

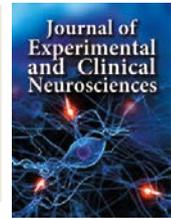


Swedish Science Pioneers

Journal of Experimental and Clinical Neurosciences

(JECNS)

www.jecns.com



Review Article

Glucocorticosteroids: Risk-Benefit Appraisals in Multiple Sclerosis and MS-Associated Optic Neuritis

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Keywords:

Corticosteroids

Glucocorticoids

Steroids

Brain atrophy

Multiple sclerosis

Optic neuritis

Treatment algorithm

Outcome measures

Adverse effects

Risk stratification

Abstract

Glucocorticosteroids/GC are the cornerstone of immunosuppression utilized for decades in the treatment of multiple sclerosis (MS) and MS-related optic neuritis (MS-ON). Steroids are often prescribed as either 'monotherapy' or add-on in structured 'polytherapy' regimens or concomitant with other immunosuppressants and/or immunomodulatory drugs, depending upon the disease situation. This review focuses on the pharmacologic corticosteroids, such as methylprednisolone, that are prevalently utilized in MS care. Among other aims, the treatment effects on dynamic patterns of cerebral atrophy, optic nerve inflammation and neurodegeneration are evaluated, and a risk stratification of patients with MS and MS-ON is presented. It provides details on selected case reports, as well as pivotal clinical studies and attributable significant (clinically important) outcomes. It then addresses primarily the outcomes related to demyelination or neurodegeneration, myelin repair or neuroregeneration, and the undesirable such safety issues as ataxia, avascular necrosis, infections, and cerebral atrophy. At the end, we put together a critical assessment of both explicit and implicit observations on various treatment configurations, including NOAEL (no observed adverse effect level) dosing for reasons where it is currently unclear whether or ever a safe and effective clinical dosing of steroids is established in clinical trials for MS and MS-ON, discuss impartially the current state-of-knowledge, identify scientific data gaps, and offer a fresh perspective on how to improve the benefits and minimize the risks of steroids in multiple sclerosis.

Received: 2014-07-23

Accepted: 2014-10-03

DOI: [10.13183/jecns.v1i1.10](https://doi.org/10.13183/jecns.v1i1.10)

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Introduction

Although there are reports that multiple sclerosis (MS) can shorten life-expectancy by up to 20 years; this cannot reliably be assessed from MS registry studies, which are subject to regional selection bias from observational studies, and patient variability which itself depends upon the quality of the treatments. Most people survive past their fifties, though some 20% accumulate severe disability at 15 years and increasing to 69% by 40 years after onset [1]. In spite of disease-modifying treatments (DMT), many develop cognitive impairments, fatigue, and debilitating neuromuscular motor [2] and vision impairments [3] and some develop fatal infections which may be the major cause-of-death [4].

Glucocorticosteroids/GCs (also called glucocorticoids, corticosteroids or steroids) use in multiple sclerosis, their risk-benefit profiles and impact on the molecular pathogenic mechanisms and target cells, have not been previously critically reviewed. In recent decades, the first generation agents cortisone and hydrocortisone have steadily been replaced with the newer analogues such as prednisolone/P and methylprednisolone/MP, which are administered either intravenously or orally with other immune-modifying-therapies to treat MS attacks from an impartial viewpoint.

Corticosteroids (CS) are generally recognized as potent anti-inflammatory agents with acceptable AEs and manageable side-effects. Although radiological evidence indicates reduction or inhibition of white-matter lesions, it is unclear whether CS

treatment alone produces this result. Of note, there is a distinct subset of patients receiving CS in whom disease activity persists or worsens. Thus, it would be important to study the efficacy of GC therapy in steroid-responsive multiple sclerosis compared to steroid-resistant multiple sclerosis. Steroid-resistant MS patients were defined by the lack of improvements in neurological conditions within 30 days after high-dose methylprednisolone treatments for 2 consecutive relapses (1000 mg given intravenously for five days, presumably during each relapse).

This review compiles and summarizes datasets extracted from clinical investigations, and *ex vivo* laboratory studies mostly published in Medline, and addresses both strengths and weaknesses of GCs in the management of MS and associated complications. It highlights the effects of corticosteroids in MS and MS-ON and focuses on:

- Evaluations of the clinical uses of corticosteroids in acute relapses, treatment effects on dynamic patterns of cerebral atrophy, optic nerve inflammation, neurodegeneration clinical outcome measures; and
- Assessments of the elements of 'risk' in all its dimensions, including unintended side-effects, recent controversial reports, and unreconciled issues – to attain clues on how to mitigate risks sensibly or through implementation of sensible treatments.

We surmise that multiple risk factors (infection, differential sensitivity, etc.) impact on CS therapy outcomes, whereas the entire basis of CS use in the treatment of MS attacks is the notion that MS is an autoimmune disease. Since there is ample evidence demonstrating lack of efficacy of CS, one might consider how CS may adversely undermine the beneficial role of immune mechanism(s) in neuronal repair and disease recovery. There are also the dreaded side effects associated with CS: osteonecrosis, osteoporosis and immunodeficiency. This article provides details and insight into the current state-of-knowledge, with the hope of cultivating interest in the risk-benefit profiles of glucocorticosteroids in multiple sclerosis and optic neuritis, and recommends the critical risks to be recognized, consistently identified and mitigated.

Biological Observations, Publications, and Assessments

PubMed and online databases were searched and selected evidence-based articles were evaluated on the principles of novelty, degree of scientific controversy, medical/scientific impact, and quality of the methodology were critically analyzed. Several review articles that met the criteria were also included. Some citations were excluded because of the scope and space constraints. The outcome of four active trials currently listed in <http://clinicaltrials.gov> to determine efficacy and safety of intravenous and oral corticosteroids in MS and one study for optic neuritis are not yet available.

Corticosteroids use in multiple sclerosis

Pharmacologic GC analogs (such as methylprednisolone/MP and prednisolone/P) are being increasingly prescribed in MS and MS-ON. Corticosteroids can suppress the inflammations through their potent anti-inflammatory effects; it is important to weigh the benefits versus adverse effects of GC therapy during a particular disease course (advanced MS, PPMS, RRMS, SPMS, and MS-ON). Does a clinically-defined symptom respond better than overall disease status? Is there a significant correlation between corticosteroid therapy and risk of disease worsening?

The rationale for corticosteroids therapy is probably based on the clinical and drug-responsiveness status of the prior treatments, but may also be rooted in unsubstantiated evidence that corticosteroids inhibit cerebral atrophy, apart from suppression or elimination of destructive immunomodulatory proteins and autoreactive immune cells [5], reductions of pathogenic autoantibodies [6] and neutralizing antibodies against biologic drugs [7].

Corticosteroids can interfere with TNF-alpha activity. CS treatment has been shown to upregulate ciliary neurotrophic

factor (CNTF) which in turn inhibits the pro-inflammatory and neurotoxic effects of TNF α . In addition, CS may downregulate TNF expression but this finding has not been shown consistently in all studies [8, 9] (Table 1), perhaps due to differential GC-sensitivity in a given patient population.

Autoantibodies in MS are heterogeneous, have inconsistent activity, titers and specificities and may fluctuate in disease flare during GC treatments. Exactly which immune parameter(s) is involved in MS attacks remains elusive. Some clinically unsubstantiated evidence puts emphasis on the significance of autoantibodies. Autoantibodies in sera of MS patients (77% of progressive and 85% of relapsing-remitting) have catalytic activity against a short recombinant fragment of the myelin basic protein (peptide 81-103) [10]. Elsewhere, complement-dependent demyelinating IgG activity was found in about 30% of MS, notably in two cases attributed to antibody-mediated neurotoxicity [11].

Methylprednisolone/MP reduces levels of the poly/autoreactive antibodies in CSF [6]. High-dose methylprednisolone/MP decreases CD4+ T-cells, IgG and albumin, and increases CD8+, but only the CD4+ T-cell decline correlates apparently with early clinical benefit, and one third of the patients were non-responders [12] (Table 2). The impact of autoantibodies, in particular anti-myelin antibodies as biomarkers, appears clinically irrelevant as the target autoantigens are unknown [13].

There is revived interest in the clinical value of biologics-drugs-induced neutralizing antibodies (NAb) which are thought to blunt efficacy [14]. Contrary to some reports [7], others found insignificant NAb levels and lack of restoring the bioactivity of interferon beta (IFN β) [15, 16] (Table 2).

There is no evidence that high-dose corticosteroids suppress long-term neuronal injury and improve the disability progression after sequential relapses. Although the radiological images show considerable reductions of lesions volume during early months after GC treatment [17], the neuronal loss continues despite treatment. Consistent with this, in a recent trial (MECOMBIN) including GC and IFN β treatment, relapse frequencies decreased almost 60% during year-1, though this trend waned in years 2 and 3 [18]. The authors conclude: "there was 38% relative reduction in relapse rate and less T2-lesion accumulation in the methylprednisolone group compared with the placebo arm, this does not seem to reduce disability progression any more than interferon beta-1a" (Table 3).

In MECOMBIN, the analytical choices allow neither to discriminate the responders from non-responders nor to rule out long-term SAEs, no matter how rare. In another trial (Avonex-Steroids-Azathioprine/ASA), combining immunosuppressants and immunomodulatory drugs allowed the use of low doses to gain better outcomes. The results were disappointing, indicating increased brain atrophy, cortical lesions and pathophysiological markers [19- 21] (Table 3).

Corticosteroids use in optic neuritis

Several goals should guide any potential treatment of optic neuritis: 1. Accelerating visual recovery; 2. Improving long-term visual function; 3. Reducing relapse rate; 4. Reducing the risk of developing MS in the future. All of these goals must undoubtedly be balanced against the overarching issue of patient safety.

Systemic corticosteroids have been an important part of the management of ON. The urgency for establishing a rigorous treatment for ON came on the heels of a landmark study [22] in which the authors reported a significant risk of MS developing in patients who had presented initially with ON. While systemic steroids were already being used in the treatment of extra-ocular MS and also of ON, there was no large-scale prospective study looking at both the natural history of ON and the potential benefits of corticosteroids [23, 24] in the treatment of this condition. In 1988, the first major prospective study addressing the efficacy of systemic steroids in the treatment of ON was established. The Optic Neuritis Treatment Trial (ONTT) has become the benchmark study of ON [25].

In the ONTT, enrollees were followed prospectively for 15 years and found to have a 50% cumulative risk of developing MS. The risk of MS increased substantially in those who presented with optic neuritis associated with lesions on baseline non-contrast MR imaging of the brain. Overall, 56% had a 10-year risk of developing MS if brain lesions were present and a 22% risk, in the absence of brain lesions.

The ONTT treatment plan was organized into three randomized arms: oral prednisone vs. IV methylprednisolone followed by oral prednisone vs. placebo for 14 days. The study showed that IV steroids accelerated visual recovery; but after a month, there was no significant difference in visual acuity, color vision or contrast sensitivity between treatment and placebo arms. Another noteworthy finding of the ONTT was that patients receiving oral prednisone had a higher rate of recurrence of the ON. Other prospective studies have confirmed that IV steroids do not produce any long-term visual benefit for patients with ON [26-28].

The use of systemic corticosteroids in the treatment of MS-related ON remains controversial. There is no incontrovertible evidence pointing to a clear long-term benefit both in terms of visual recovery or occurrence of MS. In a Cochrane review [29], the authors searched all randomized trials for any form of CS used in the treatment of ON between 1950 and 2012. Based on six trials meeting their criteria for analysis, they concluded that neither oral nor IV steroids produced any benefit on visual acuity, contrast sensitivity or visual fields. In effect, they corroborated the findings of the ONTT.

In the face of substantial data arguing against the use of systemic CS, physicians continue to treat ON with CS in the US [30,31]. When surveyed, many ophthalmologists and neurologists believe that CS enhances visual recovery. In one survey, 48.4% of ophthalmologists recommended 3 days of high-dose IV methylprednisolone. 32.9% did not recommend any treatment. Neurologists appeared to have a lower threshold to treat: 87.3% of neurologists reported that they would treat acute ON with IV methylprednisolone most of the time.

MS treatment algorithm

What are the rationales for corticosteroid therapy? What evidence-based decision points encourage MS practitioners to

give GCs as a replacement or add-on to other established MS therapeutics? Does the choice for GC therapy depend upon the disease situation – or whether or not the patients respond/tolerate other medications? Can stratifying patients for individualized risks be the best predictor of the outcomes? If so, which biomarkers and clinical parameters should be utilized?

GC-induced paraclinical and clinical changes

The role of immune system in multiple sclerosis and optic neuritis is multi-faceted. One major aspect involves disruption of the blood brain barrier during MS attacks, as evidence on gadolinium (Gd)-enhanced MRI images. These images are indicative of active inflammation and often used as rationale to initiate treatments [32, 33].

In phase II studies on relapsing-remitting MS monitored for 5 years, high-dose cyclical pulses of methylprednisolone/MP [1 g/day intravenously for 5 days with oral prednisone taper for 4 days, every 4 months for 3 years then every 6 months for 2 years (pulsed IVMP group) did not affect early events in lesion formation and in fact, resulted in significantly more T2 lesions (1779 vs. 1179, p<0.0001) in pulsed IVMP group compared to patients who received IVMP only for relapses. T1 black holes and confluency of Gd-enhancing T2 lesions changed: initially datasets showed decrease in T1 lesion volume (2.7 vs. 6.7 ml) in favor of the steroid treatment arm with no significant differences in T2 lesions [34]. Subsequent analysis partially resolved the ambiguity that fewer confluent large T2 lesions (>10mm, 165 vs. 541) were accompanied by smaller T2 lesions (<5 mm, 1082 vs. 288). Although there were no apparent differences in total lesion volumes between two treatment arms at study entry, the volumes appear increased 130% more in the pulsed IVMP group than the IVMP for relapse group at the end of study period. Furthermore, when the data for both arms are combined, an average increase of 15 ml is found in total lesion volume [35]. The increased small T2 lesions may represent expanding constellations of 'newly forming' lesions or accumulating brain atrophy. This trend may reflect treatment failure, presumably because of partly new demyelination, necrosis or axonal loss in the wake of recrudescence inflammation often attended by tissue edema.

Table 1. Corticosteroids resistance and cytokines expressions in blood leukocytes of MS patients.

Test drug	Study design	No. of pts (GC only)	Dosage	Trial duration	Outcome measures	Relevant Conclusions	Strengths/Limitations	References
Methylprednisolone (±IFNβ)	open label	16 (5)	high-dose IV on day-1 to 4 and 30	30 days	Cytokines neurotrophics, MSSS	Increased CNTF expression (86%) Modestly decreased CD3+ T cells and increased B cells/macrophages	Significance of CNTF inhibition of TNFα in CNS compartment unknown	[8]
Methylprednisolone	open label	27 (22)	2 g total (1 g/d on days 1-3 or 0.5 g/d on days 1-5)	6 weeks	TNFα, EDSS	Suppression of TNFα (≥50%) production and GC-sensitivity implied in clinically improved, but 4/17 GC-resistant participants	Disease-categorized small study; no clinical follow-ups are published	[75]
Dexamethasone	cross-sectional	29	0.01-1 μM ^a (ex-vivo)	3 months (follow up)	PBMC apoptosis	T-cells, mainly CD8+, are GC resistant in relapses, and sensitive during remission	Consistent with known inhibition of GRα expression in GC-treated MS patients	[76]

Interpretation

- Optimal GR function is essential for GCs to counteract the key proinflammatory cytokines, such as TNFα. Such event to occur effectively requires active form of GC to remain stable at effect site—to offset emergence of GC resistance—without interference with myelin repair.

Annotation/Glossary:

a equivalent to physiological (0.01 to 0.1 μM) and supraphysiological or pharmacological (1 μM) dose [77].
CNTF = ciliary neurotrophic factor, a relevant protein expressed in blood leukocytes, astrocytes and myelinating Schwann cells, and is known to give trophic support to neurons; **EDSS** = expanded disability status scale; **IV** = intravenous injection; **MRI** = quantitative magnetic resonance imaging scans of lesions, typically before and after contrast agent (gadolinium) injections; **MSSS** = multiple sclerosis severity score, the evaluation takes into account EDSS and disease duration; **PBMC** = human peripheral blood monocytic cells; **TNFα** = tumor necrosis factor alpha

Corticosteroids use can lead to short-term cognitive disturbances and reversible long-term memory deficits [36, 37] apparently independent of GC dose [36]. Methylprednisolone/MP impairs explicit memory which can improve in time after cessation of therapy [38]. Others note that corticosteroids slightly impair off-line motor memory consolidations comparable to those seen in clinically depressed [39].

Corticosteroid therapy can result in decreased cytokine-producing monocytic cells and NK cells and increased B cells and macrophages in peripheral blood (Table 1). The post-CS effects suggest a possible stabilization of blood brain barrier [40]. Significant improvement in EDSS appeared independent of GC dose, but the changes in certain immunological parameters (e.g., mRNA expressions of IL-6 and IL-8 cytokines) depended upon the high-dose [41].

High-powered studies are required to determine the strength-of-associations of these outcomes. Nevertheless, the consistency-of-associations point to increased risk for the patient, particularly on neurological effects of GCs in multiple sclerosis.

Benefit-to-risk ratios: GC-related AEs

Corticosteroids are shown neither to protect nor reverse pathophysiology in multiple sclerosis. Low-dose GCs are apparently immunostimulatory, rather than immunosuppressive so that, "chronic low-dose treatment with corticosteroids may contribute to irreversible loss of brain tissue in a variety of autoimmune diseases" [5]. Moreover, low-dose steroids in combination therapies fail to slow down disability progression and cortical atrophy (Table 3). Studies on the respective disease models in rodents demonstrate that steroids treatment are lethal to axonal, ganglionic and myelinating cells, and can damage retina and visual pathway (reviewed in [42]).

In addition, corticosteroids disrupt the hypothalamic-pituitary-adrenal (HPA) axis, aggravate endogenous steroidal-hormonal hyperactivity [43] and exacerbate CNS deficits and ataxia or motor coordination disorders [39], presumably more often in GC-responsive MS than in the GC-resistant MS with aberrant/diminished GC receptor (GR). Recent investigations point out that osteonecrosis or avascular necrosis (AVN) of the femoral bone head is amongst the previously least recognized risks [44]. With a mean dose of about 6 g and a risk period of 12 months in steroid-treated patients [45], AVN may occur in upwards of 15% of patients [46].

Evidence-based decision points

Certain benefits can be improved or risk avoided by stratifying patients based on pharmacogenetic markers and modifying treatment configuration. Steroids use in MS under circumstances where co-morbidities such as Addison's disease [47] may result in additional complexities. In such situations that levels of circulating/endogenous GCs are suboptimal, modification of treatments may be necessary.

Efforts aimed at influencing multi-drug resistant genes with the rationale of enhancing drug efficacy is a sound approach, and is tested in a variety of disease. In MS, certain alleles of ATP-binding cassette transporters (ABC-B1/G2), although highly polymorphic and without apparent roles in disease susceptibility, are variably expressed in CNS tissue and leukocytes. GCs may be beneficial in a subset (14.8%) of patients by inhibiting the efflux of other immunosuppressants such as mitoxantrone [48]. A similar common polymorphism in the efflux transporter (ABCB1, C3435T) of P-glycoprotein increases susceptibility to GC-induced osteoporosis [49]. It may be useful then to give an optimal complementary dose, but the ABC-mediated effluxed steroids are not thoroughly investigated in MS.

Discussion

Corticosteroids are a key component in the management of immune-mediated conditions. Currently approved agents are based on the controversial assumption that MS is an

autoimmune disease. Whether inflammation is the cause or the consequence of demyelination and axonal loss in MS and related exacerbations remains unanswered. To date, no known biomarker of the immune system seems essential and sufficient to initiate degeneration in MS or visual pathways in MS-ON. Alternative hypotheses on the beneficial roles of activated immune cells in MS and ON disease models in animals in relations to the impacts of steroids treatments are reviewed elsewhere [42]. Our clinical assessments are aligned with the viewpoint that transient suppression of MS relapses through steroids use may inevitably carry additional risks, such as inability to control intracerebral replication of such viruses as Epstein-Barr virus (EBV) and JC polyomavirus (JCV) [50, 51], as well as induction of pro-apoptotic elements in oligodendrocyte progenitor cells (OPCs) hence hindering myelin repair and neurogenesis [42].

Corticosteroids are generally recognized to increase the risks of microbial, viral and/or parasitic infections, including potential reactivation of endogenous pathogens. Activation or reactivation of infectious squalae with CNS involvements can occur as a result of treatments with immunosuppressants or steroids. Serological findings implicate that persons exposed to EBV are at an increased risk of developing MS [52]. It is unclear whether the observed cortical layer infection with EBV—suspected in the pathogenesis of meningeal inflammation and gray matter lesions in progressive MS [53]—reflect a GC-related reactivation and/or an ensuing viral infection that began prior to MS attack. A careful interpretation of the infections in MS is prudent when immunosuppressants are involved. Most adverse effects are presumably subtle and fall into NOAELs, though most patients ultimately cannot tolerate side-effects and require modification of the treatment plan. In any case, an assessment of infections with CNS involvements before and after corticosteroids use would be useful in diagnosis, treatment and management of the disease progression in multiple sclerosis [54]. A summation of some of the above concerns with potential clinical relevance is illustrated in Figure 1 towards a risk stratification and mitigation strategy in multiples sclerosis.

Recent insights into the pathogenesis of MS reveal that the subcortical deep gray matter atrophy is common [19, 55, 56] and that "neurodegeneration in MS occurs on an inflammatory background" [57]. Patients apparently initially benefit from a burst of intensive therapy with various immunosuppressive drugs but immunosuppressants eventually fail to control the disease, the neuronal loss continuing despite these treatments.

In a long-term follow-up of a pivotal trial of IFN β , the authors assert that "excessive mortality in the placebo was largely from MS-related causes, especially, MS-related pulmonary infections" [4]. The authors conclusion might be misconstrued that an overactive autoimmunity in treatment-naive MS can lead to fatal respiratory infections, and vice versa, the immune stimulation with viral infections cause the MS attacks. Whether there are definite relations between the infections and confounding effects of IFN β , or lack thereof in the treatment arm [58] and use of immunosuppressants such as corticosteroids and mitoxantrone, were unaddressed. MS patients may be at increased risk for infections because of immunosuppressants.

An independent set of risk factors are often linked to a variety of others such as drug dosage, frequency and extent of treatment, and manufacturing issues. In addition, a high risk of bias may be intrinsic to some industry supported studies. Excepting steroids (prednisone, prednisolone), fingolimod and the new orals such as dimethyl fumarate and teriflunomide [59-61], all currently approved DMT are injectables. Injectable corticosteroids may pose additional perils related to manufacturing and/or administration of the drug. Such complications could include emboli and neurologic complications by injecting particulate steroids that have a tendency to form aggregates [62].

Another promising option instead of corticosteroids use is injectable peptides (ACTH gel), which is thought to exert immunomodulatory effects by stimulating the production of

endogenous corticosteroids through steroidogenesis, as a means to curb the relapses [63]. The rationale of this approach relies on the deregulated immune response and inflammation as a basis of the pathophysiology of MS [63-65]. However, a treatment option that falls back on a continuous stimulation and release of endogenous corticosteroids might arguably bring out the worst pharmacodynamic characteristics, such as pro-apoptotic effects on OPCs, rather than only neuroprotective activities [42]. Furthermore, elevated levels of steroids can adversely affect myelin repair: the inhibition of immune cells in the CNS may hinder clearance of the cellular debris from injurious neurons in multiple sclerosis [42].

Scientific data gaps

Corticosteroids differentially affect oligodendrocytes and neurons in both GC-resistant and GC-responsive MS [42]. Several active trials are evaluating efficacy and safety of steroids in MS and optic neuritis, while others shifting to radical approaches to determine for instance efficacy of stem-cell transplants in MS. Most studies focus on ex-vivo expanded autologous hematopoietic stem cells after intensive immunosuppressive therapy [66, 67]. Earlier trials set a precedence to utilize GCs in combination with oncologic drugs in myelosuppressive pre-conditioning or total body irradiation in myeloablative conditioning [68]. Corticosteroids in combination with potent immunosuppressants might inevitably skew the benefit-risk ratio of the stem cell therapy. The totality of evidence in such uses of CS implores a more careful consideration of their use.

Recent pivotal trials on GC treatment intervals with other DMTs have corroborated previous studies, but also indicate that a transient reversal of the lesion volume shift to excessive small lesions, cerebral atrophy, and ultimately disappointing outcomes (Table 3). It is difficult to understand why high-dose oral GC would give a better clinical outcome than intravenous GCs. Other studies conducted on small populations are inconclusive.

Difficult challenges are associated with misdiagnosis of the GC-induced perturbations in peri/extraleSIONAL tissues. Smaller size veins surrounded by inflammatory cells are newly diagnosed pathological features in MS [69]. It is tempting to hypothesize that corticosteroids can induce atrophy/necrosis in neuro-vasculature structures in a manner consistent with their well known antiangiogenic properties [70]. This might shrink the microvessels, cut off blood/nutrients supply, increase venous insufficiency, interfere with brain-wide pathway for fluid exchange, and impede waste clearance of myelin debris. GCs might then progressively accumulate new small lesions — sustain or enlarge the lesion volume in a U-shape curve manner and deteriorate MS attacks in time. These concerns might be solvent by loosening the outcome measures, such as using non-conventional MRI scans [69, 71] and tightening the analytical choices for effect estimates based on predetermined efficacy criteria. Our assessment insufficiently addresses issues pertaining to GC-mediated infections and/or reactivation of endogenous viruses and their impact on MS pathology.

One treatment algorithm recommends bolus methylprednisolone/MP injections indiscriminately for a variety of demyelinating diseases, namely fulminant MS cases, including a spectrum of diseases [(such as acute disseminated encephalomyelitis (ADEM), variants of acute hemorrhagic leukoencephalitis (AHLE or Hurst disease), as well as severe relapses of MS and other variants (tumefactive, Marburg variants, Balo concentric sclerosis, myelinoclastic diffuse sclerosis), and neuromyelitis optica (NMO)-spectrum disorders)], even though certain clinical presentations may deteriorate in spite of such treatments [72]. Other studies indicate that high-dose steroids may worsen the brain atrophy in clinically-definite MS [73] and MS-ON [74], and as described in detail in this article. While the steroids-suppressed immune cells may lose their beneficial roles in the clearance of myelin and other cellular debris in the injury pathways and hence inhibit remyelination and neurogenesis [42], do steroids exert harmful effects only on certain CNS cell types?

Table 2. Glucocorticoids effects on immune and clinical parameters in RR-MS.

Test drug	Study design	No. of pts (GC-treated)	Dosage (high-dose)	Trial duration	Outcome measures	Conclusions	Strengths/Limitations	References
Methylprednisolone/MP								
MP + IFNβ	RAC	313 (51)	1 g/day IV 3 consecutive days, bimonthly	1 year	NAb vs. IFNβ EDSS MSFC, MRI bioactivity	Decreased NAb titers Nonsignificant favorable clinical outcomes, Unfavorable BPF trend	Small NAb+ patients do not preclude theoretical benefit in a subset of MS High dropout rates (30%)	[7]
MP + IFNβ + MTX		(55)						
MP+ IFNβ	open label controlled	73 NAb+ (38 NAb+)	monthly	6 months	NAb vs. IFNβ activity Relapses	Neither changes NAb status nor restores IFNβ bioactivity, No difference in relapse rate	GC-resistance characteristics and MRI activities unexplored	[15]
MP	open label	(16)	1 g/day IV day-3 to 5 + taper 60 mg/day	2 weeks	Immune parameters EDSS	Decreased CD4+ T cells (13.5%) Increased CD8+ T cells (40%) IgG index in CSF unaffected Decreased EDSS (12%)	Marginal clinical benefit MRI activity unpublished Insufficiently powered Long-term effects unknown	[12]
MP	cross-sectional, open label	66 (26)	undisclosed	2 months	Antigen microarrays IgG index	Decreased autoantibodies vs. myelin and heat-shock proteins in CSF	Positive predictive values in relations to GC dose and epitope specificity/ spreading and clinical relevancy unclear	[6]

Interpretation

- High-dose corticosteroid may be effective in regaining bioactivity of IFNβ, if given concurrently at onset of therapy.
- GC-induced CD8+ T cells entering CNS can suppress CD4+ T cells—might also unfavorably affect myelin repair.
- GC-induced decreases in autoantibodies/T cells have no known clinically relevant beneficial effect.
- It seems inappropriate to offer GCs long-term to a large population for small a chance of clinical benefit—these studies do not justify GC use in clinical practice.

BPF = brain parenchymal fraction; **CSF** = cerebrospinal fluid; **IgG** = immunoglobulin antibodies; **IFNβ** = interferon beta; **MSFC** = multiple sclerosis functional composite score; **NAb+** = neutralizing antibody positive; **RAC** = randomized active controlled; **RRMS** = relapsing-remitting multiple sclerosis

Key points and hypotheses

- Corticosteroids can generate hyporesponsive immune cells and inhibit auxiliary elements in CNS—such as proliferations of astrocytes, dendrites density, clearance of myelin debris, myelin repair and neurogenesis.
- Resistance to corticosteroids may stem from an acquired deficit of GR and/or inactivation in lesion environment—hence blocking neuroprotective role, and tip the balance in perils of the side-effects.
- Synaptic loss and neuronal remodeling, in addition to axonal loss and brain atrophy, probably occur in GC-medicated and the residual neurological-cognitive impairments persist in GC-unmedicated MS.
- Predefined criteria for preclinical and clinical efficacy are the key to unequivocally sort out risk-benefit of corticosteroids in multiple sclerosis.

Perspective

Conventional first- and second-line DMT—including certain broad-spectrum chemotherapies (such as azathioprine, cyclophosphamide, mitoxantrone) and recombinant biologics can compromise the immune system. Although most treatments typically commence with IFNβ [61], the immune system often develops resistance to it and other biologics. Ultimately the effectiveness of such drugs wears off and results in a reduced patient compliance.

The drawbacks of approved biologics, in addition to suboptimal effectiveness, involve other difficult challenges. Implementation of diagnostics to detect, decipher and counteract autoantibodies and neutralizing antibodies against biologics are thought to improve efficacies. This burden of pre-conceived notions on neuroprotective and antioxidant effects GCs probably affects the perceptions of the most in MS community to continue (and potentially escalate) the use of GCs—without weighing in the consequences. This trend

appears active partly to complement efficacy of the DMT and largely globally for the clinicoeconomics reasons.

The absolute-/relative-risk reduction or management for the GCs use in multiple sclerosis is currently unreconciled. Additional use of GCs as auxiliary medications to enhance the effectiveness of the biologics in MS are also questionable. Novel alternative approaches to potentially overcome or reverse the insensitivity to GCs are interesting ideas and should be further researched. In the interim, rigorous guidelines are needed for the justifications of corticosteroids use in clinical practice. These can be practical steps forward to modify treatments, minimize risks, and improve benefits of therapeutics in multiple sclerosis. These assessments have also implications for other neurological disease that corticosteroids are universality utilized.

Conclusion

The preponderance of evidence suggests that there are causal relationships between corticosteroids therapy and irreversible AEs such as avascular necrosis and neurodegeneration. Corticosteroids appear overutilized, largely off-label, in multiple sclerosis, based on their commonly known anti-inflammatory effects despite marginal benefits. Individuals at low risk categories may still benefit from short pulse treatments should the rationales are traced to evidence based pharmacogenetics or personalized treatment. Prospective studies are needed to sufficiently address whether individuals with low-relapse-rates and high GC responsiveness are less vulnerable to detrimental effects of GCs than those with malignant MS or GC resistant or special populations with overleaping neurological and/or autoimmune disease, and vice-versa. The positive predictive value of surrogate biomarkers or such as MRI activities such as cortical thinning, neuronal atrophy and perilesional veins atrophy, rather than just appraisals of new and enlarged T2 lesions, need to be addressed at the individual patient

Table 3. Glucocorticoids in structured polytherapy in relapsing-remitting multiple sclerosis.

Test drug	Study design	No. of pts (GC-treated)	Dosage (oral)	Duration (follow-up) Years	Outcome measures	Efficacy summary (% improvement rate [APIR])	Strengths/Limitations	References
Methylprednisolone + IFNβ	multicenter RDBPC	longitudinal 341 (171)	High 500 mg/d 3 days monthly	3 to 4	MRI, EDSS, MSFC, MSIS	None; Decreases relapse rates (38%) and T2 lesions without clinical benefit at the study endpoint	AE SAE MP 1436 24 PL 1070 35 Tissue specific imaging and long-term risks unexplored.	[18]
	RDBPC	102 (49)	Medium 200 mg/d 5 days monthly	2	MRI activity EDSS	None; Decreases relapse rates (62%) similarly in year-1 and year-2; Decreases T2 lesions (23%)	Most frequent AEs include sleep disturbances, neurologic and psychiatric disorders; High dropout rates	[78]
Prednisone + IFNβ ± Aza	RDBPC	181 (63)	Low 2 10 mg alternate days	2	EDSS, MRI	None; Decreases T2 lesions (52%) ASA vs. IFNβ	Study rationale based on potential superiority of combination treatments with low-dose immunosuppressants	[20]
	open label	172 of 181		4	EDSS, MRI	5.5% (2-year) 0.6 (one patient, 6-year) Increases T2 LV (3-6 cm ³) and disability progression	Lesion volume probably inflated by analytical choices used for effect estimate	[21]
	post-hoc	136 of 181		2	MRI - gray matter and white matter analysis	Cortical atrophy (2.5%) develops independent of T2 LV in patients with early (48.3%) and late (28.3%) disease durations	Exhibits differential lesion accumulations and cortical atrophy as predictive markers for disease progression	[19]

Interpretation
 ■ These outcomes reject predetermined criteria for efficacy that GCs with other immunosuppressants and/or immunomodulatory agents improve pathophysiology in multiple sclerosis.

APIR = attributable percentage improvement rate (at ≤0.05 level), the numbers of patients free from the clinical disease activity, accumulation of disability and related outcome measures; **Aza** = Azathioprine; **MSIS** = multiple sclerosis impairment scale; **None** = denotes that the test drug is inefficacious based on inferences from the clinical end-point; **PL**= Placebo; **RDBPC** = randomized double blind placebo controlled

level, in relation to the use of corticosteroids—as these agents are more conveniently administered, especially among economically disadvantaged regions, than costly DMTs. There is insufficient evidence for justification of corticosteroids use in multiple sclerosis.

Conflict of interests: The authors have no conflicts of interest with this research, including the reviewed technologies, products or competitor products, and used no external funds for this research.

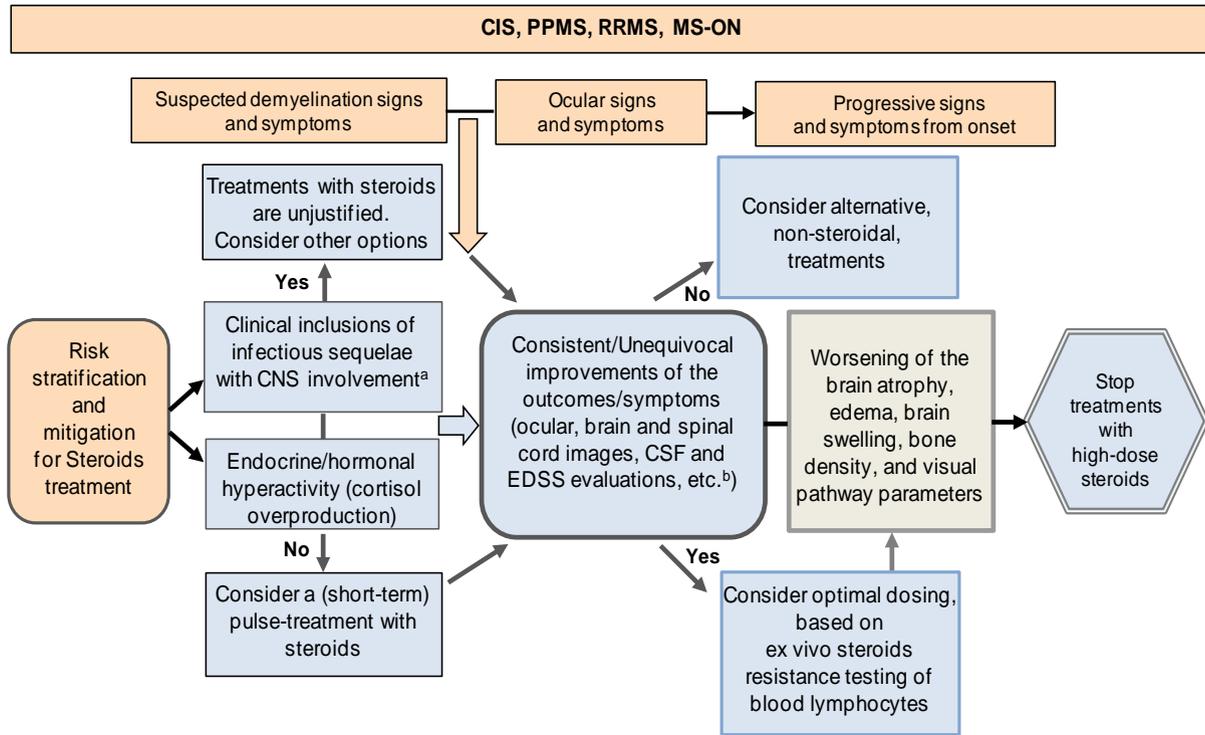


Figure 1. An algorithm for screening, monitoring, treatment and mitigating risks of steroids-associated disease progression and clinical decision-making points in CNS inflammatory demyelinating disease [clinically isolated syndrome (CIS), primary progressive (PPMS), relapsing-remitting (RRMS) multiple sclerosis, and MS-associated optic neuritis (MS-ON)] is proposed. a: Detection of infectious agents or related biomarkers, such as increased IgG and DNA loads in cerebrospinal fluid (CSF) in relations to acute, concurrent or reactivated neurotropic viruses [cytomegalovirus (CMV), Epstein-Barr virus (EBV), herpes simplex viruses (HSV-1/-2), papillomavirus, (HPV), human herpes virus types 6, 7 or 8 (HHV-6/-7/-8), parvovirus B19, varicella-zoster virus (VZV), human retroviruses (HTLV, HIV)], progressive multifocal leukoencephalopathy (PML) in JC polyomavirus (JCV) positive patients, herpetic necrotizing retinitis (caused by CMV, HSV or VZV) or ocular/neurotoxoplasmosis. b: The terms 'etc.' and 'outcome measures' are consistent with additional data requirements of sufficient quality to fulfill the revised criteria for diagnosis of MS, with respect to extensions of the recommendations of the 2010 McDonald criteria [79].

References

- Hurwitz BJ: Analysis of current multiple sclerosis registries. *Neurology* 2011, 76(1 Suppl 1):S7-13. doi: [10.1212/WNL.0b013e31820502f6](https://doi.org/10.1212/WNL.0b013e31820502f6)
- Skoog B, Runmarker B, Winblad S, Ekholm S, Andersen O: A representative cohort of patients with non-progressive multiple sclerosis at the age of normal life expectancy. *Brain* 2012, 135(Pt 3):900-11. doi: [10.1093/brain/awr336](https://doi.org/10.1093/brain/awr336)
- Volpe NJ: The optic neuritis treatment trial: a definitive answer and profound impact with unexpected results. *Arch Ophthalmol* 2008, 126(7):996-9. doi: [10.1001/archoph.126.7.996](https://doi.org/10.1001/archoph.126.7.996)
- Goodin DS, Ebers GC, Cutter G, Cook SD, O'Donnell T, Reder AT, et al: Cause of death in MS: long-term follow-up of a randomised cohort, 21 years after the start of the pivotal IFNbeta-1b study. *BMJ Open* 2012, 2(6). pii: e001972. doi: [10.1136/bmjopen-2012-001972](https://doi.org/10.1136/bmjopen-2012-001972)
- Zivadinov R: Steroids and brain atrophy in multiple sclerosis. *J Neurol Sci* 2005, 233(1-2):73-81. doi: [10.1016/j.jns.2005.03.006](https://doi.org/10.1016/j.jns.2005.03.006)
- Quintana FJ, Farez MF, Izquierdo G, Lucas M, Cohen IR, Weiner HL: Antigen microarrays identify CNS-produced autoantibodies in RRMS. *Neurology* 2012, 78(8):532-9. doi: [10.1212/WNL.0b013e318247f9f3](https://doi.org/10.1212/WNL.0b013e318247f9f3)
- Cohen JA, Imrey PB, Calabresi PA, Edwards KR, Eickenhorst T, Felton WL 3rd, et al: Results of the Avonex Combination Trial (ACT) in relapsing-remitting MS. *Neurology* 2009, 72(6):535-41. doi: [10.1212/01.wnl.0000341934.12142.74](https://doi.org/10.1212/01.wnl.0000341934.12142.74)
- Lindquist S, Hassinger S, Lindquist JA, Sailer M: The balance of pro-inflammatory and trophic factors in multiple sclerosis patients: effects of acute relapse and immunomodulatory treatment. *Mult Scler* 2011, 17(7):851-66. doi: [10.1177/1352458511399797](https://doi.org/10.1177/1352458511399797)
- Pitzalis C, Sharrack B, Gray IA, Lee A, Hughes RA: Comparison of the effects of oral versus intravenous methylprednisolone regimens on peripheral blood T lymphocyte adhesion molecule expression, T cell subsets distribution and TNF alpha concentrations in multiple sclerosis. *J Neuroimmunol* 1997, 74(1-2):62-8. doi: [10.1016/S0165-5728\(96\)00206-8](https://doi.org/10.1016/S0165-5728(96)00206-8)

10. Belogurov AA, Jr., Kurkova IN, Friboulet A, Thomas D, Misikov VK, Zakharova MY, et al: Recognition and degradation of myelin basic protein peptides by serum autoantibodies: novel biomarker for multiple sclerosis. *J Immunol* 2008, 180(2):1258-67. doi: [10.4049/jimmunol.180.2.1258](https://doi.org/10.4049/jimmunol.180.2.1258)
11. Elliott C, Lindner M, Arthur A, Brennan K, Jarius S, Hussey J, et al: Functional identification of pathogenic autoantibody responses in patients with multiple sclerosis. *Brain* 2012, 135(Pt 6):1819-33. doi: [10.1093/brain/aws105](https://doi.org/10.1093/brain/aws105)
12. Wang HY, Matsui M, Araya S, Onai N, Matsushima K, Saida T: Immune parameters associated with early treatment effects of high-dose intravenous methylprednisolone in multiple sclerosis. *J Neurol Sci* 2003, 216(1):61-6. doi: [10.1016/S0022-510X\(03\)00214-4](https://doi.org/10.1016/S0022-510X(03)00214-4)
13. Korn T, Tumani H: Patterns of intrathecal autoreactive antibodies in MS using antigen microarrays. *Neurology* 2012, 78(8):522-3. doi: [10.1212/WNL.0b013e318247fa26](https://doi.org/10.1212/WNL.0b013e318247fa26)
14. Creeke PI, Farrell RA: Clinical testing for neutralizing antibodies to interferon-beta in multiple sclerosis. *Ther Adv Neurol Disord* 2013, 6(1):3-17. doi: [10.1177/1756285612469264](https://doi.org/10.1177/1756285612469264)
15. Hesse D, Frederiksen JL, Koch-Henriksen N, Schreiber K, Stenager E, Heltberg A, et al: Methylprednisolone does not restore biological response in multiple sclerosis patients with neutralizing antibodies against interferon-beta. *Eur J Neurol* 2009, 16(1):43-7. doi: [10.1111/j.1468-1331.2008.02336.x](https://doi.org/10.1111/j.1468-1331.2008.02336.x)
16. Zarkou S, Carter JL, Wellik KE, Demaerschalk BM, Wingerchuk DM: Are corticosteroids efficacious for preventing or treating neutralizing antibodies in multiple sclerosis patients treated with beta-interferons? A critically appraised topic. *Neurologist* 2010, 16(3):212-4. doi: [10.1097/NRL.0b013e3181de4924](https://doi.org/10.1097/NRL.0b013e3181de4924)
17. Oliveri RL, Valentino P, Russo C, Sibilgia G, Aguglia U, Bono F, et al: Randomized trial comparing two different high doses of methylprednisolone in MS: a clinical and MRI study. *Neurology* 1998, 50(6):1833-6. doi: [10.1212/WNL.50.6.1833](https://doi.org/10.1212/WNL.50.6.1833)
18. Ravnborg M, Sorensen PS, Andersson M, Celius EG, Jongen PJ, Elovaara I, et al: Methylprednisolone in combination with interferon beta-1a for relapsing-remitting multiple sclerosis (MECOMBIN study): a multicentre, double-blind, randomised, placebo-controlled, parallel-group trial. *Lancet Neurology* 2010, 9(7):672-80. doi: [10.1016/S1474-4422\(10\)70132-0](https://doi.org/10.1016/S1474-4422(10)70132-0)
19. Zivadinov R, Tekwe C, Bergsland N, Dolezal O, Havrdova E, Krasensky J, et al: Bimonthly Evolution of Cortical Atrophy in Early Relapsing-Remitting Multiple Sclerosis over 2 Years: A Longitudinal Study. *Mult Scler Int* 2013, 2013:231345. doi: [10.1155/2013/231345](https://doi.org/10.1155/2013/231345)
20. Havrdova E, Zivadinov R, Krasensky J, Dwyer MG, Novakova I, Dolezal O, et al: Randomized study of interferon beta-1a, low-dose azathioprine, and low-dose corticosteroids in multiple sclerosis. *Mult Scler* 2009, 15(8):965-76. doi: [10.1177/1352458509105229](https://doi.org/10.1177/1352458509105229)
21. Kalincik T, Horakova D, Dolezal O, Krasensky J, Vaneckova M, Seidl Z, et al: Interferon, azathioprine and corticosteroids in multiple sclerosis: 6-year follow-up of the ASA cohort. *Clin Neurol Neurosurg* 2012, 114(7):940-6. doi: [10.1016/j.clineuro.2012.02.014](https://doi.org/10.1016/j.clineuro.2012.02.014)
22. Rizzo JF, 3rd, Lessell S: Risk of developing multiple sclerosis after uncomplicated optic neuritis: a long-term prospective study. *Neurology* 1988, 38(2):185-90. doi: [10.1212/WNL.38.2.185](https://doi.org/10.1212/WNL.38.2.185)
23. Spoor TC, Rockwell DL: Treatment of optic neuritis with intravenous megadose corticosteroids. A consecutive series. *Ophthalmology* 1988, 95(1):131-4. doi: [10.1016/S0161-6420\(88\)33220-3](https://doi.org/10.1016/S0161-6420(88)33220-3)
24. Brusaferri F, Candelise L: Steroids for multiple sclerosis and optic neuritis: a meta-analysis of randomized controlled clinical trials. *J Neurol* 2000, 247(6):435-42.
25. Beck RW: The Optic Neuritis Treatment Trial. *Arch Ophthalmol* 1988, 106(8):1051-3.
26. Kapoor R, Miller DH, Jones SJ, Plant GT, Brusa A, Gass A, et al: Effects of intravenous methylprednisolone on outcome in MRI-based prognostic subgroups in acute optic neuritis. *Neurology* 1998, 50(1):230-7. doi: [10.1212/WNL.50.1.230](https://doi.org/10.1212/WNL.50.1.230)
27. Sellebjerg F, Nielsen HS, Frederiksen JL, Olesen J: A randomized, controlled trial of oral high-dose methylprednisolone in acute optic neuritis. *Neurology* 1999, 52(7):1479-84. doi: [10.1212/WNL.52.7.1479](https://doi.org/10.1212/WNL.52.7.1479)
28. Trauzettel-Klosinski S, Diener HC, Dietz K, Zrenner E: The effect of oral prednisolone on visual evoked potential latencies in acute optic neuritis monitored in a prospective, randomized, controlled study. *Doc Ophthalmol* 1995, 91(2):165-79.
29. Gal RL, Vedula SS, Beck R: Corticosteroids for treating optic neuritis. *Cochrane Database Syst Rev* 2012, 4:CD001430. doi: [10.1002/14651858.CD001430.pub2](https://doi.org/10.1002/14651858.CD001430.pub2)
30. Atkins EJ, Drews-Botsch CD, Newman NJ, Calvetti O, Swanson S, Biousse V: Management of optic neuritis in Canada: survey of ophthalmologists and neurologists. *Can J Neurol Sci* 2008, 35(2):179-84.
31. Biousse V, Calvetti O, Drews-Botsch CD, Atkins EJ, Sathornsumetee B, Newman NJ, et al: Management of optic neuritis and impact of clinical trials: an international survey. *J Neurol Sci* 2009, 276(1-2):69-74. doi: [10.1016/j.jns.2008.08.039](https://doi.org/10.1016/j.jns.2008.08.039)
32. Gold R, Kappos L, Arnold DL, Bar-Or A, Giovannoni G, Selmaj K, et al: Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. *N Engl J Med* 2012, 367(12):1098-107. doi: [10.1056/NEJMoa1114287](https://doi.org/10.1056/NEJMoa1114287)
33. Lublin FD, Cofield SS, Cutter GR, Conwit R, Narayana PA, Nelson F, et al: Randomized study combining interferon and glatiramer acetate in multiple sclerosis. *Ann Neurol* 2013, 73(3):327-40. doi: [10.1002/ana.23863](https://doi.org/10.1002/ana.23863)
34. Zivadinov R, Rudick RA, De Masi R, Nasuelli D, Ukmar M, Pozzi-Mucelli RS, et al: Effects of IV methylprednisolone on brain atrophy in relapsing-remitting MS. *Neurology* 2001, 57(7):1239-47. doi: [10.1212/WNL.57.7.1239](https://doi.org/10.1212/WNL.57.7.1239)
35. Zivadinov R, Zorzon M, De Masi R, Nasuelli D, Cazzato G: Effect of intravenous methylprednisolone on the number, size and confluence of plaques in relapsing-remitting multiple sclerosis. *J Neurol Sci* 2008, 267(1-2):28-35. doi: [10.1016/j.jns.2007.09.025](https://doi.org/10.1016/j.jns.2007.09.025)
36. Uttner I, Muller S, Zinser C, Maier M, Sussmuth S, Claus A, et al: Reversible impaired memory induced by pulsed

- methylprednisolone in patients with MS. *Neurology* 2005, 64(11):1971-3. doi: [10.1212/01.WNL.0000163804.94163.91](https://doi.org/10.1212/01.WNL.0000163804.94163.91)
37. Brunner R, Schaefer D, Hess K, Parzer P, Resch F, Schwab S: Effect of high-dose cortisol on memory functions. *Ann N Y Acad Sci* 2006, 1071:434-7. doi: [10.1196/annals.1364.037](https://doi.org/10.1196/annals.1364.037)
 38. Oliveri RL, Sibilila G, Valentino P, Russo C, Romeo N, Quattrone A: Pulsed methylprednisolone induces a reversible impairment of memory in patients with relapsing-remitting multiple sclerosis. *Acta Neurol Scand* 1998, 97(6):366-9. doi: [10.1111/j.1600-0404.1998.tb05967.x](https://doi.org/10.1111/j.1600-0404.1998.tb05967.x)
 39. Dresler M, Genzel L, Kluge M, Schussler P, Weber F, Rosenhagen M, et al: Off-line memory consolidation impairments in multiple sclerosis patients receiving high-dose corticosteroid treatment mirror consolidation impairments in depression. *Psychoneuroendocrinology* 2010, 35(8):1194-202. doi: [10.1016/j.psycheneu.2010.02.005](https://doi.org/10.1016/j.psycheneu.2010.02.005)
 40. Mirowska-Guzel DM, Kurowska K, Skierski J, Koronkiewicz M, Wicha W, Kruszewska J, et al: High dose of intravenously given glucocorticosteroids decrease IL-8 production by monocytes in multiple sclerosis patients treated during relapse. *Journal of neuroimmunology* 2006, 176(1-2):134-140. doi: [10.1016/j.jneuroim.2006.03.024](https://doi.org/10.1016/j.jneuroim.2006.03.024)
 41. Mirowska-Guzel D, Gromadzka G, Kurowska K, Czlonkowska A, Czlonkowska A: Long-term effect of high doses glucocorticosteroids on mRNA expression for IL-6 and IL-8 in relapsed multiple sclerosis patients. *Immunopharmacol Immunotoxicol* 2010, 32(3):416-21. doi: [10.3109/08923970903486625](https://doi.org/10.3109/08923970903486625)
 42. Sadaie MR, Samiy N, Rosenbaum RE, Thomas GA: Steroids impact on myelin repair, neurogenesis and visual pathway in multiple sclerosis: preclinical perspectives. *J Exp Clin Neu Sci* 2014, 1(1). doi: [10.13183/jecns.v1i1.9](https://doi.org/10.13183/jecns.v1i1.9)
 43. Ysraelit MC, Gaitan MI, Lopez AS, Correale J: Impaired hypothalamic-pituitary-adrenal axis activity in patients with multiple sclerosis. *Neurology* 2008, 71(24):1948-1954. doi: [10.1212/01.wnl.0000336918.32695.6b](https://doi.org/10.1212/01.wnl.0000336918.32695.6b)
 44. Sahraian MA, Yadegari S, Azarpajouh R, Forughipour M: Avascular necrosis of the femoral head in multiple sclerosis: report of five patients. *Neurol Sci* 2012, 33(6):1443-6. doi: [10.1007/s10072-011-0914-8](https://doi.org/10.1007/s10072-011-0914-8)
 45. Koo KH, Kim R, Kim YS, Ahn IO, Cho SH, Song HR, et al: Risk period for developing osteonecrosis of the femoral head in patients on steroid treatment. *Clin Rheumatol* 2002, 21(4):299-303. doi: [10.1007/s100670200078](https://doi.org/10.1007/s100670200078)
 46. Ce P, Gedizlioglu M, Gelal F, Coban P, Ozbek G: Avascular necrosis of the bones: an overlooked complication of pulse steroid treatment of multiple sclerosis. *Eur J Neurol* 2006, 13(8):857-61. doi: [10.1111/j.1468-1331.2006.01375.x](https://doi.org/10.1111/j.1468-1331.2006.01375.x)
 47. Nielsen NM, Frisch M, Rostgaard K, Wohlfahrt J, Hjalgrim H, Koch-Henriksen N, et al: Autoimmune diseases in patients with multiple sclerosis and their first-degree relatives: a nationwide cohort study in Denmark. *Mult Scler* 2008, 14(6):823-9. doi: [10.1177/1352458508088936](https://doi.org/10.1177/1352458508088936)
 48. Cotte S, von Ahnen N, Kruse N, Huber B, Winkelmann A, Zettl UK, et al: ABC-transporter gene-polymorphisms are potential pharmacogenetic markers for mitoxantrone response in multiple sclerosis. *Brain* 2009, 132(Pt 9):2517-30. doi: [10.1093/brain/awp164](https://doi.org/10.1093/brain/awp164)
 49. Lovas K, Gjesdal CG, Christensen M, Wolff AB, Almas B, Svartberg J, et al: Glucocorticoid replacement therapy and pharmacogenetics in Addison's disease: effects on bone. *Eur J Endocrinol* 2009, 160(6):993-1002. doi: [10.1530/EJE-08-0880](https://doi.org/10.1530/EJE-08-0880)
 50. Angelini DF, Serafini B, Piras E, Severa M, Coccia EM, Rosicarelli B, et al: Increased CD8+ T cell response to Epstein-Barr virus lytic antigens in the active phase of multiple sclerosis. *PLoS Pathog* 2013, 9(4):e1003220. doi: [10.1371/journal.ppat.1003220](https://doi.org/10.1371/journal.ppat.1003220)
 51. Antoniol C, Jilek S, Schluep M, Mercier N, Canales M, Le Goff G, et al: Impairment of JCV-specific T-cell response by corticotherapy: effect on PML-IRIS management? *Neurology* 2012, 79(23):2258-64. doi: [10.1212/WNL.0b013e3182768983](https://doi.org/10.1212/WNL.0b013e3182768983)
 52. Decard BF, von Ahnen N, Grunwald T, Streit F, Stroet A, Niggemeier P, et al: Low vitamin D and elevated immunoreactivity against Epstein-Barr virus before first clinical manifestation of multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2012, 83(12):1170-3. doi: [10.1136/jnnp-2012-303068](https://doi.org/10.1136/jnnp-2012-303068)
 53. Bo L: The histopathology of grey matter demyelination in multiple sclerosis. *Acta Neurol Scand Suppl* 2009(189):51-7. doi: [10.1111/j.1600-0404.2009.01216.x](https://doi.org/10.1111/j.1600-0404.2009.01216.x)
 54. Smyk DS, Alexander AK, Walker M, Walker M: Acute disseminated encephalomyelitis progressing to multiple sclerosis: Are infectious triggers involved? *Immunol Res* 2014, 60(1): 16-22. doi: [10.1007/s12026-014-8499-y](https://doi.org/10.1007/s12026-014-8499-y)
 55. Hagemeyer J, Weinstock-Guttman B, Heininen-Brown M, Poloni GU, Bergsland N, Schirda C, et al: Gray matter SWI-filtered phase and atrophy are linked to disability in MS. *Front Biosci (Elite Ed)* 2013, 5:525-32.
 56. Eshaghi A, Bodini B, Ridgway GR, Garcia-Lorenzo D, Tozer DJ, Sahraian MA, et al: Temporal and spatial evolution of grey matter atrophy in primary progressive multiple sclerosis. *NeuroImage* 2014, 86:257-64. doi: [10.1016/j.neuroimage.2013.09.059](https://doi.org/10.1016/j.neuroimage.2013.09.059)
 57. Popescu BF, Lucchinetti CF: Meningeal and cortical grey matter pathology in multiple sclerosis. *BMC Neurology* 2012, 12:11. doi: [10.1186/1471-2377-12-11](https://doi.org/10.1186/1471-2377-12-11)
 58. Edwards S, Zvartau M, Clarke H, Irving W, Blumhardt LD: Clinical relapses and disease activity on magnetic resonance imaging associated with viral upper respiratory tract infections in multiple sclerosis. *J Neurol Neurosurg Psychiatry* 1998, 64(6):736-41. doi: [10.1136/jnnp.64.6.736](https://doi.org/10.1136/jnnp.64.6.736)
 59. Gasperini C, Ruggieri S: Development of oral agent in the treatment of multiple sclerosis: how the first available oral therapy, fingolimod will change therapeutic paradigm approach. *Drug Des Devel Ther* 2012, 6:175-86. doi: [10.2147/DDDT.S8927](https://doi.org/10.2147/DDDT.S8927)
 60. Ruggieri S, Tortorella C, Gasperini C: Pharmacology and clinical efficacy of dimethyl fumarate (BG-12) for treatment of relapsing-remitting multiple sclerosis. *Ther Clin Risk Manag* 2014, 10:229-39. doi: [10.2147/TCRM.S53285](https://doi.org/10.2147/TCRM.S53285)

61. Sorensen PS: New management algorithms in multiple sclerosis. *Curr Opin Neurol* 2014, 27(3):246-59. doi: [10.1097/WCO.0000000000000096](https://doi.org/10.1097/WCO.0000000000000096)
62. Okubadejo GO, Talcott MR, Schmidt RE, Sharma A, Patel AA, Mackey RB, et al: Perils of intravascular methylprednisolone injection into the vertebral artery. An animal study. *J Bone Joint Surg Am* 2008, 90(9):1932-8. doi: [10.2106/JBJS.G.01182](https://doi.org/10.2106/JBJS.G.01182)
63. Ross AP, Ben-Zacharia A, Harris C, Smrtka J: Multiple sclerosis, relapses, and the mechanism of action of adrenocorticotropic hormone. *Front Neurol* 2013, 4:21. doi: [10.3389/fneur.2013.00021](https://doi.org/10.3389/fneur.2013.00021).
64. Berkovich R: Treatment of acute relapses in multiple sclerosis. *Neurotherapeutics* 2013, 10(1):97-105. doi: [10.1007/s13311-012-0160-7](https://doi.org/10.1007/s13311-012-0160-7)
65. Berkovich R, Agius MA: Mechanisms of action of ACTH in the management of relapsing forms of multiple sclerosis. *Ther Adv Neurol Disord* 2014, 7(2):83-96. doi: [10.1177/1756285613518599](https://doi.org/10.1177/1756285613518599)
66. Bonab MM, Sahraian MA, Aghsaie A, Karvigh SA, Hosseinian SM, Nikbin B, et al: Autologous mesenchymal stem cell therapy in progressive multiple sclerosis: an open label study. *Curr Stem Cell Res Ther* 2012, 7(6):407-14. doi: [10.2174/1574888X11207060407](https://doi.org/10.2174/1574888X11207060407)
67. Connick P, Kolappan M, Crawley C, Webber DJ, Patani R, Mitchell AW, et al: Autologous mesenchymal stem cells for the treatment of secondary progressive multiple sclerosis: an open-label phase 2a proof-of-concept study. *Lancet Neurol* 2012, 11(2):150-6. doi: [10.1016/S1474-4422\(11\)70305-2](https://doi.org/10.1016/S1474-4422(11)70305-2)
68. Burt RK, Traynor AE, Pope R, Schroeder J, Cohen B, Karlin KH, et al: Treatment of autoimmune disease by intense immunosuppressive conditioning and autologous hematopoietic stem cell transplantation. *Blood* 1998, 92(10):3505-14.
69. Gaitan MI, de Alwis MP, Sati P, Nair G, Reich DS: Multiple sclerosis shrinks intralésional, and enlarges extralésional, brain parenchymal veins. *Neurology* 2013, 80(2):145-51. doi: [10.1212/WNL.0b013e31827b916f](https://doi.org/10.1212/WNL.0b013e31827b916f)
70. Geltzer A: When the standards aren't standard: evidence-based medicine in the Russian context. *Soc Sci Med* 2009, 68(3):526-32. doi: [10.1016/j.socscimed.2008.10.029](https://doi.org/10.1016/j.socscimed.2008.10.029)
71. Iliff JJ, Lee H, Yu M, Feng T, Logan J, Nedergaard M, et al: Brain-wide pathway for waste clearance captured by contrast-enhanced MRI. *J Clin Invest* 2013, 123(3):1299-309. doi: [10.1172/JCI67677](https://doi.org/10.1172/JCI67677)
72. Rahlmow MR, Kantarci O: Fulminant demyelinating diseases. *The Neurohospitalist* 2013, 3(2):81-91. doi: [10.1177/1941874412466873](https://doi.org/10.1177/1941874412466873)
73. Rossi S, Motta C, Studer V, Boffa L, De Chiara V, Castelli M, et al: Treatment Options to Reduce Disease Activity After Natalizumab: Paradoxical Effects of Corticosteroids. *CNS Neurosci Ther* 2014, 20(8):748-53. doi: [10.1111/cns.12282](https://doi.org/10.1111/cns.12282)
74. Hickman SJ, Kapoor R, Jones SJ, Altmann DR, Plant GT, Miller DH: Corticosteroids do not prevent optic nerve atrophy following optic neuritis. *J Neurol Neurosurg Psychiatry* 2003, 74(8):1139-41. doi: [10.1136/jnnp.74.8.1139](https://doi.org/10.1136/jnnp.74.8.1139)
75. van Winsen LM, Polman CH, Dijkstra CD, Tilders FJ, Uitdehaag BM: Suppressive effect of glucocorticoids on TNF-alpha production is associated with their clinical effect in multiple sclerosis. *Mult Scler* 2010, 16(4):500-2. doi: [10.1177/1352458509359721](https://doi.org/10.1177/1352458509359721)
76. Gold SM, Sasidhar MV, Lagishetty V, Spence RD, Umeda E, Ziehn MO, et al: Dynamic development of glucocorticoid resistance during autoimmune neuroinflammation. *J Clin Endocrinol Metab* 2012, 97(8):E1402-10. doi: [10.1210/jc.2012-1294](https://doi.org/10.1210/jc.2012-1294)
77. Ishida Y, Heersche JN: Glucocorticoid-induced osteoporosis: both in vivo and in vitro concentrations of glucocorticoids higher than physiological levels attenuate osteoblast differentiation. *J Bone Miner Res* 1998, 13(12):1822-6. doi: [10.1359/jbmr.1998.13.12.1822](https://doi.org/10.1359/jbmr.1998.13.12.1822)
78. Sorensen PS, Mellgren SI, Svenningsson A, Elovaara I, Frederiksen JL, Beiske AG, et al: NORdic trial of oral Methylprednisolone as add-on therapy to Interferon beta-1a for treatment of relapsing-remitting Multiple Sclerosis (NORMIMS study): a randomised, placebo-controlled trial. *Lancet Neurol* 2009, 8(6):519-29. doi: [10.1016/S1474-4422\(09\)70085-7](https://doi.org/10.1016/S1474-4422(09)70085-7)
79. Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, et al: Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol* 2011, 69(2):292-302. doi: [10.1002/ana.22366](https://doi.org/10.1002/ana.22366)