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EXPERT OPINION

Monophosphoryl lipid A is an lipopolysaccharide-derived Toll-like receptor 4 agonist which may improve Alzheimer's disease pathology

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Introduction: Alzheimer's disease (AD) is partly characterized by the formation of plaques composed of β-amyloid (Aβ) as a result of excessive accumulation of Aβ. Monophosphoryl lipid A (MPL) is a Toll-like receptor 4 agonist commonly used as a nontoxic, FDA-approved adjuvant in viral vaccines.
Areas covered: Previous reports had shown MPL as an effective adjuvant for Aβ vaccinations to decrease Aβ deposition. Recently, it was discovered that MPL monotherapy in APP/PS1 transgenic AD mice had beneficial effects, such as decreasing the number and size of deposits, decreasing soluble Aβ monomers and improving cognition through phagocytic activation of microglia. Unlike the parental endotoxin lipopolysaccharide (LPS), MPL stimulated microglial phagocytosis of Aβ, while only minimally increasing a proinflammatory response.
Expert opinion: MPL is a promising therapeutic option for AD treatment due to its ability to promote Aβ clearance without eliciting a strong adverse inflammatory response. Since MPL is already FDA-approved in humans, clinical application can be accelerated. Further analysis of how MPL affects other hallmarks of AD pathology such as dystrophic neurites and hyperphosphorylated tau aggregates, as well as its mechanism of action, will facilitate the understanding of the therapeutic benefits that MPL can produce.

Keywords: Abeta, adjuvant, Alzheimer's disease, β-amyloid, microglia, monophosphoryl lipid A, MPL, phagocytosis, TLR4, Toll-like receptors

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1. Introduction

Alzheimer's disease (AD) is a neurodegenerative dementia characterized by β-amyloid (Aβ) plaques and neurofibrillary tangles composed of the microtubule-associated protein tau [1]. Currently, the only FDA-approved medications for AD are cholinesterase inhibitors and memantine, both of which are considered to be only symptomatic and not disease-modifying in nature [2]. Disease-modifying drugs should target steps involved in the pathogenesis of the disease, such as tau hyperphosphorylation, increased levels of Aβ accumulation and the formation of pathogenic Aβ oligomers in AD, each representing targetable progressive changes [1,2]. Recently, it was found that the accumulation of Aβ in late-onset sporadic AD correlated with a decrease in the clearance of Aβ and not with an increased production [3]. Drugs that can stimulate the clearance of Aβ could, therefore, be of therapeutic significance. Having been pioneering attempts along this concept, clinical trials for an Aβ vaccine, AN1792, unfortunately ended prematurely due to development of T-lymphocyte meningoencephalitis in a small subset

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Article highlights.

- Increasing Aβ clearance is a potential therapeutic target for the treatment of AD.
- MPL is a nontoxic, FDA-approved adjuvant used in viral vaccines.
- MPL treatment in APP/PS1 transgenic AD mice decreased Aβ burden and restored cognition.
- The neuroprotective nature of MPL is likely due to its ability to stimulate microglial phagocytosis of Aβ without eliciting a strong proinflammatory response.
- It remains to be seen how MPL treatment can affect other markers of AD pathology, including neurofibrillary tangles.

This box summarizes key points contained in the article.

of patients [4]. Nonetheless, decreased Aβ burden in specific brain regions and lowered rates of cognitive decline were noticed in positive responders [4], suggesting that targeting the Aβ degradation/clearance pathway could still be a valid option for the treatment of AD.

Monophosphoryl lipid A (MPL) is a non-toxic Toll-like receptor 4 (TLR4) agonist that has been tested for over two decades as a safe adjuvant for vaccinations [5] and is currently FDA-approved for the formulation of a human papillomavirus vaccine [6]. As a derivative of lipopolysaccharide (LPS) found in the Gram-negative bacteria *Salmonella minnesota* [7], MPL is capable of facilitating an immune response similar to LPS but much less potently based on the effective concentration required [8]. A beneficial outcome has surprisingly emerged for AD, however, when MPL is used as a stand-alone therapy, as Michaud *et al.* recently reported [8], likely due to MPL's unique ability to preferentially stimulate TLR4-TRIF (Toll/IR-1R domain-containing adaptor inducing interferon over the proinflammatory MyD88 signaling pathway [9].

2. MPL as a potential therapeutic for AD

Two animal studies have demonstrated that MPL is a capable adjuvant for Aβ immunization. Chen *et al.* [10] demonstrated that in transgenic mice overexpressing amyloid precursor protein, immunization with $A\beta_{1-42}$ adjuvanted with MPL decreased the accumulation of brain Aβ by 60%. Although overall cognitive improvement (water maze test) was not demonstrable due to large variations in the immune response seen in the group, significant negative correlations were observed between Aβ levels and cognition and positive correlations between antibody titer and cognition [10]. Thus, in the successfully immunized animals, reduced Aβ levels appear to have led to improved cognitive function. Immunization of aged macaques with $A\beta_{1-42}$ and MPL was well tolerated with no apparent microglial activation and resulted in a shift in the size of Aβ oligomers toward smaller species [11]. Although the significance of the latter finding remains to be explored, the result suggests that Aβ antibodies induced by immunization can indeed affect Aβ's oligomeric and, consequently, pathogenic dynamics.

Recently, the effects of MPL on AD pathology were studied extensively by Michaud *et al.* [8]. Whereas previous studies used MPL as an adjuvant for Aβ immunization [10,11], Michaud *et al.* took a different approach by simply injecting MPL or LPS alone into 3-month-old APP/PS1 transgenic mice weekly for 12 consecutive weeks [8]. Although LPS had no effect on cognition (using a water T-maze) and even resulted in increased plaque load, MPL was able to decrease the number and size of plaques, decrease soluble Aβ monomers and improve cognition [8], all with less variability compared to when MPL was used as an adjuvant for Aβ vaccination [10,11].

What makes MPL uniquely effective, relative to LPS, in decreasing Aβ burden and improving cognition? Both MPL and LPS were able to acutely stimulate monocyte expansion and increase the ability of microglia and monocytes to phagocytose and internalize Aβ oligomers [8]. Unlike LPS, however, MPL did so without strongly and chronically inducing a proinflammatory response [8]. Compared to LPS, MPL induced weaker expression of proinflammatory cytokines in BV2 microglia and *in vivo* as well [8]. Consistently, MPL treatment in BV2 microglia did not stimulate the extracellular signal-regulated kinase or Jun N-terminal kinase pathways, which are associated with cytokine production, but did stimulate p38, which is associated with phagocytosis activity [8]. The ability of MPL to stimulate microglial phagocytosis without activating proinflammatory cytokines may thus explain why MPL can decrease plaque burden in APP/PS1 mice and improve cognitive function, since chronic inflammation has been shown to elevate Aβ deposition and thereby jeopardize the benefit of stimulated microglial clearance of Aβ [8].

3. Expert opinion

MPL has considerable therapeutic potential for the treatment of AD for a number of reasons. First, MPL is able to decrease the amount of soluble Aβ, an early stage in Aβ accumulation, in addition to decreasing plaque burden [8]. MPL administration also did not result in any form of chronic inflammatory response or immune tolerance, which would allow for prolonged and repeated treatments without causing toxicity or loss of efficacy [8]. The variability in the response to MPL in this study was considerably lower compared to those seen in response to coadministration of MPL with Aβ as a vaccination in previous studies, where only a subset of animals had detectable antibodies made against Aβ [10,11]. This suggests that well-regulated activation of TLR4 signaling surpasses the inconsistent efficacy of an Aβ vaccine therapy. Finally, as it already is an FDA-approved drug [6], MPL should have easier and more rapid translation into human clinical trial.

A number of additional studies will be required to understand the full scope of MPL's potential to modify the AD pathology. First, it remains to be seen if MPL alone is more potent at reducing Aβ burden and improving cognition

compared to MPL + Aβ, although the effects of MPL alone described by Michaud *et al.* [8] were more impressive than those from an earlier study done with MPL + Aβ (however, a different mouse model of AD was used [10]). It also remains to be explained how peripheral administration of MPL can affect brain Aβ levels, and if the clearance of other proteins are also affected, since this stimulation of microglial phagocytosis by MPL does not appear to be specific toward Aβ. Vascular amyloid and hemorrhaging, problems associated with earlier Aβ immunization approaches [4], should also be addressed. Additionally, the long-term effects of MPL on Aβ burden as well as other hallmarks of AD pathology, including dystrophic neurites and hyperphosphorylated tau aggregation, need to be further examined. The effects of MPL on tau are especially important since failed anti-Aβ strategies did not seem to modify tau neurofibrillary tangle pathology [12], the neuropathological marker more closely associated with cognitive decline [13]. Several studies have shown that microglial activation in mouse models of AD can clear plaques but actually enhance tau pathology [14], but early studies with MPL have yet to describe this phenomenon [8,10,11].

Previous setbacks in clinical trials targeting Aβ have cast considerable doubt on the amyloid cascade hypothesis of AD [2,4,15]. With the cost of drug development increasing prohibitively and with the spread of AD rising due to an aging demographic, finding new therapeutic uses for already FDA-approved drugs represents a cost-effective and time-efficient path leading to a new AD drug. Based on these published reports, MPL is a promising new therapeutic option for treating AD.

Declaration of interest

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