Lecanemab blocks the effects of the Aβ/fibrinogen complex on blood clots and synapse toxicity in organotypic culture

Pradeep Kumar Singh, Elisa Nicoloso Simões-Pires, Zu-Lin Chen, Daniel Torrente, Marissa Calvano, Anurag Sharma, Sidney Strickland, and Erin H. Norris

Alzheimer’s disease (AD) is a neurodegenerative dementia characterized by the accumulation of amyloid-beta (Aβ) aggregates in the brain parenchyma and in/around blood vessels (cerebral amyloid angiopathy, CAA) (1, 2). An early feature in AD is the disruption of the blood–brain barrier (BBB), which leads to the extravasation and accumulation of blood proteins within the brain, worsening AD pathology (1, 3, 4).

Human IgG had no effect on Aβ42 and added them to normal human plasma (NHP). Immunoprecipitation was performed to pull down any Aβ42 and added them to normal human plasma (NHP). Immunoprecipitation was performed to pull down any Aβ42 and added them to normal human plasma (NHP). Immunoprecipitation was performed to pull down any Aβ42; however, Aβ42 did not pull-down fibrinogen, indicating
that lecanemab blocked Aβ42/fibrinogen binding in NHP (Fig. 2 A and B). Consistent with in vitro results (Fig. 1 E–J), lecanemab corrected Aβ42-induced clot abnormalities in human plasma (Fig. 2 C–H).

Synapse loss in AD is associated with memory impairment (4, 9). For example, the reduction of presynaptic protein synaptophysin (SYP) and postsynaptic density protein-95 (PSD-95) in the hippocampus corresponds to cognitive deficits in AD (10, 11). Extravasated fibrinogen can contribute to synaptic dysfunction (1, 3, 4, 12). Therefore, we explored whether lecanemab could alter fibrinogen’s effect on Aβ42-mediated synaptotoxicity by examining the levels of SYP and PSD-95 in mouse organotypic hippocampal cultures (OHC). Treatment of OHCs with a mixture of Aβ42 protofibrils and fibrinogen reduced SYP and PSD-95 (1, 3, 4), lecanemab’s ability to mitigate Aβ42/fibrinogen-mediated synaptic changes (Fig. 2 J–K).

Moreover, lecanemab dissociated preformed Aβ42/fibrinogen complexes in human plasma (Fig. 2 L and M) and mitigated synaptotoxicity induced by preformed complexes in mouse OHCs (Fig. 2 N–P). We have shown that anti-Aβ antibodies whose epitopes overlap with fibrinogen’s binding site on Aβ can prevent Aβ/fibrinogen complex formation and dissociate Aβ/fibrinogen complexes (5), so this mechanism is not specific to lecanemab. However, aducanumab, another FDA-approved Aβ immunotherapy (2), did not dissociate Aβ/fibrinogen complexes in human plasma (Fig. 2 L and M). Therefore, lecanemab’s ability to block Aβ/fibrinogen complex formation or dissociate the complex, in addition to its ability to inhibit contact system dysfunction (13), could be some of its protective mechanisms.

The concentration of lecanemab used in our studies is higher than in the CSF of treated AD patients (14), which could be considered a study limitation. However, Aβ42/fibrinogen complexes lead to pathologies both in cerebral blood vessels and the brain parenchyma (1). Therefore, the proposed protective effect of lecanemab against Aβ42/fibrinogen-mediated vascular dysfunction is more likely dependent on the concentration of lecanemab in the patients’ blood (8).

Our findings suggest that further investigation into lecanemab’s mechanisms-of-action is necessary in AD mouse models and AD patients. Questions remain about lecanemab’s efficacy in dissociating and method of clearing Aβ/fibrinogen complexes in vivo and its mechanism in mitigating Aβ/fibrinogen-induced synaptotoxicity. Moreover, given the neurodegenerative impact of extravasated fibrin(ogen) into the brain parenchyma independent of Aβ (1, 3, 4), exploring a combinatorial therapeutic strategy using lecanemab alongside a fibrin-specific antibody (12) or another relevant target could be an effective treatment to improve upon the current AD immunotherapies.

Materials and Methods

Details of reagents and methods are included in SI Appendix.

Data, Materials, and Software Availability. All study data are included in the main text and/or SI Appendix.

ACKNOWLEDGMENTS. This work was supported by NIH grant NS106668, Samuel Newhouse Foundation, Zina Stern Fellowship, Mr. and Mrs. William J. and Pam Michaelcheck, Mr. John A. Herrmann, and May and Samuel Rudin Family Foundation. We thank Dr. Roger Vaughan and Ms. Caroline Jiang, Rockefeller University, for statistical analysis advice.
Fig. 2. Lecanemab blocks Aβ42-induced clot abnormalities and delays fibrinolysis in NHP and Aβ42/fibrinogen-mediated synaptotoxicity in mouse OHC.

(A) Biotinylated Aβ protofibrils (B-Aβ) were incubated in NHP to form complexes with fibrinogen. Lecanemab, aducanumab, buffer, or control IgG was added after 1 h. Western blot analysis shows treatment with preformed Aβ42/fibrinogen complexes reduced SYP and PSD95 levels in OHC. However, in the presence of lecanemab, the Aβ42/fibrinogen-mediated reduction in PSD-95 and SYP was minimized. (J and K) Quantification of immunoprecipitation shows that lecanemab dissociated preformed Aβ42/fibrinogen complexes while aducanumab did not. (M) Quantification of I. Data from four experiments. Changes in synaptic markers were not due to cell death as determined by propidium iodide staining.

(B–E) Clotting and fibrinolysis in NHP using turbidity assay. Lecanemab restored Aβ42-induced delayed fibrinolysis in NHP. (D) Quantification of clot lysis rate in C. (E) Quantification of maximum clot turbidity in C. (C–E) Data from seven experiments, n = 7/group. (F) Representative scanning EM of clots formed from NHP with different treatments. (Scale bar, 5 µm.) (G and H) Analyses of scanning EM showing quantifications of fibrin diameter and total area of abnormal fibrin clumps/clusters. Data from three independent experiments. (J) Western blotting shows Aβ42/fibrinogen treatment reduced SYP and PSD-95 levels in OHC. However, in the presence of lecanemab, the Aβ42/fibrinogen-mediated reduction in PSD-95 and SYP was minimized. (J and K) Quantification of I. Data from four experiments. Changes in synaptic markers were not due to cell death as determined by propidium iodide staining. (L) B-Aβ42 was incubated in NHP to form complexes with fibrinogen. Lecanemab, aducanumab, buffer, or control IgG was added after 1 h. Western blot analysis of immunoprecipitation shows that lecanemab dissociated preformed Aβ42/fibrinogen complexes while aducanumab did not. (M) Quantification of I. Data from three independent experiments. (N) Western blotting shows treatment with preformed Aβ42/fibrinogen complexes reduced SYP and PSD-95 levels in OHC, but lecanemab mitigated this effect. (O and P) Quantification of SYP and PSD-95. Data from three independent experiments. Vehicle constitutes PBS+DMSO.

Comparisons among multiple groups were performed using one-way ANOVA followed by Newman-Keuls multiple comparison test. Data are presented as mean ± SEM. ****P < 0.0001, ***P < 0.001, **P < 0.01; ns, not significant.