Journal of Integrative Neuroscience

J. Integr. Neurosci. **2024**; 23(3): 57
https://doi.org/10.31083/j.jin2303057

Opinion

Translation from Preclinical Research to Clinical Trials: Brain–Gut Photobiomodulation Therapy for Alzheimer's Disease

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Academic Editors: Cecile Moro and Gernot Riedel
Submitted: 27 September 2023 Revised: 18 November 2023 Accepted: 29 November 2023 Published: 11 March 2024

Abstract

Recently, novel non-pharmacological interventions, such as photobiomodulation (PBM) therapy, have shown promise for the treatment of Alzheimer's disease (AD). This article outlines the translation from the preclinical to clinical stages of an innovative brain–gut PBM therapy in a mouse model of AD, a pilot clinical trial involving mild-to-moderate AD patients, and a continuing pivotal clinical trial with a similar patient population. In a mouse model of AD ($A\beta_{25-35}$), daily application of brain–gut PBM therapy to both the head and the abdomen produced a neuroprotective effect against the neurotoxic effects of an $A\beta_{25-35}$ peptide injection by normalizing all the modified behavioral and biochemical parameters. The pilot clinical trial to evaluate brain–gut PBM therapy demonstrated the tolerability and feasibility of the novel PBM-based treatment for mild-to-moderate AD patients. Compared to the sham patients, the PBM-treated patients had lower Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog) comprehension sub-scores, higher forward verbal spans, and lower Trail Making Test (TMT) Part B (TMT-B) execution times, which suggest an improvement in cognitive functions. This pilot study provided important information for the design of a novel pivotal clinical trial, currently in progress, to assess the efficacy of brain–gut PBM therapy in a larger sample of AD patients. This pivotal clinical trial could demonstrate that brain–gut PBM therapy is a safe, well-tolerated, and efficient disease-modifying treatment for mild-to-moderate AD patients and that it has medical and economic benefits.

Keywords: Alzheimer's disease; neuro degenerescence; memory; neuroinflammation; amyloid; phosphorylated tau; photobiomodulation; electromagnetic; magnetic; photonics; oxidative stress

1. Introduction

Alzheimer's disease (AD) is an irreversible neurodegenerative disease for which new therapeutic strategies are urgently needed [1]. In recent years, novel non-pharmacological interventions, such as transcranial photobiomodulation (PBM) therapy, transcranial magnetic stimulation, transcranial electromagnetic treatment, transcranial direct or alternating current stimulation, and deep brain stimulation, have been developed to treat neurological and psychiatric disorders, and these interventions have demonstrated potential for application in the treatment of AD [2–9]. PBM, a safe and non-invasive therapy that utilizes red or near-infrared (NIR) light to stimulate specific mitochondrial functions [10], has known benefits, including improved tissue healing, cell survival promotion, and reduction of inflammation and oxidative stress [11,12].

The assumption of various mechanisms in AD, such as mitochondrial dysfunction [13] or inflammatory processes [14], supports the use of transcranial PBM therapy that has been used in various clinical trials demonstrating improvement in cognitive performance in persons with mild cognitive impairment (MCI) [15], improvement in the quality of life and self-independence of patients with dementia [16], and better cognitive performance of patients diagnosed with mild-to-moderate AD [17]. Furthermore, there is increasing evidence that the brain–gut axis plays an important role in neurodegenerative diseases [18], and we investigated abdominal PBM stimulation in association with the classical transcranial application. To the best of our knowledge, this type of study has not been reported elsewhere.

This article describes the preclinical to clinical translation of an innovative technology based on brain–gut PBM therapy (REGEnLIFE RGn500, RGn530, and RGn600 devices) that combines photonic and magnetic emissions in a mouse model of AD, a pilot clinical trial, and an ongoing pivotal clinical trial involving mild-to-moderate AD patients.

2. Photobiomodulation Devices

The neuro-magneto-photonic treatment used in our studies combines PBM with a static magnetic field. Low static magnetic field (SMF) stimulation has shown promise

in animal models, and transcranial magnetic stimulation with a high magnetic field has been investigated as a non-invasive therapeutic tool to treat neurological and psychiatric diseases [9]. SMF stimulation is thought to induce a long-term change in the excitability and connectivity of the stimulated brain networks by modulating membrane excitability [19–21], and its application to human subjects is safe [22]. For those reasons, we decided to combine light with a magnetic field in our therapeutic devices.

The device used in our preclinical studies is the RGn500 device (REGEnLIFE, Paris, France), which provides tri-photonic stimulation using light sources in the red and NIR spectrums, including lasers and light-emitting diodes (LEDs). The device contains an NIR laser (λ = 850 nm) combined with an NIR LED (λ = 850 nm) and a red LED (λ = 625 nm), which is surrounded by a ring-shaped magnet to create a SMF at 200 mT. The photonic emissions are pulsed (50% duty cycle) through the SMF with a total irradiance of 28 mW/cm^2 and a total fluence of 8.4 J/cm^2 for a 10-minute exposure at the skin surface. As a result, the RGn device delivers PBM therapy with the addition of an SMF, in contrast to the more common PBM used up until now.

The medical device RGn530 has been used for brain–gut PBM therapy in clinical studies. As shown in Fig. 1, it consists of a modular helmet and an abdominal belt, each of which is includes NIR lasers (λ = 850 nm, power density = 21.36 mW/cm^2), NIR LEDs (λ = 850 nm, power density = 28.76 mW/cm^2), and red LEDs (λ = 660 nm, power density = 25.46 mW/cm^2), as well as a static magnetic field (magnetic flux density = 200 mT). The helmet has a total of 60 NIR lasers, 60 IR (infrared) LEDs, and 60 red LEDs. The abdominal belt has a total of 51 NIR lasers, 51 IR LEDs, and 51 red LEDs. All photonic emissions are pulsed at a 10 Hz frequency (50% duty cycle).

3. Preclinical Research

An initial preclinical study focused on a mouse model of AD, Aβ_{25-35}. Six-week-old male Swiss mice were anesthetized with isoflurane 2.5% and injected intracerebroventricularly (ICV) with Aβ_{25-35} peptide (9 nmol/mouse) or Scramble Aβ (Sc Aβ) peptide (9 nmol/mouse) [23].

A significant disruption in memory performance was observed eight days after the Aβ_{25-35} peptide injection. Spatial working memory deficits were deduced from the decrease in the percentage of alternation in the Y-maze test, which evaluates short-term and long-term contextual memory deficits in terms of shorter step-through and longer escape latency in the passive avoidance test. Furthermore, an elevation in oxidative stress (measured by lipid peroxidation levels) and inflammation (measured by the elevation in glial fibrillary protein and tumor necrosis factor and the activation of astrocytes and microglia) and the induction of apoptosis (measured by the levels of mitochondrial Bax [pro-apoptotic] and Bcl2 [anti-apoptotic] mitochondrial markers) were observed in hippocampal tissue analyzed 9 days after the peptide injection. Characteristic markers of AD for amyloid processing (Aβ_{1-42}) and hyperphosphorylation of tau protein (pTau-Thr181) were also significantly increased in the hippocampus.

Considering the possibility of an abscopal effect from such stimulation based on developing evidence of brain–gut interactions, the treatment was applied to two sites: the head and abdomen.

The mice were manually restrained by holding their bodies down, and the photonic emitters were applied 1 cm from the shaved skin of the head and/or center of the abdomen. Three applications were tested: the top of the head as a transcranial PBM through an SMF (1 cm^2 surface), the abdomen (1 cm^2 surface) as a transcutaneous PBM through an SMF, and both the head and abdomen (2 cm^2 surface) simultaneously. Treatments were applied once a day (o.d.) or twice a day (b.i.d.) for several durations (2.5 min, 5 min, 10 min, and 20 min) for 7 days after the Aβ_{25-35} injection.

Daily application of RGn500 to both the head (at a pulse frequency of 10 Hz) and the abdomen (at a pulse frequency of 1000 Hz) for 10 min produced a neuroprotective effect against the detrimental effects of the Aβ_{25-35} peptide injection, leading to normalization of all the modified behavioral and biochemical parameters [24]. RGn500 failed to yield a beneficial effect when the treatment was localized to only the head or abdomen.

A complementary study implementing a similar device, the preclinical RGn530, has made it possible to explore the role of gut microbiota dysbiosis in AD with this new biophotonic-based therapeutic strategy [25]. Aβ_{25-35} peptide-injected mice were treated with an RGn530 preclinical device (at a pulse frequency of 10 Hz) and characterized gut microbiota. The RGn530 preclinical device has almost the same technical specifications as the RGn500 preclinical device, with the exception of the red LED (λ = 660 nm). The treatment for the mice was applied for 6 minutes for 7 days after the injection of the Aβ_{25-35} peptide. The microbiota was characterized via 16SrRNA sequencing, and a cognitive and biological evaluation was performed. Cecal content was sampled from mice under RGn treatment in the groups with the best performances at the moment of sacrifice; the content was submitted to metagenomic analysis with the use of next-generation high-throughput sequencing of variable regions (V3–V4) of the 16S rDNA bacterial gene. The analysis showed that the Aβ_{25-35} peptide injection produced significant changes in the percentage of various phila, namely *Firmicutes, Bacteroidetes*, *Tenericutes*, and *Deferribacteres*, as compared to the Sc peptide-injected animals. Daily application of RGn530 to the head and abdomen reversed the decrease in *Firmicutes* and the increase in *Tenericutes* and *Bacteroidetes* and decreased the expression of *Deferribacteres* in control and Aβ_{25-35} animals.

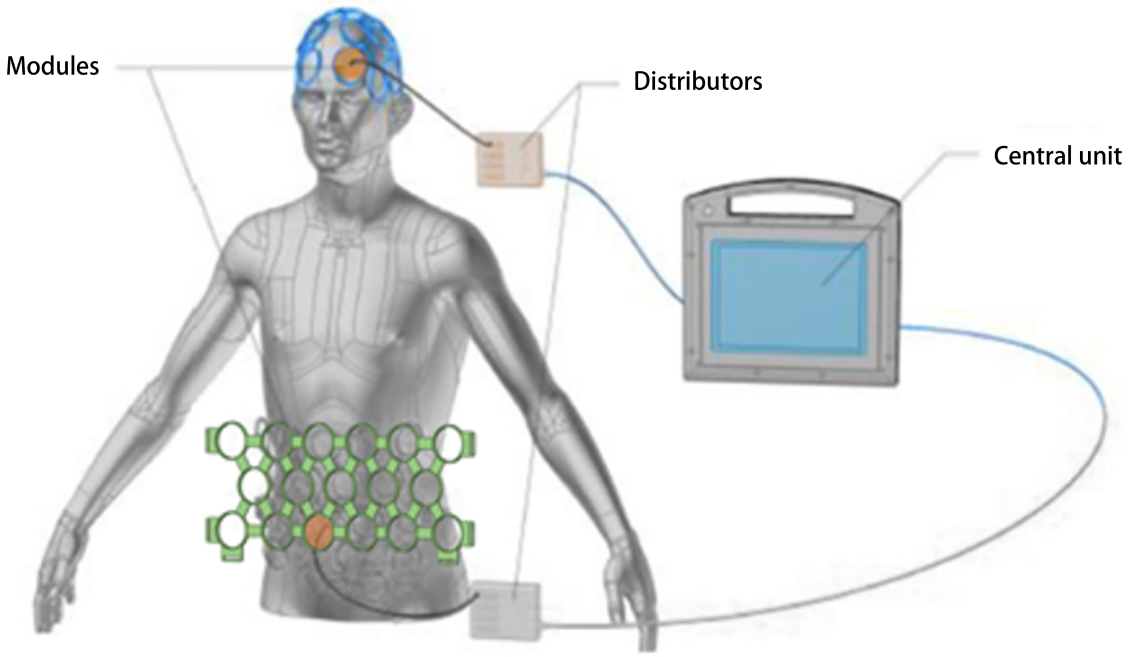

Fig. 1. Photobiomodulation (PBM) device. Main components of the PBM device (REGEnLIFE RGn530/RGn600), including the central unit, helmet, abdominal panel integrated modules, and two distributors that centralize the connections. Reprinted from Journal of Alzheimer's disease, Vol. 90. Guillaume Blivet, Aroaa Relano-Gines, Mélanieb Wachtel, Jacques Touchon. A Randomized, Double-Blind, and Sham-Controlled Trial of an Innovative Brain-Gut Photobiomodulation Therapy: Safety and Patient Compliance. Pages No. 811-822, Copyright (2022), with permission from IOS Press. The publication is available at IOS Press through https://www.iospress.com// [DOI:10.3233/JAD-220467].

4. Clinical Studies

4.1 Pilot Clinical Trial

A double-blind, randomized, mono-centered, sham-controlled pilot clinical trial [26] involving 53 individuals with mild-to-moderate AD was conducted. These patients were randomly assigned, with 27 in the brain–gut PBM group and 26 in the sham group. All participants underwent 40 treatment sessions, each lasting 25 minutes, over an 8-week period, followed by a 4-week observation period.

The brain–gut PBM therapy proved to be safe in regard to the number of recorded adverse events (AEs) (44% of the patients), which were balanced between the PBM and sham groups. The AEs were mainly mild, and no serious AEs were reported. The majority of the patients (92.5%) were highly compliant, which confirms the feasibility of the PBM treatment. Compared to the sham patients, after two months of treatment, the PBM-treated patients had lower Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog) comprehension sub-scores, higher forward verbal spans, and lower Trail Making Test (TMT) Part B (TMT-B) execution times, which suggest an improvement in cognitive functions measured at baseline that was still present two months after the end of the treatment.

4.2 Pivotal Clinical Trial

This first study provided important information for the design of the pivotal clinical trial that is currently ongoing to evaluate the cognitive benefits of the novel improved medical device RGn600 for brain–gut PBM therapy in a larger sample of AD patients [27]. The RGn600 is an improved version of the RGn530 medical device manufactured by REGEnLIFE and consists of a helmet and an abdominal belt that combine tri-photonic technology from red to near-infrared wavelengths from lasers, LEDs, and static magnetic stimulation.

In June 2023, a multicenter clinical trial, featuring a double-blind, randomized, sham-controlled pivotal clinical trial, commenced at Toulouse University Hospital. The study has enrolled a total of 108 individuals diagnosed with AD based on National Institute on Aging – Alzheimer's Associatio (NIA-AA) clinical criteria. These participants were randomly divided into a treatment group ($n = 54$) and a sham group ($n = 54$). These individuals will receive 84 treatment or sham sessions over a period of 26 weeks, each lasting 20 minutes, followed by a 26-week monitoring phase post-treatment.

The primary objective of this ongoing pivotal clinical trial is to assess the cognitive progression of patients following 26 weeks of brain–gut PBM therapy, as assessed by the ADAS-Cog global score. Secondary endpoints include the

investigation of neuropsychological functions, autonomy, overall clinical response, quality of life (AD and inflammation biomarkers), and an analysis of blood and fecal (microbiota) biomarkers, as well as the exploration of the medical and economic implications. In addition, the safety of this brain–gut PBM therapy will be rigorously evaluated.

The trial's initial patients visit occurred in July 2023, and analyses will be conducted across different sets, including the full-analysis set, per-protocol populations, and treated set.

5. Discussion and Summary

Improvement of memory performance and biochemical markers associated with AD were observed through brain-gut exposure to PBM therapy in the mouse Aβ_{25-35} model. These findings align with the reported effectiveness of PBM therapy in other studies, utilizing whole body exposure [28–30], abdominal exposure [30] or transcranial application [31–35] across diverse AD models in mice or rats. The effectiveness of PBM treatment can be evaluated by comparing the outcome to outcomes achieved with the use of daily treatments such as donepezil and other specific pharmacological substances in the same preclinical model [36]. The remarkable aspect of PBM treatment is its ability to normalize a comprehensive range of pathological factors examined in the model, encompassing memory function linked to oxidative stress, neuroinflammation, and apoptosis markers, as opposed to merely focusing on markers associated solely with amyloid or tau processes. This normalization observed in this preclinical research suggests that PBM therapy engages a multitude of mechanisms, a finding that is supported by various other studies [37]. Conversely, conventional pharmacological interventions typically operate via highly specific and limited mechanisms. Consequently, considering the complexity of the targeted pathology, it is reasonable to anticipate that the application of PBM may yield more favorable outcomes compared to a precise yet limited pharmacological treatment. Moreover, transcranial PBM has demonstrated its capacity to facilitate the implementation of novel nanotechnologies, nanomedecines and drug delivery systems. This breakthrough holds considerable promise for advancing therapeutic strategies in AD [38].

The modifications observed in bacterial abundance in the mouse Aβ_{25-35} model are similar to what has been described in patients with AD, with decreased *Firmicutes* and increased *Bacteroidetes* and *Tenericutes* [39,40], which highlights the role of the microbiome in regulating multiple neuro-chemical pathways through the highly interconnected host–microbiome system, the so-called gut–brain axis. Bacterial byproducts such as short-chain fatty acids (SCFAs) exert a number of neuromodulatory effects and act directly on gastrointestinal cells to stimulate the synthesis of hormones such as leptin and glucagon-like peptide (GLP) [41]. The gut microbiota produces a large amount of amyloid, lipopolysaccharide (LPS), and other toxins that contribute to systemic inflammation and disruption of physiological barriers. Bacterial amyloids may act as prion proteins by cross-seeding, misfolding, and enhancing native amyloid aggregation. Moreover, gut microbiota products may prime microglia, which exacerbate the inflammatory response in the central nervous system (CNS), which, in turn, results in pathologic microglial function, increased neurotoxicity, and impaired amyloid clearance. The capacity of the PBM treatment observed in this study to modify the intestinal microbiome aligns with results from other research groups [28,42,43]. More importantly, the observation that PBM normalizes dysbiosis produced by toxic peptide Aβ_{25-35} injections in our mouse model of AD suggests that it may be of therapeutic interest in the treatment of the pathology.

The initial pilot clinical study showcased the tolerability, acceptability, and practicality of the innovative PBM-centered treatment for individuals with mild-to-moderate AD. This safe and non-invasive therapeutic solution is a feasible and appealing alternative to conventional AD management approaches and, furthermore, has the advantage of potential administration within patients' homes.

The pivotal clinical trial is poised to demonstrate that REGEnLIFE's RGn600 brain–gut PBM therapy is a safe, well-tolerated, and effective disease-modifying treatment for mild-to-moderate AD patients. In addition, it is expected to demonstrate both medical and economic benefits [44].

Transcranial PBM therapy has recently emerged as a potential clinical treatment and cognitive enhancement method for various neurodegenerative pathologies, which could also increase the potential of pharmacological therapies. The association of abdominal application to transcranial PBM could provide optimal efficacy to the treatment of AD by mobilizing multiple mechanisms in synergy with clinical drug development.

Author Contributions

FJR and GB performed the literature searches, designed and wrote the paper, and contributed to the editorial changes in the manuscript. JD and JT contributed to its analysis, its critical review, and its final version approval. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

Guillaume Blivet is an employee of REGEnLIFE and owns equity. Jacques Touchon is a consultant for REGEnLIFE. François J. Roman is the director of FR Consulting. The authors declare no conflict of interest and the writing were not influenced by this relationship.

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