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A review on neurodegenerative disease: The race to develop disease modifying drugs for Alzheimer's and Parkinson's

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Abstract
Neurodegenerative disorders represent a heterogeneous group of chronic and progressively debilitating conditions that result from the gradual loss of structure and function of neurons in the central nervous system (CNS). This deterioration leads to irreversible impairments in cognition, motor control, and other vital neurological processes, frequently culminating in profound disability or death. Prominent examples include Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease, and Amyotrophic Lateral Sclerosis (ALS). Despite their clinical differences AD being primarily associated with memory decline and executive dysfunction, while PD is characterized by bradykinesia, tremors, and rigidity both share common pathological mechanisms. These include chronic neuroinflammation, mitochondrial dysfunction, oxidative stress due to reactive oxygen species imbalance, and abnormal protein misfolding or aggregation (such as amyloid-β, tau, and α-synuclein). Current therapeutic strategies are largely palliative, focusing on symptomatic relief rather than halting disease progression. In AD, treatment typically involves acetylcholinesterase inhibitors (e.g., Donepezil, Galantamine) or N-methyl-D-aspartate (NMDA) receptor antagonists (Memantine), with newer interventions such as anti-amyloid monoclonal antibodies (Aducanumab, Lecanemab) being investigated to reduce amyloid plaque burden. In PD, dopamine replacement therapy with Levodopa and dopamine receptor agonists like Pramipexole and Ropinirole remain the cornerstone of management, though they do not prevent ongoing dopaminergic neuronal degeneration. Increasing evidence highlights the role of the innate immune system, particularly microglial over activation, in driving disease progression through persistent release of pro-inflammatory cytokines including tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6). This has stimulated growing interest in the potential repurposing of Disease-Modifying Anti-Rheumatic Drugs (DMARDs), traditionally used for autoimmune conditions such as rheumatoid arthritis, as possible disease-modifying therapies. Such a shift from purely symptomatic management to immunomodulatory and neuroprotective strategies marks an emerging and promising avenue for the treatment of AD, PD, and other neurodegenerative conditions.

Keywords: Alzheimer's disease, amylotrophic lateral sclerosis, tumor necrosis factor, oxidative stress, protein aggregation

Introduction
Neurons, once terminally differentiated, possess very limited regenerative potential, which makes the central nervous system (CNS) highly susceptible to progressive and irreversible damage. The onset of neurodegenerative disorders is driven by a complex interaction of genetic factors, environmental influences, and biochemical imbalances, eventually leading to the structural and functional decline of neuronal networks. Among these disorders, Alzheimer's disease (AD) stands out as one of the most prevalent and therapeutically challenging conditions, with its global burden expected to rise substantially in the coming years. At present, pharmacological options approved by the U.S. Food and Drug Administration (FDA), such as acetylcholinesterase inhibitors and the N-methyl-D-aspartate (NMDA) receptor antagonist memantine, primarily offer symptomatic benefits without effectively halting disease progression. The characteristic pathological features of AD include the extracellular buildup of amyloid-β (Aβ) plaques and the intracellular accumulation of hyperphosphorylated tau protein forming neurofibrillary tangles. Although these abnormalities are well documented, their exact contribution to disease causation is still under debate. Increasingly, research focus has shifted toward disease-modifying approaches aimed at targeting upstream pathological mechanisms, such as persistent neuroinflammation, oxidative stress resulting from reactive oxygen species imbalance, disrupted metal ion regulation, and altered cholesterol metabolism. Recent research has highlighted the contribution of various

intracellular signaling pathways to the development of Alzheimer's disease (AD), with special attention given to the Janus kinase 2/signal transducer and activator of transcription 3 (JAK2/STAT3) axis.Experimental models have demonstrated heightened JAK2/STAT3 activity in the hippocampal region, contributing to disease progression through modulation of astrocytic function, even in the absence of overt Aβ or tau pathology [1-3].

Parkinson's disease (PD) is a long-term, progressive neurodegenerative condition marked predominantly by the selective loss of dopaminergic neurons within the substantia nigra pars compacta, a key midbrain region essential for dopamine production.Dopamine depletion disrupts the finely tuned circuitry of the (a group of nuclei in subcortical region) basal ganglia, resulting in abnormal neuronal firing patterns, pathologically increased synchrony, and aberrant oscillatory activity within interconnected regions such as the thalamus and cerebral cortex. These pathophysiological changes impair both motor control and cognitive processing. Clinically, Parkinson's disease (PD) is characterized by a constellation of motor symptoms, most notably resting tremor, cogwheel rigidity, bradykinesia, and postural instability, all of which arise from disrupted nigrostriatal dopaminergic signaling within the basal ganglia circuitry. Beyond motor impairment, PD is increasingly recognized as a multisystem disorder with diverse non-motor manifestations, including affective disturbances such as depression and anxiety, circadian and sleep-wake abnormalities, autonomic dysfunction, olfactory deficits, and progressive cognitive impairment that may evolve into Parkinson's disease dementia (PDD).The pathological hallmark of Parkinson's disease involves the intracellular accumulation of Lewy bodies, which predominantly consist of aggregated and misfolded α-synuclein fibrils, leading to synaptic dysfunction, mitochondrial impairment, and progressive neuronal toxicity.In addition to proteinopathy, several convergent pathogenic mechanisms have been implicated, including sustained microglial-mediated neuroinflammation, mitochondrial respiratory chain deficits excessive oxidative and nitrosative stress, coupled with dysfunction of the ubiquitin-proteasome degradation machinery and impaired autophagic-lysosomal clearance, collectively contribute to α-synuclein aggregation, mitochondrial dysfunction, and subsequent dopaminergic neuronal vulnerability in Parkinson's disease [4-6]. These mechanisms are now recognized as central to both familial and sporadic forms of PD.

Several key mechanisms contribute to this process

Abnormal Protein Aggregation in Neurodegenerative Disorders

Protein aggregation is a fundamental pathological process implicated in a wide spectrum of neurodegenerative diseases. It refers to the aberrant folding of specific proteins, leading to their self-association into insoluble aggregates that accumulate intra- or extracellularly, thereby disrupting neuronal homeostasis and promoting neurodegeneration. Under physiological conditions, proteins adopt precise three-dimensional conformations to execute their biological functions; however, genetic mutations, imbalance between reactive oxygen species and antioxidants, and age-related cellular changes can destabilize protein structure, exposing hydrophobic domains that predispose them to abnormal intermolecular interactions [7].

Misfolded proteins not only lose their native physiological functionality but also accumulate as neurotoxic aggregates that overwhelm the brain's proteostasis network, particularly the autophagy-lysosomal pathway and the ubiquitin-proteasome system, both of which are essential for protein quality control. Failure of these clearance mechanisms facilitates the persistence of pathogenic protein inclusions, which are characteristic of major neurodegenerative diseases: amyloid-β (Aβ) plaques in Alzheimer's disease (AD), α-synuclein-rich Lewy bodies in Parkinson's disease (PD), mutant huntingtin aggregates in Huntington's disease (HD), and inclusions containing TAR DNA-binding protein 43 (TDP-43) or misfolded superoxide dismutase 1 (SOD1) in amyotrophic lateral sclerosis (ALS) [7].

Mechanisms of neuronal damage mediated by protein aggregation can be outlined as follows:

- **ProteinMisfolding:** Genetic defects, oxidative insults, or the biochemical effects of aging can induce aberrant protein conformations. Misfolded proteins expose hydrophobic regions that abnormally interact, enhancing their aggregation propensity [7].
- **Formation of Toxic Oligomers:** Initially, misfolded monomers associate into soluble oligomers microscopically undetectable but highly neurotoxic. Oligomers are now recognized as more deleterious than late-stage fibrillar deposits, as they disrupt membrane integrity and synaptic signaling [7].
- **Accumulation into Larger Aggregates:** Progressive oligomerization results in the formation of insoluble inclusions, such as amyloid plaques in AD or Lewy bodies in PD. Inefficient clearance due to impaired proteostasis amplifies aggregate burden, initiating microglial activation, sustained neuroinflammation, and neuronal injury [7-9].
- **Interference with Neuronal Functions:** Synaptic Dysfunction:Protein aggregates impair neurotransmitter release, receptor function, and synaptic plasticity, thereby disrupting neuronal communication [8].
- Mitochondrial Dysfunction:Damaged mitochondria lead to reduced ATP production, imbalance between reactive oxygen species and antioxidants, and impaired calcium buffering. The resultant energy crisis compromises neuronal firing and accelerates oxidative injury to proteins, lipids, and nucleic acids. Dysfunctional mitochondria may release cytochrome c, triggering apoptotic cascades, or contribute to necrotic cell death with associated neuroinflammation [7-9].
- Protein Clearance Failure:Deficits in autophagic flux or ubiquitin-proteasome function exacerbate aggregate accumulation [8].
- Endoplasmic Reticulum (ER) Stress:Misfolded proteins burden the ER, impairing protein synthesis and folding capacity, further aggravating cellular dysfunction [8]. Persistent Neuroinflammation:Chronic activation of microglia and astrocytes results in the sustained release of pro-inflammatory mediators, aggravating neuronal injury [15].
- **Progressive Neuronal Loss:** The cumulative effects of synaptic impairment, metabolic collapse, proteostatic failure, and excitotoxicity ultimately culminate in neuronal death via apoptosis or necrosis, contributing to

cortical and subcortical atrophy. Clinically, this manifests as progressive deficits in cognition, memory, and motor function [8-11].

- **Excitotoxic Damage:**Overactivation of glutamatergic receptors, especially N-methyl-D-aspartate (NMDA) receptors, leads to pathological calcium influx into neurons, triggering excitotoxic cascades characterized by mitochondrial dysfunction, oxidative stress, activation of calcium-dependent proteases, and ultimately apoptotic or necrotic cell death. Elevated intracellular calcium activates proteases and phospholipases, damaging cellular membranes, cytoskeletal proteins, and nucleic acids. This process exacerbates mitochondrial dysfunction, promotes imbalance between reactive oxygen species and antioxidants, and accelerates neurodegeneration [12-14].
- **Chronic Inflammation:** Persistent glial activation drives the production of cytokines such as TNF-α, IL-1β, and IL-6, which perpetuate neuronal injury and contribute to disease progression [15].

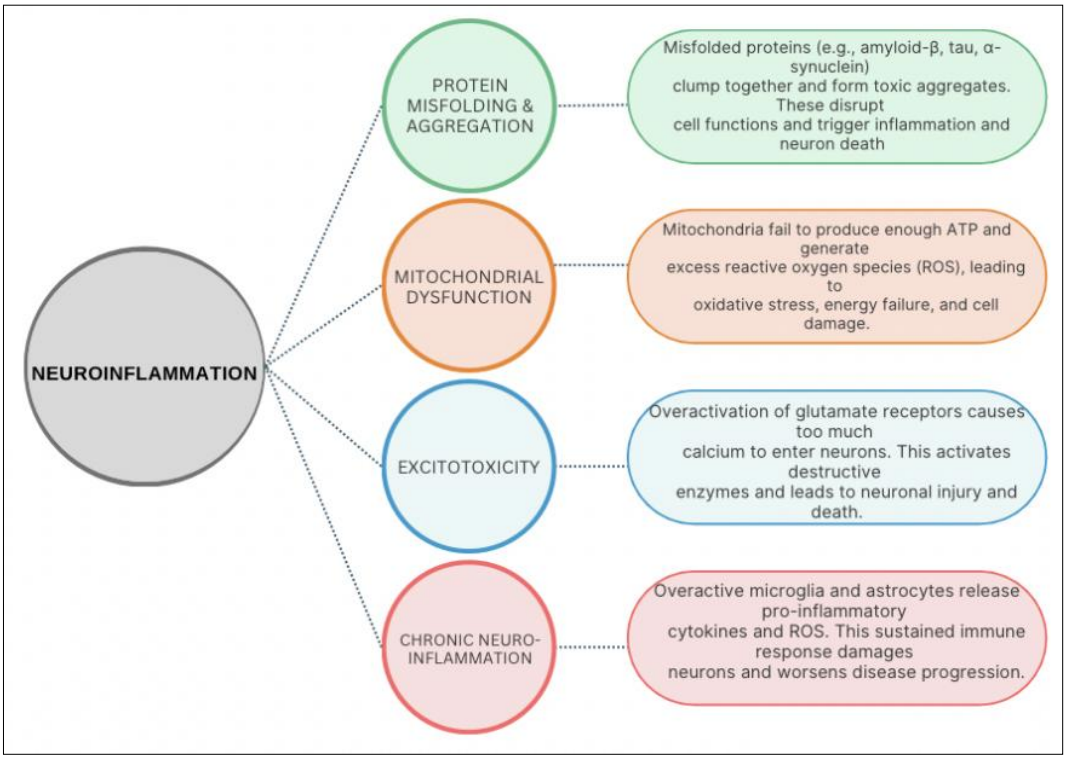

Fig 1: Pathways leading to neuronal damage

Pioneering Novel Therapeutic Strategies: Emerging Potential of Disease-Modifying Anti-Rheumatic Drugs (DMARDs) in the Management of Alzheimer's and Parkinson's Disease.

Disease-Modifying Anti-Rheumatic Drugs (DMARDs) have traditionally served as the cornerstone in managing autoimmune disorders such as rheumatoid arthritis, primarily by modulating immune responses and attenuating inflammatory cascades mentioned in figure 1. Their core pharmacological actions include suppression of aberrant immune signaling, downregulation of pro-inflammatory cytokines, and preservation of organ function. Intriguingly, mounting evidence implicates neuroinflammation not merely as a downstream consequence but as an active driver of neuronal injury in major neurodegenerative disorders such as Alzheimer's disease (AD) and Parkinson's disease (PD). This paradigm shift has sparked interest in repositioning DMARDs as potential neuroprotective agents.

Mechanistic Insights into Neuroimmune Modulation: A central pathological hallmark of neurodegeneration is the chronic overactivation of microglia, the innate immune sentinels of the central nervous system. Under physiological conditions, microglia maintain tissue homeostasis and support neuronal integrity. However, in response to pathological triggers such as misfolded protein aggregates (amyloid-β, α-synuclein), redox imbalance, or persistent inflammatory signaling quiescent microglia (M0) undergo phenotypic polarization.

M1 Phenotype (Pro-inflammatory): This state is characterized by excessive production of pro-inflammatory cytokines (e.g., TNF-α, IL-1β), chemokines, and reactive oxygen/nitrogen species, leading to oxidative stress, synaptic dysfunction, and progressive neuronal injury.

M2 Phenotype (Anti-inflammatory/Neuroprotective): This reparative state involves the secretion of anti-inflammatory mediators (e.g., IL-10, TGF-β) and neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and insulin-like growth factor-1 (IGF-1), which facilitate synaptic plasticity, neuronal survival, and tissue repair.In the context of chronic neurodegeneration, prolonged exposure to inflammatory cytokines like IL-1β and TNF-α skews microglial activity toward a sustained M1-dominant phenotype. This maladaptive polarization impairs amyloid-β clearance, amplifies neuroinflammatory cascades, and accelerates neuronal degeneration. The therapeutic rationale behind employing Disease-Modifying Anti-Rheumatic Drugs (DMARDs) in Alzheimer's and Parkinson's disease lies in

their potential to modulate neuroimmune responses reorienting microglia toward the M2 phenotype, thereby attenuating neurotoxicity while enhancing endogenous repair mechanisms.

Anakinra: A Biologic DMARD in Neuroinflammation: Anakinra, a recombinant form of the human interleukin-1 receptor antagonist (IL-1Ra), serves as a prototypical immunomodulatory agent by competitively blocking the interaction of pro-inflammatory cytokines IL-1α and IL-1β with the interleukin-1 type I receptor (IL-1R1), thereby attenuating downstream signaling cascades such as NF-κB and MAPK that drive neuroinflammation.In AD pathology, IL-1β levels are markedly elevated in amyloid plaque-rich regions, activating microglia and astrocytes, which in turn release TNF-α and IL-6. This cascade exacerbates imbalance between reactive oxygen species and antioxidants, drives tau phosphorylation, and promotes amyloidogenic processing of APP via β-secretase (BACE1). By intercepting IL-1β signaling, Anakinra attenuates inflammatory amplification loops, facilitates the M1→M2 microglial shift, and may restore amyloid-clearing capacity thereby safeguarding neuronal integrity.

Additional Neuroprotective Mechanisms of DMARDs: Beyond cytokine blockade, DMARDs influence other neurodegenerative pathways mentioned in figure 2 and 3:

- **Protein Homeostasis Restoration:** By dampening neuroinflammation, they may normalize proteasome and lysosome activity, enhancing clearance of misfolded proteins.
- **Immune Modulation:** Regulation of T-cell activity and peripheral immune infiltration into the CNS microenvironment.
- **Mitochondrial Protection:** Reduction of imbalance between reactive oxygen species and antioxidants and prevention of mitochondrial dysfunction, preserving neuronal energy homeostasis.

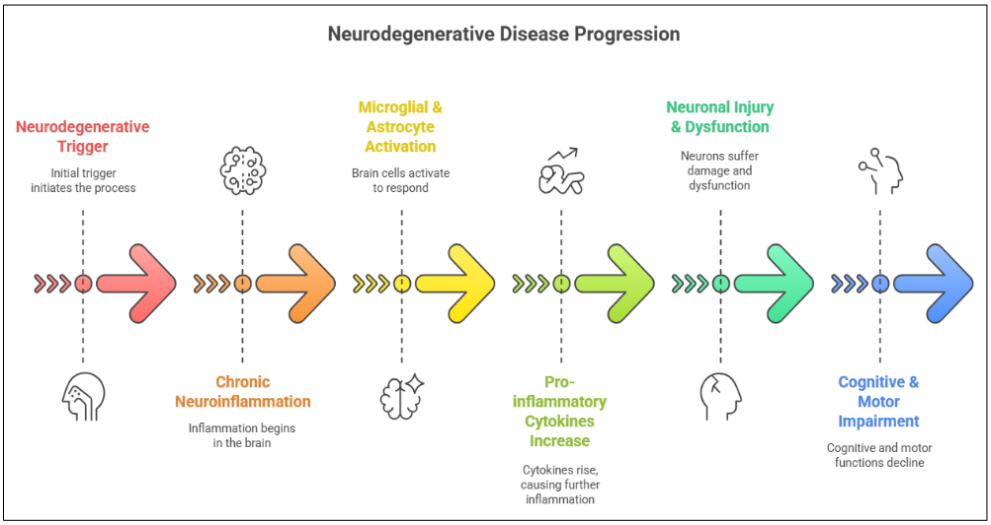

Fig 2: Pathophysiological Framework

DMARD Intervention Points

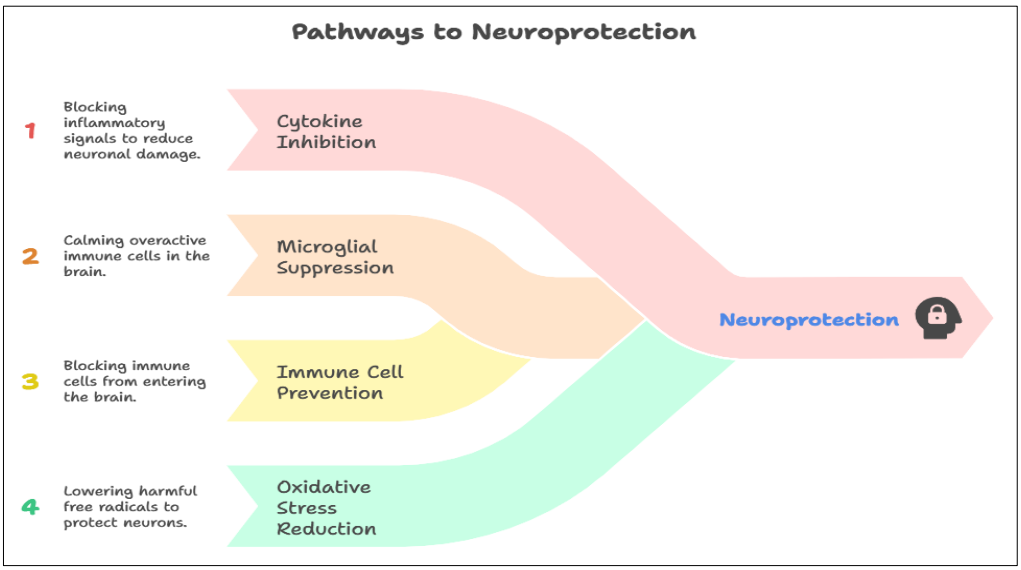

Fig 3: Pathway to Neuroprotection

Therapeutic Outcome: ↓ Inflammation, ↑ Neuronal Survival, Slower Disease Progression

Examples of DMARDs with Neuroprotective Potential

Minocycline: Minocycline, a second-generation semisynthetic tetracycline antibiotic, has garnered significant attention for its dual anti-inflammatory and neuroprotective properties, extending its therapeutic relevance beyond infectious diseases into the domain of neurodegenerative disorders. A hallmark feature of neurodegeneration is the chronic overactivation of microglia, leading to sustained neuroinflammation, imbalance between reactive oxygen species and antioxidants, and progressive neuronal injury. Minocycline exerts its neuroprotective efficacy primarily by inhibiting key intracellular signaling cascades such as the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and mitogen-activated protein kinase (MAPK) pathways critical mediators of microglial activation.

By attenuating these signaling routes, Minocycline impedes the phenotypic shift of microglia from the resting M0 state to the pro-inflammatory M1 phenotype, thereby reducing the excessive production of neurotoxic mediators including nitric oxide (NO), inducible nitric oxide synthase (iNOS), and pro-inflammatory chemokines. Furthermore, suppression of NF-κB-driven transcription of pro-inflammatory genes mitigates cytokine-mediated neuronal apoptosis. Importantly, Minocycline demonstrates an inherent ability to penetrate the blood-brain barrier (BBB), a pharmacokinetic attribute that enhances its potential utility in Alzheimer's disease, Parkinson's disease, and other neurodegenerative pathologies. These combined immunomodulatory and barrier-penetrating properties position Minocycline as a compelling candidate for therapeutic intervention in CNS disorders characterized by aberrant microglial activation [18-20].

Low-Dose Methotrexate: Methotrexate, traditionally recognized as a cornerstone disease-modifying antirheumatic drug (DMARD) in rheumatoid arthritis, has shown promise as a neuroinflammation modulator when administered at low doses. At sub-immunosuppressive concentrations, Methotrexate effectively attenuates microglial activation and curtails the release of pro-inflammatory cytokines without inducing profound systemic immunosuppression. Its mechanism of action encompasses modulation of T-cell activity, dampening inflammatory cascades, and elevating adenosine concentrations a neuromodulator with both neuroprotective and anti-inflammatory effects.

The pharmacokinetic ability of Methotrexate to traverse the BBB, particularly at low doses, further reinforces its potential in CNS disorders. Unlike high-dose regimens, which are associated with cytotoxicity, neurotoxicity, and bone marrow suppression, low-dose administration is generally well-tolerated and exerts targeted immune modulation. By mitigating neuroinflammation and limiting immune-mediated neuronal injury, Methotrexate could serve as a valuable adjunctive strategy in slowing the progression of neurodegenerative diseases [21].

JAK Inhibitors (Tofacitinib, Baricitinib): The Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway constitutes a fundamental intracellular signaling axis that integrates cytokine and growth factor inputs to regulate diverse cellular processes. This cascade is central to immune homeostasis, governing the activation and differentiation of innate and adaptive immune cells, orchestration of inflammatory signaling, and transcriptional regulation of genes involved in survival, proliferation, and programmed cell death. Dysregulated hyperactivation of the JAK-STAT pathway particularly the JAK1/JAK2-STAT1/STAT3 signaling branch has been increasingly associated with the pathogenesis of neurodegenerative disorders such as Alzheimer's disease (AD) and Parkinson's disease (PD). In these conditions, chronic microglial overactivation perpetuates neuroinflammation through sustained production of pro-inflammatory cytokines, including interleukin-6 (IL-6), interferon-γ (IFN-γ), and tumor necrosis factor-α (TNF-α). Pharmacological inhibition of JAKs with small-molecule agents such as Tofacitinib and Baricitinib offers a promising strategy to suppress aberrant cytokine-driven signaling, thereby dampening neuroinflammatory cascades and potentially slowing disease progression [22].

Mechanistically, persistent cytokine stimulation triggers phosphorylation of JAK kinases, which in turn activate STAT transcription factors via tyrosine phosphorylation. Activated STAT1/STAT3 dimers translocate to the nucleus, driving the transcription of pro-apoptotic and pro-inflammatory genes. This cascade enhances imbalance between reactive oxygen species and antioxidants, exacerbates neuronal injury, and accelerates neurodegeneration. JAK inhibitors (Jakinibs) disrupt this pathological signaling by preventing STAT phosphorylation, thereby inhibiting nuclear translocation and transcriptional activation of apoptosis-associated genes. The result is reduced neuronal loss and preservation of CNS functional integrity [22, 23].

The JAK-STAT pathway's breadth of influence engaged by over 70 distinct cytokines underscores its central role in neuroimmune dysregulation. Beyond its established relevance in autoimmune and neoplastic disorders, increasing evidence implicates its aberrant activation in PD pathogenesis, where elevated cytokine levels are consistently observed in the brain parenchyma and cerebrospinal fluid. This has positioned JAK inhibition as a rational therapeutic strategy to attenuate neuroinflammation and potentially arrest disease progression [22].

Preclinical studies have provided compelling mechanistic validation. In a PD rodent model, dopaminergic neurodegeneration was induced via intracerebral delivery of an adeno-associated viral vector encoding human α-synuclein (AAV2-α-SYN), a protein whose misfolding and aggregation are central to PD pathology. Subsequent analyses demonstrated robust JAK-STAT activation in response to α-synuclein aggregates, accompanied by heightened neuroinflammation and dopaminergic neuron loss. Administration of the selective JAK1/JAK2 inhibitor AZD1480 (AstraZeneca) via oral gavage yielded significant neuroprotective effects:

- **Inflammation arm:** 10 mg/kg/day initiated at week 2 post-inoculation for 2 weeks markedly reduced microglial activation.
- **Neuroprotection arm:** 5 mg/kg/day starting at week 4 for 4 weeks, followed by a 4-week washout, preserved dopaminergic neurons and mitigated behavioral deficits.

In vitro, mouse microglia and macrophages exposed to 500 nM α-synuclein aggregates (formed over 7 days at 37 °C) exhibited pronounced inflammatory activation, which was

effectively attenuated by AZD1480. These findings confirm that α-synuclein-induced neuroinflammation is mediated, at least in part, through JAK-STAT signaling, and that pharmacological blockade with JAK inhibitors can confer robust neuroprotection [22, 23].

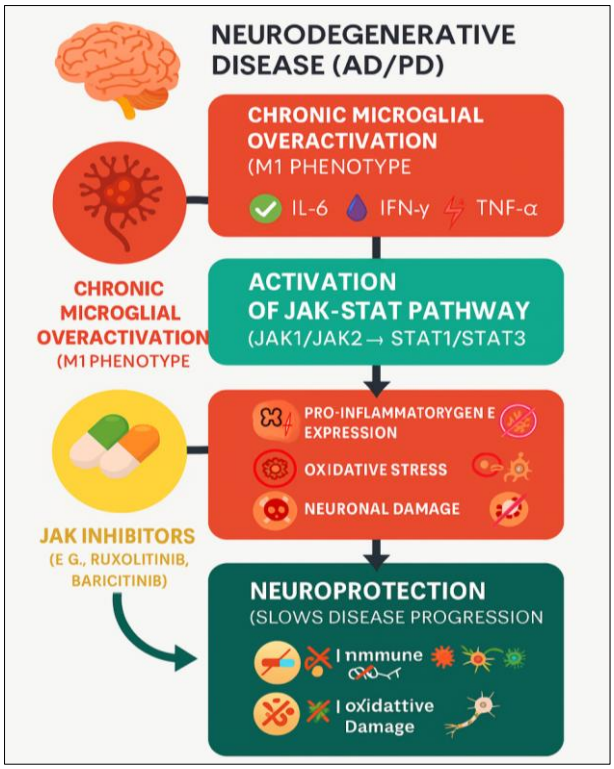

Fig 4: General pathway of JAK-STAT pathway in AD/PD

Etanercept: Etanercept is a recombinant biologic fusion protein classified among disease-modifying antirheumatic drugs (DMARDs). It is engineered by linking the extracellular ligand-binding domain of the human tumor necrosis factor (TNF) receptor to the Fc fragment of human immunoglobulin G1 (IgG1). This chimeric construct confers high-affinity binding to soluble TNF-α, thereby preventing its interaction with cell-surface TNF receptors and effectively neutralizing downstream pro-inflammatory signaling. By attenuating TNF-α-mediated activation of the NF-κB and MAPK pathways, Etanercept reduces the release of secondary inflammatory mediators, oxidative stress, and apoptosis, mechanisms increasingly recognized in the pathogenesis of autoimmune conditions as well as neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease [24-26].

Emerging evidence suggests that anti-TNF agents such as etanercept may hold therapeutic promise in Alzheimer's disease (AD) and Parkinson's disease (PD) by modulating neuroinflammation, a key driver of neuronal injury. However, the translational potential of systemic etanercept is limited by its poor penetration across the blood-brain barrier (BBB). The BBB restricts passive diffusion of molecules exceeding 400-600 Da, whereas etanercept has a molecular weight of approximately 150 kDa and lacks lipophilicity as well as intrinsic transport mechanisms, rendering conventional central nervous system (CNS) delivery inefficient [24].

To overcome this pharmacokinetic barrier, an alternative route leveraging Batson's venous plexus has been proposed. Batson's plexus is a valveless, bidirectional venous network extending from the pelvic region to the cranial cavity, in direct communication with meningeal veins and intracranial venous sinuses. Owing to the absence of valves, retrograde venous flow can be induced, particularly when patients are positioned in a mild Trendelenburg posture (head-down tilt), facilitating upward drug movement toward the CNS.

Building upon this anatomical pathway, perispinal administration has been explored as a targeted delivery technique. In this approach, etanercept is injected into the perispinal space near the cervical spine at the C5-C6 level to engage the cerebrospinal venous system, potentially bypassing the BBB and enabling indirect access to the cerebrospinal fluid (CSF) and brain parenchyma [25,26]. Unlike strategies aimed at amyloid plaque clearance, the therapeutic intent of perispinal etanercept is to recalibrate neuroimmune homeostasis, thereby attenuating ongoing neuronal injury and slowing cognitive decline [24-26].

Sargramostim (GM-CSF): Sargramostim is a recombinant therapeutic analog of granulocyte-macrophage colony-stimulating factor (GM-CSF), a multifunctional cytokine with essential roles in hematopoiesis and immune regulation. Under physiological conditions, GM-CSF drives the proliferation, differentiation, and survival of myeloid progenitor cells within the bone marrow, promoting the production of granulocytes (neutrophils, eosinophils, and basophils) as well as monocytes. These monocytes further differentiate into macrophages and dendritic cells, key effector populations that coordinate innate immune defense, antigen presentation, and the priming of adaptive immune responses. Beyond its hematopoietic role, GM-CSF also modulates microglial function and neuroimmune communication, a property that has sparked growing interest in its potential application for neurodegenerative disorders, where immune dysregulation and impaired clearance of

pathological protein aggregates are central features [27].

In the context of neurodegeneration, GM-CSF has been shown to exert immunomodulatory and neuroprotective effects by promoting regulatory T-cell (Treg) activation and enhancing clearance of misfolded proteins that contribute to neuroinflammation. By modulating the immune milieu rather than broadly suppressing it, Sargramostim has been postulated to exert neuroprotective effects in neurodegenerative disorders such as Parkinson's disease (PD) and Alzheimer's disease (AD) by modulating neuroimmune interactions, enhancing microglial phagocytic clearance of pathogenic protein aggregates, and promoting a neurotrophic milieu that may help preserve neuronal integrity and functional connectivity [27, 28].

Preliminary clinical investigations in PD patients receiving sargramostim demonstrated modest but measurable improvements in motor function, accompanied by favorable shifts in neuroimmune parameters, including increased Treg levels and function. Immune enhancement correlated with changes in serum biomarkers such as tryptophan-derived metabolites, suggesting a mechanistic link between metabolic and immunological modulation. Adverse effects were generally mild and well-tolerated, though larger and longer-term studies are required to fully characterize safety and efficacy profiles [27].

Similarly, in early-phase studies of AD, sargramostim treatment was well-tolerated and associated with improvements in cognitive performance, reduced neurodegenerative pathology, and favorable alterations in AD-related blood biomarkers. These findings challenge the long-standing paradigm that all inflammatory responses are detrimental in AD, instead supporting the hypothesis that controlled immune activation may confer neuroprotection. Nonetheless, the current evidence is limited by small cohort sizes, underscoring the need for robust, randomized clinical trials to confirm the therapeutic promise of GM-CSF-based interventions in neurodegenerative disease [28].

Leflunomide: Leflunomide is an immunomodulatory prodrug that undergoes rapid hepatic conversion to its pharmacologically active metabolite mentioned in figure 5, teriflunomide (A771726), which has demonstrated significant anti-inflammatory and neuroprotective potential in preclinical models of neurodegeneration. Its principal mode of action is the selective and reversible inhibition of dihydroorotate dehydrogenase (DHODH), a mitochondrial flavoprotein enzyme that catalyzes the oxidation of dihydroorotate to orotate, a rate-limiting step in the de novo biosynthesis of pyrimidine nucleotides. This pathway is indispensable for the generation of uridine monophosphate (UMP), the precursor for pyrimidine nucleotides such as cytidine triphosphate (CTP) and deoxythymidine triphosphate (dTTP), which are critical for DNA and RNA synthesis. Because this metabolic pathway is highly upregulated in rapidly proliferating immune cells, particularly activated T lymphocytes and microglia, DHODH inhibition by teriflunomide effectively restricts their expansion, thereby dampening pathological immune activation. In the context of neurodegenerative diseases, this translates into suppression of chronic neuroinflammation, reduction of excitotoxic and oxidative stress, and preservation of neuronal viability within the central nervous system [29].

Beyond DHODH inhibition, teriflunomide also attenuates tyrosine kinase-dependent signaling pathways, further dampening immune cell activation. In experimental autoimmune neuritis (EAN) models, leflunomide administration from disease onset completely prevented paralysis, while post-symptomatic treatment arrested disease progression and facilitated recovery. Comparative analyses demonstrated superior efficacy over azathioprine, which failed to yield significant therapeutic benefit in the same model. Histopathological assessments revealed reduced perineural immune cell infiltration, preservation of myelin architecture, and enhanced axonal integrity in leflunomide-treated animals. Moreover, treatment prevented the generation of pathogenic autoantibodies associated with demyelinating injury [29].

Remarkably, in adoptive transfer paradigms where disease-inducing immune cells were passively introduced into healthy recipients leflunomide significantly attenuated symptom severity. The addition of uridine did not abrogate its therapeutic effect, suggesting that its mode of action extends beyond mere inhibition of nucleotide synthesis. Mechanistic investigations have further demonstrated that leflunomide disrupts T-cell activation by reducing calcium influx, a pivotal step in lymphocyte signaling and effector function [29].

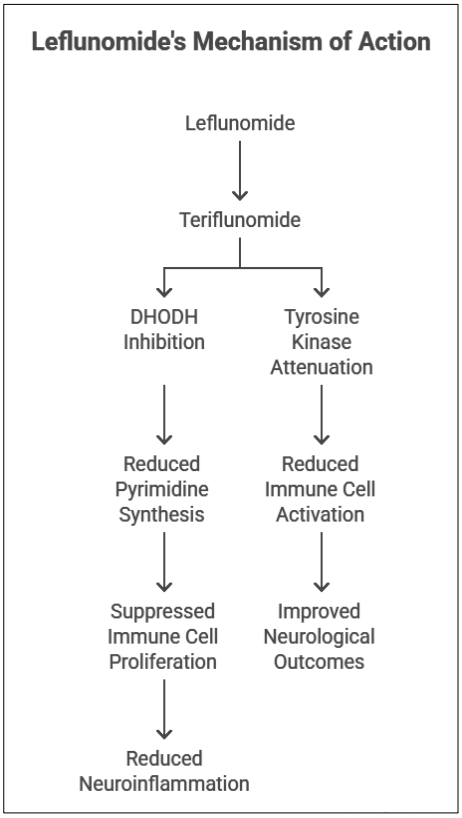

Fig 5: Leflunomide Mechanism of Action

Conclusion

Alzheimer's disease (AD) and Parkinson's disease (PD) remain the most prevalent age-related neurodegenerative disorders, imposing immense personal, societal, and economic burdens worldwide. Traditionally distinguished by unique pathological hallmarks amyloid-β and tau in AD, dopaminergic loss and α-synuclein aggregation in PD emerging evidence highlights a convergence of mechanisms that drive both conditions. Neuroinflammation, oxidative stress, mitochondrial dysfunction, and immune dysregulation form a shared pathogenic axis that sustains disease

progression. Within this framework, disease-modifying antirheumatic drugs (DMARDs) have attracted attention for therapeutic repurposing. Beyond their established role in autoimmune disorders, DMARDs demonstrate the ability to regulate microglial activity, suppress pro-inflammatory cytokines, and restore immune balance within the central nervous system. Agents such as methotrexate, JAK/STAT pathway inhibitors, TNF-α antagonists, and IL-1 blockers are under active investigation for their neuroprotective potential, with early evidence suggesting disease-modifying capacity. Clinical translation, however, presents critical challenges. Limited penetration across the blood-brain barrier, the risk of systemic immunosuppression in elderly patients, and inter-individual variability linked to genetic modifiers such as APOE4 in AD or LRRK2 in PD underscore the need for precision-based strategies. Integrating pharmacogenomics, biomarker profiling, and advanced drug delivery technologies will be essential to optimize efficacy while minimizing risks. As the repositioning of DMARDs advances from conceptual promise to clinical reality, a multidisciplinary approach bridging immunology, neurobiology, and precision medicine will be required. If successful, these agents could redefine the management of neurodegenerative diseases shifting the paradigm from symptomatic relief toward genuine disease modification and long-term neuroprotection.

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