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Review

Neuropharmacology of Lecanemab-irmb: A new drug granted in the treatment of Alzheimer's disease

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ABSTRACT

United state food and drug administration approved on 6 January 2023, Lecanemab-irmb via the accelerated approval pathway for the treatment of Alzheimer's disease. Researchers evaluated Lecanemab-irmb's efficacy in a double-blind, placebo-controlled, parallel-group, dose-finding study of 856 patients with Alzheimer's disease. Treatment was initiated in patients with mild cognitive impairment or mild dementia stage of disease and confirmed the presence of amyloid beta pathology. Patients receiving the treatment had significant dose and time-dependent reduction of amyloid beta plaque, with patients receiving the approved dose of lecanemab, 10 milligram/kilogram every two weeks, having a statistically significant reduction in brain amyloid plaque from baseline to Week 79 compared to the placebo arm, which had no reduction of amyloid beta plaque.

These results support the accelerated approval of Lecanemab-irmb, which is based on the observed reduction of amyloid beta plaque, a marker of Alzheimer's disease. The amyloid beta plaque was quantified using positron emission tomography (PET) imaging to estimate the brain levels of amyloid beta plaque in a composite of brain regions expected to be widely affected by Alzheimer's disease pathology compared to a brain region expected to be spared of such pathology.

Keywords: Alzheimer's disease, Lecanemab-irmb, amyloid beta plaque

INTRODUCTION

Alzheimer's disease (AD), the commonest cause of dementia, is a growing global health concern with huge implications for individuals and society. Alzheimer's disease is a neurodegenerative disorder marked by cognitive and behavioral impairment that significantly interferes with social and occupational functioning. AD is a progressive and fatal dementia of unknown cause characterized by loss of cognitive and physical functioning, commonly with behavior or cognitive symptoms. Cognitive decline is gradual and includes memory loss, aphasia, apraxia, agnosia, disorientation, and impaired executive function.[1-2]

Alzheimer's disease is an irreversible, progressive brain disorder affecting more than 6.5 million Americans that slowly destroys memory and thinking skills and, eventually, the ability to carry out simple tasks. While the specific causes of Alzheimer's are not fully known, it is characterized by changes in the brain-including amyloid beta plaques and neurofibrillary, or tau, tangles that result in the loss of neurons and their connections. These changes affect a person's ability to remember and think.[3-5]

Lecanemab-irmb was approved using the Accelerated Approval pathway, under which the FDA may approve drugs for serious conditions where there is an unmet medical need and a drug is shown to have an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit to patients. The results of a Phase 3 randomized, controlled clinical trial to confirm the drug's clinical benefit have recently been reported and the agency anticipates receiving the data soon.[6,7]

Indications and Uses

Lecanemab-irmb is an amyloid beta-directed antibody indicated for the treatment of Alzheimer's disease. Treatment with Lecanemab-irmb should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in clinical trials. There are no safety or effectiveness data on initiating treatment at earlier or later stages of the disease than were studied. This indication is approved under accelerated approval based on a reduction in amyloid beta plaques observed in patients treated with Lecanemab-irmb. Continued approval for this indication may be contingent upon verification of clinical benefit in a confirmatory trial.[6,7]

Dosage and Administration

Confirm the presence of amyloid beta pathology prior to initiating treatment. The recommended dosage is 10 mg/kg that must be diluted and then administered as an intravenous infusion over approximately one hour, once every two weeks. Obtain a recent (within one year) brain MRI prior to initiating treatment to evaluate for pre-existing Amyloid Related Imaging Abnormalities (ARIA). Obtain an MRI prior to the 5th, 7th, and 14th infusions. If radiographically observed ARIA occurs, treatment recommendations are based on the type, severity, and presence of symptoms. Dilution in 250 mL of 0.9% Sodium Chloride Injection, USP, is required prior to administration. Administer as an intravenous infusion over approximately one hour via a terminal low-protein binding 0.2 micron in-line filter. Injection: 500 mg/5 mL (100 mg/mL) solution in a single-dose vial, 200 mg/2 mL (100 mg/mL) solution in a single-dose vial.[6,7]

Warnings and Precautions

Amyloid Related Imaging Abnormalities (ARIA): Enhanced clinical vigilance for ARIA is recommended during the first 14 weeks of treatment with Lecanemab-irmb. The risk of ARIA, including symptomatic ARIA, was increased in apolipoprotein E ε4 homozygotes compared to heterozygotes and noncarriers. If a patient experiences symptoms suggestive of ARIA, clinical evaluation should be performed, including MRI scanning if indicated.

Infusion-Related Reactions: The infusion rate may be reduced, or the infusion may be discontinued, and appropriate therapy administered as clinically indicated. Consider pre-medication at subsequent dosing with antihistamines, non-steroidal anti-inflammatory drugs, or corticosteroids.[6,7]

Adverse Reactions

The most common adverse reactions (at approximately 10% and higher incidence compared to placebo) are infusion-related reactions, headache, and ARIA-edema.[6,7]

Mechanism of Action

Lecanemab-irmb is a humanized immunoglobulin gamma 1 (IgG1) monoclonal antibody directed against aggregated soluble and insoluble forms of amyloid beta. The accumulation of amyloid beta plaques in the brain is a defining pathophysiological feature of Alzheimer's disease. Lecanemab-irmb reduces amyloid beta plaques, as evaluated in Study.[6,7]

Effect of Lecanemab-irmb on Tau Pathophysiology

A reduction in plasma p-tau181 was observed with Lecanemab-irmb 10 mg/kg every two weeks compared to placebo in the double-blind, placebo-controlled period of the Study.[6,7]

Pharmacokinetics

Steady-state concentrations of lecanemab-irmb were reached after 6 weeks of 10 mg/kg administered every 2 weeks and systemic accumulation was 1.4-fold. The peak concentration (Cmax) and area under the plasma concentration versus time curve (AUC) of lecanemab-irmb increased dose proportionally in the dose range of 0.3 to 15 mg/kg following a single dose.

Distribution: The mean value (95% CI) for the central volume of distribution at steady-state is 3.22 (3.15-3.28) L. Elimination: Lecanemab-irmb is degraded by proteolytic enzymes in the same manner as endogenous IgGs. The clearance of lecanemab-irmb (95% CI) is 0.434 (0.420-0.451) L/day. The terminal half-life is 5 to 7 days.[6,7]

CONCLUSION

A treatment that may moderately slow mild cognitive decline and reduce amyloid-β plaques in patients with early Alzheimer's disease gained accelerated approval from the US Food and Drug Administration (FDA). Lecanemab-irmb is indicated for patients with mild cognitive impairment or mild dementia due to Alzheimer's disease.

Conflict of Interest

The author declares that there are no conflicts of interest relevant to this article.

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