

Oral antifungal therapy for chronic rhinosinusitis and its subtypes: a systematic review

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Background: The objective of the evidence base review was to systematically evaluate the literature to elucidate the potential role of oral antifungal therapy in management of chronic rhinosinusitis (CRS) and its subtypes.

Methods: Articles for inclusion were identified by query of appropriate search terms in the PubMed database. The articles were reviewed independently by 2 authors and assigned an evidence level. The composite outcome data was reviewed to determine the impact of oral antifungals in CRS.

Results: The search yielded 356 abstracts for review, retrieved 60 articles for full review, and incorporated 28 studies in this report. The majority of literature included level 4 (15) and level 5 (12) studies. One study met criteria for level 1 evidence. Most common disease entity studied was allergic fungal rhinosinusitis in 19 series; the most common antifungals reported were itraconazole and ketoconazole in 19 and 6 studies, respectively. Subjective parameters were assessed in 12 (42.8%) studies; overall, 64 (78%) of 82 patients reported symptom resolution or improvement.

Objective parameters were reported in 6 (21.4%) studies, including improvement in endoscopic findings (3), CT imaging (3), reduction in oral steroid usage (1), and less revision surgery (2). Median length of follow-up was 14.7 months (3–60).

Conclusion: The composite data suggests a potential beneficial effect of oral itraconazole and ketoconazole in patients with CRS and its subtypes. However, majority of the studies are uncontrolled case series, confounded by non-validated outcome variables. Randomized controlled trials are required to better elucidate their role in CRS. © 2011 ARS-AAOA, LLC.

Key Words:

chronic rhinosinusitis; fungal sinusitis; allergic fungal rhinosinusitis; antifungal therapy; itraconazole; ketoconazole; voriconazole; terbinafine

How to Cite this Article:

Thanasumpun T, Batra PS. Oral antifungal therapy for chronic rhinosinusitis and its subtypes: a systematic review. *Int Forum Allergy Rhinol*, 2011; 1:382–389

Chronic rhinosinusitis (CRS) represents a common chronic disorder characterized by persistent inflammation of the nose and paranasal sinuses for 3 months or longer.^{1,2} The pathophysiologic mechanisms of CRS remain poorly understood, with variety of potential etiologies being proposed, including defects in innate and acquired immunity, infectious agents (viruses, bacteria,

and/or fungi), superantigens, and osteitis.¹ Fungus, in both noninvasive (fungal ball, allergic fungal rhinosinusitis) and invasive (acute, chronic, and granulomatous invasive fungal rhinosinusitis) forms, has been recognized as a causative agent of paranasal sinus disease for almost 3 decades.³ However, this paradigm shifted with implication of fungus as the central etiologic agent in all forms of CRS.⁴ Ponikau et al.⁴ demonstrated the presence of fungus utilizing their novel culture technique in 96% of CRS patients and 100% of controls. Subsequent work has demonstrated interleukin-5 mediated eosinophilic inflammation in response to fungal antigens within the paranasal sinuses.⁵

The introduction of the fungal hypothesis has led to investigation of topical and oral antifungal therapies for CRS and its subtypes.⁶ Despite preliminary studies suggesting potential utility of topical amphotericin B irrigations,^{7,8} recent double-blind placebo-controlled randomized multicenter trial demonstrated no difference in mean visual analog scores (VAS), quality-of-life scores, nasal endoscopy

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Potential conflict of interest: P.S.B. has received research grants from ARS, Xoran Technologies, MedInvent, and Medtronic; has been a consultant to Medtronic and LifeCell.

Received: 20 February 2011; Revised: 28 June 2011; Accepted: 1 July 2011
DOI: 10.1002/alr.20088

View this article online at wileyonlinelibrary.com.

scores, or polyp scores between topical amphotericin B and placebo groups.⁹ Comparatively, the role of oral antifungals for treatment of CRS remains largely unexplored. Initial reports advocated its utility as an alternative to systemic steroids for allergic fungal rhinosinusitis (AFRS).^{10,11} Recent studies have reported improvement of symptoms, endoscopy, and computed tomography (CT) scores and reduction for need of revision surgery with oral itraconazole in patients with recalcitrant CRS or AFRS.^{12–14} With this in mind, the main objective of the present study was to systematically review the literature to better clarify the role of oral antifungal therapy in CRS and its subtypes. This, in turn, will help facilitate clinicians in more informed clinical decision-making when considering the use of oral antifungal agents in CRS patients.

Materials and methods

For this systematic review, the clinical indicator was oral antifungal therapy. The population of interest was adult patients with CRS and its subtypes (AFRS, eosinophilic mucin rhinosinusitis [EMRS], non-allergic eosinophilic fungal rhinosinusitis [NAEFRS]). The following focused clinical question (FCQ) was formulated: “In adults with refractory chronic rhinosinusitis and its clinical subsets (AFRS, EMRS, and NAEFRS) who have failed endoscopic sinus surgery and medical therapy with persistent symptoms and/or objective evidence of disease, does oral antifungal therapy improve clinical symptoms, endoscopic findings, imaging scores, and/or inflammatory markers?”

Literature search

Studies for inclusion were identified on PubMed (www.ncbi.nlm.nih.gov/pubmed) through search of the English language literature from 1983 to August 2010. A second group of studies was identified by reviewing the bibliographies of the initial group to cross-reference any missed studies. Search terms included oral antifungals and sinusitis, oral antifungals and allergic fungal sinusitis, itraconazole and sinusitis, voriconazole and sinusitis, posaconazole and sinusitis, ketoconazole and sinusitis, and fluconazole and sinusitis.

Selection the articles for inclusion

The PubMed search yielded 356 abstracts for further review. Two reviewers independently screened the abstracts and identified 32 articles that met the preset criteria for the FCQ. Query of the bibliographies cross-referenced an additional 28 abstracts, yielding 60 full-length articles for review. Thirty-two studies were excluded due to no oral antifungal treatment (26) and wrong disease entity (6). A total of 28 articles were included in the evidence-based review. The flow chart for article inclusion and exclusion process and final level of evidence is shown in Figure 1.

Assigning levels of evidence

The systematic review required the evidence-based medicine (EBM) process to assign each study with appropriate level of evidence. The studies in this review were assigned as follows: randomized controlled clinical trials (level 1), prospective cohort study or low-quality randomized trial (level 2), retrospective case-control studies (level 3), case series/reports or retrospective chart review (level 4), and expert opinion (level 5).¹⁵ Important considerations for assigning accurate level of evidence included inclusion of a comparison group and use of rigorous outcomes methodology, such as validated instrument tools, true subject randomization, prestudy power analysis, and robust statistical analysis.

Each full-length article was evaluated by 2 reviewers. Both independently evaluated the studies to determine inclusion based on the FCQ and subsequently assigned the level of evidence. Any discrepancy in the level of evidence was addressed by developing consensus among the panelists. Then, the aggregate of evidence was reviewed to assign an evidence grade for the overall body of literature according to the FCQ.

Data collection

Data accrued included median number of patients, median age, median follow-up, disease entity, fungal cultures, type of oral antifungal therapy, and duration of treatment. Outcome variables recorded included symptom outcome, endoscopic and/or CT findings, inflammatory markers, decrease in concurrent sinonasal medications, and need for additional sinus surgery.

Results

A total of 28 studies satisfied the FCQ for this review. The number of publications by decade was as follows: 1980s (3); 1990s (9); and 2000s (16). The geographic location of study origination was as follows: United States (18); Canada (3); United Kingdom (2); Netherlands (2); Saudi Arabia (2); and Australia (1). The level of evidence was designated level 4 in 15 and level 5 in 12 studies. One study was classified as level 1 (Table 1). The concordance for agreement for the 2 reviewers for the 28 studies was 100%. Statistically analysis was performed in 2 studies, being deemed statistically significant for the variables in both studies. Kennedy et al.¹⁶ reported the use of oral terbinafine on CRS patients. There were no statistically significant differences in outcomes by alteration of symptoms and radiographic finding on pretreatment and post-treatment between terbinafine and placebo groups. Chan et al.¹³ studied on oral itraconazole in 32 patients with AFRS refractory to variety of medications in the postoperative period. The comparison between pretreatment and posttreatment in Rhinosinusitis Outcome Measure-31 (RSOM-31) had statistically significant improvement in the subgroup of

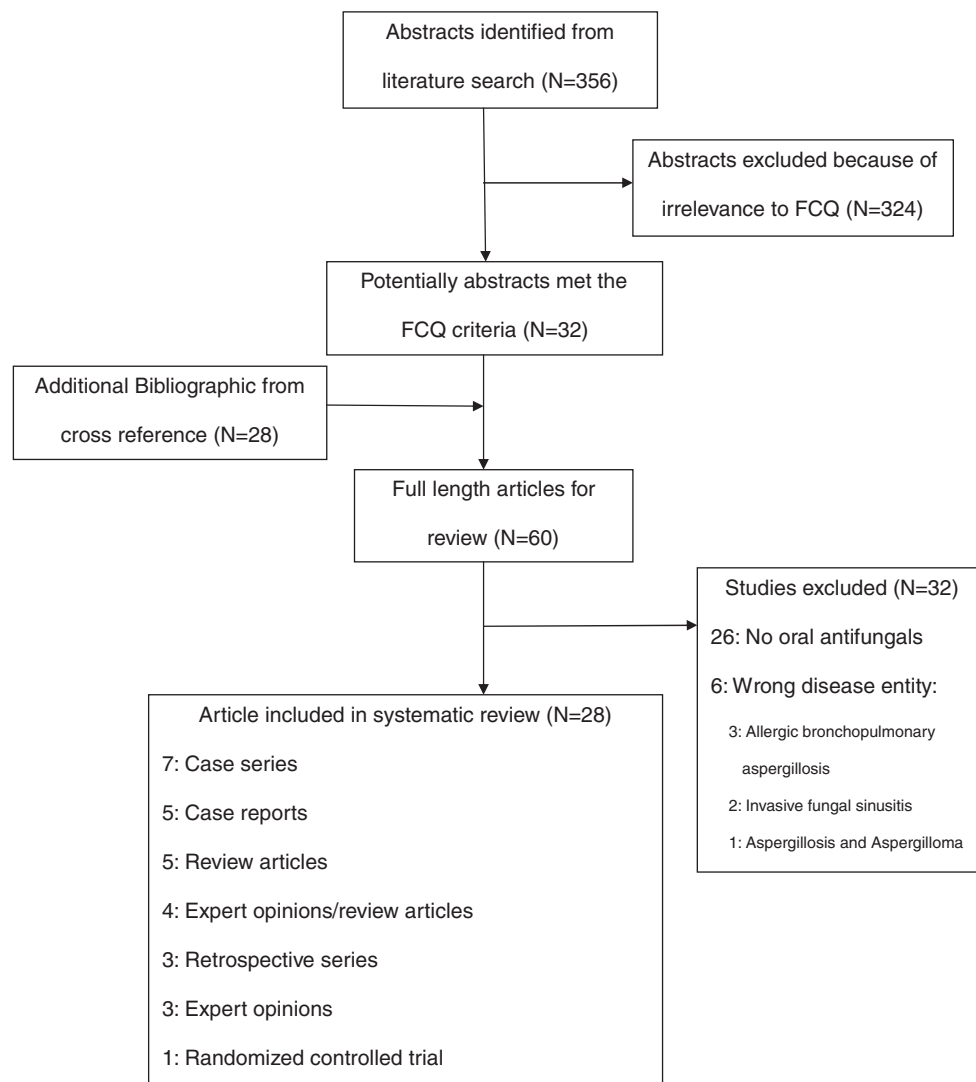


FIGURE 1. Flow chart for article retrieval process.

nasal symptoms, sleep symptoms, ear symptoms, practical problems, and emotional consequences.

The median age of subjects was 33.9 years (range, 7–57 years). Median number of patients was 4 (range, 1–137). Median length of follow up was 14.7 months (range, 3–60 months). The disease entities reported were AFRS in 19 (67.8%), CRS in 6 (21.4%), AFRS and AFRS-like syndrome in 1 (3.6%), AFRS and NAEFRS in 1 (3.6%), and AFRS with allergic bronchopulmonary aspergillosis (ABPA) in 1 (3.6%) study.

Fungal culture was reported in 22 studies with *Aspergillus* species being the most common fungal organism. The data for the fungal organisms is reported in Table 2. Oral antifungal employed were itraconazole (19), ketoconazole (6), oral antifungal not specified (2), fluconazole (1), voriconazole (1), and terbinafine (1). Oral antifungals were used as monotherapy in 56 patients and used in combination with oral and/or topical steroids in 197 patients. Oral antifungals were concurrently with immunotherapy in 1 patient.

Studies focusing on itraconazole and/or ketoconazole reported subjective parameters in 12 (42.8%) studies. Overall, 64 of 82 patients (78.0%) reported symptom resolution or improvement, while 18 patients (22.0%) experienced no change in symptoms compared to baseline. The binomial test found statistical difference between the subgroup of resolution/improvement and no improvement ($p < 0.001$).

In patients with symptom resolution or improvement, itraconazole was used as monotherapy in 44 patients, combination with oral/topical steroids in 19 patients, and combination with immunotherapy in 1 patient. For another 18 patients who did not improve, itraconazole was prescribed alone in 4 patients, whereas itraconazole was combined with topical steroids in 14 patients.

In the subgroup analysis of 25 fungal-positive cultures, symptom resolution or improvement was shown in 24 of 25 (96%). In another 9 patients of the fungal-negative cultures subgroup, symptoms resolution or improvement was demonstrated in 6 of 9 (67%).

TABLE 1. Evidence table for oral antifungal therapy in 28 articles

Year	Author	Disease entity	Number of patients	Oral antifungal	Treatment duration	Symptom outcome
1984	Farquhar et al. ³¹	AFRS	1	Ketoconazole 200 mg qd	2 months	Complete resolution of sinusitis
1987	Frenkel et al. ³⁷	AFRS	1	Ketoconazole 100 mg qd for 3 weeks and then itraconazole 100 mg qd for 32 weeks	35 weeks	Decrease nasal stuffiness and mucus production
1989	Jonathan et al. ³⁸	AFRS	4	Itraconazole (1 case)	NA	Stable after 7 months
1991	Friedman et al. ³⁹	AFRS	3	Ketoconazole (1 case)	NA	NA
1992	Daghistani et al. ³²	AFRS	5	Ketoconazole 200 mg qd (2 cases)	10 days	Symptom free: 1 case (18 months); recurrence: 1 case (1 year)
1994	Cody et al. ⁴⁰	AFRS, AFRS-like	44	Ketoconazole, miconazole, clotrimazole	NA	NA
1995	Corey et al. ⁴¹	AFRS	NA	Itraconazole	Not specified	NA
1996	Kinsella et al. ⁴²	AFRS	25	Ketoconazole (1 case), fluconazole (1 case)	NA	Symptom free (ketoconazole); recurrence (fluconazole)
1996	Morpeth et al. ⁴³	AFRS	NA	Itraconazole	Not specified	Itraconazole may be helpful in maintaining remission but prone to recurrence after withdrawal
1997	Kupferberg et al. ⁴⁴	AFRS	26	Name not provided, oral antifungals used in 3 cases, oral antifungals + steroids in 2 cases	NA	Antifungal: improve 1/3; steroid + antifungal: improve 2/2
1998	Ferguson ¹¹	AFRS	NA	Itraconazole	Not specified	NA
1998	Kuhn and Javer ⁴⁵	AFRS	2	Itraconazole	19 months (1 case), other case not specified	Both patients with improvement, relapse after discontinuation
2000	Fadl et al. ⁴⁶	AFRS	4	Itraconazole	1 month in 2 cases	Symptom free all cases
2000	Kuhn and Javer ⁴⁷	AFRS	NA	Itraconazole	Not specified	NA
2000	Andes et al. ⁴⁸	AFRS	1	Itraconazole 200 mg qd	12 months	Symptoms improved
2001	Marple ⁴⁹	AFRS	NA	Itraconazole	NA	NA
2003	Tang et al. ⁵⁰	AFRS	1	Oral and topical itraconazole	Not specified	Symptoms improved
2003	Kuhn and Swain ⁵¹	AFRS	NA	Oral antifungals	Not specified	NA
2003	Rains and Mineck ¹²	AFRS	137	Itraconazole 400 mg qd for 1 month, 300 mg qd for 1 month, 200 mg qd for 1 month ($\pm$ 2–4 additional weeks)	3 months	NA
2005	Kennedy et al. ¹⁶	CRS	53	Terbinafine 625 mg qd	6 weeks	No statistical change in symptoms
2007	Ebbens et al. ¹⁷	CRS	NA	Itraconazole, terbinafine	Not specified	Anecdotal evidence, unsure if secreted into sinus mucus
2007	Erwin and Fitzgerald ³⁵	AFRS/ABPA	1	Voriconazole	2 months, followed by 1 year course for relapse	Improved symptoms
2008	Ebbens and Fokkens ¹⁰	CRS	NA	Itraconazole, terbinafine	Not specified	NA
2008	Desrosiers and Kilty ⁵²	CRS	NA	Itraconazole	Not specified	NA

(Continued)

TABLE 1. Continued

Year	Author	Disease entity	Number of patients	Oral antifungal	Treatment duration	Symptom outcome
2008	Chan et al. ¹³	AFRS	32	Itraconazole 100 mg tid, then 100 mg qd for 2 months	3 months	RSOM-31: 9 (28%) significant improvement; 9 (28%) moderate improvement; 14 (44%) little or no change
2009	Lal and Stankiewicz ⁶	NA	NA	Itraconazole 100 mg bid or 200 mg bid	1 month intermittently between prednisone bursts	NA
2009	Rank et al. ⁵³	CRS	NA	Itraconazole	Not specified	NA
2009	Seiberling and Wormald ¹⁴	AFRS, NAEFRS	23	Itraconazole 100 mg bid	6 months	16/23 (69.6%) responded, with 11/16 (68.8%) free of disease by symptoms and endoscopy

ABPA = allergic bronchopulmonary aspergillosis; AFRS = allergic fungal rhinosinusitis; bid = two times a day; CRS = chronic rhinosinusitis; NA = not applicable; NAEFRS = non-allergic eosinophilic fungal rhinosinusitis; qd = once a day; RSOM-31 = rhinosinusitis outcome measure-31; tid = three times a day.

TABLE 2. Fungal organisms reported in 22 series utilizing antifungal therapy

Fungus	Number (%) studies
<i>Aspergillus</i>	18 (81.8)
<i>Alternaria</i>	13 (59.1)
<i>Bipolaris</i>	11 (50)
<i>Curvularia</i>	11 (50)
<i>Exserohilum</i>	7 (31.8)
<i>Cladosporium</i>	6 (27.3)
<i>Penicillium</i>	6 (27.3)
<i>Drechslera</i>	6 (27.3)
<i>Fusarium</i>	3 (13.6)
<i>Aureobasidium</i>	2 (9.1)
<i>Candida</i>	2 (9.1)
<i>Helminthosporium</i>	1 (4.5)
<i>Hyalinase</i>	1 (4.5)
<i>Rhizopus</i>	1 (4.5)
<i>Acremonium</i>	1 (4.5)
<i>Tricoderma</i>	1 (4.5)
<i>Scedosporium</i>	1 (4.5)

Objective parameters were reported in 6 studies (21.4%); these included improvement in endoscopic findings (3), CT imaging (3), less revision surgery (2), and reduction in oral steroid usage (1).

Adverse events (AEs) from itraconazole were reported in 3 retrospective studies. The majority of AEs were of mild to moderate severity, with 1 serious AE of chemical hepatitis that resolved with discontinuation of the antifungal. No cases of liver or cardiac failure were reported. The most common AE was elevation of liver enzymes (17–20%) that normalized after cessation of antifungals. The other

AEs were lower extremity swelling (2.9%), rash (2.2%), malaise (1.4%), hair loss (0.7%), nausea (0.7%), headaches (0.7%), and anaphylactoid reaction (0.7%). Kennedy et al.¹⁶ compared adverse events between terbinafine and placebo groups and noted no statistical difference. One patient did develop chest pain, though this was not considered related to the study medication.

Discussion

The majority of experts may accept the basis of CRS as a chronic inflammation process with multifactorial etiology, though the possibility of fungus as the central etiologic agent has been increasingly disputed.^{9,10,17} Initially described by Millar et al.¹⁸ in 1981 and then by Katzenstein et al.¹⁹ in 1983, AFRS represents one of the most extensively studied forms of fungal sinusitis. In 1994, Bent and Kuhn²⁰ proposed 5 criteria for the diagnosis of AFRS based on clinical findings in 15 patients: (1) nasal polypoidosis; (2) allergic mucin; (3) CT findings consistent with CRS; (4) positive fungal history or culture; and (5) type I hypersensitivity to fungi. In the same report, they highlight the challenges in managing this disease by concluding “misdiagnosis is common, recurrence rates are high, and proper treatment remains elusive.”²⁰

Controversies in the literature on the precise etiologic role of fungus, challenges in accurate diagnosis, and diversity in nomenclature to describe CRS and its subtypes underscores the challenge in devising optimal management strategy for these patients. Though the role of topical antifungals has been extensively studied in the literature, the utility of oral antifungal agents in CRS remains to be elucidated.^{7,8} To the best of our knowledge, the present study represents the first systematic review in the literature to delineate the potential role of oral antifungals in CRS.

Several important observations stem from the evidence-based review. Most of the accrued data to date on oral

antifungal therapy prescribed in CRS and its subtype is level 4 (15) and level 5 (12). The paucity of robust studies is highlighted by the mere presence of one level 1 study evaluating utility of terbinafine in CRS.¹⁶ The overwhelming evidence of the studies is grade C, given that the database is comprised mostly of retrospective case series with a median of 4 patients and relative short median follow-up of 14.7 months. A variety of CRS subtypes were studied, with AFRS being reported in 22 studies. When the aggregate data is evaluated, 64 of 82 patients (78%) reported symptom improvement or resolution ($p < 0.001$), with several select series reporting improvement of objective parameters, such as endoscopy, CT, and inflammatory markers.

Kennedy et al.¹⁶ have reported the only double-blind, placebo-controlled, multicenter study to date. Fifty-three adult CRS patients received oral terbinafine 625 mg/day ($n = 25$) or placebo ($n = 28$) once daily for 6 weeks. No statistically significant differences were noted in outcomes by change of symptoms and radiologic appearance pretreatment and posttreatment between terbinafine and placebo groups. The authors concluded that terbinafine failed to improve overall parameters in CRS patients with positive or negative fungal cultures. The authors posited that fungus may not have been a major pathologic factor. Furthermore, it is possible that terbinafine may not have maintained therapeutic levels in nasal secretions, despite the high dose. The fact that this study elected to assess response to terbinafine in all comers (both culture positive and culture negative subjects) is a potential weakness of this study. Whether exclusion of fungal negative patients would have altered the outcome is unclear and may deserve additional study.

One prospective, randomized, placebo-controlled trial of postoperative oral corticosteroids in AFRS used oral itraconazole 200 mg once daily for 12 weeks in all patients who received either oral prednisolone or placebo.²¹ The study did not meet the criteria for inclusion into this systematic review as it failed to address the FCQ. Patients were proactively treated with itraconazole with or without oral steroids in the immediate postoperative period and did not represent a refractory group as defined by the study. Interestingly, itraconazole alone did not appear to control disease. The combined itraconazole and oral steroid control had better control of disease by symptomatic and endoscopic criteria. However, 8 of 12 in the itraconazole group had partial relief of symptoms. This data would suggest that itraconazole is likely not indicated in the early postoperative period and may potentially have an additive benefit in conjunction with oral steroids. Additional trials, perhaps oral steroids compared directly to oral itraconazole, would be required to clarify these important issues.

Itraconazole, an azole oral antifungal, has been most extensively evaluated in other retrospective series.^{12–14} Itraconazole inhibits the fungal cytochrome P450 oxidase-mediated synthesis of ergosterol, a key cell membrane component. It has proven efficacy in variety of fungal infections, including invasive aspergillosis and ABPA.²² The drug is metabolized in the liver; thus, dose adjustment and peri-

odic liver function tests (LFTs) monitoring is imperative to minimize risk of hepatic dysfunction.²³ Itraconazole also has been associated with QTc prolongation and may be cardiotoxic when administered with other agents, such as cisapride, terfenadine, astemizole, and quinidine.²⁴

Rains and Menick¹² retrospectively reported 139 patients with AFRS over a 12-year period. The patient group was managed with high-dose itraconazole protocol (400 mg/day for 1 month, 300 mg/day for 1 month, and 200 mg/day for 1 month or until clear by endoscopy), coupled with short bursts of steroids and topical nasal steroids in the postoperative period. Though 69 patients (50.3%) relapsed on this protocol, additional surgery was only required in 20.5% of patients. No serious adverse events were noted with over 36,000 prescribed doses. Seiberling and Wormald¹⁴ employed oral itraconazole 100 mg twice daily in 23 patients with refractory AFRS and NAEFRS for 6 months. Nineteen patients (82.6%) responded with a decrease in symptoms and improvement of eosinophilic mucin and polyps on endoscopy. Three responders had to terminate therapy due to elevation of LFTs. Twelve of 16 responders were able to stop or decrease requirement for oral steroids, with 11 being recurrence free with mean follow-up of 15.7 months. No serious complications were attributable to oral itraconazole.

Similarly, Chan et al.¹³ evaluated oral itraconazole in 32 patients with AFRS refractory to oral and topical steroids and amphotericin B nasal spray in the postoperative period. Subjectively, RSOM-31 demonstrated significant improvement in 9 (28%), moderate improvement in 9 (28%), and little or no change in 14 (44%) patients. Twelve cases were noted to have endoscopic improvement, with no correlation between subjective and endoscopic changes. Six patients (19%) developed elevated LFTs, with 1 patient developing chemical hepatitis. The changes were reversible in all cases after discontinuation of itraconazole.

Robust clinical data on the potential utility of itraconazole is available in the ABPA literature, a chronic respiratory inflammatory process analogous to AFRS. Stevens et al.²⁵ evaluated the efficacy of itraconazole compared to placebo for 16 weeks in corticosteroid-dependent ABPA. The responses in the treatment group included reduction of corticosteroids by 50%, decrease in total immunoglobulin E (IgE) by 25%, and improvement of pulmonary function testing or exercise tolerance by 25%. The overall response was significantly higher in the itraconazole group (13 of 28 patients) compared to the placebo group (5/27 patients) at the end of treatment ($p = 0.04$). Denning et al.²⁶ reported use of itraconazole 200 mg twice daily in 6 cases of steroid-dependent ABPA. Overall, statistically significant reduction in the mean steroid dosage ($p < 0.01$), decrease in serum IgE ($p < 0.05$), and increase in forced expiratory volume in 1 second (FEV₁) ($p < 0.05$) were observed. However, most patients suffered relapses in clinical symptoms or serum IgE after discontinuation of therapy.

Additional data demonstrates that itraconazole may confer the potential to reduce eosinophilic airway

inflammation in ABPA. Wark et al.²⁷ assigned ABPA patients to obtain 400 mg itraconazole daily or placebo for 16 weeks. The itraconazole subjects demonstrated reduction in sputum eosinophils by 35% per week with no decrease in the placebo arm ($p < 0.01$). Sputum eosinophil cationic protein levels decreased with itraconazole by 42% per week compared with 23% in the placebo group ($p < 0.01$). Itraconazole reduced systemic immune activation resulting in decrease of serum IgE levels (310 IU/mL) and a decrease in IgG levels to *Aspergillus fumigatus* (15.4 IU/mL) compared with placebo. Fewer exacerbations requiring oral steroids were seen in the itraconazole group ($p = 0.03$).

These randomized clinical trials would suggest a possible role of oral itraconazole in CRS and its subtypes. The classic purported mechanism of its effectiveness has been its ability to reduce nasal fungal load and, thus, improving disease activity in CRS patients. Further, ABPA data suggest that reduction of the fungal load may decrease eosinophilia, eosinophilic cationic protein, and IgE levels, thus reducing the need for systemic steroids. Interestingly, in vitro data has also suggested possible anti-inflammatory properties. Incubation of human platelet-activating factor-activated neutrophils with various azole antimycotic agents results in statistically significant inhibition of production of leukotriene B₄, with itraconazole being the most potent.²⁸ Additionally, itraconazole has been able to magnify the anti-inflammatory effect of oral steroids by its inhibition of the hepatic P450 system, thus decreasing clearance of these exogenous steroids.²⁹ Though the primary mechanism of action of azoles is their antifungal activity, these other secondary mechanisms may further add to the beneficial effects of itraconazole.

Based on the pathophysiology and clinical similarities of AFRS to ABPA, itraconazole may potentially be considered in this subgroup refractory to surgery, and oral and/or topical steroid therapy. It may be introduced at dosages ranging from 200 to 400 mg daily for 2 to 6 months.^{12–14} LFTs must be obtained at baseline and, then, monthly while on therapy. Patients should be warned about its off-label usage and frank discussion should ensue about risks of hepatotoxicity and cardiotoxicity, carefully weighed with potential benefits. Other possible side effects include gastrointestinal reactions (nausea/vomiting), skin rash, headaches, dizziness, and pedal edema. It should be avoided in patients with preexisting cardiac or hepatic disease.

Ketoconazole and voriconazole have also been demonstrated to be effective for AFRS in select cases. Ketoconazole is an imidazole antifungal that can inhibit the growth of dermatophytes and *Candida* species and can be effective in the treatment of chronic mucocutaneous candidiasis.³⁰ Farquhar et al.³¹ reported 1 case of recurrent *Aspergillus* fungal rhinosinusitis after extensive sinus surgery. Ketoconazole 200 mg daily was introduced for 2 months resulting in complete resolution that remained in remission for 12 months after cessation of therapy.³¹ Daghistani et al.³² demonstrated benefit with ketoconazole 200 mg daily for 10 days in 2 cases of AFRS after external sinus surgery;

both patients were disease-free at 12 and 18 months, respectively.

Voriconazole is a triazole antifungal but has better bioavailability than itraconazole. It has been widely used for treatment of invasive aspergillosis in immunocompromised patients.³³ Hillard et al.³⁴ reported a retrospective case series of 13 children with concurrent cystic fibrosis and ABPA receiving oral voriconazole for mean of 22 weeks. Overall, there was improvement of lung function and decrease of total serum IgE. Erwin and Fitzgerald³⁵ reported a case of a patient with AFRS and ABPA refractory to multiple sinus surgeries, high-dose oral and inhaled steroids, and oral itraconazole. Oral voriconazole resulted in improvement of sinopulmonary complaints in 2 months. Patient remained disease-free with 1 year of voriconazole with discontinuation of oral steroids and reduction of total serum IgE and peripheral eosinophils.³⁵ Voriconazole may represent a potential option for patients unresponsive to itraconazole; however, patients should be warned of the most common adverse events, including visual disturbances (21%) and LFT elevation (12%).³⁶

Important limitations of this review must be highlighted. The systematic analysis represents a composite of several retrospective, uncontrolled studies, and precludes definitive conclusions on the role of oral antifungals in CRS and its subtypes. The inclusion criteria for refractory CRS, as decided by failure to previous surgery and medical therapy, were decided in each individual study. Furthermore, treatment of patients with variety of oral antifungals and, often in combination with other therapeutic agents, serves to further confound the data. Moreover, the outcomes generally represented nonvalidated symptom improvement, with scarcity of validated outcomes and subgroup analyses of impact of fungal-positive vs fungal-negative cultures.

Nonetheless, the aforementioned studies, especially the data derived from the ABPA literature, underscore the potential utility of oral antifungals in management of upper airway inflammatory disease. The purpose of this review is not to advocate the use of oral antifungals in management of CRS. More importantly, it serves to highlight the accrued evidence base on its efficacy in CRS and its subtypes. Further, it highlights the significant gaps that persist for outcomes data in CRS. Clinicians should carefully scrutinize the lack of randomized controlled trials and accepted treatment protocols if consideration is given to using this agent for CRS patients. The systematic review may also serve to facilitate future randomized clinical trials to better elucidate the role of oral antifungal therapy in CRS.

Conclusion

The study systematically reviewed the evidence base for oral antifungal therapy in management of CRS and its subtypes. Twenty-eight studies were identified meeting the FCQ criteria, with majority of data being level 4 and 5 on the EBM schema. Most of the retrospective data

suggests potential role of oral antifungal therapy with subjective symptom improvement being reported in 64 of 82 patients (78%). Overall, the risk of serious complications is low, though LFT elevation is common, resolving after discontinuation of therapy. Given the paucity of robust level 1 and 2 studies on the topic, future prospective clinical

trials, preferably with blinding and appropriately matched controls, will be required to better clarify the role of itraconazole and other azole antifungal agents in CRS and its subtypes. Until such stronger evidence exists, the use of systemic antifungals should only be undertaken after careful consideration. ④

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