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ALS UNTANGLED

ALSUntangled #65: glucocorticoid corticosteroids

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Abstract

ALSUntangled reviews alternative and off-label treatments for people with amyotrophic lateral sclerosis (PALS). Here we review glucocorticoids. Neuroinflammation plays a prominent role in amyotrophic lateral sclerosis (ALS) pathogenesis, so some hypothesize that glucocorticoids might be an effective ALS therapy through their immunosuppressive effects. In this paper, we review the available evidence for glucocorticoids in ALS, including one pre-clinical study with a genetic mouse model of ALS, nine case reports (ranging from 1 to 26 patients each), and four clinical trials. We also review the possible side effects (including steroid myopathy) and the costs of therapy. We graded the level of evidence as follows: Mechanism, D; Pre-Clinical, F; Cases, B; Trials, F; Risks, C. Our review of the current evidence concludes that glucocorticoids do not offer clinical benefit in ALS and confer serious risks. Thus, ALSUntangled does not recommend glucocorticoids as a treatment for ALS.

Keywords: *Amyotrophic lateral sclerosis (ALS), steroids, glucocorticoids, neuroinflammation, alternative therapy, neuropathology, excitotoxicity, SOD1*

ALSUntangled reviews alternative and off-label treatments for ALS on behalf of people with ALS (PALS). Here we review corticosteroids, for which we have had over 660 requests (1).

Overview

Corticosteroids are prescription medications that suppress the immune system, among many other effects. Corticosteroids affect T-cell function by

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promoting T-cell apoptosis, which may limit production of proinflammatory cytokines including interleukin (IL)-1, IL-2, interferon gamma, and tumor necrosis factor (2,3). Corticosteroids are approved for many indications in almost all areas of medicine (2). In neurology, they can decrease swelling caused by brain tumors and they are also used to temporarily help suppress disease activity in many autoimmune-mediated disorders including multiple sclerosis, polymyositis, chronic inflammatory demyelinating polyneuropathy, and myasthenia gravis (4–7).

The corticosteroid hormones produced by vertebrates are divided into two classes: glucocorticoids and mineralocorticoids. Glucocorticoids have broad and complex effects on the immune system, metabolism, organism development and homeostasis, among others. Mineralocorticoids impact salt and water balance (3). The focus of this paper is on the glucocorticoid effect of steroids on the immune systems. Glucocorticoids are reported as ALS treatments on various websites (8–10).

Mechanisms

Both human imaging studies and rodent neuropathological assessments confirm that neuroinflammation begins early in ALS disease progression (11) and is primarily due to the innate (rather than adaptive) immune response (12). Multiple cell types contribute to neuroinflammation in ALS, including astrocytes, microglia, T cells, dendritic cells, and macrophages. In addition to neuroinflammation, systemic inflammation is well-documented in ALS, including alterations in inflammatory cytokine production (13). Furthermore, multiple genes associated with ALS (including C9ORF72, TBK1, MAPK1, OPTN and other) are known to regulate innate immune function among other roles (11). It remains unclear whether altered inflammation is causative or secondary to another pathogenic mechanism in ALS.

Previous data in both humans and animals help elucidate the ways in which ALS disease progression is influenced by the immune system. In a mouse model of ALS (SOD1-G93A), a neuroprotective immune response dominates early in the disease course due to anti-inflammatory M2 macrophages/microglia and T-helper 2 lymphocytes, helping to protect motor neuron cell viability. Later in disease progression, when motor neuron injury accelerates, a pro-inflammatory immune response occurs, with M1 macrophages/microglia and pro-inflammatory T cells overtaking the previous neuroprotective response (12,14,15). Injection of neuroprotective regulatory T lymphocytes (Tregs) into SOD1 mice leads to increased anti-inflammatory interleukin-4 secretion and prolonged survival (15,16). Correlating with these animal models, human ALS patients with more rapidly progressive disease have lower numbers of Tregs than PALS with slower disease progression (15). Compared to healthy human controls, PALS have lower numbers of neuroprotective Tregs and higher numbers of cytotoxic CD8 and natural killer (NK) T lymphocytes (17). This suggests that treatments augmenting the neuroprotective and inhibiting the pro-inflammatory immune responses may slow disease progression in ALS.

An open-label clinical trial (NCT01884571 (18)) enrolled 31 PALS to assess the effect of immune modulation on ALS disease progression and biomarkers. PALS were treated with a combination of multiple immunosuppressants: basiliximab (20 mg IV on days 1 and 4), tacrolimus (1–5 mg twice daily titrated to goal trough 4–8 ng/mL, for 6 months), mycophenolate mofetil (titrated up to 1000 mg twice daily, for 6 months), and prednisone (methylprednisolone 125 mg IV once, then prednisone 60 mg daily tapered down to 10 mg daily over 1 month). Outcome measures included monthly ALSFRS-R. CSF cytokines including IL-2, 4, and 6 were assessed as well. Overall, this immunosuppression regimen had no effect on the rate of ALSFRS-R decline (compared to the rate of decline before treatment). In addition, no change in peripheral regulatory T lymphocyte populations was observed. Of note, CSF IL-2 levels were increased post-immunosuppression, then later decreased after cessation of treatment. The clinical implication of this finding is unclear; IL-2 maintains regulatory T lymphocytes to prevent autoimmunity as well as stimulates T lymphocytes to promote the immune response (19).

Overall, there is some evidence that the immune system is involved in ALS pathogenicity, and that pro-inflammatory immune activation is associated with more advanced disease. Animal data suggests that direct administration of regulatory T lymphocytes may prolong survival, but there is no clear evidence that corticosteroids impact regulatory T lymphocyte activity. Thus, ALSUntangled assigns corticosteroids a "Mechanisms" grade of "D". See Table 1, the Table of Evidence Grades for Glucocorticoid Corticosteroids, for a summary grade for each category reviewed: Mechanisms, Pre-Clinical, Cases, Trials, and Risks.

Pre-clinical models

In a genetic mouse model of ALS (SOD1-G93A), free or CNS-targeted liposomal encapsulated glucocorticoids were administered through weekly injections of 10 mg/kg of methylprednisolone for 9 weeks (starting at 60 days of age) and compared to saline-treated wild-type mice (20). In this study, glutathione PEGylated liposomal

Table 1. Table of evidence grades for glucocorticoid corticosteroids.

	Grade	Explanation
Mechanism	D	Glucocorticoid corticosteroids can affect specific parts of inflammation, but it is not clear that these specific parts are relevant to ALS progression (11-19)
Pre-clinical	F	Glucocorticoid corticosteroids have failed to produce clinical benefits in animal models of ALS (20-21)
Cases	B	Two PALS with a validated diagnosis experienced recovery of lost motor function on glucocorticoid corticosteroids (along with other treatments) (10, 22-25)
Trials	F	Multiple trials of glucocorticoid corticosteroids failed to produce convincing benefits in PALS (32-36)
Risks	C	More than 10% of patients experienced non-serious adverse events in previous trials (32, 34, 37-42)

methylprednisolone (2B3-201) was chosen for its ability to target endogenous glutathione transporters at the blood-brain barrier and its previous demonstrated success at CNS-targeted steroid delivery in models of multiple sclerosis. Animal weight and motor performance were measured throughout the treatment period. Mice receiving CNS-targeted corticosteroids showed reduced brainstem pathology compared to those receiving free steroids as reflected by reduced T2 hyperintensity on MRI and reduced gliosis and neuronal loss on histological examination. This provided some evidence that targeted steroid delivery to the CNS may be able to decrease pathologic changes in the CNS; unfortunately this treatment did not correlate with any clinical improvements in the mice (20). In another study using this same mouse model, recurrent stressors on the mice (which led to higher serum cortisol levels) were associated with an earlier onset of paralysis and shorter survival times (21), suggesting a possible injurious role for endogenous corticosteroids. Given this lack of clinical benefit in these animal models, ALSUntangled assigns corticosteroids a "Pre-Clinical" grade of "F".

Cases

Many of the initial case series of PALS being treated with corticosteroids are from the 1950s and 1960s. One case series followed two patients who were treated with an "adequate" dose of intramuscular cortisone, 200 mg on day one, then 100 mg daily until 3 grams were fully administered. Both patients had continued progression of their disease despite therapy (22). Another report described a patient who received intrathecal injections of hydrocortisone acetate for over a year (initially every other day for one week, then approximately weekly for 2 months, then every 2 months for 10 months, then once 6 months later) with doses ranging from 32 to 75 mg, along with a specialized diet of "unsalted fresh food" and a vitamin regimen consisting of vitamin A, vitamin D, thiamine, riboflavin, niacinamide, and ascorbic acid. The patient had a baseline disease course that had been slowly progressive for 15 years, and he primarily had diffuse fasciculations in his back and legs, left greater than right lower extremity weakness, and fluctuating lower extremity Babinski signs with no cranial nerve or upper extremity symptoms. Throughout the patient's treatment course, he noted "improvement [continuing] with each spinal". At the end of 2.5 years, his exam was largely stable (23). Given his slow 15 years of symptom progression prior to therapy, it is difficult to conclude that two-and-a-half years of stability represented a true slowing of his progression.

In another series, 26 patients received weekly intrathecal injections of 50 mg of hydrocortisone and 1000 mg of vitamin B12. Twenty-one of these were able to complete at least 16 intrathecal injections. At the end of 10 months of observation, 1 patient had improved slightly, 2 were in the same condition, 14 had become more severely affected, and 4 had died. Two patients no longer met inclusion criteria as they concurrently were taking a separate herb therapy. The 2 patients in the same condition had progressive muscular atrophy and primary lateral sclerosis, both of which can be associated with slower progression. The one patient who initially showed slight improvement had continued disease progression by month 12. This case series was thus unable to confirm convincing benefits from steroids (24).

Three additional PALS "in advanced stages of the disease" were treated with adrenocorticotropic hormone (ACTH) with an initial pulse of 100–200 mg followed by 10–20 mg of oral prednisolone daily. ACTH stimulates the release of endogenous glucocorticoids. The authors conclude that "No long term effects of the treatment could be observed… nor did it influence the expected course of the disease" (25).

In January 2013, a former Physiology professor at Wake Forest University School of Medicine (10) published an account of his purported ALS remission with the aid of anti-inflammatory medications. At age 32, he developed fasciculations in his left index finger, with rapid spread to the rest of his body. His fasciculations increased over the subsequent year, and he developed dysarthria and sialorrhea, followed by weakness and loss of coordination. He was never formally diagnosed with ALS, but he had consulted once with a neurologist who mentioned the disease. He self-administered the fluorinated corticosteroid oral triamcinolone ("Aristocort"), with which he was performing

laboratory research. Over the first week, his fasciculations reduced by 50%. He continued varied steroid treatments over the subsequent decade and noted gradual improvement in his weakness and dysarthria despite persistent fasciculations. After stopping steroid use, he lived until age 91 when he died of respiratory disease. Given he was never formally diagnosed with ALS and may have had a form of a benign fasciculation syndrome, his case is unlikely to represent true recovery from ALS due to steroid treatment.

Another person diagnosed with ALS in September 2013 with initial symptoms of dysarthric speech and fasciculations throughout his body started oral steroids for an allergic reaction and reported that his slurred speech improved after two doses (9). He later received corticosteroid injections in his lumbar spine for lower back and leg pain; he briefly experienced improved leg strength following injections, although his strength began to decline again 4 weeks later. Medical records to evaluate for concurrent radicular lumber stenosis, upper motor neuron signs, strength testing, or other features of his disease are not available. He died approximately 4 years after diagnosis. From the limited information provided, it cannot be determined whether his corticosteroid use yielded any significant clinical benefits (9).

Lastly, three Caucasian males with ALS who were admitted to the hospital for progressive dysphagia and dysarthria were treated with a 21-day course of 1–20 million units of penicillin G and 100 mg of hydrocortisone (26). One patient who was previously wheelchair-bound could reportedly walk 100 meters one week after initiation of therapy, followed by improved speech and swallowing function and dexterity in his fingers. However, he was wheelchair-bound again by week 12; he received a second 21-day course of this therapy at week 13 and maintained functional speech and swallowing through 21 weeks of follow-up. Patients 2 and 3 noted improvements in speech, swallowing and muscle coordination within one week of treatment initiation and remained stable for 16+ weeks. It is not clear whether penicillin G, hydrocortisone, or both contributed to the observed effects. Limitations of this case series include possibility of concurrent syphilis or another infection treated by penicillin G (26). For a more critical look at this paper, please refer to our previous ALSUntangled review: Penicillin-G-hydrocortisone (27).

In the online community PatientsLikeMe, six participants reported taking prednisone for their ALS (28) and two provided detailed reports. One rated effectiveness as "major" and one "moderate" (28). Five participants reported taking dexamethasone for their ALS (29). Four of these provided treatment evaluations; two reported "major" effectiveness, one "moderate" effectiveness and one "can't tell" (30). One other participant reported taking hydrocortisone for their ALS but did not provide a treatment report (31). We were unable to confirm the diagnoses or reported benefits in any of these PatientsLikeMe participants. It is worth noting that many individuals, regardless of health or neurological disease, report a small, brief, subjective improvement in strength while taking glucocorticoids.

In the cohort of confirmed "ALS reversals" being studied at Duke University, one patient reported taking prednisone and another reported taking dexamethasone during their recovery. Both these patients were taking multiple other drugs and supplements. Associations like these do not provide causality. Based upon these two validated "ALS reversals" associated with glucocorticoid corticosteroids, ALSUntangled assigns a "Cases" grade of "B".

Trials

There have been four clinical trials using corticosteroids in PALS, though none involved use of corticosteroids alone. One trial followed 16 PALS who were randomized to penicillin G/hydrocortisone (1–20 million units in escalating dose for penicillin; 100 mg hydrocortisone) versus placebo quarterly over 48 weeks. Only six PALS (40%) completed this study. There was no statistically significant benefit in ALSFRS-R progression, though there was an increased risk of thrombotic complications from IV administration (32). As mentioned above, a second trial used an open-label design to test an immunosuppression regimen including basiliximab, tacrolimus, mycophenolate, and prednisone (prednisone dose of 60 mg during days 2–7, 40 mg during days 8–14, 20 mg during days 15–21, and 10 mg during days 22–28) in 31 patients over 6 months. This treatment design limited steroid administration to the first month of treatment and included additional immunosuppressive medications (with slower onset of action) to augment the immune regulatory effect, possibly to minimize long-term side effects of corticosteroids use. Only 18 patients completed the study. There was no overall improvement in ALSFRS-R progression during treatment compared to progression before treatment (33). A third trial treated 21 PALS with prednisolone (1000 mg intravenous methylprednisolone loading dose, followed by prednisolone 100 mg every other day during months 0–3, then prednisolone 50 mg every other day during months 4–12) and azathioprine for one year. No difference was seen in survival between treated patients and matched historical controls (34). Finally, a prospective uncontrolled trial tested a steroid-containing regimen (intravenous methylprednisolone 1000 mg per day for 4

days, then oral prednisone 100 mg every other day for 4 months, then for some patients oral cyclophosphamide for 6 months) in 65 patients with "idiopathic motor neuron syndromes" (35). From the descriptions provided, is likely that this study included patients with "multifocal motor neuropathy", a lower motor neuron disease which is known to be an autoimmune (36). Among the participants most likely to have had ALS (those with both upper and lower motor neuron signs) no objective improvements in muscle strength were identified.

Based on these four negative studies, ALSUntangled assigns a "Trials" grade of "F".

Dosing, risks, costs

Glucocorticoids can differ in their potencies and dosing regiments. The frequency and intensity of side effects of steroids at higher doses limit prolonged treatment periods. For many other inflammatory diseases, steroids are started at high dosages until maximal efficacy is reached, then weaned down to a goal of less than 20 mg per day; of note, higher doses were used in several of the case studies and trials above with negative results.

The side effects of corticosteroids are common and may affect up to 30% of patients. Side effect profile and severity depend on the dose and duration of therapy (37). Common risks of steroids, particularly with doses above 20 mg per day, include increased appetite and weight gain, diabetes, hypertension, increased risk of infection, osteopenia, cataracts, glaucoma, peptic ulcer disease, and myopathy. Of note, steroid myopathy may worsen weakness in patients who are already weak due to their motor neuron disease (38); this may depend on the type of steroid delivered, whether fluorinated or nonfluorinated, and generally resolves 3–4 weeks after discontinuation of therapy (37,39). Unlike motor neuron disease, steroid myopathy typically presents with symmetric proximal weakness; creatine kinase (CK) is generally normal, and EMG may be normal or may show a non-irritative myopathy. Additionally, given risk of falls in many PALS, osteopenia may lead to an increased risk of fall injuries with broken bones including hips, which may worsen disability (40). Additional risks include unmasking underlying infections, particularly viruses and tuberculosis (41). Proper screening for underlying infectious diseases and initiation of appropriate prophylaxis with vitamin D, calcium, gastrointestinal protection, and *Pneumocystis* pneumonia protection is prudent. Bone mineral density testing should be periodically monitored (3,37).

There are no trials that use corticosteroids alone to assess adverse effects in patients with ALS, and therefore the risk of adverse effects is difficult to estimate. From the trials that used corticosteroids in PALS, intravenous administration with penicillin led to 80% developing gastrointestinal disorders and 38% developing deep venous thrombosis (32). In the trial of azathioprine and steroids, 29% of patients stopped due to side effects or personal reasons (34). The use of corticosteroids for only one month followed by non-steroid immunosuppressants was associated with fewer than 10% developing new onset diabetes or hyperglycemia (33); other adverse effects were likely secondary to disease progression or other drugs within the regimen. Still, given the frequent and potentially serious side effects from prolonged corticosteroid therapy, ALSUntangled assigns a "Risks" grade of "C".

The cost of oral corticosteroids is low; without insurance, a one-month supply of prednisone 50 mg costs approximately $12, though cost may depend on the size and type of pill purchased (42). Costs related to the administration of other corticosteroids through non-oral routes are difficult to determine as they may incur facility costs.

Conclusion

In conclusion, corticosteroids are a class of medications with wide-ranging clinical uses and well-studied effects on the immune system. ALS progression is associated with changes in immune system function, with the early disease states associated with anti-inflammatory immune markers and the advanced disease states associated with pro-inflammatory immune markers. Although treatment with corticosteroids may cause a transient change in some immune markers, both preclinical and clinical trials have failed to show any clinical benefit in ALS. Multiple individual PALS have self-reported improvement in weakness with corticosteroid treatment, but these cases have unclear generalizability and are limited by an uncertain ALS diagnosis, limited clinical data during the disease course, and heterogeneity of glucocorticoid type and dose. Although affordable and widely available, corticosteroids can have numerous side effects, and their risks are greater for higher doses or prolonged treatment. Therefore, we cannot recommend corticosteroids at this time as a way to slow ALS progression. Further research into immune system modulation in ALS is ongoing at many research centers internationally.

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Declaration of interest

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