



Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration

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ALSUntangled No. 50: Antifungal Therapy

THE ALSUNTANGLED GROUP

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RESEARCH ARTICLE

ALSUntangled No. 50: Antifungal Therapy

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ALSUntangled reviews alternative and off-label therapies on behalf of persons with amyotrophic lateral sclerosis (ALS) (PALS). Here we review the use of antifungal drugs in PALS for which we have received over 500 votes (1).

Overview

Fungi are a group of living organisms that includes yeasts, molds, and mushrooms. Like bacteria, fungi normally live on the skin and inside the gastrointestinal tract of humans, but certain forms and overgrowths can cause disease (2). For fungal infections, a number of antifungal drugs have been developed; these tend to have more side effects than antibacterial drugs (see “risks” section below). In 2006, a physician specializing in hematology and oncology named William K. Reid filed a patent for use of antifungal drugs in multiple neurologic diseases including ALS (3). He reported that he treated patients with ALS (see “cases”) with antifungals (usually voriconazole), sometimes in combination with other methods (3,4). More recently, a research group in Spain has reported finding evidence of fungal infection in the central nervous system (CNS) of patients with ALS (reviewed in Refs. (5–7); see “mechanism”).

Mechanism

Multiple antifungal drugs, including voriconazole, penetrate the CNS and can be used to treat fungal infections of the CNS (8). Therefore, we will focus this “mechanism” section on the plausibility of the hypothesis that a CNS fungal infection contributes to ALS disease. Specific antifungal drugs are discussed in “dosing.”

Dr. Reid first hypothesized that ALS is caused by a fungal “opportunistic infection” occurring because of an immunodeficient state. He reported that some of the PALS that he treated had laboratory evidence of immunosuppression including a low lymphocyte count and low IgG antibodies (3,4). This is an intriguing hypothesis; however, research has indicated that total IgG levels (9,10) are normal in PALS. Lymphocytes are frequently measured as a part of routine laboratory tests ordered by outpatient primary care providers; low total counts have not been associated with ALS. Immune system dysregulation may play a complex role in the pathophysiology of ALS; however, immunodeficiency is not thought to be a feature of this dysregulation (11). If PALS were truly immunodeficient, theoretically there would be more apparent manifestations of infection with not just fungi, but also bacteria and/or viruses.

One research group in Spain has reported evidence of mixed fungal infections in the CNS of PALS (12–14). They claim to have found a small quantity of yeast-like DNA and antigens in the frontal cortex neurons, spinal cord neurons, and CSF of PALS. There are several problems with this work. The possible fungal products were of inconsistent appearance and the antigens occasionally appeared to form structures that have never been seen in any disease before (i.e. “endomycosomes”). The authors used polyclonal antibodies they made and not commercially available monoclonal antibodies against fungi (12–24). This is concerning because polyclonal antibodies are less specific in terms of what they detect; in other words, the fungal-like antigens detected might not be truly fungal. In other articles, the same researchers claimed to find evidence of

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Note: this paper represents a consensus of those weighing in. The opinions expressed in this paper are not necessarily shared by every investigator in this group.

fungal infection in patients with Alzheimer's disease (15–22), Parkinson's disease (13), and multiple sclerosis (23,24). Finally, crucial details are missing from these reports, including whether included patients were known to have fungal infections near the ends of their lives, or about the intervals and storage procedures between deaths and autopsies (where contamination might have occurred). To date, we have not found any other researchers who have attempted to replicate these results.

If there truly are fungi in the brain of PALS, these may not be infections. Some researchers believe that the central nervous system may be home to its own microbiome. Several papers have been published from different research groups reporting the presence of a “CNS microbiome” (25–28) and some institutions are now attempting to build databases of the “CNS microbiome” (29–31). The existence of a “CNS microbiome” would explain why possible fungi were found in the CNS of multiple neurological disease patients and healthy patients. If there is a “CNS microbiome” (analogous to the gut microbiome), it could plausibly be altered in neurological diseases. It is unknown, however, if modifying the “CNS microbiome” would lead to a therapeutic benefit for any disease.

Given the uncertain nature of the relationship between ALS and fungi, ALSUntangled assigns a “mechanism” grade of D.

Pre-Clinical Models

There are no pre-clinical models relevant to ALS that explored the role of fungal infections or antifungal drugs. Therefore, ALSUntangled assigns a “pre-clinical models” grade of U.

Cases

The only cases we could find of PALS taking antifungals were reported by Dr. Reid. In a patent application, Dr. Reid described five middle-aged patients diagnosed with ALS who also had laboratory evidence suggestive of a porphyria (disorders of the hemoglobin synthesis pathway). Most were quadriplegic and ventilator dependent. The four patients treated with the antifungal drug voriconazole at 200–300 mg twice daily by mouth experienced small benefits in hand or wrist movement. No other symptomatic benefits were reported. The fifth patient treated with the antifungal itraconazole did not benefit. Some of the patients were also treated with blood filtration with activated charcoal or with the bile acid sequestrant cholestyramine, but not with both (3). A later report submitted by Dr. Reid to a non-peer reviewed website discussed five patients with ALS

treated with voriconazole, plasma exchange (PLEX), and sometimes intravenous immunoglobulin (IVIG). The first patient was quadriplegic and ventilator dependent. There was no initial improvement in ALS symptoms with any of the antifungal drugs amphotericin B, fluconazole, or voriconazole. When the first patient received voriconazole, PLEX, and IVIG in combination, there was some functional improvement in one hand. The second patient, also end-stage, had some improvements in leg movement and respiratory function with voriconazole and PLEX treatment. The third patient was “paralyzed from the waist down” and experienced some improvements in “motor function”, but details were not provided. The fourth patient had a plateau in disease progression after treatment with voriconazole, PLEX, and IVIG. The fifth patient with bulbar-onset ALS had substantial improvements in respiratory function after treatment with 5 d of voriconazole and PLEX (4).

It is difficult to know if small functional improvements in PALS are due to a treatment. The natural course of ALS often has modest functional improvements that are not sustained (32). The follow-up period of Dr. Reid's small group of patients is not stated, but it is implied to be short. The publications were not peer-reviewed, and we were not able to obtain medical records to verify the diagnosis or reported improvements in these cases. The reported laboratory signs of immunodeficiency seen in many of these patients are not consistent with ALS. Of potential interest, previously published small case series of PALS receiving either PLEX (33–36) or IVIG (37,38) have reported that these treatments are not beneficial when given alone. Based on these unverified cases, ALSUntangled assigns antifungal drugs a “cases” grade of D.

Trials

There are no trials of antifungal drugs in patients with ALS. Therefore, ALSUntangled assigns a “trials” grade of U.

Dosing and Costs

There are multiple antifungal drugs that can be used for CNS infections including liposomal amphotericin B, fluconazole, and voriconazole. The exact regimen varies based on the fungus targeted (39). Both *Malassezia* and *Candida* species have similar general treatment recommendations for CNS infections; i.e. initial treatment with intravenous liposomal amphotericin B (weight-based dosing) and then switching to oral fluconazole (400–800 mg per day). Voriconazole is used in some cases (400 mg per day). In less severe cases,

Table 1. Table of evidence for antifungals.

	Grade	Explanation
Mechanis	D	Antifungals are effective at treating CNS fungal infections. The existence of fungi in the CNS of PALS has not been proven. Even if present, the relevance of this to the pathophysiology of ALS and the therapeutic potential of antifungal drugs in ALS remains uncertain
Pre-clinical	U	There are no studies of antifungal drugs in pre-clinical models of ALS
Cases	D	A small case series published without peer-review reported short-term small functional benefits in PALS. We were unable to obtain the medical records to review
Trials	U	There are no trials of antifungal drugs in PALS
Risks	D/F	Antifungal drugs very commonly cause side effects which are sometimes serious. There is high potential for dangerous drug–drug and drug–supplement interactions, including with riluzole

oral fluconazole may be sufficient in monotherapy (40,41). It is plausible but unknown if oral fluconazole alone would be sufficient to treat a hypothesized chronic fungal infection of the CNS (if such an infection even exists). A typical 8-day course of liposomal amphotericin B without any complications would cost approximately \$4500 USD (42). Oral fluconazole would cost approximately \$75 USD per month and oral voriconazole would cost approximately \$400 USD per month (43,44).

Risks

In non-ALS patient populations, adverse effects of antifungal drugs are common and sometimes serious. It is unknown if there are additional adverse effects of antifungals that are specific to PALS. Liposomal amphotericin B very commonly causes nonspecific flu-like symptoms. Some patients (15%) have clinically significant nephrotoxicity that can lead to kidney failure (45,46). Side effects associated with oral fluconazole are usually mild including headache and GI distress (47). Oral voriconazole side effects include hair loss and nail changes (75%), changes in vision (30%), fever, nausea, and rash. Skin cancer and severe life-threatening skin reactions have been reported with voriconazole (48–50). Patients taking antifungal therapy should be carefully monitored if taking riluzole. Like riluzole, all antifungal drugs may increase transaminase enzyme levels which are a marker of liver damage (51,52). Voriconazole has recommendations to test transaminase levels weekly for the first month and then monthly (48). Fluconazole and voriconazole both have many substantial drug–drug and drug–supplement

interactions because they are metabolized by the CYP450 enzyme system (47,48,53,54). Based on the above discussion, ALSUntangled assigns antifungal drugs a “risks” grade of D/F (Table 1).

Conclusion

It is unknown if fungi exist in the brain of PALS. If they do exist, it is unknown if they have any pathogenic effect, and unknown if antifungal drugs would modify ALS disease progression. There are no pre-clinical ALS model studies, verified ALS cases, or ALS clinical trials to suggest that antifungals would be of any significant benefit to PALS, and these medications can cause harm. At this time, we strongly discourage PALS from taking antifungal drugs for their ALS disease. We hope in the future that independent laboratories will look for fungi in the CNS of PALS using more appropriate experimental methods.

Declaration of interest

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