POINT OF VIEW

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Potential use of glucocorticosteroids in *CSF1R* mutation carriers — current evidence and future directions

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ABSTRACT

We recently found that glucocorticosteroids (GCs) have protective effects in *CSF1R* mutation carriers against developing symptomatic *CSF1R*-related leukoencephalopathy. Our findings were subsequently confirmed in a mouse model study.

We have received many questions from patients, their families, patient organisations, and healthcare practitioners about the optimal type of GCs, the dose, the route of administration, and application timing. This paper attempts to answer the most urgent of these questions based on our previous studies and personal observations. Despite the promising observations, more research on larger patient groups is needed to elucidate the beneficial actions of GCs in *CSF1R* mutation carriers.

Keywords: leukoencephalopathy, glucocorticosteroids, spheroids, hereditary

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CSF1R-related leukoencephalopathy (CRL) is an autosomal dominant neurodegenerative disease with worldwide prevalence, rapid progression, and an ominous prognosis, with death ensuing within a few years [1]. Currently, treatment options are limited to supportive care and possibly hematopoietic stem cell transplantation [2]. Our previous observations on pathogenic *CSF1R* mutation carriers exposed to long-term immunosuppressive therapy who did not develop symptomatic disease prompted us to evaluate the effects of glucocorticosteroids (GCs) on the disease course [3].

We conducted a retrospective cohort study on 41 *CSF1R* mutation carriers, of which eight took GCs for various unrelated medical reasons at the *asymptomatic stage* of the disease [4]. We found that individuals exposed to GCs were less likely to develop symptomatic disease, or to become dependent in the activities of daily living, and less frequently had white matter lesions and corpus callosum involvement on neuroimaging [4]. Our findings were confirmed in an animal model, in which mice carrying an inactivated allele of *CSF1R* and exposed to GCs did not develop symptomatic disease, nor demyelination, neurodegeneration nor microgliosis, on neuropathological evaluation [5].

These promising results from our studies on a possible protective effect of GCs against symptomatic CRL sparked considerable interest among patients, their families, patient organisations, and healthcare practitioners. We have received many questions about the optimal type of glucocorticosteroid, the dose, the route of administration, and application timing in asymptomatic and symptomatic *CSF1R* mutation carriers. We suggested that more research needs to be done before implementing GCs in clinical practice [4]. Generally speaking, there is limited interest within the pharmaceutical industry in performing clinical trials on already FDA-approved medications. Even more importantly, conducting such a medication trial would take many years (definitely beyond the timeframe of currently conducted medication trials). Based on our previous studies and personal observations, we here attempt to answer the most important questions.

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Our thoughts presented below have significant limitations and must be read only as our personal views, and not as forming any recommendations or guidelines.

GCs differ in terms of their anti-inflammatory potency, hormonal activity (mainly mineralocorticoid effects), and duration of hypothalamic-pituitary-adrenal axis suppression (HPA) (ranging from hours to days) [6, 7]. Based on the duration of HPA axis suppression, GCs are classified as short-acting (hydrocortisone), intermediate-acting (prednisone, prednisolone, methylprednisolone, triamcinolone), or long-acting (dexamethasone, betamethasone) [7]. It is important to note that as GC effects are mainly mediated through intracellular and nuclear mechanisms, their therapeutic effects persist beyond their plasma elimination time [6, 8]. Chronic GC therapy is associated with a number of side effects, including increased mortality, psychiatric (anxiety, irritability, mood liability, insomnia, psychosis), cognitive (memory impairment), musculoskeletal (osteoporosis, fractures, myopathy), endocrine (adrenal suppression, Cushingoid features), metabolic (hyperglycaemia, diabetes, dyslipidemia, obesity), cardiovascular (hypertension), ophthalmological (cataracts, glaucoma), gastrointestinal (gastritis, peptic ulcer disease, dyspepsia), dermatological (skin thinning, purpura, red striae), and immunosuppressive (predisposition to infection) complications [7].

In addition, GCs may interact with other non-steroid medications, leading to decreased or increased exposure to GCs or non-steroid medications, resulting in a higher risk of side effects and drug toxicity [7]. As the harm associated with GC therapy and GC-related toxicity depends on the dose and duration of the therapy, the goal is the lowest effective dose for the shortest duration [7, 9]. Short-term GC courses (i.e. less than two weeks) are unlikely to suppress the HPA axis, and steroid tapering is not needed [10, 11]. In most studies, adverse effects have been linked to long-term treatment with a prednisone equivalent daily dose of more than 5–7.5 mg [8]. In a recent consensus paper of the European League Against Rheumatism's task force group, the authors concluded that a daily dose of ≤ 5 mg prednisone equivalent conveyed an acceptably low level of harm in rheumatic diseases, with the exception of patients at high risk for cardiovascular disease (i.e. older age, male sex, obesity, hypertension, diabetes, dyslipidemia) [9]. A daily prednisone equivalent dose of > 10 mg was linked with elevated harm, whereas the benefit-risk balance of daily prednisone equivalent doses between 5 and 10 mg was determined by patient-specific conditions (i.e. risk factors, comorbidities) [9]. The general risk of GC-related complications is higher in older individuals with concurrent medical problems, unhealthy lifestyles, those who smoke, have high alcohol consumption, and bad nutrition [8, 9]. The risk of GC-related complications can be lowered by adopting healthy behaviours such as regular physical exercise, a healthy diet (low in saturated fat and sodium), stopping smoking, lower alcohol consumption, sufficient vitamin D and calcium intake, and weight loss [9]. Monitoring for potential complications, preventive and therapeutic measures is recommended to address the most common serious GC-related side effects [9]. Influenza, pneumococci, and herpes zoster vaccinations are proposed in patients on chronic GC therapy [9]. Patients at high risk for osteoporosis may be prescribed bisphosphonates, osteoanabolic drugs, or selective oestrogen receptor modulators, whereas statins and angiotensin-converting enzyme inhibitors may benefit patients at high cardiovascular risk [9].

Therefore, the ultimate benefit-*versus*-risk balance depends on the GC therapy regimen (dose and duration) and the individual patient profile.

Based on basic science studies, at least partial preservation of microglia is a prerequisite for GCs to exert their positive effects in CRL [4, 5]. In line with this, we demonstrated the beneficial effects of GCs in asymptomatic human and mouse *CSF1R* mutation carriers [4, 5]. The age at GC therapy onset ranged from 21–50 years, with a median 34.5 years in our retrospective clinical study [4], and 3 months in the mouse model study [4], which corresponds to 20 human years [12, 13]. In the clinical study, the group treated with GCs was heterogeneous regarding the type of medication, dose, route of administration, therapy duration (median of 14.5 years, range 2–25 years), and mono- or poly-GC therapy [4]. In the animal study, the mice received slow-release subcutaneous prednisone 1.8 mg/kg/day for 12 months [5], corresponding to human exposure of 0.146 mg/kg (8.75 mg in a 60-kg adult) [5, 14] for 30 years [12, 13].

It is challenging to convert subcutaneous prednisone to its oral equivalent, as such a formula is not available for humans. However, another glucocorticoid, dexamethasone, is converted in a 1:1 or 0.825:1 ratio between oral and subcutaneous applications [15]. Hence, the translated dose from the mouse model study [5] equals an approximate oral daily prednisone dose of 7.2–8.75 mg/kg in a 60-kg (132 lbs) adult human.

The age at onset in CRL has been previously calculated at 43 ± 11 years (mean ± 1 SD, range 18–78 years) for both sexes [16]. Women develop symptomatic disease on average seven years earlier than men, with an age at onset of 40 ± 10 compared to 47 ± 11 years (mean ± 1 SD), respectively [16]. One possible explanation for the observed dichotomy in symptomatic onset may be hormonal differences. As some studies have shown that men display higher cortisol levels compared to women [17, 18], we hypothesise that physiological differences in GCs levels between men and women may lead to later symptomatic onset in men.

The age at onset may also depend on *CSF1R* mutation, and kindred studies may help in better understanding genotype-phenotype associations and predicting the timing of symptomatic disease onset in carriers of specific mutations. Ideally, the GCs would be initiated a few years before the predicted symptomatic onset, limiting the lifetime exposure to GCs. However, in carriers of *CSF1R* mutations that are not well characterised, a general (based on all *CSF1R* mutation

carriers) [16] age at onset would determine the GCs initiation. The application of age at onset encompassing two standard deviations (2 SD) would allow the inclusion of c.95% of all cases. Thus, starting ages for prophylactic GCs initiation of 20 years for women and 25 years for men seem reasonable.

We speculate that GCs could also be of potential benefit in the early stages of CRL when a substantial fraction of microglia still functions properly. As no systematic studies have addressed GCs use in symptomatic *CSF1R*, we searched the literature and our records for reports of symptomatic CRL mutation carriers treated with GCs, finding a total of 12 patients (Tab. 1). Unfortunately, in most cases, the information on the GC regimen was scarce. However, as more than half of the cases (n = 7) received GCs for misdiagnosed multiple system sclerosis, it can be assumed that it was a pulse therapy. The timing of the treatment varied, but in most cases, patients received GCs when they were already severely affected. Three cases received repeated courses of intravenous methylprednisolone followed by oral therapy with downward titration starting in the first two years of their disease, and did not benefit from the treatment [19, 20]. However, they presented rapidly progressive phenotypes, and could have been already advanced when initially exposed to GCs. In the whole group, a lack of benefit was observed in all but one case, who received pulse therapy with GCs and immunoglobulins, "which slightly relieved his dementia symptoms" [21]. However, the improvement in this patient is questionable, because at the 3-month follow-up, the authors noted worsening of the symptoms [21]. Based on arguments from the previous studies, we speculate that GCs may also be beneficial at the early stages of symptomatic disease; however, no benefit can be expected at the advanced stages of the disease, when already most microglia are damaged and dysfunctional; and not as a one-time dose (pulse therapy). More studies are needed to gain insight into these important aspects in the early disease stages of CRL.

The annual incidence of short-term oral GC treatment in the United States has been estimated at 7%, with approximately one in five adults receiving at least one course of therapy in three years for various medical reasons [22]. The chronic oral GC intake has been estimated at 0.6–1.2%, with more than 70% of patients using prednisone [23, 24].

Due to systemic action, high bioavailability, non-invasiveness, and relatively low cost, oral prednisone would be the first choice among GCs for use in *CSF1R* mutation carriers. Since most serious side effects are associated with prednisone equivalent doses of higher than 5 mg/day, we speculate that the initial oral dose for asymptomatic *CSF1R* mutation carriers would not exceed 5 mg per day. Repeated short-term courses would obviate the need for steroid tapering, and limit the side effects.

Any biomarkers of disease progression would be invaluable for deciding upon the optimal timing of GC initiation, monitoring the therapy effects, and allowing appropriate titration of GCs according to individual needs. However, the role of both non-specific (e.g. neurofilament light chain, glial fibrillary acidic protein, tau protein) or specific to microglia (e.g. positron emission tomography imaging of the translocator protein, not yet discovered proteins unique to microglia) biomarkers is yet to be verified in *CSF1R* mutation carriers. Thus, an annual comprehensive clinical assessment with neurological, neuropsychological, and neuroimaging (preferably with 7 Tesla magnetic resonance imaging [25]) evaluations, remains the best strategy to monitor asymptomatic *CSF1R* mutation carriers, detect early first signs of conversion from asymptomatic to symptomatic disease, and monitor symptomatic disease progression.

Given all these considerations, we hypothesise that the starting GC regimen in asymptomatic *CSF1R* mutation carriers would include a 7-day prednisone course of 5 mg per day every 3–4 months. However, if signs of disease progression are detected, as they are today by means of neurological, neuropsychological, or neuroimaging (7-Tesla brain MRI) assessments, or by means of biomarkers as they may be tomorrow, an intensified GC regimen would be introduced. That could involve an increased duration of GC courses, an increased daily dose, or a transition to more potent GCs (e.g. methylprednisolone pulses).

Despite the promising results from earlier studies, more research on larger patient groups is needed to elucidate the beneficial actions of GCs in asymptomatic and symptomatic *CSF1R* mutation carriers. We cannot exclude that an unidentified confounder impacted upon previous observations, particularly the clinical ones, which were based on a small number of patients. As a randomised clinical trial would be challenging, in terms of time, cost and ethics, a retrospective meta-analysis based on a multicentre collaboration is the ultimate means we would use to provide further evidence, or a lack thereof. Additional basic science studies of novel targets downstream of GCs are underway. The last decade has seen the discovery of the genetic cause underlying the disease; hopefully, our observations will hasten the emergence of preventive therapy.

Table 1. Demographic, genetic, and clinical characteristics of symptomatic patients with *CSF1R*-related leukoencephalopathy treated with glucocorticosteroids (based on literature review and our records)

No	Paper	Sex	Ethnicity	CSF1R mutation	Age at onset	Initial diagnosis	Clinical course	Treatment	Age at treatment	Benefit
1	Sundal et al. [19, 20]	F	Norwegian	c.1754-2A > G (splicing mutation)	38 years	Multiple sclerosis	Rapid progression, bedridden at 41 years, died six months later	Three courses: intravenous methylprednisolone (1,000 mg/day for three days) followed by oral prednisolone 60 mg/day with downward titration over three weeks	38–41 years	None
2	Sundal et al. [19, 20]	F	Norwegian	c.1754-2A > G (splicing mutation)	36 years	Multiple sclerosis	Rapid progression, bedridden at 38 years, died at 40 years	Three courses of intravenous methylprednisolone (1.000 mg/day for three days) followed by oral prednisolone 60 mg/day with downward titration over three weeks; Interferon β-1b 44 μg three times/week for six months	37–39 years	None
3	Inui et al. [26]	M	Japanese	Arg777Gln	24 years	Multiple sclerosis	Enteral feeding tube at 30 years; bedridden with occasional respiratory support at 32 years	Methylprednisolone, cyclophosphamide	N/A	None
4	Saitoh et al. [27]	F	Japanese	Ile782Thr	28 years	HDLS	Rapid progression, wheelchair-bound at 1.5 years from onset	Methylprednisolone pulse therapy (1,000 mg/day for three days)	29 years	None
5	Kitani-Morii et al. [28]	F	Japanese	Ile794Thr	20 years	Multiple sclerosis	Rapid progression, wheelchair-bound at 21 years	Intravenous and oral glucocorticosteroids, plasmapheresis	20 years	None
6	Konno et al. [29]	F	Japanese	Gly589Arg	37 years	Multiple sclerosis	Rapid progression, bedridden at 41 years	Glucocorticosteroids, interferon β-1b	N/A	None
7	Konno et al. [29]	F	Japanese	Gly589Arg	30 years	N/A	Rapid progression, severe dementia at 31 years	Glucocorticosteroids	31 years	None
8	Konno et al. [29]	F	Japanese	c.2442 + 5G > A (splicing mutation)	27 years	N/A	Progressive gait disturbances, frontal lobe dysfunction, spasticity, alien hand syndrome by 28 years	Glucocorticosteroids	28 years	None
9	Shi et al. [21]	M	Chinese	p.His899fs (frame-shift mutation)	42 years	HDLS	Dependent in activities of daily living in second year of disease	Glucocorticosteroids (pulse therapy), immunoglobulin	43 years	Slight improvement of dementia, but then worsening at 3-months follow-up
10	Breningstall & Asis [30]	M	N/A	Gln481Term	14 years	Inflammatory or metabolic disorder	Fast progression, incapable of independent walking at three months after presentation, gastrostomy at eight months after presentation	Glucocorticosteroids	14 years	None
11	(unpublished)	F	White European	Gly589Glu	47 years	Multiple sclerosis	Rapid progression, wheelchair = bound at 48 years, died at 49	Three courses: — intravenous — methylprednisolone (1,000 mg/day for five days) followed by — oral therapy for one week	48–49 years	None
12	(unpublished)	F	White European	Gly589Glu	42 years	Multiple sclerosis	Rapid progression, wheelchair-bound at 43 years	Intravenous glucocorticosteroids	44 years	None

F— female; HDLS — Hereditary diffuse leukoencephalopathy with spheroids; M — male

Article information

Conflict of interest: *None.*
Data availability statement: *Additional data that supports the findings of this study is available from the corresponding author, ZKW, upon reasonable request.*
Ethics statement: *The patient data was collected and investigated under approval by the Mayo Clinic institutional review board (1087-98 and 21-006198) and by means of a literature review. We confirm that we have read the Journal's position on issues involved in ethical publication, and affirm that this work is consistent with those guidelines.*
Authors' contributions:
1. Research project: A. Conception, B. Organisation, C. Execution;
2. Statistical analysis: A. Design, B. Execution, C. Review and critique;
3. Manuscript preparation: A. Writing of first draft, B. Review and critique;
JD: 1A, 1B, 1C, 3A, 3B; ERS: 1A, 1B, 1C, 3B; VC: 1A, 1B, 1C, 3B; ZKW: 1A, 1B, 1C, 3B.
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