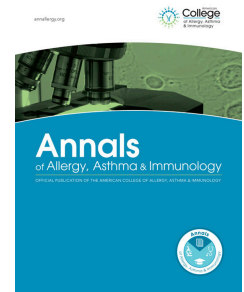


Accepted Manuscript

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PII: S1081-1206(19)30456-9

DOI: <https://doi.org/10.1016/j.anai.2019.06.012>

Reference: ANAI 2934

To appear in: *Annals of Allergy, Asthma and Immunology*

Received Date: 24 May 2019

Revised Date: 13 June 2019

Accepted Date: 17 June 2019

Please cite this article as: Mahdavinia M, Batra PS, Codispoti C, Mepolizumab utility in successful aspirin desensitization in aspirin-exacerbated respiratory disease in a refractory case, *Annals of Allergy, Asthma and Immunology* (2019), doi: <https://doi.org/10.1016/j.anai.2019.06.012>.

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Title: Mepolizumab utility in successful aspirin desensitization in aspirin-exacerbated respiratory disease in a refractory case

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Key words: Chronic Rhinosinusitis(CRS), biologics, Aspirin exacerbated respiratory disease, Mepolizumab, desensitization

FINANCIAL DISCLOSURE: This study was conducted by internal departmental funding by Rush University. MM is supported by research grants from Brinson Foundation, NIH and Medtronic. PSB is supported by a research grant from Medtronic.

Clinical trial registration: not applicable

CONFLICT OF INTEREST: authors have no conflict of interest to report

Word count: 1100

Tables: 1

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Aspirin-exacerbated respiratory disease (AERD) is a severe respiratory syndrome characterized by asthma, chronic rhinosinusitis with nasal polyposis (CRSwNP), and sensitivity to nonsteroidal anti-inflammatory drugs (NSAID) including aspirin manifested by acute upper and lower respiratory symptoms with exposure to this class of medications. (1) The prevalence of AERD is reported in 5.5% to 12.4 % of adult asthmatics, and rises to 21% when NSAID hypersensitivity is determined by provocation. (2-4) The management of asthma and CRSwNP in AERD should follow international guidelines including use of combination inhaled corticosteroid and long acting beta-2 agonists (ICS/LABA), leukotriene-modifying drugs (LTMD), nasal corticosteroids, nasal saline irrigations and short-term antibiotics and oral steroids as needed.(5) However, it is well documented that CRSwNP in AERD patients is substantially more resistant to pharmacological and surgical treatment.(6, 7) Currently, aspirin desensitization followed by daily use of high-dose aspirin is the accepted standard of care for AERD patients.

Multiple new biologic agents have emerged as possible agents for treatment of eosinophilic and allergic asthma. There are currently five biologics approved by the U.S. Food and Drug Administration for use in asthma; four of them are approved for patients with eosinophilic asthma and one for moderate to severe allergic asthma. Two previous studies have suggested that anti-IgE monoclonal antibody (omalizumab) and anti-IL-5 monoclonal antibody (mepolizumab) can be helpful in treatment of AERD. A study on the efficacy of omalizumab in AERD, showed that omalizumab resulted in significant reduction of both upper and lower airways symptoms, as well has reduction in asthma exacerbations and asthma related hospitalizations. (8) A retrospective study on use of mepolizumab showed that this medication is efficacious as an adjunct treatment for patients with AERD. (9) Here we report a case of refractory AERD

with severe lower airway response to ASA, who could only be desensitized after addition of an anti-IL-5 agent.

A 36 year old male with a history of AERD was referred to Allergy/Immunology from his rhinologist. Patient admitted to asthma and nasal polyposis diagnosed at 22 years old. His first reaction to aspirin was at 23 years of age when he ingested Excedrin (containing aspirin, acetaminophen and caffeine) that triggered a severe asthma exacerbation that poorly responded to multiple albuterol treatments and resulted in respiratory failure as well report of throat swelling requiring racemic epinephrine and hospitalization for 3 days. Patient reported his oxygen saturation decreased to below 80%. All NSAIDs have been avoided since this reaction. At 26 years of age he became anosmic. He has had a total of 4 functional endoscopic sinus surgeries; at 24, 26, 34 and 35 years of age. His asthma, was reported as controlled (ACT=22) on budesonide/formoterol combination 160/4.5 twice per day and montelukast 10 mg daily. His peripheral blood eosinophil count was 0.60 thousand cells/mL (12%). His immunoglobulin-E was 138.0 kU/mL. His skin prick test was only positive to Alternaria mold.

At presentation his sinus CT scan obtained 4 months after latest FESS, showed recurrence of severe mucosal disease. Decision was made to proceed with aspirin challenge following the fifth FESS. This was planned to be done in medical intensive care unit (MICU) due to his reported history of hospitalization and throat swelling with aspirin, 4 weeks after his surgery. Patient was admitted to MICU as planned. His baseline forced expiratory volume in 1 second (FEV1) was 3.57 L (83% of predicted). Results of desensitization are shown in Table 1. Approximately 90 minutes after his 81 mg aspirin dose, his FEV1 dropped to 1.98 L (46%). He became symptomatic with rhinorrhea, sneezing, cough and wheezing. Nebulized albuterol treatment was given with antihistamines and nasal decongestants. However, he continued to have extensive wheezing and shortness of breath despite multiple doses of albuterol. Four hours later his FEV1 remained decreased 1.85 L (43%) despite bronchodilator treatments every two

hours. An intravenous methylprednisolone dose of 60 mg was given. He remained symptomatic and the FEV1 did not improve even 5 hours after the dose. This halted the first day of aspirin challenge. Overnight he received 2 additional doses of methylprednisolone 60 mg and scheduled albuterol every 4 hours. By 8am on day 2 of desensitization he was asymptomatic and feeling well. His FEV1 had improved to 3.76 L (87%). The provoking 81 mg dose of aspirin was given again. There was no change in FEV1 after 30 and 60 minutes, but 90 minutes later his FEV1 decreased to 2.3 L (57%). He was again given albuterol, antihistamines and nasal decongestant with no improvement in FEV1 or shortness of breath. Approximately 4 hours after the provoking 81 mg dose, his FEV1 remained decreased at 3.01 L (70%). Desensitization was stopped due to his discomfort. There was no pharyngeal swelling in examination, but he continued to have wheezing for almost 48 hours despite scheduled albuterol. He was started on prednisone course with follow-up in Allergy/Immunology. On his follow up appointment, he was started on tiotropium and omalizumab 300 mg. His asthma was initially controlled, but he experienced increased symptoms of sinusitis (yellow-green mucous discharge, PND and sinus pain). He was started on prolonged course of low-dose prednisone; 5mg per day. Although decision was made to repeat aspirin challenge on omalizumab, it could not be done due to two asthma exacerbations while on omalizumab in a 3-months period. Five months after starting omalizumab, patient needed another FESS due to severe recurrence of CRSwNP. At this point omalizumab was stopped and he was started on mepolizumab 100mg monthly injections along with the same regimen of ICS/LABA, montelukast and nasal steroid irrigations. One month after his last FESS he was again admitted to MICU and the same ASA desensitization protocol was reinitiated (Table 1). Again he had a reaction at 81mg dose, but this time with 25% decrease in FEV1 which was rapidly reversed after use of albuterol. He subsequently tolerated the repeated dose of ASA in 90 minutes and was successfully desensitized to full dose ASA. He was discharged and continued with 650mg ASA twice per day afterwards with no further symptoms. In the past 24 months following his desensitization he has been on mepolizumab 100mg monthly, high dose

ICS/LABA , montelukast 10mg daily and nasal steroid irrigations. His ASA dose is now decreased to 325 twice per day. Since desensitization he has not needed further sinus surgery or oral prednisone for asthma exacerbation, and has had no increase in nasal polyp burden.

This case represents the first report of successful aspirin desensitization on mepolizumab in a patient that failed earlier trial of desensitization. Although most of AERD patients can be successfully desensitized to aspirin, this is not the case in some severe cases such as our patient with more severe and steroid dependent asthma. This report supports the use of anti-IL-5 monoclonal antibody in patients who have previously failed aspirin desensitization. This study raises the question should anti-IL-5 monoclonal antibody therapy be used as either a therapeutic bridge to complete safe aspirin desensitization for those with more advanced disease and severe asthma or in all patients with AERD to provide the most efficacious treatment for preventing exacerbations and need for recurrent surgeries.

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Table 1A: First (1A) and second (2B) attempt of ASA desensitization off and on Mepolizumab

1A:		
Time	Aspirin doses, mg	Symptoms after ASA dose
Day 1		
8 am	20mg	none
10 am	40.5*	none
1 pm	81	37% drop in FEV1 Rhinorrhea, cough, congestion
4-8 pm		Sustained 39% drop in FEV1
Day 2		
8 am	81mg	30% drop in FEV1 Rhinorrhea, cough, congestion
10 am-4 pm		Sustained 20 % drop in FEV1 Rhinorrhea, cough, congestion
6 pm		Discharged home on oral steroids
2A		
Time	Aspirin doses, mg	Symptoms after ASA dose
Day 1		
8 am	20mg	none
10 am	40.5*	none
1 pm	81	25% drop in FEV1 Rhinorrhea, nasal congestion Reversed with treatment
4 pm	162	none
Day 2		
8 am	325 mg	none
Day 3		
8 pm	Started 650mg BID at home	none