Antifungal Treatment and Chronic Rhinosinusitis

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Chronic rhinosinusitis (CRS) is an inflammatory disease with a multifactorial etiology. Antifungal therapy is not routinely used to treat it. However, evidence implicating fungi in some forms of CRS recently has been published. Controversy exists as to whether fungi identified in sinonasal cultures are always pathogenic. Immunologic evidence supporting the role of fungi in the pathogenesis of CRS is also debated. Topical antifungal therapy is more widely used than oral therapy, with amphotericin B irrigation being the most common. Although some studies show benefit from this irrigation, others refute the efficacy. Although oral antifungal agents are used uncommonly, itraconazole is the most commonly used drug. The efficacy of oral itraconazole in CRS has never been assessed in a clinical trial. Given the current evidence, the use of antifungals to treat CRS is controversial and has limited indications.

Introduction

Background

The etiology of chronic rhinosinusitis (CRS), a chronic disorder of the sinonasal mucosa, is poorly understood, although we know that it is inflammatory. A multifactorial basis involving genetic predisposition, infection, and atopy has been proposed. However, how this inflammation is precipitated is only partially understood. The role of pathogens such as viruses, bacteria, and fungi in the induction or propagation of the disease process, and how to treat them, is also incompletely understood.

Role of fungi in chronic rhinosinusitis

CRS is associated with eosinophilic infiltrates in the sinonasal mucosa [1]. Although fungi have been associated with diseases of the paranasal sinuses for more than two decades, only recently have they been implicated in the pathogenesis of CRS [2–4]. Surgical specimens from CRS patients have shown fungi on histology [4,5]. However, airborne and other fungi also have been found in sinonasal tissue of normal controls. It is hypothesized that patients with CRS have a unique response to these ubiquitous fungi that distinguishes them from normal controls. A nonallergic, noninvasive interleukin (IL)-5–mediated response to fungi leading to an eosinophilic inflammation of the sinonasal mucosa is proposed to occur in patients with CRS [6].

Chronic rhinosinusitis, eosinophilic mucus chronic rhinosinusitis, and allergic fungal rhinosinusitis: the same disease or distinct pathologies?

CRS caused by fungus may or may not be an entity distinct from allergic fungal sinusitis (AFS). Pathophysiologically, AFS is also an eosinophilic inflammatory reaction to fungal antigens [7]. Attempts have been made to differentiate AFS from the other subtypes of CRS [8]. Eosinophilic mucus chronic rhinosinusitis (EMCRS) comprises CRS patients with eosinophilic mucin. EMCRS is further subclassified into nonallergic fungal eosinophilic sinusitis; nonallergic, nonfungal eosinophilic sinusitis; and AFS. Nonallergic fungal eosinophilic sinusitis is characterized by positive fungal culture and eosinophilic mucin but no noted fungal allergy. Nonallergic, nonfungal eosinophilic sinusitis comprises patients with EMCRS who are negative for fungal allergy and fungal culture. However, some authors question this classification and propose that all these subtypes may represent different phases of the same disease process. Allergen-specific IgE (to *Aspergillus* or *Alternaria* spp) presents in allergic and nonallergic forms of CRS, and "allergic" fungal disease cannot always be distinguished from "ordinary" CRS [9].

Antifungal Therapy in Chronic Rhinosinusitis

Rationale

Proponents of antifungal therapy argue that the therapy eradicates ubiquitous fungi in the sinonasal mucosa, decreases eosinophilic inflammation, and clears CRS. However, as noted in the classification of EMCRS, fungi may not always be isolated in cultures. It is against the

background of this conundrum that the role of antifungal therapy in managing CRS needs to be assessed.

Topical antifungal therapy

Ponikau et al. [10] first proposed using amphotericin B nasal irrigations for treating CRS in 2002. The same group first published a single-arm, open-label cohort study in 1999 (reviewed in [9]). Amphotericin B solution (100 μg/mL; 20 mL twice daily) was used for sinus irrigation by 51 patients with CRS for 3 to 17 months. Their outcome measures included subjective symptoms, endoscopic examination, and CT findings. Seventy-five percent of the patients showed improvement in symptoms and endoscopic findings. Statistically significant radiologic improvement was noted in 13 patients with CT scans. On endoscopy, 35% of patients became completely disease free.

Ricchetti et al. [11] confirmed these findings in an unblinded, uncontrolled study of 74 patients with CRS with nasal polyposis. Patients performed nasal lavage with 20 mL of a 100-μg/mL amphotericin B suspension in each nostril twice daily for 4 weeks. All patients also continued their saline nasal lavage and conventional topical corticosteroid spray. After antifungal nasal lavages, total disappearance of nasal polyposis was observed in 29 patients (39%).

However, the benefits of amphotericin B irrigation were refuted in a randomized, double-blind clinical trial carried out by Weschta et al. [12] in 2004. Seventy-eight patients with CRS with nasal polyps were enrolled, 60 of whom completed the study. Patients with AFS were excluded. Patients were instructed to instill a spray (amphotericin or control) as two puffs delivered four times daily for 8 weeks. Each puff was calculated to deliver 100 μL of the solution. Using a concentration of 3 mg/mL of amphotericin, a total daily dose of 4.8 mg of amphotericin B was administered to those in the study arm. The primary outcome was defined as a 50% reduction in pretreatment CT score. Secondary outcome variables included a symptom score, a quality-of-life score, and an endoscopy score. Before and after treatment, nasal lavages were examined for fungal elements by polymerase chain reaction assays and culture. In the control group, no positive response was observed, and only 2 of 28 patients in the amphotericin B group responded. The symptom scores were actually worse after amphotericin B therapy ($P < 0.005$). Other outcome measures did not differ between the treatment groups. The authors concluded that amphotericin B spray in the described dosing and schedule was ineffective and even worsened patient symptoms.

Ponikau et al. [13] then carried out a double-blind, randomized, placebo-controlled trial published in 2005. The authors increased the concentration of amphotericin B to 250 μg/mL and used 20 mL of that solution twice daily for 6 months in 30 CRS patients. Their primary outcome measure was CT findings. Secondary outcomes were endoscopic examination, symptom scores, and intranasal inflammatory markers. Twenty-four patients completed the 6 months of treatment. Patients receiving amphotericin B achieved a statistically significant reduction in mucosal thickening on CT. Statistically significant improvement in endoscopic scores was seen in the amphotericin B group compared with the placebo group. The intranasal mucus levels of eosinophil-derived neurotoxin and IL-5 (markers for eosinophilic inflammation) showed a statistically significant reduction in the amphotericin B group and an increase in the placebo group. However, there was no difference between the amphotericin B and placebo groups in symptom scores, and two study patients complained of nasal burning.

With these conflicting results, a double-blind, placebo-controlled, multicenter trial was conducted to clarify the role of intranasal antifungal drugs in the treatment of CRS. The results were published by Ebbens et al. [14••] in 2006. A total of 116 patients with CRS (with or without nasal polyps) were instructed to instill 25 mL of amphotericin B (100 μg/mL) or placebo into each nostril twice daily for 3 months using a standard commercial nasal douching device. Patients with AFS were excluded. To guarantee access to the sinonasal mucosa, only patients with previous endoscopic sinus surgery were included. Primary outcomes included a reduction in total visual analogue scale (VAS) and nasal endoscopy score. Secondary outcome measures included peak nasal inspiratory flow, polyp scores, quality-of-life scores, and individual VAS scores. After 13 weeks of treatment, no significant difference was noted between the amphotericin B and placebo groups on mean VAS scores, quality-of-life scores, peak nasal inspiratory flow values, nasal endoscopy scores, or polyp scores. The study concluded that amphotericin B nasal lavages in the described dosing and time schedule did not reduce clinical signs and symptoms in patients with CRS and did not add any benefit to use of intranasal steroids or irrigations. The authors proposed that fungi are innocent bystanders in CRS pathogenesis in immunocompetent patients.

Weschta et al. [15•] also examined the effect of nasal antifungal treatment on eosinophil cationic protein (ECP) and tryptase levels in nasal lavage samples from patients with CRS and nasal polyps. In a prospective, double-blind, placebo-controlled clinical trial, 76 patients were selected, 60 of whom completed the study. Six patients withdrew because of minor adverse events, and 10 dropped out for other reasons. Nasal treatment with amphotericin B or saline control was carried out for 8 weeks. Nasal lavages were performed before and after treatment. Fungal elements were assessed by culture and polymerase chain reaction assays. ECP and tryptase levels were determined by fluorescent enzyme immunoassay. The study found no correlation between cell activation markers and detection of fungus before treatment. Nasal amphotericin B treatment had no effect on levels of ECP or tryptase in nasal lavage samples. Also, successful fungus eradication, defined as fungus detection before but not after treatment, did not influence nasal ECP or tryptase levels. The

authors concluded that neither topical amphotericin B therapy nor fungal state before and after treatment had any significant influence on activation markers of nasal inflammatory cells in CRS.

In 2004, Shin and Ye [16] studied inflammatory markers in CRS patients with polyps. Nasal polyps were collected before and 4 weeks after treatment with 100-mg/L topical amphotericin, 50-μg/mL topical amphotericin B, or normal saline. The cytokine (IL-5; IL-8; interferon-γ; regulated on activation, normal T cell expressed and secreted [RANTES]) content of polyp homogenates was determined by enzyme-linked immunosorbent assay. Nasal polyps were found to contain large amounts of cytokines (IL-5, IL-8, and RANTES) compared with normal inferior turbinates. After 4 weeks of treatment, IL-5 levels tended to decrease, but this difference was not statistically significant.

Impact of the concentration of amphotericin B

There was a significant difference in the Weschta et al. [12], Ponikau et al. [13], and Ebbens et al. [14••] studies in terms of the concentration of amphotericin B used (3 mg/mL vs 250 μg/mL vs 100 μg/mL, respectively), total dose, and method of delivery (spray vs 20-mL irrigation with bulb syringe vs 25-mL instillation with a commercial nasal douching device, respectively). Shirazi et al. [17•] studied the effect of various concentrations of amphotericin B nasal irrigation on actively growing fungi in vitro. Ten fungi species common in the nasal cavity were cultured on plates. Each fungus was exposed to 20 mL of amphotericin B irrigation at concentrations of 100, 200, or 300 μg/mL or sterile water twice daily for 6 weeks. Each plate was subcultured weekly to examine for viable fungi. The authors found that fungal growth was not arrested in the 100-μg/mL amphotericin B and sterile water groups at the end of 6 weeks. Use of the 300- and 200-μg/mL amphotericin B solutions successfully eradicated viable fungi, as they showed failure of subcultured fungi to grow at 5 and 6 weeks, respectively. They concluded that nasal amphotericin B irrigation is ineffective in killing fungi in vitro at a concentration of 100 μg/mL over a 6-week period. Only concentrations of 200 and 300 μg/mL prevented fungal growth at the end of the study.

Liang et al. [18••] recently published the results of another double-blind, randomized, placebo-controlled trial to evaluate the efficacy of intranasal amphotericin in CRS patients without nasal polyps. Patients were randomly assigned to receive irrigation with amphotericin B solution (20 mg in 500 mL of normal saline) or placebo (dye in 500 mL of normal saline) for 4 weeks. The outcome measures were quality-of-life scores, nasal endoscopy, and bacterial and fungal cultures. Seventy patients were enrolled, 64 of whom completed this study. Significant improvement was noted in the amphotericin B group, both in endoscopic and quality-of-life scores. The placebo group also showed significant improvement in quality-of-life scores. However, quality-of-life scores were significantly lower in the amphotericin B group than in the placebo group after 2 weeks of treatment. They remained lower after 4 weeks, although the difference was not significant. No significant differences were seen in endoscopic scores and bacterial or fungal culture rates between the two groups after treatment. The study concluded that amphotericin B irrigation improved symptoms and endoscopic scores but did not show superiority to saline irrigation alone in patients with CRS without nasal polyps.

Effect of amphotericin on mucociliary clearance

Questions also have been raised about the safety of amphotericin B use and its effect on the nasal mucosa. Gosepath et al. [19] studied whether antiseptic, antibiotic, and antifungal topical solutions (including amphotericin B) used in CRS treatment influence nasal mucociliary clearance by affecting the ciliary beat frequency (CBF) of nasal respiratory cells. In a prospective study, nasal respiratory cells were harvested from healthy individuals. CBF was measured while cells were perfused with cell culture medium and the respective topical solution. Controls were perfused with cell culture medium only. Video interference contrast microscopy was used to monitor CBF. A decrease in CBF occurred after application of all topical solutions. Except for clotrimazole, all solutions showed significantly stronger effects at high concentrations compared with diluted solutions. The authors cautioned that the dose-dependent ciliotoxic effects indicated the need for careful selection of adequate drug concentration for topical nasal therapy.

Hofer et al. [20] found that treatment for 20 minutes with amphotericin B diluted in saline to 0.1 mg/mL produced no decrease in CBF. In contrast, both amphotericin B diluted in distilled water and distilled water without additives lowered CBF by approximately 50%. This decrease was not reversible with reincubation in saline. They recommended that dilution of amphotericin in physiologic solvents be considered to prevent ciliotoxic effects.

Oral antifungal agents

Oral antifungal drugs have been used to treat CRS, but few studies have been reported in the literature. Kennedy et al. [21] evaluated the antifungal terbinafine in patients with CRS in a randomized, double-blind, placebo-controlled, multicenter pilot study. Fifty-three adults with CRS received terbinafine, 625 mg/d, or placebo once daily for 6 weeks. Sinus secretions were collected at screening for mycology. CT was graded at baseline and 6 weeks. Patients recorded symptoms on a VAS and completed the Rhinosinusitis Disability Index. The authors found positive fungal cultures in 41 of 53 patients. Treatment with terbinafine failed to improve symptoms or radiographic appearance, even when nasal irrigation samples were positive for fungus on culture. The authors proposed that the fungi isolated were not a major pathologic factor. It was also possible that even at a high dose, terbinafine did not maintain therapeutic levels in the nasal secretions. These

results were also similar when only patients with positive fungal cultures were evaluated in the efficacy analysis.

Although itraconazole is one of the more commonly used oral antifungal drugs, the role of oral itraconazole in CRS therapy has never been studied in a clinical trial. Rains and Mineck [22] carried out a retrospective chart review on 139 AFS patients. The study characterized the typical AFS patient seen over a 12-year period and described a treatment protocol using endoscopic sinus surgery, high-dose itraconazole, low-dose bursts of oral corticosteroids, and topical corticosteroids. Although 50.3% of patients experienced recurrence, reoperation was required in only 20.5% of 83 patients. There were no serious adverse effects attributed to itraconazole or to the combination therapy.

Personal Experience

The senior author of this paper (Dr. Stankiewicz) uses a 4-week intensive treatment protocol for medical therapy of CRS. This is a combination of 4 weeks of oral antibiotics with twice-daily topical nasal steroids and saline irrigations. He also uses an oral steroid burst (40- to 60-mg taper over 10–14 days) and intermittent topical nasal decongestant rotation (5 days on, 3 days off). He does not use oral or topical antifungal therapy routinely in operated or non-operated CRS patients. He rarely uses antifungal therapy, even when there is clinical evidence of fungus, preferring instead topical and/or oral anti-inflammatory medications.

Dr. Stankiewicz's experience with nasal amphotericin B lavages has not been very successful when he has used the commercially available 100-μg/mL preparation, even when used up to 6 months. The treatment is expensive, and disease recurs after treatment is stopped. In patients with medically unresponsive CRS, it is important to first create a surgical pathway through which topical medication can be delivered to the sinonasal mucosa. Thus, any obstructive lesions due to fungal disease, such as polyps or enlarged middle turbinates, must be addressed with surgery before topical medications can be expected to treat CRS effectively. Saline nasal irrigations to clear mucopurulence and fungal debris must be used before instillation of topical nasal drops or antifungal irrigation. Once the obstruction has been addressed surgically, we prefer to use a combination of topical tobramycin–dexamethasone drops. The steroid component of the drop is effective in decreasing sinonasal inflammation and inhibiting the inflammatory effects of resident fungi. This combination is commercially available as an ophthalmic solution. Excellent results are obtained when patients are compliant with the prescribed regimen. The tobramycin component is effective against gram-negative bacteria such as *Pseudomonas* spp that often replace the normal sinonasal commensals in the postsurgical sinus cavities. Patients are advised that this medication is not US Food and Drug Administration approved for use in the nose or to treat CRS. Patients are instructed to dispense the medication in the nose with a nasal dropper in the Moffett (head down forward) [23] or the Mygind (head hanging) positions [24]. The tobramycin–dexamethasone drops are initially used as four drops in each nostril twice daily for 3 to 4 weeks in the postoperative patient. This is then tapered to every other week or 1 week per month as a twice-daily or once-daily dose as the clinical appearance improves. These drops also may be used in a rotation with steroid nasal sprays, with the tobramycin–dexamethasone drops used for 1 week and the steroid nasal spray for 3 weeks. Interspersed prednisone bursts may be used orally every 4 to 5 months at the physician's discretion. Very occasionally, a daily low dose of prednisone (5 mg) is used in the difficult patient.

In some recalcitrant cases, bursts of oral itraconazole for 1 month (100 mg 4 times/d or 200 mg twice daily) between oral prednisone bursts are used. The authors have no experience using itraconazole topical irrigation. This irrigation is not available commercially, as it is reported to be an unstable solution.

Conclusions

Antifungal agents have limited use in treating CRS, and their routine use is not justified based on the conflicting data in the literature. Further studies need to be carried out to determine whether changes in amphotericin B concentration, dosage, and duration of therapy improve CRS symptoms. The role of oral antifungal agents also needs to be assessed in clinical trials.

Disclosure

No potential conflicts of interest relevant to this article were reported.

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