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Sinusitis in patients on tumor necrosis factor alpha inhibitors

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Abstract

Background—Tumor necrosis factor alpha (TNF- α) inhibitors have revolutionized treatment of many inflammatory diseases. Sinusitis after initiation of TNF- α inhibitors has been observed, but has not been well described in the literature. We aim to characterize the clinical features of sinusitis in patients on anti-TNF- α therapy.

Methods—This is a retrospective chart review of 28 patients on a TNF- α inhibitor diagnosed with sinusitis by otolaryngologists at Duke University. Patient demographics, sinusitis characteristics, and treatment course were studied by chart review.

Results—The prevalence of sinusitis diagnosed and treated by an otolaryngologist was less than 1%. Of the 28 patients studied, 12 (42.9%) had a history of preexisting sinusitis and 16 (57.1%) had new-onset sinusitis. 71.4% were diagnosed with chronic rhinosinusitis without polyps (CRSsNP), with disease mainly involving the maxillary and ethmoid sinuses. No patients had major extrasinus complications or required hospital admission or intravenous (IV) antibiotics. 35.7% (n = 10), including 44% (7/16) of new-onset patients required a surgical intervention after initiating anti-TNF therapy. 14.3% (n = 4) of the cohort had improvement in sinonasal symptoms after stopping, changing, or holding doses of the TNF- α inhibitor.

Conclusion—Anti-TNF- α therapy can be associated with new-onset sinusitis, mainly CRSsNP. Overall, the percentage of patients on a TNF- α inhibitor seeking consultation from an otolaryngologist is low. While some patients with new-onset sinusitis will require surgery, modification of anti-TNF- α therapy should be considered as an option in the medical management of these patients.

Keywords

sinusitis; chronic rhinosinusitis; functional endoscopic sinus surgery; FESS; immunodeficiency; rhinosinusitis; balloon dilation

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Tumor necrosis factor alpha (TNF- α) inhibitors have revolutionized the treatment of many immune-related chronic inflammatory diseases such as rheumatoid arthritis (RA), Crohn's disease, ankylosing spondylitis, psoriatic arthritis, and ulcerative colitis.^{1–5} These agents bind to TNF- α , preventing it from interacting with the TNF receptor. There are currently 5 agents approved for use: infliximab (a chimeric, monoclonal antibody); etanercept (a synthetic TNF receptor-Fc fusion protein); adalimumab (a fully human monoclonal antibody); certolizumab pegol (a PEGylated Fab fragment of a humanized monoclonal antibody); and golimumab (a human monoclonal antibody).

TNF- α is a glycoprotein that exists as a 26-kDa homotrimeric transmembrane protein found on the surface of inflammatory cells (ie, macrophages, T-lymphocytes, natural killer cells) and non-inflammatory cells (ie, smooth muscles cells and fibroblasts). It is released in a soluble form as a homotrimer of 17-kDa monomers. TNF- α is proven to be a key pro-inflammatory cytokine in the pathogenesis of many inflammatory and autoimmune diseases, and its inhibition has shown to reduce inflammation.⁶ However, TNF- α also plays a role in host immune defense and response to local injury. It is essential for the formation and maintenance of granulomas, clearance of intracellular microbes by macrophages, and response to viral pathogens.⁷ Thus, TNF- α inhibitors have been associated with a number of adverse effects, including an increased risk of serious infections.^{8–12} In most observational studies and randomized controlled trials, these serious infections are defined as bacterial and opportunistic infections requiring hospital admission or intravenous (IV) antibiotics. These infections include tuberculosis reactivation, *Pneumocystis pneumonia*, and septicemia from *Streptococcus pneumoniae*.¹³ However, the frequency and characteristics of other infections such as sinusitis are not as well understood.

The development of sinusitis after initiation of TNF- α inhibitors has been observed, but its clinical features and disease course are not well characterized in literature. Clinical studies have reported an increased incidence of sinusitis in patients with RA treated with infliximab (17% vs 6%).¹⁴ A longitudinal study of treatments for RA reported that etanercept increased the risk of sinus disease. The U.S. Food and Drug Administration (FDA) reports the incidence of sinusitis associated with infliximab to be 14% (vs 8% in the placebo arm).¹⁵ For adalimumab, the rate of sinusitis was 11% (vs 9% in the placebo arm).¹⁶ Only 2 small case series have described clinical features of new onset sinusitis after the commencement of anti-TNF- α therapy.^{17,18} In this study, we aim to characterize sinusitis, both new onset and preexisting, in patients on anti-TNF- α therapy.

Patients and methods

Data collection

This was an institutional review board (IRB)-approved retrospective study of patients diagnosed by an otolaryngologist at Duke University Medical Center with acute or chronic sinusitis between October 1, 2010 and October 1, 2014. Using the Duke Enterprise Data Unified Content Explorer (DEDUCE) query tool, patients were chosen by International Classification of Diseases, 9th Revision (ICD-9) codes for acute and chronic sinusitis and concurrent administration of 1 of the 5 available TNF- α inhibitors.

Subjects met the inclusion criteria if they had been on TNF- α inhibitor therapy for more than 30 days at the time of diagnosis of acute or chronic sinusitis. The inclusion criteria for chronic rhinosinusitis (CRS) were symptoms (any 1 or a combination of nasal discharge, congestion, hyposmia, facial pressure) for more than 12 weeks with mucosal thickening on computed tomography (CT) or inflammation in the middle meatus or sphenoid recess on nasal endoscopy. The inclusion criteria for acute sinusitis were symptoms for more than 10 days but less than 12 weeks, with objective evidence on CT or endoscopy. Demographics as well as pertinent medical and surgical history were collected. The type of TNF- α inhibitor prescribed, indication for therapy, and duration from initiation of therapy to diagnosis of sinusitis were evaluated. If the patient reported onset of symptoms, regardless of treatment, prior to initiation of TNF- α inhibitors, this was considered to be a “preexisting” sinusitis.

Clinical characteristics of the patients’ sinusitis were also extracted from the medical records. These included endoscopic findings and imaging findings. Items from the Lund-Kennedy endoscopy scoring system were considered positive endoscopic findings.¹⁹ Any mucosal thickening on CT or magnetic resonance imaging (MRI) was noted to represent a positive finding. Sinus culture results were collected if available. Sinusitis was classified as acute rhinosinusitis—single episode (ARS-single), acute sinusitis >1 episode (ARS-multiple), chronic rhinosinusitis without nasal polyps (CRSsNP), or chronic rhinosinusitis with nasal polyps (CRSwNP).

Treatment course was examined as well. Patients were grouped into either medical treatment alone or surgical plus medical treatment. The number and type of sinus surgery (functional endoscopic sinus surgery [FESS] vs balloon dilatation [BD]) were recorded. We assessed whether the patient required an alteration in their anti-TNF- α therapy (ie, discontinued, switched to another agent, or held).

Statistical analysis

Statistical analysis was performed with SPSS (version 22; IBM Corp., Armonk, NY). Descriptive statistics were performed to summarize the patients’ demographics, types of sinusitis, and treatments. All continuous variables such as duration of therapy were summarized using means/medians, standard deviations (SDs), and ranges. Categorical variables were described using counts and percentages. Associations between categorical variables were examined using chi-square tests. Phi coefficients greater than $r = \pm 0.3$ and $p < 0.05$ were considered significant.

Results

Patient demographics and characteristics

A total of 3052 patients were found to be on a TNF- α inhibitor in the Duke University system during the study period. Of these, 55 patients were seen by an otolaryngologist for acute or chronic sinusitis. However, 27 patients were excluded: 13 did not have a positive finding on endoscopy or imaging; 11 were treated for sinusitis prior to starting the TNF- α inhibitor with no further follow-up; and 3 had incomplete records. In total, 28 patients met

the inclusion criteria. This group included 22 females and 6 males, with a mean age of 47.7 ± 16.9 years (range, 10 to 72 years). Of the patients, 75% (n = 21) were white and 21.4% (n = 6) were African American.

The most common indication for treatment with anti-TNF- α therapy was RA (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), plaque psoriasis (7.1%, n = 2), and other diseases (14.3%, n = 4), which included hidradenitis suppurativa and seronegative arthritis. 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, 18 were on anti-inflammatory medications in addition to the TNF- α inhibitor; 11 were on methotrexate, 6 were on prednisone, 6 were on hydroxychloroquine, and 2 were on 6-mercaptopurine.

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. The most common sinusitis types were CRSsNP (71.4%, n = 20) and ARS-multiple (17.9%, n = 5) (Table 1). In the group with new-onset sinusitis, the median duration of treatment with anti-TNF- α agents until diagnosis of sinusitis was 22.5 months (interquartile range [IQR], 2.25 to 112.75 months) and the most commonly diagnosed form of sinusitis in this subgroup was CRSsNP (62.6%, n = 10), followed by ARS-multiple (31.3%, n = 5). Diagnosis and treatment were performed by 7 different otolaryngologists within the Duke Health System.

Endoscopy, imaging, microbiology

On endoscopic exam, the most common findings included mucosal edema (42.9%, n = 12) and discharge (32.1%, n = 9) (Table 2). Those with new-onset sinusitis were more likely to have mucosal edema (56.3% vs 25%) and discharge (37.5% vs 25%) on endoscopic exam than those with preexisting sinusitis. However, this was not statistically significant.

For those patients with imaging studies (n = 21), mucosal thickening was most commonly found in the maxillary sinus (53.4%, n = 11), anterior ethmoid sinus (33.3%, n = 7), and posterior ethmoid sinus (28.6%, n = 6) (Table 3). Comparison of imaging findings showed no statistical differences between patients with new-onset and preexisting sinusitis.

Culture results were available for 10 patients. *Staphylococcus aureus* (SA) was the most common organism, found in 9 of the 10 samples. Methicillin-sensitive SA was found in 5 samples, and methicillin-resistant SA was found in 4 samples. Gram-negative organisms, including *Pseudomonas*, *Klebsiella*, *Enterobacter*, and *Citrobacter* were the next most common organism, found in 7 of 10 samples. Coagulase-negative *Staphylococcus* was found in one sample.

Course of treatment

Six of the 28 patients (21.4%) underwent a modification in anti-TNF- α therapy (ie, discontinued the medication, switched to another agent in the same class, or suspended treatment doses temporarily) due to sinusitis. Four of those 6 experienced improvement in symptoms. When comparing anti-TNF- α therapy discontinuation rates in both patient

subgroups, we found that a higher proportion of patients in the new-onset group underwent a modification in therapy with improvement (18.8%, n = 3) compared to the group with preexisting sinusitis (8.3%, n = 1).

A summary of surgical management can be found in Table 4. Overall, 35.7% (n = 10) of patients required a surgical procedure while on anti-TNF- α therapy. Of the 16 patients with new-onset sinusitis, 7 (43%) eventually required surgical intervention, while 3 of the 12 patients (25%) with prior sinusitis required surgery. Surgical management consisted of both FESS and BD.

Discussion

This is the largest study to date reporting the association of anti-TNF- α therapy with sinusitis. The prevalence of sinusitis in patients taking a TNF- α inhibitor according to our diagnostic criteria was less than 1% in our study population. In addition, we found that the median time to presentation is 22.5 months. The true incidence is likely higher, and the median time to presentation is likely shorter, given that sinusitis, especially acute sinusitis, is often treated by primary care physicians. An interval of weeks to 3 months for development of new-onset sinus symptoms after initiation of anti-TNF- α therapy has been reported.^{17,18} Prevalence rates in the literature vary depending on the study and the agent, but range anywhere from 2% to 17%.^{14–16} While all 5 anti-TNF medications have the same mechanism of action, sinusitis rates may differ between the agents. Further studies are needed to detect such differences.

The most commonly diagnosed form of sinusitis in our patient population was CRSsNP, consistent with a smaller published series.¹⁸ The maxillary and anterior ethmoid sinuses were the most frequently affected on imaging, and *Staphylococcus aureus* and gram-negative organisms were the most commonly cultured pathogens. Overall, there did not seem to be any characteristic features of new onset sinusitis that set this entity apart from our general sinusitis population. Endoscopy and imaging findings between new-onset sinusitis and preexisting sinusitis were not significantly different. Microbiology findings were consistent with published studies.²⁰ Interestingly, 13 of the initial 55 patients in our search query had sinonasal symptoms but did not exhibit positive endoscopic or imaging findings on further workup. This suggests that some of these patients may have developed viral upper respiratory infections as a result of their TNF- α inhibitor therapy, consistent with manufacturers' data. Therefore, antibiotics should be used judiciously for these patients.

Overall, about one-third of patients required surgical management while on TNF- α therapy, including 43% of patients with new onset sinusitis. This is an important point of discussion with patients, especially with those who are deciding whether to continue with TNF inhibitor therapy in the setting of sinusitis and other possible adverse effects. At the same time, discontinuing, switching, or temporarily suspending the medication was done in 6 patients and led to subjective improvement of symptoms in 4 patients. Our results suggest that modification of TNF- α inhibitor therapy should be considered as an option in the medical management of these patients. This requires close coordination of care with patients' rheumatologists.

The limitations of this study include the small sample size, which was not powered to make statistically reliable comparisons between new-onset sinusitis and preexisting sinusitis. The retrospective design and lack of quality-of-life instruments make it impossible to assess differences in outcomes after surgery and to know whether improvement or worsening after initiation or discontinuation of anti-TNF therapy was statistically significant. Moreover, clinical assessments and treatment regimens were not uniform, since patients were treated by multiple otolaryngologists.

Another limitation is that cases were queried through a third-party software application (DEDUCE), rather than a manual search of the electronic medical record system. This method is time-saving but may not detect every patient who meets the study criteria. Last, many of the patients in the cohort were on concomitant immunosuppressive drugs (ie, methotrexate, prednisone). Therefore, we cannot isolate the true effects of TNF- α inhibitors on the development of sinusitis. However, studies suggest the effect of these other immunosuppressive drugs on the development of sinusitis is minimal. Common treatments for RA such as methotrexate and prednisone do not increase the likelihood for sinusitis, and may even improve signs and symptoms.²¹ Furthermore, patients on methotrexate and infliximab showed a higher rate of sinusitis when compared to patients on methotrexate alone.¹⁴

Conclusion

Anti-TNF- α therapy can be associated with new-onset sinusitis, mainly CRSsNP. Overall, the percentage of patients on a TNF- α inhibitor seeking consultation from an otolaryngologist is low. While some patients with new-onset sinusitis will require surgery, modification of anti-TNF- α therapy should be considered as an option in the medical management of these patients.

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TABLE 1

Sinusitis type for subgroup of patients without a prior history of sinusitis and in entire cohort *

Sinusitis type	Patients with new-onset sinusitis (n = 16)	Total cohort (n = 28)
ARS-single	1 (6.3)	1 (3.6)
ARS-multiple	5 (31.3)	5 (17.9)
CRSsNP	10 (62.6)	20 (71.4)
CRSsNP	0 (0)	2 (7.2)

* Values are n (%).

ARS-multiple = >1 episode of acute sinusitis; ARS-single = acute rhinosinusitis-single episode; CRSsNP = chronic sinusitis without nasal polyps; CRSsNP = chronic sinusitis with nasal polyps.

TABLE 2Comparison of endoscopic findings in patients with and without a history of sinusitis on anti-TNF- α therapy *

Endoscopic findings	Patients with preexisting sinusitis (n = 12)	Patients with new-onset sinusitis (n = 16)	Total cohort (n = 28)
Polyps/polypoid changes	1 (8.3)	0 (0)	1 (3.6)
Mucosal edema	3 (25.0)	9 (56.3)	12 (42.9)
Discharge	3 (25.0)	6 (37.5)	9 (32.1)
Scarring, synechiae	1 (8.3)	0 (0)	1 (3.6)
Crusting	2 (16.7)	3 (18.8)	5 (17.9)

* Values are n (%). Value of $p > 0.05$ for all findings.

TNF- α = tumor necrosis factor α .

TABLE 3Comparison of imaging findings in patients with and without a history of sinusitis on anti-TNF- α therapy*

Involved sinuses	Patients with preexisting sinusitis (n = 9)	Patients with new-onset sinusitis (n = 12)	Total cohort (n = 21)
No significant findings	4 (44.4)	4 (25.0)	8 (38.1)
OMC opacification	1 (11.1)	3 (18.8)	4 (19.0)
Anterior ethmoid	2 (22.2)	5 (31.3)	7 (33.3)
Maxillary	4 (44.4)	7 (43.8)	11 (53.4)
Posterior ethmoid	2 (22.2)	4 (25.0)	6 (28.6)
Sphenoid	2 (22.2)	2 (12.5)	4 (19.0)
Frontal	1 (11.1)	3 (18.8)	4 (19.0)
Pan-sinusitis	0 (0)	0 (0)	0 (0)

* Values are n (%). Value of $p > 0.05$ for all findings.

OMC = osteomeatal complex; TNF- α = tumor necrosis factor α .

TABLE 4

Surgical management of subjects*

	Patients with pre-existing sinusitis (n = 12)	Patients with new-onset sinusitis (n = 16)	Total cohort (n = 28)
Sinus surgery prior to initiating TNF- α therapy	10 (83.3)	NA	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 ^a	1.83	0.71	1.07

* Values are n (%).

^aValue of $p < 0.05$.FESS = functional endoscopic sinus surgery; TNF- α = tumor necrosis factor α .