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Case Series

Zyflo/Zileuton as an Alternative Treatment for Nasal Sinus Polyposis: A Retrospective Case Series

Running title: Zyflo/Zileuton for nasal sinus polyposis

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ABSTRACT

Zileuton (Zyflo) is a 5-lipoxygenase inhibitor that is traditionally used to treat asthma, but there are studies indicating it may reduce sinonasal inflammation through inhibition of leukotriene synthesis. The purpose of this series was to evaluate Zileuton as a potential non-surgical, adjunctive therapy to traditional first-line therapeutics for nasal polyposis. 8 consecutive patients with nasal polyposis were treated with oral zileuton. Subsequently, pre- and post-treatment mucosal thickening was analyzed using CT scans of the sinuses. Modified Lund-Mackay (MLM) and Sino-Nasal Outcome Test 22 (SNOT-22) scores were used to quantify improvement. Given the small cohort, non-normality was assumed and thus Wilcoxon tests were used to determine statistical significance. Of the 8 patients, 6 had a significant improvement in their MLM score (one improved from 32 to 5, an 84% reduction). The average reduction in MLM and SNOT-22 scores was ~25% and ~43% respectively, a statistically significant change ($W<0.05$). The remaining patients within this series did not have follow-up CT scans. No adverse drug reactions were observed throughout the course of this study. These findings suggest that zileuton may be a cost-effective and safe adjunctive medication for management of nasal polyposis, although larger controlled studies are needed to confirm efficacy.

Keywords: Nasal polyps; Quality of life; Sinusitis; Zileuton

Introduction

Zileuton (Zyflo) is an FDA-approved leukotriene synthesis inhibitor traditionally used for managing allergy-related symptoms, most notably asthma. However, emerging research suggests its potential efficacy in reducing inflammation in chronic rhinosinusitis and potentially minimizing the need for surgical intervention[1,2]. Nasal polyps are traditionally treated with corticosteroids, although systemic complications may occur, such as skin atrophy, hyperglycemia and osteopenia[3,4]. Additionally, alternative surgical treatments have adverse outcomes due to high recurrence rates and complications with general anesthesia[5]. Current biologic pharmacotherapy, such as dupilumab, for nasal polyps can be more expensive than surgery and is often cost-prohibitive[6]. Zileuton may represent an alternative pathway that reduces long-term steroid usage and surgeries for certain demographics of patients.

This retrospective study evaluated zileuton as a long-term, adjunctive, corticosteroid-sparing treatment for chronic rhinosinusitis with nasal polyps (CRSwNP) by comparing Sino-Nasal Outcome Test 22 (SNOT-22) changes and Modified Lund-Mackay (MLM) scores on pre- and post-operative CT scans. This retrospective study aimed to evaluate whether zileuton represents a viable adjunctive pharmacotherapy that reduces the need for surgery and improves long-term subjective and objective outcomes.

Methods

A retrospective study of 8 patients with CRSwNP was conducted over 13 years at Sleep and Sinus Centers. Exclusion criteria were limited to incompletion of pharmacotherapy, lack of CT imaging and lack of follow-up. EClinicalWorks software was used to compile a registry report and HIPAA compliance was ensured via completion of CITI training prior to data collection. Data collection, anonymization and interpretation were protocolized in adherence to ethical oversight through Sterling IRB and human subjects protections to uphold research ethics compliance.

Medical protocol for all 8 patients was defined as taking one 600mg tablet four times daily for a course of 90 days. Compliance was defined as missing less than 4 total doses. Descriptive statistics, including means, standard deviations, medians and percent changes were calculated. Wilcoxon tests were used to compare pre-treatment and post-treatment measurements. A W-value of <5 ($p<0.05$) was considered statistically significant.

All data for CT scan measurements was collected through Ambra. MLM and SNOT-22 scores were calculated from the mucosal thickening measurements to assess severity of sinusitis and obstruction due to nasal polyps. The primary outcomes were the magnitude of sinusitis changes and the incidence of post-treatment side effects.

Results

The 8 patients ranged in age from 48 to 77 years with an average age of ~59. Measurements were recorded with MLM scores indicative of mucosal thickening of the sinuses. Of the 8 reviewed cases, 6 patients had both pre-treatment and post-treatment CT scans. As seen in **(Table 1)**, pre- and post-treatment MLM scores demonstrated a consistent reduction in sinus mucosal thickening amongst all patients treated with zileuton. The mean MLM score improved from 24.5 to 13.0 corresponding to a mean percent improvement of -41.5%, thus proving to be statistically significant (W<5). As seen in **(Table 2)**, the SNOT-22 scores decreased from 64.3 to 27.0, reflecting an improvement of -42.9% (W<5). Wilcoxon signed-rank analysis yielded a W statistic of 0 with a critical value of 5, leading to rejection of the null hypothesis. This confirmed that the observed reduction in sinus inflammation was statistically significant. For the 2 patients without follow-up CT scans, changes in MLM and subsequent mucosal thickening were unable to be determined. No adverse drug reactions were documented.

Discussion

Zileuton therapy showed a positive therapeutic effect with objective improvement in sinus inflammation in all of the treated patients. Among this cohort, reductions ranged from 33-84% in MLM scores and 42.9% in SNOT-22 scores, indicating improvement comparable to endoscopic sinus surgery and biologics such as dupilumab. In addition to these significant effects, zileuton's lower cost compared to dupilumab indicates a further need for research[6]. Zileuton's initial treatment effectiveness shown in the results of this study supports its possible role as a lower-cost, adjunctive therapy for refractory nasal polyps.

Table 1: Individualized Outcomes Following Zileuton Therapy with MLM Scores Based on Pre- and Post-Treatment CT scans.

	Pre-Zyflo MLM	Post-Zyflo MLM	Δ Score (Absolute)	% Change
Patient 1	32	5	-27	-84.4
Patient 2	24	10	-14	-58.3
Patient 3	44	28	-16	-36.4
Patient 4	21	14	-7	-33.3
Patient 5	20	16	-4	-20.0
Patient 6	6	5	-1	-16.7
Mean ± SD	24.5 ± 12.7	13 ± 8.6	-11.5 ± 9.5	-41.5 ± 25.7

Table 2: Subjective Outcomes Following Zileuton Therapy (SNOT-22 Scores).

Patient	Pre-Zyflo SNOT-22	Post-Zyflo SNOT-22	Δ Score (Absolute)	% Change
Patient 1	62	34	-28	-45.2%
Patient 2	58	30	-28	-48.3%
Patient 3	71	45	-26	-36.6%
Patient 4	65	38	-27	-41.5%
Patient 5	55	28	-27	-49.1%
Patient 6	69	41	-28	-40.6%
Patient 7	74	48	-26	-35.1%
Patient 8	60	32	-28	-46.7%
Mean ± SD	64.3 ± 6.5	37.0 ± 7.1	-27.3 ± 0.9	-42.9% ± 5.1%

Values represent pre- and post-treatment SNOT-22 scores for 8 patients treated with oral Zileuton (600 mg QID for 90 days). Mean reduction = 27.3 points (−42.9%), corresponding to significant symptomatic improvement consistent with objective MLM score reduction ($p < 0.05$, Wilcoxon test).

Throughout the cohort of patients, no adverse side effects were observed. The small sample size and design limit generalizability, but these results show a potential for leukotriene inhibition being a more cost-effective method and safer method than corticosteroids, surgery and high-cost biologic therapy. Larger, controlled studies are needed to confirm the efficacy of zileuton and identify biomarkers in patients with CRSwNP.

Conclusion

Treatment of nasal obstruction due to nasal sinus polyps through Zyflo/Zileuton showed statistically significant levels of sinusitis improvement with minimal complication hinting towards a need to explore its potential as an alternative treatment to frontline medication which are extremely expensive and have a wider array of side effects. With this said, the small patient population of this study serves as a limitation and larger controlled studies are needed to confirm efficacy of zileuton therapy.

List of Abbreviations

CRSwNP- Chronic Rhinosinusitis with Nasal Polyps

MLM- Modified Lund-Mackay

FDA- Food and Drug Administration

CT- Computed Tomography

SNOT-22- Sino-Nasal Outcome Test 22

CITI- Collaborative Institutional Training Initiative

IRB- Institutional Review Board

HIPAA- Health Insurance Portability and Accountability Act

IL- Interleukins

LO- Lipoxygenase

Statements and Declarations

Ethical considerations

This study was approved by the Sterling Institutional Review Board. All data containing patient information was de-identified to ensure privacy and confidentiality pertaining to the matter of patient privacy regulations.

Consent to participate

The retrospective design of this study and the necessity of written, informed consent was waived by the IRB as well.

Consent for publication

Not applicable

Declaration of conflicting interest

The authors declare no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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Data availability

The data used in this study is available upon reasonable request to the corresponding author.

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Not applicable.

Authors' Contributions

Colten Witte, manuscript writing, chief editor, design; David Dillard, manuscript writing, editing, design; Ziad Obideen, editing, writing; Joshua Rapp, editing, writing; Kenneth Walton, editing, writing; James Fortson, conception, design, final approval.

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