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REVIEW

Neuroinflammation as a Potential Therapeutic Target in Alzheimer's Disease

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Abstract: Although amyloid-β (Aβ) peptide accumulation is considered as a key early event in the pathogenesis of Alzheimer's disease (AD), the precise pathophysiology of this deadly illness remains unclear and no effective remedies capable of inhibiting disease progression have been discovered. In addition to deposition of extracellular Aβ plaques and intracellular neurofibrillary tangles, neuroinflammation has been identified as the third core characteristic crucial in the pathogenesis of AD. More and more evidence from laboratory and clinical studies have suggested that anti-inflammatory treatments could defer or prevent the occurrence of AD. In this review, we will discuss multifaceted evidence of neuroinflammation presented in AD and the newly emerged anti-inflammatory targets both in pre-clinical and clinical AD.

Keywords: Alzheimer's disease, neuroinflammation, disease-modifying therapy, anti-inflammatory treatment

Alzheimer's Disease and Its Current Treatment Status

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that represents the commonest cause of dementia in the elderly. Worldwide, approximately 47 million people are estimated to suffer from dementia of which most are affected with AD. The number of dementia patients are expected to double every 20 years, and thereby this number is anticipated to grow to 131.5 million in 2050.[1] As such, urgent development of diagnostic methods and intervention strategies effective early in the disease course is warranted.[2] Although amyloid-β (Aβ) peptide accumulation is considered to be a key early event in the pathogenesis of AD, the precise pathophysiology of this deadly illness remains unclear and no remedies capable of successfully inhibiting disease progression have been discovered.

Converging evidence from both genetically at-risk cohorts and clinically normal older individuals suggests that the pathogenesis of AD begins years before the clinical diagnosis of dementia is established. Over time, the definition of AD has changed from a traditionally symptom-based disease entity to a clinico-biological construct encompassing a 15–20 year preclinical phase, a 3–6 year prodromal period and a terminal dementia stage.[3] In 2018, the updated National Institute on Aging and the Alzheimer's Association (NIA-AA) AD research framework defined the illness according to the Amyloid/Tau/Neurodegeneration (AT(N)) classification system.[4] This symptom-agnostic classification scheme effectively evidences the biological state of AD utilizing relevant pathophysiological biomarkers.[5]

The AT(N) framework reflects the spatiotemporal evolution of the illness, postulating that Aβ deposition (A) is the earliest pathophysiological event that is followed by tau pathology (T) and, subsequently, neurodegeneration (N).[4] However, as AD is multifactorial and polygenic in nature, neuroinflammation, axonal degeneration, synaptic dysfunction and microvascular pathology are also considered to play critical roles in its pathogenesis and progression. Hampel et al recently expanded the AT(N) framework into an ATX(N) classification where X represents novel candidate biomarkers. Inflammatory biomarkers, for instance, may be utilized to create an ATI(N) framework.[5]

To date, no therapeutics capable of reversing or hindering the progression of AD have been described. Pharmaceuticals approved for use in AD management include cholinesterase inhibitors (donepezil, galantamine,

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rivastigmine) and non-competitive N-methyl-D-aspartate antagonists (memantine); these compounds can only temporarily alleviate symptoms already apparent in the dementia stage.[6] Although more than 99% of AD drug trials do not meet efficacy endpoints, the first Phase 3 clinical trial of sodium oligomannate (GV-971) was successfully completed in China.[7] This trial revealed GV-971 to possess significant efficacy in improving cognition and the compound was approved for treatment of mild-to-moderate AD.[8] A North American phase 3 trial is currently ongoing. Aducanumab, a fully human IgG1 recombinant monoclonal antibody directed against aggregated soluble and insoluble forms of Aβ, was co-developed by Biogen and Eisai under license from Neuroimmune for the treatment of AD and was approved on June 7, 2021 in the United States.[9] According to the prescribing information provided by the American Food and Drug Administration (FDA), treatment should be initiated in patients suffering mild cognitive impairment (MCI) or mild dementia stage.

The low success rate of potential AD drugs stems in large part from its complicated pathogenesis as well as an incomplete understanding of numerous pathologic pathways relevant to disease progression.[10] According to an analysis of the 2021 AD drug development pipeline by Cummings et al, therapeutics can be divided into symptomatic or disease-modifying therapies (DMTs).[2] As they target more diverse biological processes, DMTs are more frequently studied. Although Aβ and tau protein are major targets, inflammation, synaptic plasticity, neuroprotection, and bioenergetics are targets of most of the remaining agents currently in development. Anti-inflammatory compounds currently compose the largest percentage of DMTs in all phases of clinical trials.[2]

The Neuroinflammation in AD

In addition to deposition of extracellular Aβ plaques and intracellular neurofibrillary tangles, neuroinflammation has been identified as the third core characteristic crucial in the pathogenesis of AD.[11] Accumulating evidence suggests that neuroinflammation, as well as activation of microglial cells and astrocytes, plays an important role in AD pathogenesis.[12] Although whether or not inflammation itself is an initiator or consequence of the disease process, its importance in AD is undeniable.

Epidemiological Evidence of Neuroinflammation

Since the 1990s, several epidemiological and observational studies have indicated that exposure to nonsteroidal anti-inflammatory drugs (NSAIDs) protects against AD. The Baltimore Longitudinal Study of Aging revealed a 60% risk reduction among patients who used NSAIDs for more than 2 years and a 35% risk reduction among those who used NSAIDs for less than 2 years.[13] The Cache County Study similarly revealed a risk reduction of approximately 55% among patients who used NSAIDs for more than 2 years.[14] The Cardiovascular Health Cognition Study reported NSAIDs use to be associated with a lower risk of dementia and especially of AD (37% risk reduction).[15] The Rotterdam Study revealed a significantly decreased risk of AD among NSAIDs users of 2 or more years in duration (ie, 80% sparing).[16] The Multi-Institutional Research in Alzheimer's Genetic Epidemiology (MIRAGE) study revealed a risk reduction of 36% and protective effects of NSAIDs exposure to be more pronounced among APOE-Ɛ4 carriers.[17] The Canadian Study of Health and Aging showed that use of any NSAIDs was significantly associated with 26% sparing of AD.[18] Consistent data underscore that the greater the duration of NSAIDs exposure prior to clinical AD diagnosis, the greater the sparing effect. In 2018, Zhang et al summarized data from 16 cohort studies and revealed that NSAIDs use is moderately protective against AD as compared to control (19% risk reduction).[19]

Genetic Evidence of Neuroinflammation

Increasing evidence suggests that susceptibility to AD is determined by a complex interaction between environmental and genetic factors. Based on age of onset and heredity, AD is classified into early-onset (EOAD), late-onset (LOAD) and familial or sporadic AD. Furthermore, *APP, PSEN1* and *PSEN2* are well-known to be autosomal dominant familial AD genes.[20,21] However, monogenic AD is only a small portion (<5%) of cases with the vast majority of patients suffering sporadic or polygenic AD. Genes relevant to AD have been detailed using techniques such as genome-wide association studies (GWAS), whole exome sequencing and whole genome sequencing. More than 40 independent genomic loci have been identified, in which more than half of gene variants are implicated in innate immune and

microglial functions.[22] These include triggering receptor expressed on myeloid cells 2 (*TREM2*), cluster of differentiation 33 (*CD33*), complement component (3b/4b) receptor 1 (CR1), EPH receptor A1, bridging integrator 1 (BIN1) and the MS4A family.[21]

The R47H variant of TREM2 was found to be a risk factor for LOAD with an odds ratio of 4.5 based on GWAS data.[23] An immunoglobulin (Ig) superfamily receptor expressed on various cells of the myeloid lineage, TREM2 is exclusively expressed by microglia within the central nervous system, with higher expression in the hippocampus, spinal cord and white matter.[24] Functional TREM2 has been suggested to enhance the rate of phagocytosis of microglia, modulate relevant inflammatory signaling and control microglial cell proliferation and survival.[23] In AD brain, TREM2 expression is upregulated in the early stages of disease, possibly in an effort to clear Aβ and thus serving a protective effect; however, its expression may exert a pathogenic influence in the later stages of AD via over-activation of the inflammatory responses.[25]

Another top-ranked risk gene of LOAD identified using GWAS, CD33 has an effect size much smaller than that of APOE or TREM2 and belongs to the sialic acid-binding immunoglobulin-like lectins family (Siglecs).[26] In the brain, CD33 is exclusively expressed by microglia and infiltrating macrophages. Activation of CD33 results in phosphorylation of immunoreceptor tyrosine-based inhibition motifs (ITIM) that inhibit cellular functions such as phagocytosis. Single nucleotide polymorphisms of CD33 have been implicated in modulating AD susceptibility and the pathology of LOAD, with rs3865444 and rs12459419 being the main variants.[27–30] Expression of CD33 was observed to be increased with the rs3865444C allele, and was associated with an increased risk of AD. The minor A allele form of rs3865444 was found to be associated with a reduced risk of AD (overall odds ratio of 0.89).[31,32]

Biofluids Markers of Neuroinflammation

Many studies previously reported differences in cerebrospinal fluid (CSF) or peripheral blood inflammatory markers between AD patients and controls. The recent meta-analysis and systematic review of inflammatory markers in AD and MCI by Shen revealed increased peripheral levels of high-sensitivity C reactive protein, interleukin-6 (IL-6), soluble tumor necrosis factor receptor 1 (sTNFR1), soluble tumor necrosis factor receptor-2 (sTNFR2), alpha1-antichymotrypsin (α1-ACT), IL-1β, and soluble CD40 ligand; as well as increased CSF levels of IL-10, monocyte chemoattractant protein-1 (MCP-1), transforming growth factor-beta 1, soluble triggering receptor expressed on myeloid cells 2 (sTREM2), YKL-40, α1-ACT, nerve growth factor and visinin-like protein-1 (VILIP-1) in AD patients as compared with controls.[33] YKL-40, and the sTREM2 have proven to be the most promising candidate markers in relation to inflammation/astroglia activation in neurodegenerative dementias. And CSF YKL-40 is the best-established astrocytic biomarker.[34]

YKL-40, also known as chitinase-3-like protein-1 or human cartilage glycoprotein 39 (HC-gp39), is a glycoprotein expressed by several cell types including macrophages and vascular smooth muscle cells.[35] Immunohistochemical analysis of the human AD brain by Craig-Schapiro et al revealed YKL-40 labeled astrocytes near a subset of amyloid plaques, implicating YKL-40 involvement in the neuroinflammatory response to Aβ deposition.[36] A recent study on YKL-40 expression in human brain tissue identified a subset of astrocytes as the source of YKL-40 in AD as well as tauopathies such as frontotemporal dementia.[35] Similarly, CSF YKL-40 is considered to be a surrogate marker of neuroinflammation in AD.[37] Clinical cross-sectional studies have reported increased concentrations of CSF YKL-40 not only among patients suffering AD dementia but also among those in the preclinical and prodromal stages of this disease.[38] A longitudinal cohort study by Janelidze et al revealed CSF YKL-40 levels to be elevated during the preclinical, prodromal and dementia stages of AD in addition to concomitantly high levels of CSF t-tau and p-tau, particularly in Aβ-positive individuals.[39] These data thus highlight the value of YKL-40 as a potential neuroinflammatory biomarker for the diagnosis of AD.

Neuroimaging of Neuroinflammation

Increased microglial activation and reactive astrocytosis have been consistently reported in both rodent models of AD and AD patients. Recent advances in non-invasive imaging such as positron emission tomography (PET) have greatly facilitated study of inflammatory mechanisms in vivo at both pre-clinical and clinical stages of AD.[40]

One particular protein that has attracted great attention in elucidating neuroinflammation in vivo is the 18 kDa translocator protein TSPO.[41] This protein, formerly known as the peripheral-type benzodiazepine receptor or peripheral benzodiazepine binding site, is located on the outer mitochondrial membrane. Under physiological conditions, central nervous system TSPO expression is relatively low, but in response to inflammatory stimuli, its expression is strongly upregulated. Importantly, PET tracers have been used to not only elucidate the effect of neuroinflammation on CNS disorders but also to investigate the efficacy of novel anti-inflammatory treatments. Currently, TSPO PET imaging is the most widely used in vivo method for inferring microglial activation status. The most widely used first generation TSPO tracer, [^{11}C]-R-PK11195, was reported to be associated with Aβ accumulation in patients with MCI and AD as compared to healthy controls, thus correlating with deficits in functional network connectivity, grey matter atrophy and cognitive decline.[42–44]

Microglia-Mediated Synapse Dysfunction in the Early Stage of AD

Synapses are fundamental structures of neural circuits that transmit information between neurons, and the appropriate activation or inhibition of synapses are fundamental for the proper brain function. Synaptic dysfunction has been proved as an early event in AD, and synaptic loss (also known as synaptic pruning) is regarded having the best correlation with cognitive decline in its disease progress.[45] Hong et al have demonstrated that intracerebroventricular injections of oligomeric Aβ could induce synaptic engulfment by microglia in hippocampus of AD mice at 3 to 4 months of age, prior to plaque deposition. They further found that Aβ oligomers (oAβ) failed to induce synapse loss in complement protein C3 receptor (CR3) knock out mice as they did in wild-type mice, which suggests that CR3 is necessary for oAβ-dependent engulfment of synapses by microglia. Microglia eliminate synapses through the complement pathway.[46]

Therapeutic Targets of Neuroinflammation in Pre-Clinical AD

Tumor Necrosis Factor Alpha as a Therapeutic Target

Tumor necrosis factor alpha (TNF-α), released by microglia, is a major pro-inflammatory molecule implicated in the pathogenesis of AD.[47] It plays a dual role via its interaction with various receptors including the 55-kDa TNF receptor 1 (TNFR1) and the 75-kDa TNF receptor 2 (TNFR2).[48] Whereas TNFR1 predominantly mediates pro-inflammatory effects, TNFR2 is neuroprotective, exerting both immunoregulatory and neuroregenerative effects. The transmembrane form of TNF-α (tmTNF) activates both TNFR1 and TNFR2, while its soluble form (sTNF) mainly activates TNFR1.

Modulating pro-inflammatory effects induced by TNF/TNFR signaling can be achieved at the ligand or receptor level. Acute intracerebral delivery of the anti-TNF-α antibody infliximab (150 μg) to 12-month-old APP/PS1 mice induced a rapid and transient reduction in Aβ load and levels of tau phosphorylation.[49] Subcutaneous administration of the anti-TNF-α fusion protein etanercept (30 mg/kg) in an acute Aβ25–35-infused mouse model of AD resulted in improved cognitive outcome measures and reduced hippocampal TNF-α levels.[50]

Novel therapeutics aimed at more selective inhibition of sTNF/TNFR1 signaling or TNFR2 activation are in development. Dong et al evaluated the therapeutic potential of the TNFR2 agonist EHD2–scTNFR2 and the TNFR1 antagonistic antibody ATROSAB in a mouse model of NMDA-induced neurodegeneration.[51] Both EHD2–scTNFR2 and ATROSAB were found to reduce the regional extent of macrophage or microglial activation at the site of the lesion, protect cholinergic neurons and neocortical innervations against NMDA-induced excitotoxicity, as well as restore affected cholinergic memory function.

The brain-permeant biologic XPro1595, a second-generation TNF-α inhibitor, targets only sTNF. MacPherson et al found that peripheral administration of XPro1595 modifies neuroimmune cell profiles, decreases Aβ plaque load and rescues impaired long-term potentiation in 5×FAD mice.[52] Chronic intracranial infusion with XPro1595 was also noted to strongly suppress microglial activation in aged rats.[53]

Triggering Receptor Expressed on Myeloid Cells 2 (TREM2) as a Therapeutic Target

As discussed above, sTREM2 is considered to be a potential biomarker of neuroinflammation relevant to the pathogenesis of AD. Transgenic TREM2-deficient 5×FAD mice expressing the human R47H variant of TREM2 exhibited impaired microglial

activation and recruitment to Aβ plaque.[54] Soluble TREM2 (sTREM2) released from microglial membrane was found in plaques and neurons of 5×FAD mice with the common variant of TREM2, but not among animals with the R47H variant.

Direct stereotactic injection or adeno-associated virus-mediated transfection of recombinant sTREM2 protein revealed that sTREM2 reduces plaque load and rescues functional deficits of spatial memory and long-term potentiation. Importantly, sTREM2 enhances microglial proliferation, migration, and clustering in the vicinity of amyloid plaques, increases the uptake and degradation of Aβ and reduces amyloid deposition in a 7-month-old 5×FAD mouse model.[55] The researchers further studied the impact of sTREM2 administration on hippocampal synaptic plasticity by inducing long-term potentiation (LTP). The results showed that the LTP impairment of 5×FAD mice was ameliorated when acute hippocampal slices pre-incubated with sTREM2 protein as compared with the vehicle control. Taken together, these data indicate a protective role of sTREM2 against amyloid pathology and synaptic plasticity.[55] The relationship between TREM2 deletion and tau pathology seems similar to what is known in regards to amyloid pathology.[56]

A TREM2-agonizing antibody (AL002a) developed by Alector was found to activate TREM2 signaling in vitro and immune responses in vivo when injected intracranially or intraperitoneally.[57] Wang et al recently investigated the impact of an anti-human TREM2 agonistic monoclonal antibody (AL002c) in common variant (CV) knockout or the R47H variant knockout 5XFAD mice. They found that a single intraperitoneal injection of AL002c expanded unique sub-populations of metabolically active and proliferating microglia in both model mice, as assessed by single-cell RNA-seq (scRNA-seq). Microglia were more activated and proliferative in response to AL002c in R47H mice than CV mice. Prolonged administration of AL002c was found to reduce filamentous plaques, which consist of Aβ aggregates with little β-sheet conformation and branched amyloid fibrils that protrude into the brain parenchyma, causing severe axonal swelling, as well as neurite dystrophy, influence behavior and temper the microglial inflammatory response.[58] As such, AL002 remains a promising candidate for AD therapy.

CD33 as a Therapeutic Target

Using in vitro experiments, Griciuc et al found that the BV2 microglial cell line, previously found to efficiently take up and degrade exogenously added Aβ42, decreases Aβ42 uptake upon transfection with a WT-CD33 construct.[59] A significant reduction in insoluble Aβ42 levels and brain Aβ plaque burden of APPSwe/PS1ΔE9/CD33$^{-/-}$ mice in which the CD33 gene was knocked out was similarly noted. Intracerebroventricular injection of an adeno-associated virus vector-based system encoding an artificial microRNA targeting CD33 (miRCD33) into a APP/PS1 mouse model was found to reduce CD33 mRNA and TBS-soluble Aβ40 and Aβ42 levels in brain tissue.[59] Thus, CD33 is a promising novel target for drug development for AD.

Non-Steroidal Anti-Inflammatory Drugs

Several NSAIDs have been studied in AD mouse models with varied results. Lim and Yan reported that chronic orally administration of ibuprofen to Tg2576 mice overexpressing human amyloid precursor protein (APP) reduces total brain Aβ levels, plaque burden and neuroinflammation.[60,61] However, Jantzen et al did not find any reduction in Aβ burden after treating Tg2576 mice with the same regimen.[62] Indomethacin received in drinking water was found to significantly reduce hippocampal and cortical Aβ(1–40) and Aβ(1–42) levels.[63] Nimesulide and celecoxib, both selective COX-2 inhibitors, were tested in Tg2576/PS1 mice but found to not exert significant effects as compared with placebo in terms of Aβ load.[62,63] Another selective COX-2 inhibitor, MF-tricyclic, was shown to restore memory function in Tg2576 mice over-expressing APP and block Abeta-mediated inhibition of long-term plasticity.[64] Ettcheto et al recently evaluated the effects of dexibuprofen (DXI), the active enantiomer of ibuprofen, on the progression of AD in female APPswe/PS1dE9 (APP/PS1) mice.[65] Results revealed that chronic orally administration of DXI improves peripheral parameters associated with insulin resistance. More specifically, decreased neuroinflammation, activation of the non-amyloidogenic pathway and improved synaptic plasticity were found to be characteristic in the setting of long-term DXI administration. Most above studies did not test the behavioral changes except the one by Kotilinek et al.[64] In the study, the non-selective NSAIDs, ibuprofen and naproxen, and the selective COX-2 inhibitor, MF-tricyclic, all showed benefits of restoring memory function in Tg2576 mice over-expressing APP. These studies indicate that peripheral administration of certain NSAIDs, including ibuprofen, indomethacin, MF-tricyclic and dexibuprofen can significantly inhibit amyloid formation

and deposition. The exact mechanisms of NSAIDs administration on the process of AD pathogenesis remains unknown. It has been postulated that some NSAIDs target pathological hallmarks of AD by interacting with several pathways, including the inhibition of cyclooxygenases and activation of the peroxisome proliferator-activated receptor γ, and some can inhibit BACE1 gene transcription.[66]

Small Molecules Targeting Proinflammatory Cytokines

Over-production of proinflammatory cytokines has been implicated as a key contributor to the pathophysiology progression in AD, and several small molecules have been studies in AD animal models with positive neurologic outcomes.

p38 alpha mitogen activated protein kinase (MAPK) is a key contributor to microglia proinflammatory cytokine production in response to a variety of stressor stimuli, including $A\beta_{1\text{-}42}$.[67] MW01-2-069A-SRM(069A) is a CNS-penetrant, non-toxic, orally bioavailable, small molecule inhibitor of p38 alpha MAPK. Oral administration of the compound at a low dose resulted in attenuation of excessive proinflammatory cytokine production in the hippocampus back towards normal, as well as the resultant synaptic dysfunction and behavioral deficits in an AD mouse model.[68]

MW01-2-151SRM [2-(4-(4-methyl-6-phenylpyridazin-3-yl) piperazin-1-yl) pyrimidine] (also termed MW-151), an aqueous-soluble, small molecule, developed by Hu, showed significant efficacy in an AD-relevant mouse model of human Aβ-induced injury. A single, daily oral administration at a low dose (2.5 mg/kg) for 2 weeks can effectively suppress the Aβ-induced up-regulation of the proinflammatory cytokines interleukin-1β (IL-1β), TNFα) and S100B, reduce the activation of GFAP-positive astrocytes and F4/80-positive microglia, with resultant attenuation of the loss of synaptic marker proteins (eg, synaptophysin and PSD-95) and cognitive deficits.[69] The benefit was latter approved by Bachstetter AD's study, which showed that MW-151 treatment attenuated the increase of microglial and astrocyte activation and proinflammatory cytokine production in the cortex and yielded improvement of synaptic plasticity at early stage of AD mouse model.[70]

Clinical Anti-Inflammatory AD Treatment Strategies

Although amyloid and tau protein remain important therapeutic targets, inflammation is rapidly attracting increased attention in both preclinical and clinical researches.

TNF-α Inhibition

A next-generation TNF inhibitor, XPro1595 readily neutralizes soluble sTNF without affecting tmTNF or TNF receptors.[71] Inmune Bio, Inc. recently announced the preliminary results of a 12-week, open-label phase 1b study of XPro1595 (weekly injections of 0.03, 1.0 or 3.0 mg/kg) in mild-to-moderate AD patients (NCT03943264); findings revealed a 40.6% reduction in arcuate fasciculus inflammation. The arcuate fasciculus is a major white matter anterior/posterior tract containing long and short fibers that connects the frontal, parietal and temporal lobes and is important for language and short-term memory. While CSF p-tau181 (tau phosphorylated at threonine 181, pT181) is an established biomarker of AD, reflecting abnormal tau metabolism in the brain. A recent study by Janelidze et al suggests that pT217 has higher discriminative accuracy for AD and a stronger correlation with amyloidosis and cognitive decline.[72] In this study, patients treated with XPro1595 exhibited reduced neurodegeneration as determined by a decrease in CSF pT217. In addition, XPro1595 was found to improve the white matter MRI metrics, including a 16% improvement in radial diffusivity, a biomarker of remyelination, and increase white matter volume after 3 months of treatment. A XPro1595 Phase II study for patients suffering mild AD with neuroinflammation and patients carrying the APOE4 allele suffering MCI is being planned.

TREM2 as a Therapeutic Target

Phase I study (INVOKE) data for the safety and tolerability of AL002 revealed it to generally be safe and well tolerated by healthy adults. Furthermore, levels of CSF sTREM2 and soluble CSF-1R prior to and 48 hours after intravenous infusion of AL002 revealed a dose-dependent decrease of sTREM2 and an increase in soluble colony stimulating factor 1 receptor levels after administration of a single dose. Due to its promise as an AD therapy, a Phase 2 randomized, double-

blind placebo-controlled study evaluating the efficacy and safety of intravenous AL002 administration in patients suffering early AD is currently ongoing (INVOKE-2; NCT04592874).

CD 33 as a Therapeutic Target

AL003 is an antibody, which targets sialic acid binding Ig-like lectin 3 (SIGLEC 3, also known as CD33). In 2019, the INTERCEPT study (NCT03822208), a phase I trial evaluating the safety, tolerability, pharmacokinetics, pharmacodynamics and immunogenicity of AL003 in both healthy controls and patients suffering mild-to-moderate AD was initiated. To date, no results have been reported.

Nonsteroidal Anti-Inflammatory Drugs

Epidemiological and observational studies have revealed that NSAIDs use significantly reduce the risk of developing AD. However, results of clinical double-blind, randomized, placebo-controlled NSAID trials evaluating celecoxib, ibuprofen, naproxen, rofecoxib and tarenflurbil in mild-to-moderate AD patients yielded negative results.[73] The initial period of NSAID use seems to be an important determinant of disease outcome. These results also suggest that inflammatory responses present at the early pathophysiological process of AD, even is one of initiators of the disease.

In 2015, ALZT-OP1, a combination of the inhaled mast cell stabilizer cromolyn (ALZT-OP1a) and oral ibuprofen (ALZT-OP1b), was investigated as a treatment for early AD in a Phase III clinical trial (COG-NITE; NCT02547818). A randomized phase I/II study of ALZT-OP1 combination therapy in AD and normal healthy volunteers (NCT04570644) was likewise completed; study results, however, have not been published to date.

Other Clinical Anti-Inflammatory Treatment Strategies for AD

Neural insulin resistance likely plays an important role in the pathogenesis of AD. As such, NE3107 (17α-ethynyl-androst-5-ene-3β,7β,17β-triol; formerly known as HE3286), an oral small molecule and blood–brain barrier-permeable anti-inflammatory insulin sensitizer, was found to increase insulin sensitivity, decrease postprandial glucose levels, normalize HbA1c and restore metabolic homeostasis in obese type 2 diabetes patients. A Phase III, double blind, randomized, placebo-controlled multicenter study of NE3107 in mild-to-moderate AD subjects is currently ongoing (NCT04669028).[74]

Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) is a family of redox-sensitive transcriptional factors; their activation influences the pathophysiological inflammatory processes relevant to AD as well as amyloidogenesis. Many polyphenols including curcumin, resveratrol, pterostilbene, punicalagin, macranthoin G, salidroside, 4-O-methylhonokiol, and several alkaloids such as galantamine, glaucocalyxin B, tetrandrine, berberine, oridonin and anatabine have been shown to be potent NF-κB inhibitors in AD models and thus possess significant anti-inflammatory effects.[75] The first published randomized, double blind, placebo-controlled study of curcumin in AD patients was conducted in Hong Kong (NCT00164749). There were no differences in MMSE scores or blood biomarkers among groups after 6 months treatments.[76] In another 24-week phase II randomized, double blind, placebo-controlled study, Curcumin 3 Complex® (Curcumin, bisdemethoxycurcumin, and demethoxycurcumin mixture) was applied to mild-to-moderate AD (NCT00099710).[77] The results showed no differences between treatment groups in clinical or biomarker efficacy measures. The negative results may due to its low bioavailability and selection of AD subjects at an advanced stage. The phase 2 clinical trial (NCT01383161) which was designed to determine the effects of the curcumin supplement on age-related mild cognitive impairment after 18 months' treatment, has been completed. They found that daily oral Theracurmin (containing 90 mg of curcumin) twice daily led to improved memory and attention. The FDDNP-PET findings suggest that symptom benefits are associated with decreases in amyloid and tau accumulation in brain regions modulating mood and memory.[78] A phase II study involving curcumin and yoga therapy evaluating veterans at risk for AD is currently ongoing (NCT01811381).

Future Prospects of Targeting Inflammation in the Setting of AD

Available epidemiological, genomic, bioinformatic and neuroimaging data provide sufficient evidence confirming that neuroinflammation plays a critical role in the pathogenesis and progression of AD. Targeting of neuroinflammation is

potentially an extremely effective strategy for AD prevention and therapy during the preclinical stage prior to the occurrence of significant neuronal loss. Several phase I/II clinical trials evaluating the targeting of TNF-α, TREM2 or CD33 have shown promising results. As reported data remain controversial, and most of the AD clinical trials—including those investigating anti-inflammatory compounds failed, longitudinal studies enrolling large cohorts of participants with accurate clinical and biomarker-based characterizations are needed to identify potentially effective anti-inflammatory targets and drugs relevant to AD therapy. Therefore, multimodal biomarkers-drug codevelopment pipelines are strongly recommended for future clinical trials. Moreover, developing effective quantitative techniques for biomarker detection are urgent for disease progress monitoring and treatment evaluation, such as the Mass Synaptometry for single synapse analysis,[79] the TSPO-PET imaging for microglial activation.[41]

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Disclosure

The authors report no conflicts of interest in relation to this work.

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