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NEUROINFLAMMATION IN STROKE: THERAPEUTIC TARGETS AND EMERGING PHARMACOLOGICAL STRATEGIES- A COMPREHENSIVE REVIEW

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ABSTRACT

Stroke is a time-critical neurological disorder in which vascular occlusion or vessel rupture initiates a complex cascade extending beyond the primary vascular insult. In ischemic stroke, restoration of blood flow is essential, but reperfusion can intensify oxidative stress, blood–brain barrier (BBB) disruption, microglial activation, leukocyte recruitment, cytokine release, inflammasome activation and secondary neuronal injury. Neuroinflammation is therefore both a driver of tissue damage and a component of later repair. This duality explains why broad immunosuppression has been difficult to translate into effective stroke therapy. The therapeutic opportunity increasingly lies in selective, time-dependent modulation of inflammatory pathways rather than complete suppression of immunity. This review synthesizes current evidence on the cellular and molecular architecture of post-stroke neuroinflammation and evaluates established, investigational and emerging pharmacological strategies. Major targets include microglial activation and phenotypic reprogramming; damage-associated molecular pattern signalling through HMGB1/TLR4/NF-κB; the NLRP3 inflammasome and pyroptosis; IL-1β, IL-6 and TNF-α signalling; leukocyte adhesion and neutrophil extracellular traps; matrix metalloproteinases and BBB dysfunction; oxidative stress–inflammation coupling; sphingosine-1-phosphate signalling; regulatory T-cell pathways; and the gut–brain immune axis. Particular attention is given to translational evidence from human trials of minocycline, fingolimod, natalizumab, IL-1 receptor antagonism and edaravone dexborneol. The 2026 EMPHASIS trial has materially strengthened the clinical evidence base for minocycline, although neuroinflammation-targeted treatment remains adjunctive rather than a replacement for reperfusion. Emerging approaches include NLRP3 inhibitors, NET-directed therapy, IL-6 pathway modulation, targeted drug delivery, immunometabolic interventions, microbiome-based strategies, regulatory T-cell enhancement, and non-invasive vagus nerve stimulation. The major translational challenges are timing, cellular specificity, disease heterogeneity, sex and age effects, infection risk, BBB penetration and the need to distinguish damaging inflammation from reparative immune responses. Future stroke pharmacology is likely to move toward biomarker-guided, combination and phase-specific immunomodulation integrated with reperfusion and neurorehabilitation.

KEYWORDS: ischemic stroke; neuroinflammation; microglia; NLRP3 inflammasome; HMGB1; TLR4; cytokines; neutrophils; blood–brain barrier; immunomodulation; neuroprotection; pharmacological targets.

1. INTRODUCTION

Stroke remains one of the major causes of death and long-term disability worldwide. Contemporary acute management has been transformed by intravenous thrombolysis and mechanical thrombectomy, yet substantial disability persists because many patients present outside treatment windows, have incomplete reperfusion, or develop secondary injury despite successful recanalization. Neuroinflammation is increasingly recognized as one of the mechanisms that links the original ischemic insult with infarct expansion, edema, BBB failure, hemorrhagic transformation and impaired recovery.[1-4]

The inflammatory response is not a single event. It begins within minutes to hours of cerebral ischemia, evolves during reperfusion and continues for days to weeks. Damaged neurons, endothelial cells, astrocytes and microglia release danger signals that activate innate immune pathways. Microglia rapidly change their transcriptional and metabolic state, endothelial cells express adhesion molecules, and circulating neutrophils and monocytes enter the injured territory. Cytokines, chemokines, complement components, proteases, ROS and extracellular DNA then reinforce the response.[2,5]

Importantly, inflammation is not uniformly harmful. Early inflammatory signalling can remove damaged cells and initiate repair, while later immune responses can support angiogenesis, synaptic remodeling and tissue recovery. The concept of simply "blocking inflammation" is therefore too crude. The more useful therapeutic question is which inflammatory signal should be inhibited, in which cell, at which stage, and for how long.[3,6]

This review focuses primarily on ischemic stroke and ischemia–reperfusion injury, while noting selected principles relevant to intracerebral hemorrhage. The purpose is to integrate mechanistic biology with pharmacological and translational evidence and to identify targets most likely to support future clinical development.

2. Neuroinflammation after stroke: pathophysiological framework

2.1 Initiation by ischemia and reperfusion

Loss of cerebral blood flow causes ATP depletion, ion-pump failure, membrane depolarization, glutamate accumulation, calcium influx and mitochondrial dysfunction. These events promote ROS generation and cell death. When blood flow is restored, oxygen and inflammatory substrates re-enter injured tissue. Reperfusion therefore has a paradoxical role: it is indispensable for salvaging threatened tissue but may amplify oxidative and inflammatory injury.[2,7]

Necrotic and stressed cells release DAMPs such as HMGB1, extracellular ATP, heat-shock proteins and nucleic acids. These signals activate pattern-recognition receptors on microglia, astrocytes, endothelial cells and infiltrating leukocytes. TLR4 and related receptors stimulate NF-κB and MAPK signaling, increasing transcription of cytokines, chemokines and adhesion molecules.[7-9] This creates a feed-forward loop in which cellular damage generates inflammatory signals that cause further cellular damage.

2.2 Microglia: the first-line immune regulators

Microglia are resident CNS macrophage-like cells and among the earliest immune responders to ischemia. They migrate toward the lesion, change morphology and rapidly alter gene expression. Historically, activated microglia were described as M1-like pro-inflammatory or M2-like anti-inflammatory cells. This binary model remains useful for teaching but is now considered an oversimplification because single-cell and transcriptomic studies demonstrate multiple dynamic states that vary with time, location and metabolic context.[5,10]

Early excessive microglial activation can increase TNF-α, IL-1β, IL-6, ROS and nitric oxide, aggravating neuronal death and BBB dysfunction. Conversely, later microglial programs can promote phagocytosis, debris clearance, trophic support, angiogenesis and synaptic remodeling. Consequently, therapeutic strategies are shifting from indiscriminate microglial depletion toward selective reprogramming of harmful states while preserving repair-associated functions.[5,10,11]

2.3 Astrocytes and microglia–astrocyte crosstalk

Astrocytes respond to ischemia through changes in calcium signalling, metabolism, cytokine production and reactive gliosis. They can support neuronal survival and BBB integrity, but reactive astrocytes may also release inflammatory mediators and contribute to glial scar formation. Microglia and astrocytes communicate bidirectionally through cytokines, chemokines, extracellular vesicles and complement-related signals. This crosstalk is increasingly viewed as a therapeutic node because modulating one cell type may alter the inflammatory state of the other.[12]

2.4 Peripheral immune-cell recruitment

Endothelial activation increases expression of selectins, ICAM-1 and VCAM-1, enabling leukocyte rolling, adhesion and transmigration. Neutrophils are among the earliest recruited cells and can release proteases, ROS and NETs. Monocytes/macrophages subsequently enter the brain and may either amplify inflammation or participate in repair depending on phenotype and timing. T cells, B cells and regulatory T cells contribute to later immune regulation.[2,13,14]

Neutrophils are particularly important because their functions bridge inflammation and thrombosis. NETs consist of extracellular DNA decorated with histones and proteases. In ischemic stroke they can stabilize thrombi, interfere with fibrinolysis, damage endothelial cells and activate additional inflammatory pathways. Thus, NETs provide an attractive target for combined thrombo-inflammatory therapy.[13,15]

3. Major therapeutic targets in stroke neuro inflammation

3.1 HMGB1–TLR4/RAGE signaling

HMGB1 is a nuclear protein that becomes extracellular after cell injury or active secretion by immune cells. Extracellular HMGB1 can engage TLR2, TLR4 and RAGE, thereby activating NF-κB-dependent inflammatory transcription. HMGB1 is released early after ischemia and can contribute to cytokine production, MMP activation and BBB disruption.[8,9,16]

The therapeutic challenge is that HMGB1 is biologically context dependent. Different redox states can produce different receptor interactions and biological effects, and HMGB1 may also participate in later repair. Complete systemic neutralization may therefore be less desirable than temporally restricted inhibition of its damaging early signaling. Experimental approaches include HMGB1-neutralizing antibodies, inhibitory peptides and TLR4 antagonism. These remain preclinical or early translational strategies rather than established stroke treatments.[8,16]

3.2 NF-κB and MAPK pathways

NF-κB and MAPK pathways are central transcriptional hubs linking pattern-recognition receptors to inflammatory cytokines, adhesion molecules and enzymes. Because these pathways are downstream of multiple receptors, they are attractive targets but also risky: broad inhibition could suppress protective host responses. Preclinical studies suggest that selective modulation in microglia or vascular endothelium may be preferable to systemic blockade.[5,7]

Potential pharmacological approaches include inhibitors of upstream TLR signalling, IKK/NF-κB signalling and selected MAPK pathways. Many natural products and repurposed compounds have shown effects in experimental stroke through these mechanisms, but reproducibility, bioavailability, dose equivalence and pharmacokinetic translation remain major limitations.

3.3 NLRP3 inflammasome and pyroptosis

The NLRP3 inflammasome is a multiprotein innate immune complex that integrates danger signals including ROS, potassium efflux, mitochondrial dysfunction and extracellular ATP. Its activation promotes caspase-1 activity, maturation of IL-1β and IL-18, and gasdermin-D-dependent pyroptotic cell death.[17,18]

NLRP3 inhibition is among the most intensively investigated pharmacological approaches in experimental ischemic stroke. MCC950, a selective NLRP3 inhibitor, has reduced infarct progression and inflammatory signalling in several animal studies. Importantly, recent translational work has identified increased NLRP3 expression in leukocytes and cerebral endothelium before recanalization and suggests that the pathway may influence infarct progression during large-vessel occlusion.[19] Nevertheless, preclinical results have not been uniformly positive, and inflammasome biology differs between models. NLRP3 inhibitors therefore require rigorous pharmacology and biomarker-driven clinical testing before routine use.

3.4 IL-1β/IL-1 receptor signalling

IL-1β is a potent inflammatory mediator downstream of inflammasome activation. It promotes leukocyte recruitment, endothelial activation and secondary tissue injury. Anakinra, a recombinant IL-1 receptor antagonist, has been evaluated in small stroke studies and systematic reviews suggest acceptable short-term safety with biological evidence of inflammatory modulation.[20,21]

The early randomized phase II trial of IL-1 receptor antagonist in acute stroke demonstrated reductions in inflammatory biomarkers and suggested possible clinical benefit, particularly among patients with cortical infarction. The evidence remains insufficient for routine use, but IL-1 signalling is one of the more clinically tractable inflammatory targets because receptor antagonism is already established in other diseases.[20]

3.5 IL-6 signaling

IL-6 is associated with stroke severity and poor outcomes and may contribute to endothelial activation, immune-cell recruitment and systemic inflammatory responses. Tocilizumab, an IL-6 receptor antibody, is therefore being investigated experimentally. Recent multicenter preclinical work has shown that IL-6 receptor blockade can have context-dependent effects, with age and sex influencing response.[22,23]

These findings illustrate a broader principle: a target can be mechanistically valid but therapeutically complex. IL-6 participates in host defence and tissue repair, and systemic blockade could increase infection risk. Clinical translation will likely require careful selection of patients with strong inflammatory signatures rather than unselected treatment of all stroke patients.

3.6 TNF-α signalling

TNF-α contributes to leukocyte adhesion, endothelial dysfunction, BBB permeability and neuronal injury. Experimental TNF-α inhibition has produced neuroprotective signals, but clinical development is complicated by the central role of TNF in immune defence and the poor ability of some biologics to penetrate the CNS. TNF inhibition may be more feasible when peripheral inflammation is a major driver, but evidence in acute stroke remains preliminary.[24]

3.7 MMPs and BBB dysfunction

MMP-2 and MMP-9 degrade extracellular-matrix and tight-junction components and are implicated in BBB breakdown, cerebral edema and hemorrhagic transformation. MMP-9 is particularly relevant after reperfusion and thrombolysis. Direct MMP inhibition has shown experimental benefit but has encountered the classic problem of pathway pleiotropy and toxicity. More selective approaches aimed at upstream inflammatory signalling or localized delivery may provide better therapeutic windows.[25,26]

3.8 Oxidative stress as an inflammatory amplifier

Oxidative stress and neuroinflammation form a reciprocal cycle. ROS activate redox-sensitive inflammatory pathways, while inflammatory cells generate additional ROS. Antioxidant therapy may therefore indirectly suppress inflammation. Edaravone, a free-radical scavenger, and edaravone dexborneol are

important examples of multitarget neuroprotection. A phase III trial showed better 90-day functional outcomes with edaravone dexborneol than edaravone alone, and subsequent phase III evidence has supported benefit with sublingual administration.[27,28]

The clinical significance is that a successful adjunctive strategy does not necessarily have to inhibit one cytokine. Modulation of several linked injury pathways may be advantageous, provided safety and reproducibility are demonstrated.

Table 1: Principal neuroinflammatory targets and pharmacological opportunities.

Target/pathway	Major mechanism	Representative strategy	Evidence status	Key limitation
Microglial activation	Cytokine/ROS production; phenotypic reprogramming	Minocycline; metabolic/epigenetic modulators	Clinical + preclinical	Non-specificity; timing
HMGB1–TLR4/RAGE	DAMP sensing → NF-κB/MAPK	HMGB1 blockade; TLR4 antagonists	Mainly preclinical	Biphasic biology; host defence
NLRP3 inflammasome	IL-1β/IL-18 maturation; pyroptosis	MCC950 and next-generation inhibitors	Preclinical/ translational	Model heterogeneity
IL-1 pathway	Endothelial activation; leukocyte recruitment	Anakinra/IL-1Ra	Early clinical	Small trials; infection concern
IL-6 pathway	Systemic and CNS inflammatory signalling	Tocilizumab	Preclinical	Age/sex effects; infection risk
TNF-α	BBB dysfunction and inflammatory amplification	TNF inhibitors	Preclinical/early clinical	CNS penetration; immune suppression
Leukocyte adhesion	Immune-cell entry into injured brain	Natalizumab/anti-adhesion approaches	Clinical trials	Limited efficacy; safety
NETs	Thrombo-inflammation; BBB injury	DNase I; PAD4/DPP1 inhibition	Preclinical/emerging	Optimal timing and specificity
MMPs	Tight-junction/ECM degradation	Selective MMP inhibition	Preclinical	Broad MMP functions
S1P signalling	Lymphocyte trafficking	Fingolimod	Pilot clinical	Immunosuppression; bradycardia
Oxidative stress	ROS-mediated inflammatory amplification	Edaravone dexborneol	Clinical evidence	Regional availability; mechanism is multitarget
Treg pathways	Immune suppression and repair	Treg expansion / adoptive strategies	Preclinical	Timing, dose, durability

4. Pharmacological strategies: established, repurposed and emerging

4.1 Minocycline: from experimental neuroprotection to contemporary clinical evidence

Minocycline is a lipophilic tetracycline with anti-inflammatory actions that are partly independent of its antimicrobial activity. It crosses the BBB and can inhibit microglial activation, reduce inflammatory mediators, attenuate MMP activity and influence apoptotic and oxidative pathways.[29,30]

Early experimental studies suggested a relatively broad therapeutic window, and small clinical trials generated interest. Meta-analyses of earlier randomized studies were suggestive but heterogeneous.[31] The major development in 2026 is the EMPHASIS multicenter randomized trial, which enrolled patients with acute ischemic stroke within 72 hours and evaluated minocycline in addition to routine treatment. The trial was designed to provide more definitive evidence than earlier small studies.[32] The result is clinically important because it tests an inexpensive repurposed drug against contemporary stroke care rather than against outdated treatment paradigms. Nevertheless, interpretation should consider the study population, timing, dosing, background reperfusion therapy and generalizability beyond the trial setting.

Minocycline should therefore be viewed as a leading example of how neuroinflammation-targeted therapy can progress from mechanism and animal models to pragmatic clinical testing. It also demonstrates the need to evaluate functional outcomes, not merely cytokine concentrations or infarct volume.

4.2 Fingolimod and sphingosine-1-phosphate modulation

Fingolimod is an S1P receptor modulator that sequesters lymphocytes in lymphoid tissues and reduces their migration into inflamed sites. Pilot stroke trials suggested that fingolimod, when added to standard therapy or alteplase, could reduce circulating lymphocytes, lesion burden and some early neurological measures.[33,34]

The concept is attractive because it targets the peripheral arm of neuroinflammation rather than directly

suppressing resident microglia. However, fingolimod can cause bradycardia and immunosuppression and is not an established acute stroke treatment. Larger trials, reproducibility across populations and careful infection monitoring are needed.

4.3 Leukocyte adhesion blockade: natalizumab

Natalizumab blocks α4 integrin and was evaluated because leukocyte-endothelium adhesion is a key step in inflammatory cell entry. The phase II ACTION trial did not demonstrate a reduction in infarct growth, although some secondary functional outcomes were encouraging.[35] ACTION II subsequently failed to confirm benefit and actually showed lower odds of excellent outcome with natalizumab than placebo.[36] This negative translational example is important: reducing leukocyte trafficking is biologically plausible, but the timing, cellular target and degree of blockade may be inappropriate. It also demonstrates that an apparently attractive pathway can fail when tested in heterogeneous human stroke.

4.4 IL-1 receptor antagonism

Anakinra provides a pharmacologically clean test of IL-1 signalling. Early randomized evidence showed reductions in CRP, IL-6 and leukocyte measures and suggested safety. A systematic review of clinical studies through 2023 concluded that IL-1 receptor antagonism was generally well tolerated, while emphasizing that evidence remains limited and heterogeneous.[20,21] Future trials should use biomarker enrichment, early administration and standardized functional endpoints.

4.5 Edaravone dexborneol

Edaravone dexborneol combines an antioxidant component with dexborneol and is intended to provide broader cytoprotection. In a large phase III comparison with edaravone alone, the combination produced a higher proportion of favorable 90-day functional outcomes.[27] A later phase III trial of sublingual edaravone dexborneol versus placebo also reported improved 90-day outcomes without a major difference in overall adverse-event frequency.[28] More recent thrombectomy-focused evidence has extended evaluation into the reperfusion era.[37]

The principal lesson is that oxidative stress and inflammation should not be viewed as separate therapeutic domains. A multitarget agent may be more robust than a single cytokine inhibitor because ischemia activates interconnected pathways simultaneously. However, the magnitude of benefit, population-specific effects and applicability across healthcare systems require independent confirmation.

4.6 Antioxidant and metabolic approaches

Other antioxidant approaches include uric acid supplementation, mitochondrial protectants and agents that influence NADPH oxidase, mitochondrial ROS or cellular energy metabolism. The URICO-ICTUS trial suggested that uric acid could reduce early ischemic worsening in selected thrombolysed patients, with possible benefit related to collateral circulation.[38] However, neuroprotective strategies that depend strongly on tissue delivery illustrate why BBB permeability and collateral status must be considered when designing trials.

Metabolic reprogramming of microglia is another emerging strategy. AMPK, mTOR, HIF-1α and mitochondrial pathways can influence whether microglia adopt inflammatory or reparative states. These targets are promising but require caution because metabolism also controls neuronal survival and systemic physiology.

5. Emerging pharmacological and immunological strategies

5.1 Next-generation NLRP3 inhibitors

MCC950 has served as a proof-of-concept tool, but future development requires molecules with improved brain exposure, pharmacokinetics and selectivity. The most attractive approach may be to intervene during the hyperacute period before extensive inflammasome amplification. Recent evidence showing NLRP3 elevation before endovascular reperfusion supports the idea that pre-recanalization treatment could be particularly valuable.[19]

Potential advantages include simultaneous reduction of IL-1β, IL-18 and pyroptosis. Potential risks include suppression of host defence and uncertainty about whether inflammasome activation is equally pathogenic in every patient. Biomarkers such as circulating or lesion-associated NLRP3 signatures could eventually identify responsive patients.

5.2 NET-targeted therapy

NETs are an especially attractive target because they connect thrombosis, inflammation and BBB injury. Experimental strategies include DNase I to degrade extracellular DNA, PAD4 inhibition to reduce NET formation and inhibition of neutrophil serine-protease activation. Recent work has also explored targeted nanoparticles that home to neutrophils and deliver anti-NET payloads.[13,15,39]

The central translational issue is specificity. Neutrophils are important for host defence, and excessive suppression could increase infection risk. A successful strategy may therefore need to disrupt pathological NET formation without eliminating normal neutrophil functions.

5.3 Regulatory T cells and pro-resolving immunity

Tregs suppress excessive immune activation through IL-10, TGF-β and cell-contact mechanisms. Experimental evidence indicates that Tregs can reduce inflammatory injury in the acute phase and support repair during later recovery. Current strategies include adoptive Treg

transfer, pharmacological expansion and mucosal tolerance approaches.[40]

The concept differs from conventional anti-inflammatory treatment because it aims to restore immune balance rather than suppress one mediator. Major challenges include producing a predictable cell product, selecting the optimal time window, avoiding generalized immunosuppression and determining whether effects persist long enough to influence functional recovery.

5.4 Gut–brain axis and microbiome-directed therapy

Stroke can alter intestinal motility, epithelial permeability and microbial composition. Conversely, gut-derived metabolites and immune signals can influence systemic inflammation, BBB integrity and post-stroke recovery. Microbial products such as short-chain fatty acids, indole metabolites and lipopolysaccharide can influence TLR signalling, T-cell differentiation and microglial states.[41,42]

Potential interventions include probiotics, prebiotics, defined microbial consortia, dietary manipulation and metabolite replacement. These approaches are appealing because they may influence both peripheral immunity and CNS inflammation. However, microbiome interventions are difficult to standardize because baseline diet, geography, antibiotic exposure, age and comorbidities all alter microbial composition. Therefore, future studies should use mechanistic biomarkers rather than relying only on generic measures of microbiome diversity.

5.5 Tryptophan–kynurenine–AHR signalling

Tryptophan metabolism generates kynurenine-pathway metabolites as well as serotonin and microbial indoles. Some metabolites are neuroactive and can modify oxidative stress, excitotoxicity and immune responses. The aryl hydrocarbon receptor (AHR) is one potential regulatory node linking microbial metabolites to immune phenotype. Recent reviews identify IDO, TDO, TPH and AHR as possible therapeutic targets, but clinical translation is still at an early stage.[43]

5.6 Vagus nerve stimulation and the cholinergic anti-inflammatory pathway

The vagus nerve can modulate systemic inflammation through neural control of immune signalling. Non-invasive auricular VNS is therefore being studied as a non-pharmacological adjunct with pharmacological implications because it can alter inflammatory cytokine profiles without systemic immunosuppression. In the NUVISTA randomized study of large-vessel occlusion stroke, transcutaneous auricular VNS reduced aggregate pro-inflammatory cytokines and IL-6 compared with sham stimulation, although the trial was small and was not powered for definitive functional efficacy.[44]

This approach is particularly relevant to future combination therapy: neuromodulation could be paired with reperfusion or targeted anti-inflammatory drugs to reduce inflammation while preserving immune competence.

5.7 Targeted drug-delivery systems

The BBB is both a biological barrier and a pharmacological opportunity. Nanoparticles, liposomes, exosomes and cell-homing systems may improve delivery of anti-inflammatory molecules to the ischemic brain or to specific immune-cell populations. Neutrophil-homing lipid nanoparticles carrying an inhibitor of neutrophil protease activation represent an example of this direction.[39]

Targeted delivery could reduce systemic toxicity and allow lower drug doses. However, manufacturing complexity, pharmacokinetic variability, immune reactions, tissue accumulation and regulatory requirements remain substantial barriers. Clinical development will need standardized characterization of particle size, payload, biodistribution and long-term safety.

6. Clinical translation: what has and has not worked

The clinical record shows a recurring pattern: inflammatory targets are biologically convincing, but successful translation is uncommon. Several factors explain this gap. First, human stroke is heterogeneous in mechanism, infarct size, collateral circulation, age, sex, diabetes, infection status and reperfusion status. Second, inflammation changes rapidly; an intervention that is beneficial at 6 hours may be harmful at 6 days. Third, preclinical models often use young, otherwise healthy animals and standardized occlusion, whereas clinical populations are older and have multiple comorbidities.[3,45]

The negative natalizumab experience demonstrates that blocking leukocyte trafficking does not necessarily reduce infarct expansion. Conversely, minocycline provides an example of a repurposed, BBB-penetrant anti-inflammatory agent that has progressed to large-scale clinical testing. Edaravone dexborneol illustrates the potential of multitarget cytoprotection. Fingolimod demonstrates that peripheral immune modulation can affect stroke biology, but safety and reproducibility remain issues.[27,32-36]

The most promising future trials should therefore combine conventional clinical endpoints with mechanistic biomarkers. Candidate biomarkers include IL-6, CRP, HMGB1, MMP-9, NLRP3-related signatures, neutrophil-to-lymphocyte ratio, NET markers and inflammatory transcriptomic profiles. Imaging markers of BBB permeability and infarct evolution can provide complementary evidence.

Table 2: Selected translational evidence for neuroinflammation-targeted interventions.

Intervention	Target/mechanism	Human evidence	Overall interpretation
Minocycline	Microglial activation; MMPs; inflammatory/oxidative pathways	Large 2026 EMPHASIS RCT	Most mature repurposing candidate; interpretation should follow full trial context
Anakinra	IL-1 receptor blockade	Small randomized studies + systematic review	Biologically active and apparently tolerable; efficacy not definitive
Fingolimod	S1P-mediated lymphocyte sequestration	Pilot randomized trials	Proof of peripheral immune modulation; larger efficacy evidence needed
Natalizumab	α4-integrin/leukocyte adhesion blockade	ACTION and ACTION II	Did not establish benefit; important negative translational lesson
Edaravone dexborneol	Antioxidant + anti-inflammatory multitarget cytoprotection	Phase III trials	Clinical benefit reported in Chinese trials; external validation desirable
Uric acid	Antioxidant/free-radical scavenging	URICO-ICTUS	Possible benefit in selected reperfusion-treated patients; not routine standard
Tocilizumab	IL-6 receptor blockade	Preclinical SPAN evidence	Promising mechanistic target; human efficacy not established
taVNS	Cholinergic anti-inflammatory pathway	Small randomized NUVISTA study	Biological anti-inflammatory effect; efficacy remains exploratory

7. Time-dependent therapeutic model

The therapeutic value of an anti-inflammatory drug is likely to depend on when it is given. A practical conceptual model is:

- Hyperacute phase (minutes–hours): DAMP release, oxidative stress, endothelial activation and microglial priming dominate. Therapies that prevent inflammasome activation, oxidative amplification or neutrophil-mediated thrombo-inflammation may be most relevant.
- Early acute phase (hours–days): leukocyte recruitment, cytokine amplification, BBB breakdown and edema become prominent. Selective IL-1/IL-6 modulation, microglial reprogramming and NET-targeted therapy may be useful.
- Subacute phase (days–weeks): debris clearance, angiogenesis, synaptic remodeling and adaptive immune responses become increasingly important. Broad immunosuppression may be counterproductive; Tregs and pro-resolving strategies become more attractive.
- Recovery phase (weeks–months): immune signalling interacts with neuroplasticity and tissue remodeling. Strategies that support resolution rather than suppression may be preferable.

This temporal framework also explains why clinical trials should avoid treating neuroinflammation as a static variable. Serial sampling and repeated biomarker measurements are more informative than a single baseline inflammatory value.

8. Precision pharmacology and patient selection

A major future direction is precision immunomodulation. Not every patient with stroke has the same inflammatory phenotype. Patients with large infarcts, delayed reperfusion, extensive BBB disruption, high neutrophil activity or systemic inflammatory priming may have greater opportunity for benefit. Conversely, patients with small infarcts and rapid reperfusion may have little additional inflammatory injury and could experience only the adverse effects of immunomodulation.

Biological heterogeneity also occurs across age and sex. Recent experimental work with IL-6 receptor blockade demonstrates sex-specific responses in aged animals, while inflammatory profiles differ substantially with diabetes and other metabolic conditions.[22,23,46] Trial design should therefore prespecify subgroup analyses and avoid assuming that a single dose-response relationship applies to all patients.

Pharmacodynamic biomarkers should ideally show target engagement. For example, a NLRP3 inhibitor trial should measure inflammasome-related markers; a T-cell trafficking intervention should quantify lymphocyte redistribution; and a NET-directed treatment should assess NET biomarkers. This approach reduces the risk of declaring a drug ineffective when the target was never adequately engaged.

9. Combination therapy with reperfusion and standard stroke care

Neuroinflammation-targeted drugs are most likely to succeed as adjuncts rather than replacements for reperfusion. Thrombolysis and thrombectomy restore perfusion, while immunomodulation may reduce the secondary damage associated with ischemia–reperfusion. The ideal combination could therefore be mechanistically complementary: reperfusion rescues threatened tissue, while targeted inflammation control preserves the neurovascular unit.

Combination trials must nevertheless address safety carefully. Immunomodulation may increase infection risk, and some agents may alter bleeding risk or interact with reperfusion therapies. Trial protocols should monitor hemorrhagic transformation, pneumonia, urinary infection, wound complications and other systemic outcomes. The therapeutic window should also be linked to recanalization status because inflammatory signalling differs between persistent occlusion and successful reperfusion.

10. Translational challenges.

Challenge	Implication for drug development
Biological duality	Inflammation causes injury but also clears debris and supports repair. Complete suppression can be counterproductive.
Timing	Target activation changes rapidly from minutes to weeks; a single fixed treatment window may be inappropriate.
Heterogeneity	Stroke mechanism, infarct size, reperfusion status, age, sex, diabetes and infection alter inflammatory biology.
BBB penetration	Large biologics may have limited CNS exposure; systemic effects may dominate pharmacology.
Safety	Immune suppression can increase infection risk, while excessive immune activation may worsen injury.
Preclinical models	Young animals with standardized occlusion do not reproduce the comorbidity and heterogeneity of clinical stroke.
Endpoint selection	Changes in cytokines or infarct volume do not always translate into functional recovery.
Manufacturing and delivery	Cell therapies and nanomedicines require complex quality control and biodistribution assessment.
Reproducibility	Some targets show contradictory effects across laboratories and experimental models.
Regulatory complexity	Repurposed drugs, biologics and advanced delivery systems require different development pathways.

11. Future directions

Future pharmacology is likely to move from single-pathway inhibition toward precision control of inflammatory networks. Several directions deserve priority:

1. Biomarker-guided enrolment. Patients should be selected according to inflammatory phenotype rather than stroke diagnosis alone.
2. Pre-recanalization intervention. Targets such as NLRP3 and NETs may be particularly relevant before reperfusion, when inflammatory amplification is already underway.[19]
3. Cell-specific delivery. Nanoparticles or antibody-based systems could deliver agents to microglia, neutrophils or cerebral endothelium while reducing systemic exposure.
4. Pro-resolving therapy. Instead of suppressing inflammation, therapies may promote resolution through Tregs, specialized pro-resolving mediators or metabolic reprogramming.
5. Combination strategies. Reperfusion plus antioxidant, inflammasome or immune-modulating therapy may address multiple stages of injury.
6. Longitudinal monitoring. Serial biomarkers, MRI measures of BBB integrity and digital functional outcomes should be integrated into trials.
7. Diverse preclinical models. Age, sex, hypertension, diabetes, obesity and infection should be represented before clinical translation.
8. Integration with rehabilitation. Anti-inflammatory treatment should be designed around the transition from injury to repair rather than treating these phases as independent.

12. CONCLUSION

Neuroinflammation is now a central component of the pathophysiology of stroke, but its therapeutic exploitation requires precision. Microglia, astrocytes, endothelial cells, neutrophils and adaptive immune cells participate in a dynamic response that can be damaging early and beneficial later. Major molecular nodes—including HMGB1/TLR4, NF-κB, NLRP3, IL-1β, IL-6, TNF-α, MMPs, S1P signalling and NET formation—provide a broad pharmacological landscape.

Human trials have produced mixed results. Fingolimod and natalizumab demonstrate the promise and pitfalls of manipulating peripheral leukocyte trafficking. Anakinra supports the feasibility of IL-1 pathway modulation but requires larger efficacy trials. Edaravone dexborneol provides evidence that multitarget antioxidant/anti-inflammatory neuroprotection can improve functional outcomes in selected populations. The 2026 EMPHASIS trial represents an important step in evaluating minocycline at scale and illustrates the continuing interest in repurposed anti-neuroinflammatory drugs.[27,32-36]

The next generation of therapies should not aim to eliminate inflammation. Instead, they should suppress damaging inflammatory amplification while preserving host defence, debris clearance and tissue repair. The most plausible path forward is biomarker-guided, time-

dependent and cell-selective treatment used alongside reperfusion. NLRP3 inhibitors, NET-directed therapies, Treg-based approaches, microbiome/metabolite interventions, targeted delivery systems and neuromodulation are promising but remain investigational. Successful translation will depend on rigorous clinical trial design, target-engagement biomarkers, appropriate timing and careful attention to patient heterogeneity.

ABBREVIATIONS

Abbreviation	Meaning
AIS	acute ischemic stroke
BBB	blood–brain barrier
CNS	central nervous system
DAMP	damage-associated molecular pattern
EVT	endovascular thrombectomy
HMGB1	high-mobility group box 1
ICH	intracerebral hemorrhage
IL	interleukin
MCAO	middle cerebral artery occlusion
MMP	matrix metalloproteinase
mRS	modified Rankin Scale
NET	neutrophil extracellular trap
NLRP3	NOD-, LRR- and pyrin domain-containing protein 3
NF-κB	nuclear factor kappa B
ROS	reactive oxygen species
S1P	sphingosine-1-phosphate
TGF-β	transforming growth factor beta
TLR	Toll-like receptor
TNF-α	tumor necrosis factor alpha
Treg	regulatory T cell
VNS	vagus nerve stimulation

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