



Sinusitis in patients concurrently on tumor necrosis factor alpha inhibitors

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Abstract

Objective: Tumor necrosis factor alpha (TNF- α) inhibitors have revolutionized treatment of many impairing inflammatory diseases. We aim to characterize the features of sinusitis in patients concurrently on anti-TNF- α therapy and their treatment course.

Methods: This is a retrospective chart review of 28 patients diagnosed with sinusitis by a Duke otolaryngologist while on a TNF- α inhibitor. Descriptive statistics and bivariate analysis were performed with SPSS (Version 22, Chicago, IL). Phi correlation coefficients greater than $r = \pm 0.3$ and $p \leq 0.05$ were considered significant.

Results: Of the 28 patients studied, 12 (42.9%) had a history of sinusitis prior to initiation of anti-TNF- α therapy and 16 (57.1%) had no prior history. 71.4% (n=20) of patients were diagnosed with chronic rhinosinusitis without polyps and 17.9% (n=5) had recurrent acute sinusitis. In the group with no prior history of sinusitis, the median time from drug initiation to diagnosis of sinusitis was 22.5 months (IQR: 2.25-112.75). Overall, 14.3% (n = 4) of the cohort stopped, changed, or held doses of the drug due to sinusitis. 35.7% (n=10) of patients required a surgery or procedure, which included functional endoscopic sinus surgery (FESS) (25%, n=7) and balloon dilatation (10.7%, n=3).

Conclusion: Anti-TNF- α therapy can be associated with development of sinusitis, especially chronic sinusitis. While surgery was sometimes necessary, discontinuation of anti-TNF- α therapy due to recurrent sinusitis was not necessary in most cases.

Background

- Tumor necrosis factor alpha (TNF- α) inhibitors have revolutionized the treatment of many immune-related chronic inflammatory diseases.
- There are five agents approved for use: infliximab, etanercept, adalimumab, certolizumab pegol, and golimumab
- TNF- α is a key proinflammatory cytokine in the pathogenesis of many inflammatory and autoimmune diseases
- Its inhibition has shown to reduce inflammation¹.
- TNF- α also plays a role in host immune defenses and responses to local injury.
- Thus, TNF- α inhibitors have been associated with a number of adverse effects, including an increased risk of serious infections².
- However the frequency and characteristics of less serious infections, such as sinusitis, are not as well understood.
- The development of sinusitis after initiation of TNF- α antagonists has been observed³⁻⁴, but its clinical features and disease course are not well characterized in literature. In this study, we aim to characterize sinusitis, both new onset and preexisting, in patients concurrently on anti-TNF- α therapy.

Methods

- Retrospective study of 28 patients diagnosed at Duke University with acute or chronic sinusitis by an otolaryngologist between October 1, 2010 and October 1, 2014 while concurrently receiving TNF- α inhibitor therapy.
- Demographics, pertinent medical and social history were collected
- Characteristics of the patients' sinusitis and treatment course including subjective symptoms, endoscopic findings, computed tomography (CT)/magnetic resonance imaging (MRI) findings and sinus culture results were collected
- Sinus disease at time of initial diagnosis was classified into acute rhinosinusitis -single episode (ARS-single), acute sinusitis - >1 episode (ARS-multiple), chronic sinusitis without nasal polyps (CRSwNP), and chronic sinusitis with nasal polyps (CRSwNP)
- Statistical analysis was performed with SPSS (Version 22, Chicago, IL).
- Associations between categorical variables were examined using chi-squared tests. Phi coefficients greater than $r = \pm 0.3$ and $P \leq 0.05$ were considered significant.

Results

Table 1: Sinusitis types in patients without a prior history of sinusitis and in entire cohort. ARS-single = acute rhinosinusitis-single episode, ARS-multiple= acute sinusitis - >1 episode, CRSwNP= chronic sinusitis without nasal polyps, CRSwNP= chronic sinusitis with nasal polyps

Sinusitis type	Patients without a prior history of sinusitis (n=16) n, (%)	Total cohort (n=28) n, (%)
ARS-single	1, (6.3)	1, (3.6)
ARS-multiple	5, (31.3)	5, (17.9)
CRSwNP	10, (62.6)	20, (71.4)
CRSwNP	0, (0)	2, (7.2)

Table 2: Changes in therapy in patients with and without a history of sinusitis, while on anti-TNF- α therapy

	Patients with prior history of sinusitis (n=12), n, (%)	Patients without prior history of sinusitis (n=16), n, (%)	Total cohort (n=28), n, (%)	Phi correlation coefficient (P value)
Changes in TNF-α therapy	1 (8.3)	3 (18.8)	4 (14.3)	
Discontinued	1, (8.3)	0, (12.5)	1, (3.6)	*
Switched to another agent in same class	0, (0)	1, (6.3)	1, (3.6)	*
Held due to sinusitis then restarted	0, (0)	2, (6.3)	2, (7.1)	*
Sinus surgery prior to initiating TNF-α therapy	10 (83.3)	0, (0)	10, (35.7)	*
Sinus surgery during TNF-α therapy	3 (25.0)	7 (43.8)	10 (35.7)	*
FESS	2, (16.7)	5, (31.3)	7, (25.0)	*
Balloon dilatation	1, (8.3)	2, (12.5)	3, (10.7)	*
Total number of operations/procedures	n = 12	n=7	n = 19	
1	7, (58.3)	6, (37.5)	13, (46.4)	*
2	2, (16.7)	1, (6.3)	3, (10.7)	*
3	1, (8.3)	0, (0)	1, (3.6)	*
4	2, (16.7)	0, (0)	2, (7.1)	*
Average number of procedures per patient	1.83	0.71	1.07	-0.626 (0.027)

- The study included 22 females and 6 males, with a mean age of 47.7 years (SD: 16.9), ranging from 10 to 72 years
- 75% (n=21) of the patients were Caucasian and 6% (n=6) were African American
- The most common indication for anti-TNF- α therapy was rheumatoid arthritis (50.0%, n=14), followed by Crohn's disease (14.3%, n=4), ulcerative colitis (7.1%, n=2), psoriatic arthritis (7.1%, n=2), and plaque psoriasis (7.1%, n=2)
- Etanercept (46.4%, n= 13), infliximab (28.6%, n=8), adalimumab (21.4%, n=6), and golimumab (3.6%, n=1) were the prescribed TNF- α inhibitors. No patients were prescribed certolizumab pegol
- Of the 28 patients, 12 (42.9%) had a history of sinusitis prior to initiation of anti-TNF- α therapy and 16 (57.1%) had no prior history of sinusitis
- In the cohort with no prior history of sinusitis, the median duration of treatment with anti-TNF- α until diagnosis of sinusitis was 22.5 months (IQR: 2.25-112.75)
- The most common symptoms were nasal discharge (50%, n=14), nasal congestion (46.4%, n=13), post nasal drip (42.9%, n=12), facial pressure and/or pain (39.3%, n=11), and headache (32%, n=9).
- Patients without a prior history of sinusitis were significantly more likely to present with nasal discharge (68.8% vs. 25%, $p=0.02$) than patients with preexisting sinus disease.
- On endoscopic exam, the common findings included mucosal inflammation and edema (42.9%, n=12) and discharge (32.1%, n=9)
- Culture results were available for six patients, with five patients having growth of multi-drug resistant bacteria (three in patients with a prior history and two in patients with no prior history).
- For those patients with a CT scan (n=21), the most common CT sinus finding was mucosal thickening of the maxillary sinus (53.4%, n=11), anterior ethmoid (33.3%, n=7), and posterior ethmoid (28.6%, n=6).

Discussion

- This is the largest study to date reporting the association of anti-TNF- α inhibitor therapy with sinusitis.
- The most common types of sinusitis were CRSwNP and ARS-multiple
- The median time from initiation of therapy to diagnosis of sinusitis was 22.5 months
- Discontinuation of the drug, switching to another agent in the same class, or holding doses occurred in 14.3% of patients, suggesting that cessation of TNF- α antagonist may not always be necessary, contrary to prior reports³⁻⁴
- Patients with no prior history of sinusitis were more likely to discontinue anti-TNF- α therapy and/or undergo surgical management. However, this was not statistically significant
- The limitations of this study:
 - Small sample size and retrospective study design
 - Unable to determine incidence of sinusitis after starting anti-TNF- α therapy.
 - Overestimation of percentage of chronic and recurrent acute sinus disease.
 - Cannot isolate the effect of TNF- α antagonists from the effect of concurrent immunosuppressants on the development of sinusitis.

Conclusion

- This study provides further evidence that anti-TNF- α therapy can be associated with the development of sinusitis, especially chronic rhinosinusitis without nasal polyps.**
- While surgery was sometimes included in the treatment regimen, discontinuation of anti-TNF- α therapy due to sinusitis was not deemed necessary in most cases.**
- Further studies with a larger sample size will be required to fully characterize the effects of anti-TNF- α therapy on the course of sinusitis.**

Acknowledgments

We thank Dr. Laura Ding and Dr. Maragatha Kuchibhatla for their guidance in statistical analysis. We are grateful for the assistance of Erika Juhlin, Amy Walker, and Stephanie Brinson in the process of IRB approval and DEDUCE queries.

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