aducanumab was able to cross the blood-brain obstruction, enter the brains of transgenic mice, and tie to AÎ² within the brain parenchyma, in this manner diminishing levels of solvent and insoluble AÎ². Aducanumab essentially hindered AÎ² poisonous quality and improved phagocytosis and cell survival in 10-month-old transgenic AD animal model APPPS1-21 mice treated at A dose of 10mg/kg per week for 4 months [13].

After recognizing the obvious effect of aducanumab, people began to try to improve the intracranial level of aducanumab. In the experiment of AD model APP23 mice, it was proved that aducanumab combined with ultrasound treatment could restore the cognition of APP23 mice through ultrasonic scanning of intravenously injected microvesicles. It can temporarily open the blood-brain barrier, thus facilitating the entry of aducanumab into the brain [14].

Aducanumab experiments in Tg2576 mice revealed that the therapy can dose-dependently reduce the deposition of Aβ plaques in 9-month-old mice. However, for 22-month-old mice, this effect was not significant, suggesting that it is better at preventing Aβ accumulation than clearing already formed amyloid plaques. [15].

In a Phase Ib double-blind, randomized, placebo-controlled trial, Aducanumab demonstrated significant efficacy in improving symptoms in patients with mild cognitive impairment and AD-related diseases [13]. Based on this, Aducanumab was approved for Phase III clinical studies. Further double-blind trial results showed that its efficacy was equally significant, including 196 subjects [16]. Aducanumab can significantly reduce the volume and number of Aβ plaques in the brain, and effectively improve the clinical manifestations of patients with early or mild AD [16]. At the same time, its performance in clinical and biomarker tests also confirmed its safety and reliability.

4.1.2 Lecanemab

Aducanumab and Lecanemab are both monoclonal antibody drugs that emphasize reducing the accumulation of Aβ in the brain. Due to their extremely high adsorption capacity, these drugs can specifically capture and remove soluble Aβ proteins in the brains of patients with early Alzheimer‘s disease (AD), thereby reducing the formation of Aβ plaques.

In the clinical trial of Lecanemab, researchers first focused on the safety and tolerability of the drug in AD patients. The results showed that regardless of the dose, lecanemab showed good tolerability, and under magnetic resonance imaging (MRI) evaluation, the incidence of ARIA-E/H (edema E, hemorrhage H) was not significantly different from that of the placebo group [17]. In addition, another double-blind study found that a dose of 10 mg/kg of lecanemab given every two weeks significantly reduced the level of Aβ in the patient‘s brain compared with the placebo group after 72 weeks, which provided strong support for the positive therapeutic effect of lecanemab [13].

The monoclonal antibody lecanemab, developed in recent years, may be expected to become an effective treatment

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for Alzheimer‘s disease (AD). Studies have shown that the drug can significantly reduce the Aβ content in the brain, delay cognitive decline, and reduce the incidence of amyloid-related imaging abnormalities (ARIA-E), showing good therapeutic effects and safety. However, the results of some clinical trials are not satisfactory, and its clinically significant benefits have not yet been confirmed for patients who have obvious or early symptoms of dementia. Therefore, more in-depth efficacy and safety studies of lecanemab are needed to fully evaluate its application value in the field of AD treatment.

3.2 Therapies Based on the Cholinergic Hypothesis

The cholinergic hypothesis focuses more on the function and damage of the cholinergic system. However, damage to the cholinergic system may be A link in the multifactorial pathogenesis of Alzheimer‘s disease, so protection of the cholinergic system and other potential therapeutic targets need to be considered in addition to MAB drugs targeting Aβ when treating AD.

There are relatively few monoclonal antibodies produced for AD based on the cholinergic hypothesis, because most of the AD drugs currently on the market are not monoclonal antibodies developed directly based on the cholinergic hypothesis, but AChEI drugs, which reduce the hydrolysis of acetylcholine by inhibiting acetylcholinesterase, thereby increasing the concentration of acetylcholine in the synaptic gap. Improve cholinergic neurotransmission function. However, these drugs do not directly target the neurotransmitter defects in the cholinergic hypothesis.

3.3 Other Drugs

4.3.1 Donanemab

Donanemab, an approved anti-AD monoclonal antibody, slows or hinders the progression of Alzheimer’s disease (AD) by reducing the accumulation of Aβ. A rigorous Phase II clinical study, using a randomized, double-blind, placebo-controlled design, evaluated the safety and efficacy of donanemab in patients with early AD. Subjects were randomly assigned to donanemab or placebo groups and followed up regularly to observe the efficacy. The experimental results revealed that donanemab can significantly reduce the level of Aβ in cerebrospinal fluid and blood, demonstrating its ability to clear Aβ deposits. In addition, the donanemab treatment group showed improvements in cognitive and functional assessments compared with the placebo group. However, some patients treated with high doses developed amyloid-related imaging abnormalities, and some patients in both groups unfortunately died [6]. This suggests that we need to further optimize the dose and safety, and also indicates that the drug is not yet suitable for large-scale production.

4.3.2 Crenezumab

Crenezumab, A humanized IgG4 monoclonal antibody designed to bind to a variety of Aβ forms, ranging from oligomers to fibril to plaques, effectively targets and removes excess Aβ from the body. In particular, it showed A 10-fold higher affinity for soluble Aβ oligomers, which are the core facilitators of Aβ-related neurotoxicity. Therefore, crenezumab is not only able to block the further aggregation of Aβ, but also actively promotes the breakdown of oligomers that have been formed, thereby reducing neurotoxicity at the source [18].

In addition, crenezumab achieved a significant improvement in safety over traditional IgG1 monoclonal antibodies. It can effectively prevent the vasculo-related side effects that may be caused by IgG1 monoclonal antibodies, such as antidrug-mediated brain edema (ARIA-E), amyloid-associated imaging abnormalities - bleeding (ARIA-H), and complement dependent cytotoxicity. By significantly reducing the risk of ARIAs (anti-drug antibody associated adverse events), crenezumab provides A safer and more reliable option for the treatment of Aβ-associated diseases, significantly enhancing the safety of treatment and patient tolerability [19]. In two Phase I studies in healthy people, crenezumab demonstrated excellent tolerability and an acceptable safety profile, allowing participants to tolerate it well [20]. However, when the study advanced to a Phase 3 clinical trial, despite enrolling as many as 750 patients in the prodromal to mild AD stage, the results were disappointing. No significant differences were observed between the crenezumab and placebo groups in the trial [18], a clear indication that the drug did not show significant efficacy in treating and relieving symptoms of AD.

4. Conclusion

This paper reviewed the latest advances in monoclonal antibody therapy for AD, with emphasis on aducanumab, lecanemab, and donanemab. Through a detailed analysis of their mechanism of action, effectiveness, and safety, the study emphasized the differences in their approaches to targeting amyloid accumulation. For instance, Ducanumab, which has been shown to be effective in reducing amyloid plaques, has been shown to be associated with an increased risk of brain swelling. By comparing the two drugs, the study found that although they share the same objective of reducing amyloid plaques, their safety and effectiveness are a reflection of the ongoing challenge of developing a universal therapy for Alzheimer‘s. Adu-

canumab's aggressive approach to amyloid reduction can provide rapid results, but raises long-term safety concerns. The results of this study reveal the great potential of monoclonal antibodies in the treatment of AD, especially in solving the problem of amyloid protein pathology. By comparing the effects of aducanumab, lecanemab, and donanemab, the study highlights the potential of each drug to be more effective, providing valuable insights into individualized treatment strategies. This comparison not only underscores the importance of continuing research on monoclonal antibody therapy, but also highlights the need for a multi-factorial approach to Alzheimer's, which integrates both amyloid-targeting strategies and efforts to preserve cholinergic system function.

But the scope of the study is not unlimited. Although the hypothesis of amyloid has been thoroughly investigated, the cholinergic hypothesis and other possible contributing factors have not been investigated in the same depth. The main focus of this paper is on amyloid-targeting drugs, rather than on the wider spectrum of therapies that may complement or enhance the action of monoclonal antibodies. But the long term effects of such therapies are still unclear, as are their interactions with other treatments commonly used in Alzheimer's treatment. Safety profiles, though discussed, need to be further investigated, especially with regard to the risk of side effects, such as cerebral edema and hemorrhage.

The analysis of this paper provides significant insights into the current state of the art of monoclonal antibody therapy, but also opens up a number of important avenues for future research. Moving forward, it'll be vital to conduct longitudinal considers to examine the combined impacts of amyloid-targeting and cholinergic treatments. Such research should seek to understand how the various approaches work together to provide a more holistic approach to AD. In addition, with the development of new monoclonal antibodies and other treatment strategies, it is important to focus on improving the understanding of AD. In summary, although this paper has made significant contributions to the understanding of monoclonal antibodies for AD, it also recognizes the need to explore a broader approach to the treatment of Alzheimer's.

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