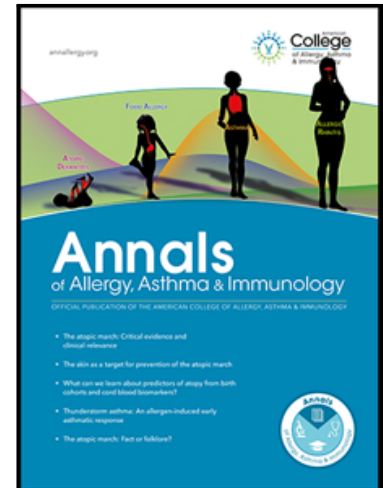


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Dupilumab Improves Alcohol Tolerance in Aspirin Exacerbated Respiratory Disease

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Key words

Dupilumab; AERD; Alcohol

Abbreviations

AERD Aspirin-exacerbated respiratory disease

Aspirin-exacerbated respiratory disease (AERD) presents with a triad of nasal polyps, asthma, and aspirin/NSAID sensitivity. It is characterized by often recalcitrant type 2 inflammation with dysregulated arachidonic acid metabolism, mast cell activation, and blood and airway eosinophilia[1]. In addition to characteristic respiratory reactions with cyclooxygenase-1 inhibitors, patients with AERD often demonstrate alcohol sensitivity. Up to 75% of patients with AERD suffer from upper airway symptoms (sneezing, rhinorrhea, nasal congestion) while 51% have lower respiratory symptoms (wheezing, dyspnea)[2] that are not specific to the type nor amount of alcohol ingested. The prevalence was similar in another survey of 190 respondents with AERD in which 77% reported reactivity to alcohol[3]. The mechanism remains unknown but may be due to polyphenols present in the alcohol, which are known inhibitors of COX-1. Patients with lower airway symptoms with alcohol ingestion are far more likely to develop lower respiratory reactions to aspirin,

supporting this phenomenon as a manifestation of the inflammatory microenvironment in AERD[2]. Interestingly, aspirin desensitization improves alcohol-induced respiratory symptoms in AERD[4].

Dupilumab is a fully human VelocImmune®- derived monoclonal antibody that binds the interleukin-4 receptor- α , and inhibits IL-4 and IL-13 signaling pathways. Emerging data suggests the efficacy of dupilumab in ameliorating sino-pulmonary inflammation in AERD[5, 6] and it can also impact the severity of alcohol-induced symptoms in these patients[5].

We describe our institutional experience with six AERD patients who reported complete resolution of alcohol-induced respiratory symptoms while on therapy with dupilumab. Patients were excluded from analysis if they were concomitantly receiving long term high dose aspirin therapy and in the absence of alcohol-induced symptoms at baseline. The cohort consisted of 3 females and 3 males, with a mean age of 52.8 years. Five patients had challenge-proven aspirin sensitivity and one patient was diagnosed based on a convincing history of NSAID/aspirin intolerance, and the mean time since diagnosis was 6.2 years. Patients had an average of 5 prior sinus surgeries. Five patients had been previously desensitized to aspirin but were unable to tolerate therapy or discontinued due to inadequate symptomatic improvement. All patients were on a baseline regimen of nasal corticosteroids as well as inhaled corticosteroid/ long acting β -agonist inhalers for asthma. Clinical characteristics of the cohort are outlined in Table 1.

All six patients described respiratory symptoms elicited by a few sips to one full alcoholic beverage, and two patients had a latency period of 10-15 minutes prior to symptom onset. Three patients stated that reactions were most prominent with consumption of red wine.

The most common symptoms were nasal congestion and rhinorrhea (100%), and shortness of breath/wheezing (33%). Following initiation of dupilumab, all six patients noted complete resolution of alcohol-triggered sino-nasal and pulmonary symptoms. Patients 1 and 2 (Table 1) even stated that they were able to tolerate multiple (>2) alcoholic beverages without any symptoms as compared with intolerance to merely a few sips prior to therapy. Notably, Patient 3 (Table 1) had a previous history of amyloid congestive heart failure and was hospitalized for an acute congestive heart failure exacerbation after five months of dupilumab therapy. Dupilumab was discontinued at this time, and she was transitioned to benralizumab. While she had noted improved alcohol reactions on dupilumab, alcohol-induced sino-nasal symptoms recurred upon switching biologics highlighting the role of dupilumab in maintaining this tolerance.

Dupilumab was also very effective at improving other sino-pulmonary manifestations of AERD, and the mean SNOT-22 improved from 54.2 at baseline to 21.2 after an average of 14.7 months of treatment. The rate of asthma exacerbations decreased from an average of 3.2 in the year prior to dupilumab to 1.0 following therapy. There were no treatment-related adverse events other than the heart failure exacerbation attributed to dupilumab but this was not confirmed.

Aspirin desensitization has been a therapeutic option for patients with AERD, and has been shown to improve alcohol tolerance[4]. However, all of the patients in the current study did not tolerate or did not derive benefit from aspirin therapy. In these cases, dupilumab is an option for improved symptom control. In a previous case series of 10 patients with AERD, 7 noted symptoms with alcohol consumption, while only 1 of 8 who consumed alcohol had symptoms after dupilumab therapy [5]. Yet it remains unclear if there exists a dose

dependent relationship, or if these patients could tolerate different types of alcohol. In this small case series, an improvement in alcohol tolerance was noted in all six cases of refractory AERD with a history of multiple sinus surgeries each, in parallel with marked improvement of sino-pulmonary symptoms. Furthermore, some denied any dose-dependent response, tolerated multiple drinks within a single period. While the mechanism remains unknown, dupilumab likely suppresses the downstream effects of alcohol-related COX-1 inhibition. Cysteinyl leukotrienes and mast cell mediators such as PGD₂ may play key roles in these reactions[2]. A prospective study of dupilumab in ten subjects with AERD showed a rapid decrease in urinary LTE₄ levels on therapy[5]. While aspirin desensitization does not downregulate LTE₄ production, its effects are thought to be mediated by decreased airway responsiveness to LTE₄[7] and decreased PGD₂ expression. Furthermore, the loss of alcohol tolerance in switching from dupilumab to benralizumab in Patient 3 suggests that alcohol sensitivity in AERD may be driven by interleukin 4 receptor positive cells, rather than interleukin-5 receptor cells, such as eosinophils.

In contrast with our observations, a few case reports have discussed patients with atopic dermatitis treated with dupilumab who developed new onset facial flushing after drinking alcohol[8, 9]. The reactions occurred minutes after ingesting alcohol and self-resolved in about 20-30 minutes. A proposed mechanism is that dupilumab may modulate the formation of cytochrome P450 which metabolizes alcohol, thus increasing acetaldehyde and causing facial flushing similar to patients with ALDH2 deficiency. No mention of upper airway reaction was noted in these patients and likely to act through a different mechanism of alcohol sensitivity than in our patients.

Improved alcohol tolerance may be a motivating factor for some to undergo or continue with dupilumab therapy. These patients were able to increasingly participate in social situations with friends and family. Future investigations into the underlying mechanism with mediator analysis including mast cell products and cysteinyl leukotrienes will help characterize this unique treatment response

Conflicts of Competing Interest

None

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None

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Table 1. Demographics and clinical characteristics:

Patient Number	1	2	3	4	5	6
Age	58	45	55	40	61	58
Sex	M	M	F	M	F	F
Medical History	chronic sinusitis, nasal polyps, AERD, and severe persistent asthma	chronic sinusitis, nasal polyps, AERD, and severe persistent asthma	severe persistent asthma, chronic sinusitis, nasal polyps, and AERD, amyloidosis	Severe persistent asthma, chronic sinusitis, nasal polyps, AERD, seasonal allergies	Severe persistent asthma, chronic sinusitis, nasal polyps, AERD, hypertension	Severe persistent asthma, chronic sinusitis, nasal polyps, AERD, hypertension, hyperlipidemia
Dupixent dosage	300mg every 2 weeks	300mg every 2 weeks	300mg every 2 weeks	300mg every 2 weeks	300mg every 2 weeks	300mg every 2 weeks
Baseline AEC (10E3/mcl)	?	2200	490	1400	1007	750
Baseline serum IgE (IU/mL)	?	?	?	?	832	770
Reason for aspirin therapy discontinuation	Gastrointestinal side effects	Lack of benefit	Orthopedic surgery	N/A	Lack of benefit	Gastrointestinal, cardiac side effects
Alcohol ingestion symptoms	Nasal congestion, rhinorrhea, dyspnea	Nasal congestion, rhinorrhea	Nasal congestion, rhinorrhea	Nasal congestion, rhinorrhea, wheezing	Nasal congestion, rhinorrhea	Nasal congestion, rhinorrhea
Type of alcohol that elicits symptoms	Wine	Beer	Sips of red wine	One glass of wine, two beers	Red wine	Sips of red wine, champagne
Duration of dupilumab	18 months	18 months	5 months	16 months	21 months	22 months
Improvement of alcohol symptoms after dupilumab	Yes	Yes	Yes	Yes	Yes?	Yes