Review Article

Biologic therapies versus surgical management for aspirin-exacerbated respiratory disease: A review of preliminary data, efficacy, and cost

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Abstract Aspirin-exacerbated respiratory disease (AERD) patients with CRSwNP suffer from reduced quality of life, reduced economic productivity, and higher risk of depression and sleep dysfunction. These patients often require frequent medical and surgical therapy, including functional endoscopic sinus surgery for recalcitrant disease. Given this severity, anti-type 2 biologic treatments are being investigated for use in this subgroup of patients with CRSwNP, including Omalizumab and Dupilumab. Preliminary data suggests that SNOT-22 related quality of life improvements following treatment with biologics are comparable to the current standard of care in the short term, but there is a lack of long-term data and standardized regimen that makes direct comparison difficult. Biologic therapies additionally require continuous use to avoid recurrence, and currently cost many times more than existing medical or surgical therapies.

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Aspirin-Exacerbated Respiratory Disease (AERD) is a type 2 (Th2)-mediated inflammatory disease characterized by chronic rhinosinusitis (CRS), nasal polyposis, rhinorrhea and asthma exacerbated by nonsteroidal anti-inflammatory drugs (NSAIDs) or acetylsalicylic acid (aspirin/ASA).[1] From a rhinologic standpoint, AERD patients are recognized as a subset of patients CRS with nasal polyps (CRSwNP), with AERD affecting approximately 1% of the United States population.[2] Broadly, CRSwNP patients demonstrate derangements of several Th2 pathways, including

dysregulation of the interleukin (IL)-4, IL-5, and IL-13. Cytokine levels are altered systemically, in the nasal mucosa, and in polyp tissue itself, while mast cells and eosinophils are also increased locally.[3–6] From a rhinologic standpoint, patients with AERD are often considered to be among the most difficult to treat CRS patients, due to severity and disease recalcitrance.6 This is reflected at the cellular and molecular level; nasal polyps from patients with AERD have over 3 times as many eosinophils and higher IL-5 concentrations when compared to polyps taken from subjects with non-AERD CRS.[7,8]

Non-biologic treatment of AERD

In general, treatment for CRSwNP consists of control of symptoms and inflammation utilizing topical steroids, oral steroids, decongestants, and ultimately, functional endoscopic sinus surgery for disease that has failed medical management.[9] While AERD is classically thought to be less responsive to surgery, more recent publications have demonstrated similar short-term benefits of FESS in AERD compared to CRSwNP overall.[10–12] Quantitative endoscopic, radiographic, and patient-reported outcome measures have repeatedly demonstrated significant improvement following surgical intervention in AERD patients. This includes significant improvement in SNOT-22 scores in several studies,[11,13,14] which is the most widely used reporting tool for sinonasal quality of life across several subdomains. Awad et al[10] further demonstrated improvements after FESS of Lund-Mackay CT scores in 41 patients with AERD, while Jang et al[11] showed improvement in Lund-Kennedy endoscopy scores. Improvements in AERD quality of life are often robust following FESS, and durability of benefit is a subject of study. Patients with AERD often require frequent surgical interventions for durable control of symptoms.[15] These patients are significantly more likely to require revision surgery than those with non-AERD CRSwNP, and these additional surgeries are often necessary earlier in the postoperative period.[16] Furthermore, while relative improvements in endoscopic scores are observed following FESS, the literature suggests that AERD patients start off with substantially worse scores and postoperative scores remain higher among AERD patients than those of operated patients with CRSwNP as a whole.[11]

Aspirin desensitization is an additional therapeutic intervention that has proven to be extremely beneficial for AERD patients. Many of the adverse reactions seen in AERD stem from aberrations in the cyclooxygenase (COX)-1 pathway, and dose-escalation challenges using aspirin can be performed under medical supervision until a derive benefit from aspirin desensitization, which results in a reduction in both upper and lower airway symptoms.[17] Following therapy, subjects take daily high-dose aspirin in the maintenance phase, which prevents hyperreactivity and can reduce or delay growth of nasal polyps in a majority of subjects.[17] However, some AERD patients are unable to tolerate the desensitization procedure itself or daily aspirin therapy, while a minority of patients do not see significant improvements even following aspirin desensitization.[17,18] Finally, if a patient misses consecutive daily doses of maintenance aspirin, an additional desensitization procedure is often required, making strict adherence to a daily regimen paramount.

Biologic therapies

Given the Th2 phenotype of CRSwNP, novel biologic therapies that target Th2 pathways and cytokines have become a subject of increased interest for the management of AERD. However, these therapies are associated with very high costs, and are often dosed on a bi-monthly or monthly basis. Five main anti-type 2 biologics have been approved for asthma: Omalizumab, Mepolizumab, Reslizumab, Benralizumab and Dupilumab. Dupilumab has additionally been approved for the treatment of severe atopic dermatitis, and more recently, CRSwNP.[3] Several pilot studies and retrospective analyses have examined the effects of these biologics specifically in patients with AERD (Table 1).

Table 1 Summary of relevant studies of biologic therapies in AERD UPSIT: University of Pennsylvania Smell Identification Test.

Author	Biologic therapy	AERD subjects	Length of therapy	Significant endpoints
Jean et al.[19]	Omalizumab	29	6–12 mo.	↓ yearly steroid use
Hayashi et al.[20]	Omalizumab	21	3 mo.	↓ urinary LTE_4, PGD_2M ↓ daily systemic corticosteroid dose ↓ nasal symptom scores (visual analog scale)
Tuttle et al.[21]	Mepolizumab	14	5.5 mo (median)	↓ SNOT-22 score (17.7 ± 4.9 points) ↓ absolute eosinophil count
Stevens et al.[22]	Reslizumab	1	8 mo.	↓ ECP, CCR3, and CLC expression
Laidlaw et al.[23]	Dupilumab	19	4 mo.	↓ SNOT-22 score (≈25 points) ↓ nasal polyp score, Lund-Mackay score ↓ morning nasal congestion/obstruction score ↑ UPSIT score

Omalizumab

IgE is a potent inducer of eosinophilia, and Omalizumab works by directly neutralizing IgE. In CRSwNP, Omalizumab both decreases nasal polyp size and improves objective CT scan scores.[24–26] While AERD pathophysiology does not demonstrate a prominent role of IgE in the development of symptomatology, initial studies show that patients with AERD on Omalizumab derive some benefit, suggesting that the therapeutic effect of this biologic may be more complex than initially thought. Initial hypotheses involve reduction in expression of IgE receptors on mast cells, with corresponding suppression of mast cell activation and eosinophilic inflammation.[20] Jean et al[19] demonstrated that AERD patients showed a reduction in number of steroid courses required for symptom management, while Hayashi et al[20] examined the effects of Omalizumab in 21 adults with AERD, and found significant symptomatic improvement in 18 of these patients, with three subjects classified as non-responders. Notable reductions in urinary LTE4 and PGD2M, two inflammatory biomarkers, were seen following Omalizumab therapy. This was accompanied by decreased hospitalizations, decreased daily doses of systemic corticosteroids, and improvement in subjective nasal symptom scores. Improvement on Omalizumab occurred in a rapid fashion; over one-half of the enrolled subjects saw improvement in the first week after initiation of therapy.

Anti-IL-5 biologics (Mepolizumab, Reslizumab)

Mepolizumab, Reslizumab, and Benralizumab all function through IL-5 antagonism, as IL-5 induces eosinophilia by potentiation of eosinophil recruitment, activation, and survival. In 2018, Tuttle et al[21] examined a non-blinded, non-randomized, and non-placebo-controlled group of 14 subjects with AERD who received at least 3 treatments with 100 mg of Mepolizumab for the treatment for severe asthma. Subjects demonstrated decreases in absolute eosinophil counts, significant reductions in daily glucocorticoid dosing, and a significant reduction in SNOT-22 score. Timing of data collection was variable, and subjects received between 3 and 11 doses of Mepolizumab over a median period of 5.5 months. While these findings indicate possible rhinologic benefit of Mepolizumab in AERD, the variability and retrospective nature of the study limits generalizability.

Reslizumab has not been extensively studied in AERD; Stevens et al[22] reviewed the effects of Reslizumab in a single AERD patient. This patient had nasal polyp tissue and blood collected prior to treatment and 8-months post therapy. Eosinophilic cationic protein levels and eosinophil lysophospholipase gene expression fell 25-fold, with reduced peripheral eosinophilia. However, the patient ultimately required sinus surgery for recalcitrant symptomatology.

Dupilumab

IL-4 and IL-13, two additional cytokines associated with the Th2 phenotype, have structural similarities and signal utilizing a heterodimeric receptor. Both cytokines induce local IgE production. IL-4 primarily controls IgE class switching, differentiation of lymphocytes, and upregulation of IgE receptors on a variety of cell types.[27,28] IL-13 also has a broad array of effects. It plays a prominent role in epithelial differentiation, causing decreased ciliation and goblet cell metaplasia with resultant mucus secretion and fibrosis. It further causes hyperresponsiveness and leakiness of the tissue itself, in addition to propagating chemokine secretion.[28] These broad and complementary effects of IL-4 and IL-13 are in part inhibited by Dupilumab, which blocks the shared receptor component for IL-4 and IL-13.[9]

Dupilumab is the first biologic to receive approval for CRSwNP,[23] with a larger study by Bachert et al[5] demonstrating improvement in objective and patient reported outcomes. Corresponding reductions in circulating IgE, eotaxin, and eosinophilic cationic protein, a potent inducer of epithelial damage, were also observed,[29] while chemokine ligand 18 (CCL18), which is chemotactic for TH2 cells, was decreased in nasal polyp tissue following Dupilumab treatment.[30] Interestingly, there is a transient increase in peripheral eosinophilia observed with Dupilumab, possible related to downregulation of eosinophilic migration from the bloodstream into the nasal tissue by chemotaxis.[5]

Laidlaw et al[23] recently examined the cohort of 19 AERD patients from the overall Phase 2 dupilumab trial for CRSwNP. Subjects received 300 mg of Dupilumab subcutaneously every two weeks, evaluating outcomes after 16 weeks. AERD patients expectedly had worse objective and subjective baseline disease, in addition to a decreased sense of smell, when compared to the aspirin-tolerant CRS patients in the trial. AERD patients saw significant reductions in nasal polyp score, Lund-Mackay score, morning nasal congestion and obstruction scores, and improvement in the University of Pennsylvania Smell Identification Test (UPSIT) scores.

Costs of AERD treatments

While many of the above studies list promising preliminary data for the treatment of AERD patients with biologic therapies, albeit with small numbers of patients, the high cost of these treatments may prohibit their widespread use. Annual wholesale acquisition costs of the 5 approved biologics range between $30 000 and $40 000.[31] Current surgical standard of care is effective in producing significant improvements in quality of life, but direct cost and benefit comparisons between surgical therapies and biologic therapies is extremely difficult based upon the current literature. There is a lack of long-term follow up for AERD subjects who have been studied to this point, so direct comparison between post-treatment SNOT-22 scores and durability of treatment benefits is currently infeasible. Furthermore, the current biologic treatment regimens are non-standardized. Given these limitations, cost comparisons cannot be made utilizing Markov modeling and true cost-effectiveness analyses, but some general trends can be observed.

Estimates have placed an average annual healthcare cost of chronic rhinosinusitis overall at 8.6 billion dollars per year in the United States.[32] These costs primarily arise

from medical management and ambulatory care, while surgical intervention and inpatient care represents a smaller fraction of this spending.[33] However, patients with AERD are significantly more costly to treat than those with non-AERD CRS, due to a higher number of inpatient visits, a higher rate of procedures, and increased prescriptions.[34] Given that AERD patients are operated on more frequently, they are often cited as patients in whom biologic therapy would be most likely to be cost effective. Several studies have attempted to calculate average costs of FESS in CRSwNP; a systematic review of several studies found a mean total cost of $8968 for uncomplicated FESS,[35] and others have reported a similar range.[36,37] Budesonide lavages, often used as medical management following surgical intervention, are quoted at approximately $440 per year (Medi-Span, 2019). This is contrasted with annual costs of $39 048 for Omalizumab, $37 293 for Mepolizumab, $31 637 for Reslizumab, $30 889 for Benralizumab, and $38 110 for Dupilumab.[31] Based on this data, even frequently-rendered surgical treatment is likely to be significantly cheaper than biologic therapy on an annual basis.

Given the disparity in costs, it thus follows to examine associated quality of life benefits when comparing surgical intervention versus biologic therapy in AERD. The Quality-Adjusted Life Year, or QALY, is a general measure of disease burden that is used to assess improvements following a therapeutic intervention. Aspirin desensitization has been found to cost approximately $6768 per QALY gained,[38] while FESS costs between $5900 and $13 800 per QALY gained.[39,40] While QALY data is not available for AERD CRSwNP patients treated with biologics, in asthma, the biologic therapies cost between $300 000 and $400 000 per QALY gained.[9] The SNOT-22 is also a validated quality of life instrument for which some short-term preliminary data is known for biologic therapies in the treatment of AERD CRSwNP (Table 1), with improvements between 17 and 25 points in the SNOT-22 following treatment.[21,23] In a meta-analysis of over 3000 patients, mean change in SNOT-22 following endoscopic sinus surgery was found to be 23 points,[41] and patients with worse preoperative SNOT-22 scores, including those with AERD, were found to have larger post-operative SNOT-22 improvement.[41] Thus, it is a reasonable assumption that biologic therapies do not produce short-term improvements in sinonasal quality of life that vastly exceed those achieved with surgical management.

Quantitative cost-effectiveness analysis will be possible once longer-term trials have been performed to determine durability of benefit for biologics, choice of drug, necessary length of therapy, and standardized treatment regimens. Based on metaregression, SNOT-22 scores rise each year following surgery,[41] and this may be magnified in AERD, as 90% of CRSwNP patients with AERD experience recurrence of polyps and would thus require repeat surgery. If biologic therapies are used as adjunctive medical management, or if there are reductions in systemic corticosteroid dosages used by these patients, then this should additionally be factored into future cost-effectiveness models. Finally, a severe limitation of any cost analysis is that drug prices, as well as procedural costs, are often based on charges rendered which are then negotiated by payers to achieve a true, final cost. When this is taken into account, median true cost of intermediate-to-full FESS ranges between $3716 and $4 281, a substantially lower figure than those cited in other studies.[42] These dramatic variations in figures cited would have large effects on cost-effectiveness models, and should be interpreted accordingly.

Conclusions

AERD patients with CRSwNP have a reduced quality of life, reduced economic productivity, and higher risk of depression and sleep dysfunction.[39,43,44] These patients often require frequent medical and surgical therapy, including functional endoscopic sinus surgery for recalcitrant disease. Anti-type 2 biologic therapies, including Omalizumab and Dupilumab, are being investigated in CRSwNP to determine effectiveness for disease management. Given the severity of AERD, this is a group of patients that could potentially derive benefit from biologic therapies. Preliminary data suggests that SNOT-22 related quality of life improvements following treatment with biologics are comparable to the current standard of care in the short term, but there is a lack of long-term data and standardized regimen that makes direct comparison difficult. Furthermore, biologic therapies can be prohibitively expensive, require continuous use to avoid recurrence, and cost many times more than existing medical or surgical therapies.

Declaration of Competing Interest

Author Alan D. Workman, MD MTR has no conflict of interest to disclose. Author Benjamin S. Bleier, MD has consultant relationships with Olympus, Medtronic, Karl Storz, Sinopsys, Baxter, and 3D Matrix and receives royalties from Theime. He holds patents for "Treatment of Sinusitis Through Modulation of Cell Membrane Pumps" (Non-provisional USP assigned to MEEI), "Inhibition of Cystatins for the treatment of Chronic Rhinosinusitis" (Non-provisional USP), and "Methods of delivery pharmaceutical agents" (US 13/561,998). Dr. Bleier is working with industry to develop source control solutions for endoscopic procedures which may include an equity position in the future.

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