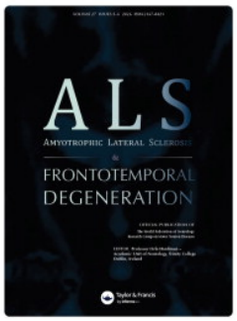

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ALSUntangled #84 – ivermectin

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CASE REPORT

ALSUntangled #84 – ivermectin

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Abstract

ALSUntangled reviews alternative and off-label treatments for people living with amyotrophic lateral sclerosis (PALS). In this review, we explore the possibility of using ivermectin to slow ALS progression. Ivermectin's ability to modulate neuroinflammation and excitotoxicity give it plausible mechanisms for treating ALS, though it does not get into the brain very well. One preclinical study demonstrated that ivermectin lengthened lifespan within a mouse model of mSOD1 genetic ALS. This finding has not been replicated. The 2 PALS we found who had data comparing ALSFRS-R progression on and off ivermectin appeared to have no benefit from it. We found no trials of ivermectin in PALS. Ivermectin is low cost and generally well tolerated with most adverse effects being mild and transient, but serious side effects can rarely occur, and it has not been carefully studied in PALS. We cannot at present endorse ivermectin as an ALS treatment.

Keywords: *Ivermectin, off-label use, alternative therapy*

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ALSUntangled reviews alternative and off-label treatments on behalf of people with ALS (PALS). Within this review we examine the potential utilization of ivermectin for which we have had 50 requests (1).

Overview

Ivermectin is a broad-spectrum antiparasitic treatment that has been used in both human and veterinary medicine for several decades (2). It belongs to the avermectin class of antiparasitic compounds, which are derived from a soil dwelling bacterium, *Streptomyces avermitilis* (3). Ivermectin is clinically used to combat numerous parasitic diseases including but not limited to strongyloidiasis, onchocerciasis, scabies, lice, pediculosis, and various forms of filariasis (4). Its wide antiparasitic activity and high safety profile have placed it on the World Health Organization's list of essential medicines (5). Each year, approximately 250 million people use this drug to treat effect debilitating parasitic diseases, especially within developing countries where these infections are most prevalent (6). The discovery that led to the development of ivermectin is widely recognized for its transformative impact on global health, which earned the 2015 Nobel Prize in Physiology or Medicine (7).

Ivermectin exerts its antiparasitic effects by allosterically modulating inhibitory glutamate gated chloride (GluCl) channel activity in invertebrates, which increases cell membrane permeability to chloride ions. This increased permeability eventually leads to hyperpolarization, paralysis, and death of parasites (8,9). Humans have a limited distribution of GluCl channels, which helps ivermectin effectively target parasites while maintaining a high safety profile. Additionally, ivermectin inhibits conductance of gamma-aminobutyric acid (GABA)-gated chloride channels in *Ascaris suum*, a common nematode parasite (10). This interaction works synergistically with GluCl channel modulation to enhance ivermectin's s antiparasitic effects (11).

In addition to ivermectin's effectiveness as an antiparasitic, it has also demonstrated strong potential in anti-inflammatory, anti-cancer, and antiviral applications (6,8). The anti-inflammatory properties of ivermectin are attributed to its inhibition of nuclear factor-kappa B (NF-κB), signal transducer and activator of transcription 3 (STAT3), and interferon-dependent pathways, which consequently decreases expression of proinflammatory cytokines (12). Clinically, these anti-inflammatory properties have been employed in the therapeutic management of rosacea, a chronic inflammatory skin condition for which topical ivermectin is an FDA approved treatment (13). Ivermectin's theoretical anti-cancer activity arises from its ability to induce apoptosis, inhibit cell cycle progression, and modulate signaling pathways that enhance the efficacy of conventional chemotherapeutic agents (14,15). Ivermectin's antiviral activity has been a source of significant research and controversy, specifically with regard to SARS-CoV-2, the virus that causes COVID-19. Ivermectin inhibits viral transport and replication *in vitro* of several viruses including HIV-1, Zika virus, dengue virus, West Nile virus, and SARS-CoV-2, but clinical evidence has been inconsistent and therefore requires further investigation to demonstrate efficacy (16,17). The mechanism of anti-viral activity involves inhibiting viral replication and nuclear transport by importin α/β1-mediated nuclear transport, which numerous viruses exploit to enter host cell nuclei (18,19). Collectively, these additional clinical uses of ivermectin highlight its therapeutic potential beyond the realm of antiparasitic activity.

Within the context of ALS, there is a 2007 patent for the use of ivermectin and its derivates in the treatment of ALS (described in reference 6). However, as we will demonstrate, the potential use of ivermectin for treating ALS remains highly speculative. More research is needed to understand any possible therapeutic benefits for modulating ALS pathogenesis and progression.

Mechanistic plausibility

The pharmacokinetics of ivermectin present a potential challenge for use as a therapeutic for central nervous system (CNS) pathologies including ALS due to its poor availability in the mammalian brain. This limitation is primarily attributed to ivermectin's high affinity for P-glycoprotein, an ATP-dependent efflux transporter highly expressed on the blood-brain barrier (BBB) that actively extrudes ivermectin from the CNS (20,21). Therefore, despite being able to penetrate the BBB, ivermectin is only present transiently in the CNS before being pushed back into general circulation. Pharmacokinetic studies in animal models have confirmed that this transport mechanism maintains a low CNS concentration of ivermectin after systemic administration. Attempts to increase brain levels by inhibiting P-glycoprotein have shown potential, but carry the risk of toxicity due to excessive drug accumulation in the CNS (22). Despite this potentially limiting factor, ivermectin does influence two mechanisms believed to be important in ALS pathogenesis: neuroinflammation (23) and excitotoxicity (24).

Neuroinflammation

The anti-inflammatory effects of ivermectin are exerted primarily by inhibiting NF-κB and STAT3 signaling pathways which significantly reduce the production of proinflammatory cytokines including

tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6), and interleukin 1 (IL-1) (12). Inhibiting these pathways leads to a reduction in both systemic and central inflammatory responses which are associated with (though not yet proven to cause) ALS disease severity and progression (25,26). NF-κB is functionally linked to genes associated with genetic ALS (27). NF-κB activation has also been observed in multiple cell types within ALS models, including microglia, astrocytes, and neurons (28). STAT3 has been observed in the motor neurons, astrocytes, and microglia of SOD1 mouse models and PALS (29). In summary, ivermectin's effects on NF-κB and STAT3 activation present a plausible therapeutic mechanism for treating ALS.

Ivermectin can also modulate neuroinflammation by inhibiting microglial activation, a hallmark feature of ALS pathology (30). The immunomodulatory effect of ivermectin on microglia is thought to occur through the positive allosteric modulation of the purinergic P2X4 receptor. Through this interaction, ivermectin promotes a phenotypic shift in microglia from a proinflammatory to an anti-inflammatory state, which suppresses accumulation and enhances the clearance of inflammatory lipid mediators such as lysophospholipids (31). In preclinical models of autoimmune encephalitis and brain radiation necrosis, ivermectin treatment decreased microglial density in inflamed CNS tissue (31,32). Although this reduction in microglial activation is not in an ALS model, the immunomodulatory properties of ivermectin presents a potential complementary mechanism to the anti-inflammatory inhibition of NF-κB and STAT3 signaling pathways.

Excitotoxicity

Excitotoxicity is a key pathological feature of ALS that is driven by excessive glutamate signaling, which ultimately leads to motor neuron degeneration (24). The clinical significance of excitotoxicity within ALS is highlighted by the beneficial effects of riluzole, an FDA approved therapeutic for ALS pathology. Riluzole primarily exerts its modulatory effects on excitotoxicity by reducing glutamate release and inhibiting postsynaptic AMPA and NMDA receptor activation (24,33). Although ivermectin does not act as a direct antagonist of glutamate receptors, preclinical studies indicate that it may protect against excitotoxic injury by modulating the balance between excitatory and inhibitory neurotransmission. Ivermectin functions as a positive allosteric modulator of the $GABA_A$ receptor, which enhances inhibitory signaling and counteracts glutamatergic overactivation (34). Additionally, ivermectin attenuates AMPA mediated excitotoxicity via downstream signaling pathways, especially through the P2X4 receptor (35). Collectively, the modulating effects of ivermectin on excitotoxicity present a mechanism of action that may be relevant to ALS pathogenesis.

With regard to ivermectin's pharmacokinetic limitations, recent research suggests that peripheral targeting of inflammation can affect the CNS without requiring the therapeutic to travel into the brain (36). To this end, it is feasible that any anti-inflammatory effects of IVM in the periphery may have a beneficial effect on the CNS. This is less likely to occur in regard to excitotoxicity for which the presence of the therapeutic is required at the neurons.

Given ivermectin's ability to modulate neuroinflammation and excitotoxicity, we assign a table of evidence (TOE) "Mechanisms" grade of B (Table 1). However, we caution that ivermectin has not yet been shown to modulate these mechanisms in classic pre-clinical models of ALS, nor in PALS.

Preclinical data

One study, conducted by Van Den Bosch et al. in 2007 examined the effects of ivermectin both in vitro and in vivo (35). The in vitro section examined whether ivermectin protected against AMPA receptor mediated excitotoxicity in cultured motor neurons. Artificial induction of excitotoxicity within these cultures led to significant cell death, but preincubation with ivermectin for at least eight hours conferred nearly complete protection. Notably, this protective effect was absent when ivermectin was administered concurrently with the excitotoxicity-inducing agent, indicating that pretreatment was essential for its efficacy.

The in vivo section of this study utilized mutant $SOD1^{G93A}$ transgenic mice, a common model of genetic ALS, to explore the effects of ivermectin on survival and pathology (35). The mice received oral ivermectin via drinking water at concentrations of 2.4, 4.8, or 12 mg/L beginning at 50 days of age (prior to symptom onset). The 4.8 and 12 mg/L treatment groups had statistically significant increases in lifespan by 6.2% and 9.1% respectively, compared to the control (solvent-treated) group. The study also performed histological analysis of the 12 mg/L ivermectin treatment group's lumbar spinal cord at 120 days, which revealed a significantly greater number of large motor neurons and a larger area occupied by axons in lumbar ventral roots versus untreated controls. This study demonstrated that despite poor ivermectin CNS availability, it still had a significant impact on motor neuron health in mammalian brains.

In a different study, ivermectin was delivered to zebrafish models of mSOD1 and C9ORF72 genetic ALS (37). Treatment at 1 uM from 2 to 5 days post fertilization reduced a marker of heat

Table 1. Table of evidence for ivermectin as an ALS treatment.

Category	Grade	Explanation
Mechanism	B	Ivermectin interacts with numerous biological mechanisms that are theoretically relevant to ALS progression, such as neuroinflammation and excitotoxicity, but suffers from potential pharmacokinetic limitations. These mechanisms have not been demonstrated in classic ALS preclinical models or in PALS.
Preclinical	B	Ivermectin prolonged survival in a single well-designed study using a mutant SOD1 transgenic mouse model of ALS.
Cases	F	We found 2 PALS in the ALS Therapy Development Institute's ALS Research Collaborative database who reported starting ivermectin during follow up. Neither had objective evidence of improvements.
Trials	U	No published clinical trials of ivermectin in ALS
Risks	U	Pharmaceutical grade ivermectin at standard dosing regimens appears generally safe and well tolerated. However, there are no data to confirm the safety and tolerability of these regimens in PALS. There are no data in any population using chronic daily dosing (as would likely be necessary to treat a neurodegenerative disease)

shock activation. What this means for PALS is unclear, as, unlike these zebrafish models, they do not appear to have overactive heat shock activation (38).

Based upon the above-described mSOD1 mouse study, which is well-designed but has yet to be replicated, we assign a TOE "Preclinical" grade of B (Table 1).

Data in PALS

Cases

Within the ALS Therapy Development Institute's ALS Research Collaborative Database, we found 2 PALS who reported starting ivermectin during their follow up. PALS report their own treatments and ALSFRS-R scores in this Database (39). Members of our team (AP, FV) calculated the ALSFRS-R slopes in these 2 PALS during their treatment with ivermectin and compared them to periods when they were not taking it. We found no differences in slopes, though the duration of treatment may have been too short to see a difference (3 months of treatment in 1 participant, 1 month of treatment in the other). We found no other reported cases of ivermectin use PALS. Therefore, we assign an ALSUntangled TOE "Cases" grade of F.

Trials

We found no published trials of ivermectin use for PALS. Therefore, we assign an ALSUntangled TOE "Cases" grade of U.

Dosing, risks and costs

Ivermectin is commercially available in an oral tablet formulation with doses typically ranging from 150 to 200 μg/kg given as a single dose or over a few days for most of its indications (40). Minor reported side effects include rash, headache, edema, and ocular complaints (2,11). In an American cohort taking various formulations of ivermectin, including veterinary formulations, off-label for COVID-19, serious adverse events were documented including confusion, ataxia, seizures, and hypotension (41). Neurotoxicity is usually rare because ivermectin is a substrate for P-glycoprotein, which limits BBB penetration. However, co-administering ivermectin with P-glycoprotein inhibitors or interactions with genetic P-glycoprotein polymorphisms may increase the risk of neurotoxicity (2,42,43). Ivermectin is primarily metabolized by CYP3A4 (44); therefore other medications that induce or inhibit CYP3A4 may have an impact on the concentration of ivermectin. Since there is so little data on ivermectin use in PALS, optimal dosing (if any) and side effect profile are unknown. Indeed, ivermectin can induce oxidative stress and mitochondrial dysfunction leading to apoptosis in cancer cells (45); if it does this in motor neurons, it could exacerbate ALS progression.

Overall, pharmaceutical grade ivermectin used at standard dosing regimens is generally well tolerated. However there are no safety or tolerability data from PALS. There are no safety or tolerability data from any population taking ivermectin daily for long periods of time, as would likely be necessary for the treatment of a neurodegenerative disease. Thus, we assign a TOE 'Risks' grade of U (Table 1). dosing information and safety data in PALS.

At standard dosing and formulations, ivermectin is relatively inexpensive with 3 and 6 mg doses costing approximately $5 and $15 respectively (46).

Conclusion

Ivermectin has plausible mechanisms for modulating ALS pathways, particularly by decreasing neuroinflammation via inhibiting NF-κB and STAT3 signaling pathways and also by modulating excitotoxicity via $GABA_A$ and P2X4 receptor interactions. One preclinical demonstrated modest neuroprotective effects in a mSOD1 mouse model of genetic ALS; this has not been replicated. The 2 PALS we found who had data comparing ALSFRS-R progression on and off ivermectin appeared to have no benefit from it. We found no trials of ivermectin in PALS. While ivermectin is inexpensive and generally well tolerated some formulations are associated with serious side effects and

there are no safety data from PALS or from any population taking it daily for long periods of time (as would likely be needed to treat a neurodegenerative disease). Based on the limited preclinical data and lack of clinical evidence, we cannot recommend the use of ivermectin to treat ALS at this time.

Author contributions

CRediT: **BENJAMIN HELMOLD**: Investigation, Writing – original draft; **CARMEL ARMON**: Writing – review & editing; **MICHAEL BENATAR**: Writing – review & editing; **TULIO BERTORINI**: Writing – review & editing; **MARK BROMBERG**: Writing – review & editing; **ANDREW BROWN**: Writing – review & editing; **JAVIER MASCIAS CADAVID**: Writing – review & editing; **OLIMPIA CARBUNAR**: Writing – review & editing; **GREGORY T. CARTER**: Writing – review & editing; **JESSE CRAYLE**: Writing – review & editing; **EVA FELDMAN**: Writing – review & editing; **JULIETTE FOUCHER**: Writing – review & editing; **JONATHAN GLASS**: Writing – review & editing; **ETHAN GREENSTEIN**: Writing – review & editing; **SARTAJ JHOOTY**: Writing – review & editing; **NAN JIANG**: Writing – review & editing; **NOAH NATHAN KOCHEN**: Writing – review & editing; **CHRISTOPHER MCDERMOTT**: Writing – review & editing; **NATASHA OLBY**: Writing – review & editing; **GARY PATTEE**: Writing – review & editing; **DEVON PORTER**: Writing – review & editing; **ALAN PREMASARI**: Data curation, Formal analysis; **ANUSHA RAO**: Writing – review & editing; **DYLAN RATNER**: Writing – review & editing; **KIM STAATS**: Writing – review & editing; **ELIA TITO**: Writing – review & editing; **FERNANDO VIEIRA**: Data curation; **PAUL WICKS**: Writing – review & editing; **RICHARD BEDLACK**: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Writing – review & editing.

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Data availability statement

There is no dataset associated with this manuscript

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