

Rethinking corticosteroid therapy in autoimmune neurology

Strapline

Teoh and colleagues assess corticosteroid treatment regimens in autoimmune neurological disease in the light of available preclinical and clinical evidence, highlighting current gaps in the literature that are important to consider when designing future therapeutic approaches.

Corticosteroids: a legacy in need of a rethink

Since their introduction into clinical practice in the 1940s, corticosteroids (CSs) have been a cornerstone of the therapeutic arsenal for neuroinflammatory disorders, including autoimmune encephalitis (AE), multiple sclerosis (MS), neuromyelitis optica spectrum disorder (NMOSD), and myelin-oligodendrocyte glycoprotein antibody-associated disease (MOGAD) during acute attacks and for relapse prevention.

During acute neuroinflammatory episodes, the first-line immunotherapies alongside CSs include intravenous immunoglobulin (IVIG) and plasma exchange (PLEX). These treatments can be used sequentially or in combination. Some studies suggest that treatment with PLEX and CSs yields better outcomes than CS monotherapy in NMDAR-antibody encephalitis, which is similar to the results in other antibody-mediated conditions like NMOSD.¹ The evidence regarding long-term management is evolving with the emerging use of novel immunotherapy in several clinical trials and case series, which prompts the question of the role of CSs in current clinical practice.

Key questions remain untested and unanswered: In acute attacks or relapses, 1) Are higher doses of CS more effective than lower doses and is there a “ceiling effect”? 2) What factors influence individual responses to CS?; For relapse prevention, 1) What is the optimal CS regimen? 2) What are the best strategies for optimal response and minimising CS complications? In systemic conditions such as ANCA-associated vasculitis, there continues to be an active debate about whether high-dose IV Methylprednisolone (MP) should be used at all. The trend favours minimising CS exposure to reduce complications such as diabetes, infections, and neuropsychiatric side effects. Similarly, in neuroinflammatory disorders, a

critical unmet need exists to define evidence-based CS use and refine treatment strategies for better patient outcomes.

Corticosteroid mechanisms

Genomic versus non-genomic mechanisms

CSs exert their effects on immune cells via both genomic and non-genomic mechanisms. The genomic pathway involves transactivation, by promoting gene transcription of metabolic regulators, and transrepression, which silences proinflammatory transcription factors and reduces proinflammatory cytokine production and prostaglandin synthesis (Figure 1A). Transactivation is responsible for many of the detrimental effects of CSs caused by activating genes involved in carbohydrate, lipid, and protein metabolism. The interplay between these pathways is highly intricate as transactivation can also enhance anti-inflammatory mediators. Genomic effects require hours or days before changes at cellular, tissue, or organism levels become evident.² But if so, how does high-dose CS achieve rapid clinical effects in acute neuroinflammatory conditions? Non-genomic mechanisms are one possible explanation. They modulate inflammatory and immune cells through three nuclear-independent pathways: 1) non-specific interactions with the cell membrane; 2) non-genomic effects mediated by the cytosolic glucocorticoid receptor (cGCR) and 3) effects dependent on membrane-bound GCR (mGCR) (Figure 1A).²

These combined actions suppress various functional capabilities of immune cells such as neutrophils, B cells, and CD4⁺ T cells by reducing their availability and effector functions.³

A further important aspect of CS activity in neuroinflammatory conditions is the selective permeability of the blood-brain barrier (BBB). CS-BBB permeability is directly proportional to lipophilicity and inversely related to the number of hydrogen bonds formed in an aqueous solution. Among commonly used CSs, a methyl group on methylprednisolone (MP) and a fluoride side chain on dexamethasone enhance hydrophilicity and CNS penetration (Figure 1B).⁴ This has important implications for CS choice for maximising effectiveness whilst minimizing side effects.

The “big shot”

‘Very high-dose’ CS therapy (prednisone-equivalent of >100 mg per day) and ‘pulse’ therapy (prednisone-equivalent of ≥ 250 mg per day, usually given for 1–5 days) are widely used for acute treatment of CNS autoimmune disorders, most common being MP (250-1000mg) and, in certain countries, dexamethasone (50-200mg). These doses saturate all GR, eliciting the full spectrum of genomic effects while also modulating receptor pharmacodynamics (receptor offloading and re-occupancy) and altering receptor synthesis and expression. Notably, receptor saturation is thought to enhance therapeutic benefit through additional non-genomic mechanisms.²

In most conditions, pulse CS therapy is followed by oral prednisolone at 1–2mg/ kg/day with a gradual taper, often overlapping with long-term immunotherapy if indicated.¹ However, the dose of pulsed CS and optimal duration, tapering rate, dose and CS formulation required to maintain disease remission remain unknown. Future research should focus on refining CS treatment protocols by integrating disease-specific immunobiology (e.g. autoantibody subclass), risk stratification using clinical/paraclinical features or biomarkers.^{5,6} These approaches will help to determine the optimal CS regimen for different diseases.

Autoimmune encephalitis

During the acute phase of AE, second-line agents (e.g., rituximab and cyclophosphamide) are added when there is an inadequate response to first-line therapy and to serve as bridging therapy to prevent early relapses. However, supportive evidence for other immunotherapies, such as proteasome inhibitors (bortezomib) and interleukin (IL)-6 inhibitors (tocilizumab) remains limited. Moreover, there is lack of robust data to guide maintenance immunotherapy in AE.¹

Beyond immunotherapy, the challenges of treating AE are epitomised by the differing CS responses observed in NMDAR and LGI1 antibody encephalitis (AbE). A retrospective study of NMDAR AbE demonstrated that first-line immunotherapy (CS, IVIG and/or PLEX) with/without tumour removal resulted in improvement for 53% of patients at four weeks. Notably, CS monotherapy showed suboptimal efficacy, whereas combination with other first-line immunotherapies yielded better functional outcomes. In contrast, LGI1 AbE is highly responsive to CS treatment. Whilst faciobrachial dystonic seizures (FBDS) resolved in only

10% of patients on antiseizure medications, immunotherapy—70–75% of which involved CS—resulted in resolution in 51% of cases at 30 days and 88% at 90 days.⁷ The rapid onset of CS non-genomic activities and modulation of BBB permeability may explain often rapid seizure resolution (Figure 1A).⁴ It is unclear whether non-genomic modes of action are enabling better outcomes at 30 and 90 days or whether this is due to synergy between CS and other immunosuppressants.

The variable responses to CS may stem from differences in predominant immunoglobulin (IgG) subclasses. NMDAR-AbE is associated primarily with IgG1, whereas LGI1-AbE is driven by IgG4.⁷ However, it is equally possible that distinct contributions of other immune cell types, including T cells, could underlie this difference.

Furthermore, CS responses are highly cell-type dependent, an often-overlooked factor in CNS autoimmune disorders, where different immune cell populations drive pathology. In one study, the transcriptional response to CS varied markedly between cell types, with haematopoietic cells, particularly neutrophils, showing the strongest response, followed by CD4⁺ T cells, B cells, monocytes and non-haematopoietic cells (Figure 1B).³ Given that CS effects on CD4⁺ T cells are greater than on B cells, this may partly explain their suboptimal efficacy in antibody-mediated diseases.

Additionally, CSF autoreactive B cells have been demonstrated in patients with NMDAR and LGI1-AbE. These pathogenic autoantibodies are either produced peripherally before transferring into the CSF and brain parenchyma or produced intrathecally, establishing a compartmentalised immune response.⁶ Given this, we would predict that the ability of specific CS agents to reach therapeutic concentrations in the CSF is important in effectively treating CNS autoimmune disorders characterised by CSF-resident autoreactive B cells. This in turn suggests that the BBB penetration potential of specific CS is an important consideration when deciding on an appropriate immunotherapeutic regimen.

Current AE treatment guidelines for adults are largely based on cohort studies: some retrospective and some prospective. CS is the preferred treatment in cases such as demyelinating MRI patterns (suggesting AE-demyelination overlap), dotted or radial enhancement (CLIPPERS or autoimmune GFAP astrocytopathy), LGI1-AbE, and suspected or confirmed paraneoplastic AE with T-cell-mediated inflammation.¹ Collectively, these

findings underscore the importance of tailoring CS-based therapies to the distinct immunopathological features of each AE subtype rather than relying on a uniform treatment approach.

Optimizing corticosteroid use in neuroinflammatory disorders: insights from MS, NMOSD, and MOGAD

The use of high-dose CS to treat acute optic neuritis (ON) and multiple sclerosis (MS) is largely based on the findings from the Optic Neuritis Treatment Trial (ONTT). The study demonstrated that intravenous methylprednisolone (250 mg every 6 hours for 3 days) followed by oral prednisone (1 mg/kg daily for 11 days) given within 8 days of onset improved visual field outcomes significantly at one month compared to oral prednisone (1 mg/kg daily for 14 days). However, there was little difference in the ultimate degree of clinical recovery following a relapse.⁸ With the advent of disease-modifying treatment (DMT), CS use in MS has been limited to a short course in early disease with early introduction of DMT, which has improved the outcome of MS patients. This model needs exploring in other areas where targeted therapies are available.

In NMOSD, autoantibodies against the astrocyte water channel aquaporin-4 (AQP4)-IgG penetrate the CNS, leading to astrocyte destruction and BBB breakdown. During acute attacks, high-dose CS broadly suppresses the immune system and helps to restore BBB integrity.² However, subsequent use of CS therapy following an acute attack remains challenging due to the lack of evidence to guide optimal dosing and duration. One study found that rapid tapering (≤ 10 mg within one year and/or ≤ 5 mg within two years after clinical attacks) was associated with a higher relapse rate compared to slower taper (36.7% vs 17.7%, $P = 0.02$).⁹ Notably, this study did not account for patients receiving combination therapy with other immunomodulators.

Since 2019, four targeted therapies—eculizumab, inebilizumab, satralizumab, and ravulizumab—have been approved for AQP4-IgG-positive NMOSD to reduce the risk of relapses. These agents exhibit a faster onset of action compared to conventional immunomodulators, raising questions about the continued reliance on prolonged CS use. There is however, limited guidance on how CS tapering should be adjusted in the context of

these newer therapies and further studies in larger patient cohorts are needed to determine the optimal dosing and duration of CS in patients receiving targeted therapies.

MOGAD was once considered a monophasic disease, however, recent studies have shown that relapse rates were 47% at 6–24 months and 72% at 5 years. The decision to institute maintenance immunotherapy in MOGAD is more nuanced due to disease heterogeneity. Currently, there is no novel maintenance immunotherapy approved for use in MOGAD. Among traditional immunotherapy, B-cell depleters (20%) are the most used, followed by oral prednisolone (15%) and azathioprine (12%). Given the risks associated with prolonged CS exposure, a more targeted and proactive approach prioritising early immunosuppressive therapy for high-risk patients rather than extended CS tapers may be a more effective strategy. One study has shown that maintaining a prednisone dose of ≥ 12.5 mg/day (0.16 mg/kg/day in children) for at least three months resulted in a 79% reduction in relapse risk and extending prednisone beyond three months did not confer additional relapse protection.⁵

Can we replace corticosteroids?

CS toxicity is an enduring challenge in both research and clinical practice. Can we redesign their use in CNS autoimmune disorders for better efficacy and fewer side effects? Emerging strategies offer promising alternatives (Figure 2).

Early intervention in acute disease phases could disrupt inflammatory cycles before they become chronic. Cytokine-targeted immunotherapies such as Tocilizumab [anti-IL-6R monoclonal antibodies (mAbs)], demonstrate rapid efficacy (response within a week), and its combined use with CS, IVIG, rituximab, and tumour removal (T-SIRT protocol) within the first month is associated with better outcomes at one year in NMDAR-AbE.⁷

Could we retain the anti-inflammatory power of CSs while minimizing their toxicity? Novel agents such as selective glucocorticoid-receptor agonists (SEGRAs), selective glucocorticoid-receptor modulators (SEGRMs), and liposomal glucocorticoids have the potential to reshape treatment paradigms.²

Decades of high-dose CS use may be giving way to a more strategic, lower-dose approach. In ANCA-associated vasculitis (AAV), the PEXIVAS (Plasma Exchange and Glucocorticoids in Severe ANCA-Associated Vasculitis) trial confirmed the noninferiority of the reduced-dose oral CS regimen compared with the standard-dose regimen, with lower rates of serious

infections.¹⁰ The success of Avacopan has led to further reduction in CS use in AAV.¹⁰ Studies with lower dose CS regimens are needed in CNS autoimmune disease, and this may offer a chance to deliver effective treatment whilst reducing the side effects associated with high dose CS treatment, particularly when using more CNS-penetrant types of CS therapy.

Conclusion

We highlight in this article the lack of evidence guiding the use of CS in CNS autoimmune disorders, particularly regarding the choice of CS, induction and maintenance regimens, and tapering strategies. Current practices often overlook disease-specific immunobiology, host pharmacodynamics, cell-dependent effects, glucocorticoid receptor (GR) isoform variability, and differences in BBB penetration. While CS remains a potent immunomodulator, its long-term use results in considerable morbidity. With the advent of targeted therapies, we need to re-evaluate the role of CS to optimize outcomes and design studies to identify ideal CS regimens for each neuroinflammatory disease. Well-designed clinical trials are necessary to improve the evidence on tailoring CS therapy to maximise benefits whilst minimising adverse effects.

Crystal Sing Chiek Teoh,¹ Shirish G Dubey^{2,3,†} and Adam E. Handel^{4,5,†}

1 Department of Neurology, Queen's Medical Centre, Nottingham University Hospital, Nottingham NG7 2UH, UK

2 Department of Rheumatology, Oxford University Hospital, Oxford OX3 7HE, UK

3 Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford OX3 7LD, UK

4 Department of Neurology, John Radcliffe Hospital, Oxford University Hospital, Oxford OX3 9DU, UK

5 Oxford Autoimmune Neurology Group, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford OX3 9DU, UK

[†]These authors contributed equally to this work.

Correspondence to: Dr Adam E. Handel

Full address: Oxford Autoimmune Neurology Group, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford OX3 9DU, UK

E-mail: adam.handel@ndcn.ox.ac.uk

Running title: Rethinking corticosteroids in neurology

Short biographies:

Crystal Teoh is a Neurology Specialist Registrar working in Nottingham.

Shirish Dubey is a Consultant Rheumatologist working in Oxford with expertise in vasculitis and connective tissue disorders.

Adam Handel is a Consultant Neurologist running the Oxford encephalitis clinic and leads a research group studying autoimmune encephalitis.

Funding

A.E.H. is funded by the National Institute for Health Research (NIHR) Oxford Health Biomedical Research Centre (BRC), the Medical Research Council (United Kingdom) [MR/X022013/1] and MyAware. The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.

Competing interests

A.E.H. has received previous research funding from UCB-Pharma and Argenx. S.G.D. is part of advisory boards for Boehringer Ingelheim and Abbvie. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

References

1. Abboud H, Probasco JC, Irani S, et al. Autoimmune encephalitis: proposed best practice recommendations for diagnosis and acute management. *J Neurol Neurosurg Psychiatry*. 2021;92(7):757-768. doi:10.1136/jnnp-2020-325300

2. Stahn C, Buttgereit F. Genomic and nongenomic effects of glucocorticoids. *Nat Clin Pract Rheumatol*. 2008;4(10):525-533. doi:10.1038/ncprheum0898
3. Franco LM, Gadkari M, Howe KN, et al. Immune regulation by glucocorticoids can be linked to cell type-dependent transcriptional responses. *J Exp Med*. 2019;216(2):384-406. doi:10.1084/jem.20180595
4. Chen TC, Mackic JB, McComb JG, Giannotta SL, Weiss MH, Zlokovic BV. Cellular uptake and transport of methylprednisolone at the blood-brain barrier. *Neurosurgery*. 1996;38(2):348-354. doi:10.1097/00006123-199602000-00023
5. Trewin BP, Brilot F, Reddel SW, Dale RC, Ramanathan S. MOGAD: A comprehensive review of clinicopathological features, therapy and outcomes in 4699 patients globally. *Autoimmun Rev*. 2025;24(1):103693. doi:10.1016/j.autrev.2024.103693
6. Ramanathan S, Brilot F, Irani SR, Dale RC. Origins and immunopathogenesis of autoimmune central nervous system disorders. *Nat Rev Neurol*. 2023;19(3):172-190. doi:10.1038/s41582-023-00776-4
7. Trewin BP, Freeman I, Ramanathan S, Irani SR. Immunotherapy in autoimmune encephalitis. *Curr Opin Neurol*. 2022;35(3):399-414. doi:10.1097/WCO.0000000000001048
8. Gal RL, Vedula SS, Beck R. Corticosteroids for treating optic neuritis. *Cochrane Database Syst Rev*. 2012;4(4):CD001430. Published 2012 Apr 18. doi:10.1002/14651858.CD001430.pub3
9. Takai Y, Kuroda H, Misu T, et al. Optimal management of neuromyelitis optica spectrum disorder with aquaporin-4 antibody by oral prednisolone maintenance therapy. *Mult Scler Relat Disord*. 2021;49:102750. doi:10.1016/j.msard.2021.102750
10. Massicotte-Azarniouch D, Canney M, Karnabi P, et al. Glucocorticoid Minimization in Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis: An International Survey of Clinicians. *Kidney Med*. 2024;6(8):100858. doi:10.1016/j.xkme.2024.100858

Figure legends

Figure 1 Molecular pathways of CS action. A) Genomic and non-genomic actions of CS: Genomic actions. In their inactive state, GR exists as multimeric complexes. CS enters the cell via GR transporter and binds to cGR, triggering receptor activation, dimerisation and nuclear translocation with subsequent transactivation or transrepression. Non-genomic actions: 1) Interaction with cellular membrane: CS alters the function of membrane-associated proteins, with rapid reductions in calcium and sodium cycling across membranes, and decreases in ATP production by mitochondria; 2) CS-cGR complex inhibition of PLA2: This reduces arachidonic acid production; 3) CS-mGR complex inhibition of enzymatic activities: Lymphocyte-specific protein tyrosine kinase and Fyn, components of the mGR–multimeric complex, are inhibited by CS binding. These proteins are crucial in initiating T-cell receptor signaling, cytokine synthesis, and cellular migration or proliferation. B) Current paradigm of factors influencing CS effects: i) Cell-dependent effects: Hematopoietic cells showed a stronger CS-induced transcriptional response: neutrophils > CD4⁺ T cells > B cells > monocytes; ii) GR isoforms: Research has mainly focused on GR α and GR β , which are isoforms of GR derived from alternative splicing of exon 9. GR α is the biologically active isoform, whereas GR β lacks helix 12 and hence is not capable of binding CS but expression of a splice variant of GR β can influence CS sensitivity via its dominant negative effects on GR α function; iii) Drug-CSF/brain penetration: CS – BBB penetration in decreasing order, MP > Dexamethasone > Prednisolone/hydrocortisone; iv) Disease heterogeneity: Inter-individual variability in CS response varies by CS levels, immune dysregulation and differential receptor sensitivity. Abbreviations: AP, activator protein; cGR, cytoplasmic glucocorticoid receptor; GRE, glucocorticoid receptor element; HSP, heat shock protein; IL, interleukin; mGR, membrane glucocorticoid receptor; MAPK, mitogen-activated protein kinase; NF κ B, nuclear factor κ B; PLA2, phospholipase A2; Src, steroid receptor coactivator; TK, tyrosine kinase; TNF, tumour necrosis factor.

Figure 2 Emerging strategies for CS use in CNS autoimmune disorders. Abbreviations: mAb, monoclonal antibodies; JAK, Janus Kinase; BTK, Bruton's tyrosine kinase