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Severe Asthma:
Changing the Game

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Introduction

Asthma is common, with a prevalence of about 18% worldwide and 7.7% in the US.[1,2] Asthma is associated with significant morbidity, accounting for nearly 12 million hospital stays, and emergency department and office visits in 2016 and mortality, including 10.5 deaths per million in the US.[1,2] Prevalence is higher in the Black community than in Whites, and while those of Hispanic ethnicity carry a lower overall prevalence, the Puerto Rican community has a higher prevalence than Blacks, Whites, or other Hispanics.[2,3] Adults with asthma (≥18 years) experience higher rates of death, and 3% to 10% of adults generate 60% of associated health care costs.[2,4,5] These alarming numbers fostered clinical phenotyping and pathologic endotyping to develop evidence-based diagnostic and treatment guidance. The National Asthma Education and Prevention Panel published the first expert guidelines in 1991, and its 2007 update acknowledged immune and genetic factors, the potential of biomarkers, and need for stepped therapy approaches.[6] By 2014, the European Respiratory Society/American Thoracic Society (ERS/ATS) Task Force drafted guidelines specific to "severe" or hard-to-control asthma as a discrete entity, and in 2018 the Global Initiative for Asthma (GINA) published its first guide explicitly for the management of difficult-to-treat and severe asthma.[7,8]

Cluster phenotyping groups patients according to age of onset, race/ethnicity, lung function, obesity, presence of atopy, levels of control, and smoking history. Analyses established several phenotypes, including allergic subtypes and nonatopic disease, each displaying different causes, natural histories and response to therapy.[9-11] Further investigation within this decade found less subjective endotypes, with characteristic molecular pathways, associated biomarkers, and corresponding precision therapies.[3,11-14] Additionally, rapid advances in genetics and epigenetics have produced interesting insights into polymorphisms associated with heritability, treatment resistance, airway epithelial expressions potentially related to asthma susceptibility, and genetic modification by pollutants, all points of possible intervention.[11,15] Indeed, a genetic source (GATA-3) for inflammatory endotypes is now targeted with an investigational antisense oligonucleotide therapy.[16,17]

Difficult-to-control asthma vs severe asthma

Reports indicate that 50% of asthma patients in the US have suboptimal control, of whom 85% to 90% have difficult-to-control asthma, while the rest suffer severe or refractory asthma.[9,18] Difficult-to-control asthma refers to situations where the lack of control is due to factors other than intrinsic severity of the disease itself, such as poor adherence to controller therapy, suboptimal inhaler technique, modifiable environmental triggers, and/or comorbidities complicating asthma.[4,9] When these modifiable factors have been addressed and excluded, but the patient still reports symptoms of poor control despite high-dose inhaled corticosteroid (ICS) and other controller(s), particularly if they have 2 or more acute exacerbations a year, then the patient is considered to have severe or refractory asthma.[4,19]

Case #1

"Jenny", a 15-year-old Black adolescent female, presents with complaints of awakening 1 to 2 nights per week with asthma symptoms, difficulty breathing with exercise, and a nonproductive cough. She mentions that she is a gymnast and her coach thinks she is being lazy. She was diagnosed with asthma at around age 6 and managed with nebulized budesonide until age 10 when she switched to a metered-dose inhaler (MDI). She has chronic, year-round allergies that worsen with high oak and cedar pollen counts. She also describes a history of eczema between the ages of 5 and 8 years. No other significant history or recent illnesses.

Medications:

- mometasone furoate HFA MDI, 200mcg, 1 puff BID
- albuterol HFA MDI, 2 puffs 15 minutes before workout and 1-2 puffs q4-6 h prn
- fexofenadine, 60-mg tab, 1 tablet BID
- montelukast, 10-mg tab, 1 tablet daily
- triamcinolone acetonide AQ, 2 sprays each nostril daily

Examination:

Significant only for expiratory wheezes throughout both lungs

Spirometry:

- Prebronchodilator FEV_1/FVC=0.78; FEV_1=75% predicted
- Postbronchodilator FEV_1/FVC=0.84; FEV_1=90% (represents 18%, and 240 mL improvement)

Prior to starting asthma therapy, reversibility through pre- and postbronchodilator FEV_1, spirometry with a ≥12% and 200 mL improvement is consistent with an asthma diagnosis but does not rule out comorbidities.[10,20] Incomplete reversibility may suggest asthma–chronic obstructive pulmonary disease (COPD) overlap phenotype in the appropriate clinical setting and older age group.[4,10,21] In select patients with suspected asthma but baseline normal spirometry without a bronchodilator response, the bronchoprovocation or challenge tests (methacholine, histamine, mannitol, etc) may be helpful to rule out asthma if normal.[10,13,20] However, in Jenny's case, her dry cough, exercise-induced bronchoconstriction, audible wheezing, and significant improvement in spirometry postbronchodilator confirm the diagnosis of asthma.

Labs/studies:

- Asthma control test (ACT)=14
- FeNO (fraction of exhaled nitric oxide)=55 ppb
- Complete blood count (CBC) with differential: absolute eosinophil count=100 cells/µL
- Total IgE=340 IU/dL
- Radioallergosorbent test (RAST) IgE (+): oak, various grasses, mold, dust mite, cockroach, cat dander

The Asthma Control Questionnaire (ACQ >1.5) or the Asthma Control Test (ACT <20) as well as the recently validated Asthma Impairment and Risk Questionnaire (AIRQ) are useful tools to help determine asthma control.[1,19,22] Jenny's ACT score of <15 is consistent with uncontrolled asthma. Normal, intermediate, and high FeNO levels are categorized as: low/normal: <25 ppb (adults), <20 ppb (children); intermediate: 25 to 50 ppb (adults), 20 to 35ppb (children); or high: >50 ppb (adults), >35 ppb (children).[23,24] Jenny's FeNO of 55 ppb indicates ongoing and significant type 2 inflammation, predicts patients who will likely respond to corticosteroids, or cues a lack of ICS and leukotriene receptor antagonist (LTRA) compliance.[10,12,24,25]

Upon further questioning, it is discovered that Jenny has now taken responsibility for her own asthma care and is no longer supervised by her mother. Jenny admits to often forgetting to take her controller ICS inhaler, hates the taste of her nasal spray so she rarely takes it, bought a new fluffy comforter, and only sporadically cleans her room. While she uses her albuterol for nighttime symptoms, she is embarrassed to use it at school and the gym because she often gets teased.

Poor adherence and improper inhaler technique account for approximately 80% of uncontrolled asthma.[3,4] Inhaler technique should be routinely observed during office visits, as approximately 50% of patients fail to receive a complete dose due to inadequate inspiration of dry powder inhalers or poor timing of actuation/inhalation with MDIs.[26,27] Other identified failures include loading of device, ensuring adequate medication is present, removing the cap, holding the inhaler properly upright and sealing lips around the mouthpiece, all of which may improve with in-person demonstrations and multimedia educational interventions.[26] Confusion is understandable given the plethora of unique inhaler devices, as illustrated in **Figure 1**. Changing the level of current therapy (eg, adding a long-acting $ß_2$-agonist [LABA] or increasing ICS dose) is not needed in the setting of suboptimal compliance and self-management, although sometimes trying a different type of inhaler remains an option.[9]

Another modifiable target is exposure to triggers.[1] The National Heart, Lung, and Blood Institute (NHLBI) guidelines place emphasis on ensuring patient education regarding these areas at each visit to ensure control goals are being met.[3,6] Techniques to manage exacerbations from cold weather, exercise, stress, and allergen exposure should be reinforced.[1,10] While inhaler technique is observable, ensuring that a prescription is actually filled and utilized is challenging. Both controller and reliever prescription refill history might provide a picture of compliance as some

FIGURE 1: Inhalers and nebulizers

Figures courtesy of the WipeDiseases Foundation at https://wipediseases.org.

estimates state that <50% of controllers are ever picked up, and high rates of short-acting β_2-agonist (SABA) refills are associated with hospitalization and death.[14,28,29] Inhalers with electronic monitoring devices (EMDs) that log and transmit time of use are available.[10,14,30] Some patients simply need an inhaler that is best for their coordination capabilities, or is less costly, while others may be forgetful about using and refilling their medications or do not like the associated side effects.[10,30]

Jenny's greatest issues are poor adherence to medications and suboptimal avoidance of her known asthma triggers (ie, new "fluffy comforter" and dusty room). Motivational interviewing practices as outlined by Saha et al. (www.aap.org/en-us/Documents/practicesupport_aap_mi_asthma_allergy_webinar.pdf) and technology (eg EMDs and Propeller/AsthmaMD®apps) help elucidate better information and gain buy-in to improve patient understanding and participation in self-management, while also assisting in allergen management.[30-32] Involving the patients in choosing treatments that fit their lifestyle and needs is now a readily available option through an online Shared Decision Making tool by CHEST (**https://asthma.chestnet.org/sdm-tool/**).[33] Joint development of a personalized action plan comes highly recommended as a proven way to reduce exacerbation and mortality risk.[10,20]

Treatment plans developed in conjunction with Jenny and her mom: Change to fluticasone mist nasal spray, loratadine every morning (remembers meds at breakfast); agrees to use mometasone as prescribed (programmed her phone to remind her and has set the inhaler by her toothbrush) and says she will use albuterol prior to going to the gym. She acknowledges the need to replace her comforter with a washable blanket, use dust/mite covers on her bedding, remove rugs, and keep her room clean.

She is now willing to talk about asthma with her friends and coach. Sent home with written action plan.

Six-week follow-up visit: Symptoms controlled, and ACT is 22.

T2-high inflammatory endotype

In contrast to difficult-to-control asthma, severe asthma encompasses disease intrinsic pathophysiology requiring high dose ICS and other agents to maintain control, or remains uncontrolled, despite good compliance, appropriate inhaler technique and adequate treatment of contributing factors.[4,19] Severe asthma is defined as consistent use of high-dose ICS (Steps 4-5 of GINA guidelines, or equivalent) and any 1 of the following: (1) symptoms remain burdensome; (2) ≥2 bursts of oral corticosteroids (OCS) in the prior year; (3) ≥1 hospitalization for exacerbation in the prior year; (4) FEV_1/FVC <0.80 and/or FEV_1 <60% predicted; or (5) loss of control with tapering attempts from high-level therapies.[8,10,13,21,34,35] Importantly, stepped therapy categories as a measure of severity need to be understood within the context of varying definitions of "high dose" and age-based steps between guidelines, as well as limitations imposed by fixed dose combination inhalers.[1,8,9]

Around 5% to 10% of patients with asthma suffer from severe asthma, 1% to 2% of whom are considered treatment refractory.[9] Of adults with severe asthma, 71% are women, 4% to 21% exhibit aspirin sensitivity with nasal polyposis, and those with gradually-developing obesity as well as the black race predominate.[3,34,36] Asthma's episodic nature distinguishes it from most other chronic respiratory conditions, with airway edema and bronchoconstriction triggered by exposures to allergens, irritants, cold air, medications, or recent infection.[19] Two key physiologic components underpin the asthma disease state as a whole: (1) the inflammatory response as exemplified in **Figure 2**, and (2) changes in the airway structures over time as shown in **Figure 3**.[37] Endotyping has helped define differing inflammatory branches within the cascade, the path of which is determined by genetics, trigger type and the specific immune cells with accompanying mediators activated.[19] Practitioners may find the animated tour of T2-high inflammatory pathways at **https://hcp.wipediseases.org/lungdon/** of great value to increase understanding.[38]

The inflammatory cascade involves various innate and adaptive immune cell modulators.[11,12] Thymic stromal lymphopoietin (TSLP) is released when the epithelium is breached by allergens, activating mast cells, antigen-presenting dendritic cells, eosinophils and, to some degree, innate lymphoid groups 2 cells. TSLP also activates T-helper 2 (Th2) cells with their cytokines IL-4, IL-5, and IL-13 to stimulate production of IgE while further recruiting eosinophils.[11,19,25,37] Other nonallergic triggers, such as infection, smoke, or pollutants, more prominently stimulate epithelial release of IL-25 and IL-33, as well as TSLP, to

FIGURE 2: Inflammatory cascade

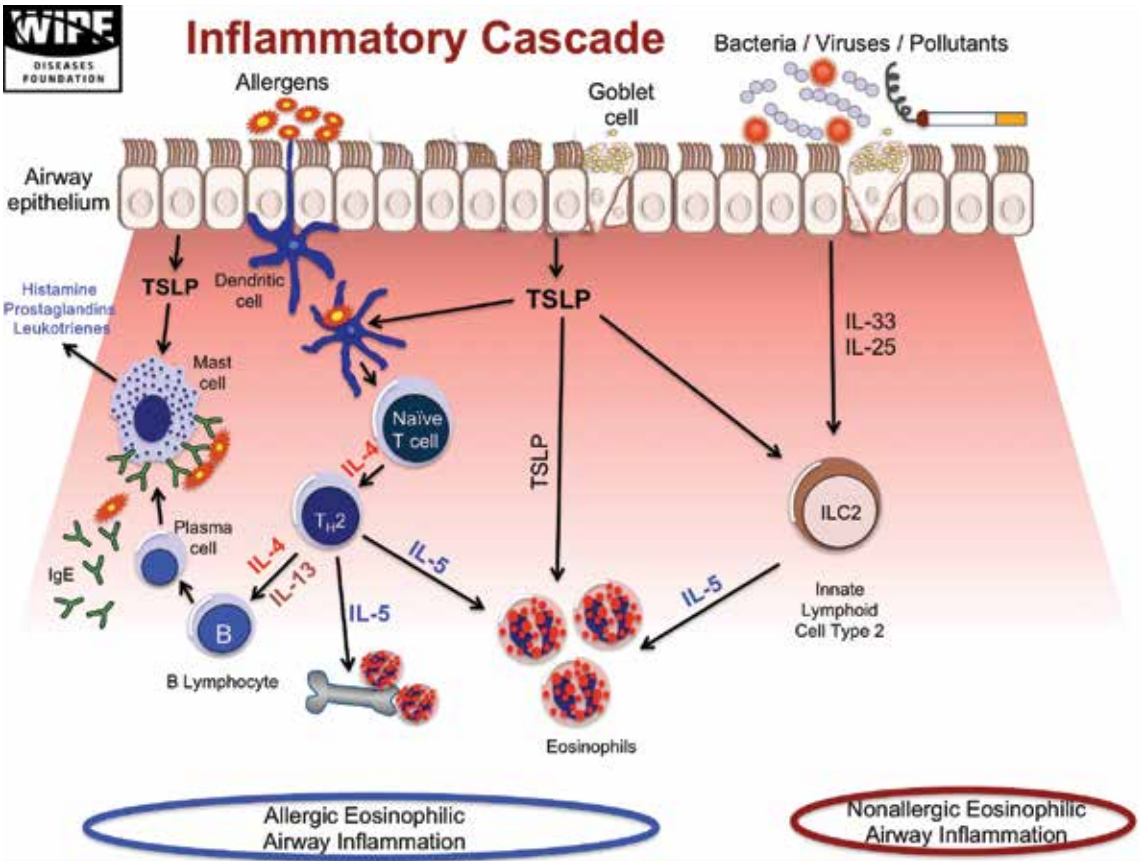
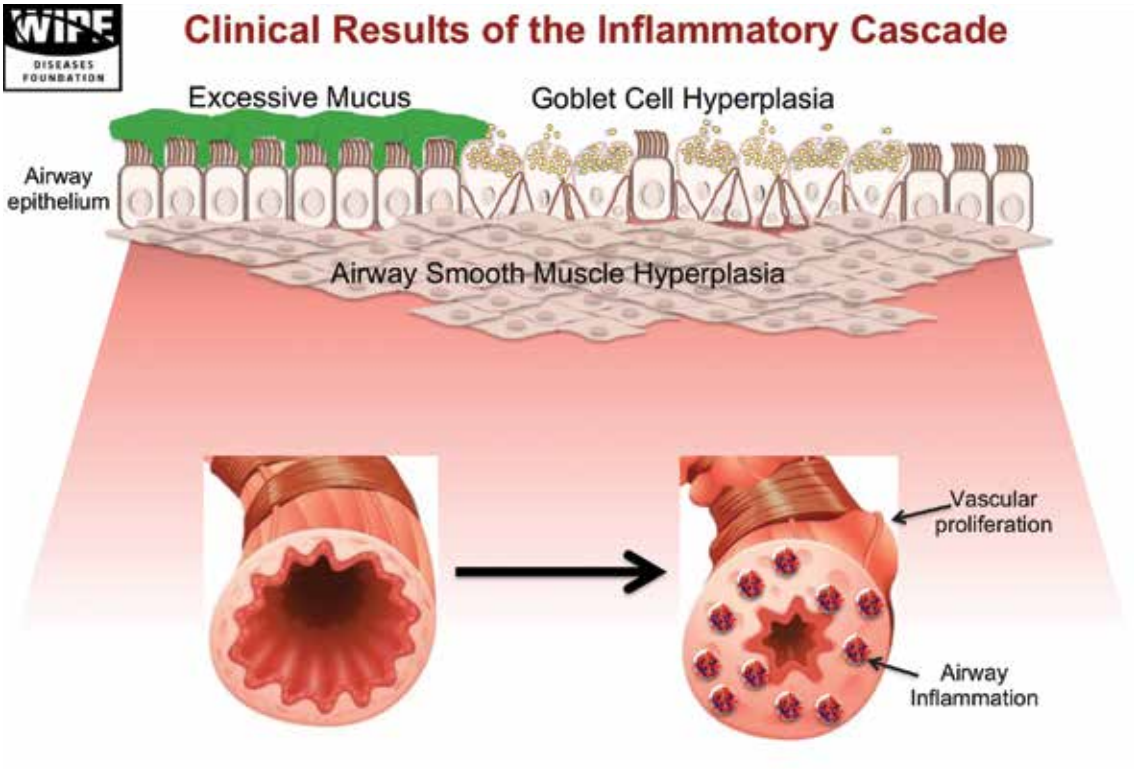


FIGURE 3: Clinical results of the inflammatory cascade



Figures courtesy of the WipeDiseases Foundation at https://wipediseases.org.

activate ILC2s that stimulate eosinophil production via IL-5, IL-9 and IL-13.[11,37,39] Often described as T2-high asthma, with atopic or nonatopic subtypes, this endotype's further branching is based on immunoglobulin E, eosinophils, and other biomarkers.[9,14,25,39] Other suspected players that may prove useful for therapeutic intervention include epithelial interferon-b and lipoxin A4's role in natural inflammatory truncation.[4,11,17] Inflammatory milieu lay the foundations for airway wall changes, resulting in mucus plugs, air trapping, and smooth-muscle hyperresponsiveness.[11]

Airway walls change as inflammatory mast cells, monocytes, neutrophils, basophils, and macrophages with their various cytokines/chemokines infiltrate the tissues.[11] IL-13 causes proliferation and hyperresponsiveness of smooth muscle.[11,28] Goblet cells overproduce and expand into new territory in response to IL-4, IL-9, and IL-13 and increase mucus production.[11] As surface columnar cells separate from the basal layer, the subepithelial reticular lamina becomes layered with repair collagens, periostin, fibronectin, and other connective tissues to cause thickening and loss of elasticity.[4,11] Neogenesis of vasculature, neuronal, and smooth-muscle cells occurs in response to a host of epidermal growth factors, such as neurotrophins and vascular endothelial factor, from the epithelium.[11] The resultant remodeling reduces responsiveness to bronchodilators and increases hyperreactivity.[10]

Several measurable biomarkers, along with defined levels, coordinate to help endotype disease, and identify severity, treatment response, and even compliance.[21,24, 34] FeNO ≥50 ppm in adults indicates high severity and likelihood of eosinophilic T2-high asthma, while <25 ppb was proven more useful in ruling out eosinophilia as increased age, smoking and upper respiratory infection can contribute to elevated levels.[24,25,36] One suggested cutoff is FeNO ≥30 ppb in adults to confirm T2-high over T2-low probability.[9] The most recent GINA Difficult-to-Treat and Severe Asthma Recommendations utilize ≥20 ppb to support anti-IgE monoclonal antibodies (mAbs), and ≥25 ppb for anti-IL4 or anti-IL5 mAbs, choice and monitoring, while ERS/ATS 2020 recommends a blood eosinophil ≥150 µL to guide anti-IL5 initiation.[1,40]

Eosinophils in the blood or airway are more reliable indicators of T2-high asthma, both allergic and nonallergic, proving useful in predicting successful treatment with corticosteroids, anti-IL5 and anti-IL4/13 treatments.[10,12] High sputum counts (>2% to 3%) are often listed in literature, however the expense, difficulty, and high contamination rates associated with sputum analysis make blood levels a more clinically useful marker.[14,19,24,25,41] Blood levels ≥150 cells/µl suggest T2 inflammation.[4,10,24] Cutoffs for study inclusion range from >150-300 cells/µl, the lower end of the range being more closely associated with atopy and the higher linked to non-atopic high mortality.[24,25] Patients with severe asthma with high IgE levels (30-700 IU/mL) with atopy based on a positive skin-prick test (SPT) or RAST-specific IgE are usually responsive to anti-IgE treatment. Those with eosinophils ≥300 cells/µl are usually more responsive and appropriate for anti-IL5 treatment.[1,12,14,25] GINA recommendations suggest an eosinophil count of ≥150 cells/µL as an indicator for anti-IL4/13 therapy as response rates were not impacted if eosinophils were ≥300 cells/µL.[1,4] Steroid suppression of eosinophils can skew results, so steroid-free measurements should be considered when possible.[36]

As with Jenny, atopic T2-high asthma usually begins in childhood and is often associated with eczema, a familial tendency, and identifiable aeroallergen triggers with comorbid chronic rhinosinusitis (CRS).[1,10,11,36] Atopy is present in 50% to 60% of all asthma cases, allergic rhinitis in 55% to 68% of severe asthma, with 2/3 of asthmatic children and a predominance of Black patients being represented.[13,34,42] High IgE levels are indicative of atopy, including subendotypes such as fungal sensitivities, whereas extreme levels (≥1000 IU/mL), or aspirin intolerance should be further investigated and treated accordingly.[9,34,36,42] Antigen-specific IgE via RAST gives confidence in the allergic component and combines with high eosinophils to confirm atopic T2-high endotype and predict good response to corticosteroids and biologics, while her serum IgE can be used to properly dose omalizumab if needed in the future.[1,4,10,25,41] Even in adult onset, it is important to check for allergy status through RAST or SPT as two-thirds are found unable to recall a documented history and serum IgE is known to decrease with age.[20,29]

For severe T2-high atopic patients, several therapeutic choices exist. For medications, Step 4 GINA recommendations include high-dose ICS for a limited time, with a long-acting muscarinic agonist (LAMA) or LTRA add-on, or medium-dose ICS/LABA combination for baseline controllers; NHLBI Step 4 or 5 corresponds with this approach and further recommends OCS as a controller.[1,35]

The first biologic asthma therapy, omalizumab, is used in atopic asthma to bind and reduce the IgE-mast cell complex.[9,17] Initially Food and Drug Administration (FDA) approved in 2003 for ages ≥12 years and IgE ≥30 IU/mL, exacerbation decreased by 25% to 35% in clinical trials, with greatest improvement in those with FeNO ≥19.5 ppb (50%), high eosinophils and periostin.[4,9,24] Eventually approved in ages ≥6 years, the National Institute for Health and Care Excellence now recommends it as add-on treatment for those requiring frequent or continuous oral corticosteroid (OCS).[43,44] One Cochrane review showed omalizumab significantly reduced exacerbations, hospitalizations, and the need for ICS in those with moderate-to-severe asthma.[44] This review indicated equivocal results on OCS and $ß_2$-agonist use, but other studies demonstrated reduced OCS and rescue dosing as well as improved lung function and life-quality.[1,28,44] Adverse effects were minimal and statistically lower compared to placebo with injection-site reactions being the most common; a black-box warning for anaphylaxis remains despite a 0.14% occurrence, and concerns over malignancy risks appear unfounded.[28,44] McQueen et al

evaluated cost-effectiveness assessments comparing omalizumab to "usual care" and found variable, though mostly positive, patterns in omalizumab patients and indicating the need for more standardized analysis.[45] Aside from cost-savings, if omalizumab is steroid-sparing overall, this represents potential long-term benefits in children by reducing bone, adrenal, and growth complications.[29] Not all eligible patients will respond to omalizumab, and pretreatment IgE levels are not predictive of response, so it is recommended that patients be reassessed at 16 weeks.[9,25] Should Jenny progress to a severe state, she could benefit from this option.

Case #2

"Michael" is a 28-year-old Hispanic man who suffered a cold that turned into "bronchitis" approximately 5 months ago, causing his asthma to flare and requiring 2 courses of OCS. He has had asthma since age 7 that was controlled with fluticasone propionate HFA MDI, 110mcg daily and albuterol MDI, 1-2 times/month until the age of 22 when he changed to fluticasone/salmeterol Diskus 250/50mg twice daily due to loss of control, which restored him to good control. Today, he presents with the following complaints: now using albuterol 1-2 times/day, awakens 1-2 nights/week with cough and wheezing.

Interview finds that he demonstrates good inhaler technique, is a nonsmoker, has no pets, no known exposure to pollutants and has taken aspirin without problems. His ACT score=12.

Spirometry:

Postbronchodilator FEV_1/FVC, 0.78; FEV_1, 80% predicted (10% improvement)

Labs:

- FeNO=60 ppb
- IgE=170 IU/dL with RAST-negative (no allergies)
- Blood eosinophils=530 cells/µL

Nasal endoscopy reveals the presence of polyps and Michael begins fluticasone propionate nasal spray, 93mcg and tiotropium Respimat, 1.25mcg 2 puffs daily, but his ACT only improves to 18.

There is about 50% overlap between atopic and non-atopic disease.[9] Non-atopic disease with elevated eosinophils typically develops in later life, generally involves lower IgE levels, and is associated with nasal polyps and aspirin sensitivity.[10] Nasal polyposis should be explored. Although nasal steroids could produce improvement, nasal endoscopy and paranasal computed tomography (CT) assist with finding nasal polyps that are strongly associated with asthma phenotypes.[11,42,46] CRS is a significant factor (40% to 50% prevalence in asthma) which, along with symptomatic gastroesophageal reflux disease (GERD) and obstructive sleep apnea (OSA), is associated with high exacerbation rates. The presence of these comorbidities should be investigated, and these concomitant conditions should be aggressively managed prior to stepping up therapy for uncontrolled asthma.[34,42]

Eosinophilic asthma with no indication of an allergic component and those who are atopic but fail the medication options discussed above may attempt any of the new anti-IL5 mAbs.[29] While Michael's IgE level is elevated, his RAST(-) suggests that he may not respond well to omalizumab.[1,40] In contrast, one of the anti-IL5 monoclonal antibodies (mepolizumab, reslizumab, or benralizumab) or the anti-IL4 (dupilumab) would be better options for Michael. Mepolizumab and reslizumab bind IL-5 directly, while benralizumab binds to the IL-5α receptor, which causes involution, thereby blocking activation, all preventing eosinophil degranulation and significantly decreasing eosinophil counts.[4,9,19,28] All 3 are shown to reduce exacerbations and OCS use, but other measures, such as FEV_1, quality of life, and symptom control scoring were best improved for patients selected for severity, defined either by extreme eosinophil levels (blood) and dependence on OCS or high-dose ICS.[9] As such, their current role seems best suited for recurrent exacerbations, resistance to steroid tapering, and baseline (off of OCS) blood eosinophils ≥300/µL.[1,21] A Cochrane review demonstrated that all 3 reduced exacerbations by about 50% and increased mean prebronchodilator FEV_1 from 0.08 to 0.11 L.[28] Benralizumab and mepolizumab appear to exert a greater effect as the baseline blood eosinophils and exacerbation history increases.[4,9,19] Reductions in blood eosinophil count are rapid and nearly complete with all anti-IL5 mAbs, and this marker may be monitored to evaluate effectiveness, but it should be noted that this decline may not reflect clinical results.[9,19] Long-term safety remains to be determined, but current evidence suggests they are all well tolerated, often with fewer adverse events than placebo.[9]

A novel approach to managing T2-high inflammation is the IL-4α mAb, dupilumab, which truncates IL-4/13 signaling and decreases IgE production by 40% but temporarily elevates blood eosinophils, thought to be due to a block of migration into the tissues that eventually self-regulates.[4,9,28,47] Initially FDA-approved in 2017 for moderate-to-severe atopic dermatitis, it received updated approval in October 2018 for add-on maintenance of moderate-to-severe eosinophilic or OCS-dependent asthma for ages ≥12 years.[48] Studies show a 60% to 80% reduction in exacerbations, improved FEV_1, greater control, and reduced FeNO and IgE.[4,9,28] Subsequently, dupilumab has been approved for atopic dermatitis in children ≥6 years and for CRS in adults with nasal polyps[48,49] Though phase 3 trials recruited patients regardless of blood eosinophil counts and beneficial effects were observed at all levels, a greater response corresponded to higher counts (≥150 cells/µL with incremental increase when ≥300 cells/µL).[47,50] Similar effects on FeNO were also observed such that good response occurred in those with baseline FeNO, 25-50 ppb, but better when FeNO, ≥50 ppb.[47]

TABLE 1: Biologic therapies in severe asthma

	Omalizumab	Mepolizumab	Reslizumab	Benralizumab	Dupilumab
FDA approval for asthma by age[49,51,53,54,55]	≥6 years old	≥6 years old	≥18 years old	≥12 years old	≥12 years old
mAb target[49,51,53-55]	IgE antagonist	IL-5 antagonist	IL-5 antagonist	IL-5α receptor binder	IL-4α antagonist
Dose in asthma[49,51,53-55]	Every 2 or 4 weeks sub-Q dosing based on IgE level and body weight in kg: 75-375 mg	• ≥12 years old: 100 mg sub-Q every 4 weeks • 6-11 years old: 40 mg sub-Q every 4 weeks (available as auto-injection)	3 mg/kg intravenous infusion over 20-50 minutes every 4 weeks	30 mg sub-Q every 4 weeks x 3 doses, then every 8 weeks (available as auto-injection)	• 400 mg sub-Q followed in 2 weeks by 200 mg QOW, <OR> • 600 mg sub-Q followed by 300 mg QOW* (available as auto-injection)
Adverse drug events[49,51,53-55]	≥2% arthralgias and body pain, fatigue, dizziness, earache, dermatitis, pruritus, injection site reaction, headache, nasopharyngitis	≥3% headache, injection site reaction, back pain, fatigue, influenza, urinary tract infection, upper abdominal pain, pruritis, eczema, muscle spasms	>2% oropharyngeal pain >1% myalgia, +mild ↑CPK Infusion reactions 2.2% musculoskeletal pain, spasm, fatigue	≥3%: headache, pharyngitis, pyrexia, urticarial hypersensitivity reactions 2.2% injection site reactions	≥1%: injection site reactions, oropharyngeal pain, eosinophilia
Incidence of anaphylaxis†	0.14% blackbox warning[44,51]	Postmarketing reports only[53]	0.3%, blackbox warning[54]	Postmarketing reports only[55]	<1% in pivotal trials[49]

Warnings are common to all regarding the potential for helminthic infections, and the treatment thereof, development of immunogenicity, and the need for gradual steroid reduction.[4,39,51,53,54,55]

*Higher dose recommended in concomitant OCS use or co-morbid atopic dermatitis[49]

†Omalizumab and reslizumab recommend an adequate post-administration monitoring period and the capability to emergently manage anaphylaxis.[51,54]

The QUEST trial improvements in FEV_1 were rapid, with peak effect by Week 6 and sustained for 52 weeks. Injection site reactions were greater with dupilumab vs placebo, and the most frequent ADEs reported (≥5%: URI, bronchitis, influenza, headache) were outpaced those in the placebo group.[47] VENTURE showed that dupilumab significantly reduced glucocorticoid use in steroid-dependent asthmatics and compared to placebo while maintaining high-dose ICS with either LABA or LTRA.[50]

Choosing a mAb in severe asthma can be difficult and may be more influenced by insurance and cost limitations than objective determinants (**Table 1**). Omalizumab has a proven track record in atopic disease, successfully used in a small number of pregnant patients, and now supersedes other preferred controllers in the GINA Step 5 recommendations for children ≥6 years, but may be restricted when IgE levels are not elevated.[1,9,51] Women who become pregnant can participate in the **mothertobaby.org/** registry in trialing any of the biologic therapies.[52] Anti-IL5s offer differing dosage routes and self-administration options (mepolizumab-ab, approved in children ≥6 years) while clearly offering a greater benefit in highly eosinophilic steroid-dependent presentations, yet OCS may need to be stopped if feasible to assess baseline eosinophils.[1,9] Dupilumab could be an option in atopic (like Jenny) and non-atopic (like Michael) patients, especially in light of steroid-sparing effects, but it is new and direct comparison to other mAbs is lacking.[9] None have been found to permanently alter disease course or induce long remissions and their optimal duration and long-term effects are not yet known.[9,12,28]

Although tiotropium is the only LAMA approved by the FDA at this time, recent studies of other inhaled LAMAs (glycopyrronium, umeclidinium, etc.) demonstrate the benefits of these agents in patients with symptomatic asthma; therefore, the benefits are likely a class effect.[28,56] Additionally, they are shown to inhibit airway hyperresponsiveness, contribute anti-inflammatory properties, and have successfully improved lung function when added to ICS/LABA

combinations.[9,29,36] Their use in non-atopic, asthma-COPD overlap is better defined, though they may be used in un-endotyped patients or those for whom OCS use is a concern.[1] Other add-on therapies to consider include LTRAs and theophylline, both of which are deemed less effective than adding a LABA, with theophylline not recommended in children.[1,29]

Azithromycin is now recognized by both ERS/ATS and GINA as an option for adults who remain symptomatic despite Step 5 controllers.[1,9,40] With both antibiotic and anti-inflammatory properties, it has shown some success in reducing exacerbations in eosinophilic and neutrophilic asthma.[10,29,36] GINA and ERS/ATS only recommend a trial of low-dose (250 mg TIW) therapy in adults with either T2-high or T2-low after full discussion of the risks and awareness that this is off-label with the patient.[1,36,40]

Treatment plan for Michael: 4-month trial of mepolizumab, 100 mg sub-q every 4 weeks. Upon follow-up, though blood eosinophils=0 cells, he continues to need OCS and his ACT=18, indicating inadequate response. Could consider changing to another anti-IL5 agent or to dupilumab and continue to reassess. If he continues to have an inadequate response, further options include azithromycin or low-dose continuous OCS.

T2-low endotype

T2-high describes approximately 37% to 55% of patients with severe asthma, leaving a significant group who do not benefit from T2-high precision interventions.[14,28] Cohort studies have identified patients with either mixed or low T2 biomarker levels, instead having high sputum neutrophil counts or paucigranular sputum, and these so-called T2-low patients exhibit the highest resistance to all forms of corticosteroid therapy.[19,39,57.58] Without solid biomarkers for this endotype, the lack of typical T2-high indicators is their current defining characteristic.[9] Neutrophilic subtypes are found to be particularly treatment-refractory and recent advances in characterizing this immune pathway are opening doors to new treatment options, but as mentioned, sputum analysis is not commonly available in clinical settings.[12,24.39] Some theorize an immune shift toward an IL-17/Th17 cascade.[24,25] Obesity is increasingly linked to IL-17 with ILC3 cells.[39,58] Future development of IL-17 and IL-8 measurements as biomarkers may further classify, and provide treatments for, this difficult endotype.[39]

Case #3

Jane is a 36-year-old White woman, BMI=39 kg/m^2, who recalls having childhood asthma that she "outgrew" in puberty. About 1 year ago, symptoms returned, and she started budesonide/formoterol MDI, 160/4.5 mg 2 puffs twice a day. After 6 weeks of no improvement, tiotropium Respimat 1.25mcg 2 puffs daily, was added. Two months later, her symptoms were not better and nasal stuffiness worsened. She recalls past allergens as dust mites and oak. Frequent triggers for a wheezy cough include cold temperatures, strong smells, and laughing. She had taken prednisone 20 mg daily for 2 weeks over a month ago with no improvement, and was tapered off.

Upon interview and exam, comorbidities other than obesity are ruled out. Her current ACT score=12.

Jane's labs, tests, and biomarkers

- CBC with differential: absolute eosinophil count= 50 cells/μL
- IgE=15 IU/dL
- FeNO=15 ppb
- SPT (-)

Jane's case offers a glimpse into how phenotyping and endotyping create a conflicting picture. T2-low encompasses a large share of asthma (39% to 50%), yet cannot be endotyped to the same degree as T2-high due to a lack of measurable biomarkers.[14] Instead, this group is typified by a high degree of severity with steroid resistance, obesity (particularly women with early-onset history), 13% to 20% crossover with COPD (especially in smokers and those ≥50 years old), and possible vitamin D deficiency.[4,20,21,39,58] Additionally, 10% to 15% of severe, corticosteroid-refractory asthma show T2-high/low overlap with mixed biomarkers.[57] Early-onset atopic disease, even in those experiencing remissions, leaves lasting reductions in lung function and permanent airway remodeling 25% of the time, with a loss of airway recoil, and imparts an increased risk of asthma return with possible concomitant COPD in adulthood and near-fatal exacerbations.[11,13,34]

Airway IL-8, IL-17 and IFN-γ are suspected cytokines targetable for treatment, yet study medications have not produced favorable results for patients who have not been prescreened for the presence of these biomarkers; brodalumab, an anti-IL17 mAb not approved by the FDA, provided improvement in a subset of patients with greater pretreatment reversibility.[4,10,14,57,58] Immunosuppressants (methotrexate, azathioprine, cyclosporine) have been attempted as steroid-sparing add-ons but are no longer recommended.[4,10] Some of these patients have responded well to azithromycin trials.[4,9,21] A more invasive option, bronchial thermoplasty, reduces smooth-muscle mass, proven to reduced exacerbations and increase life-quality for up to 5 years, but this is done in concert with disease registry through specialized centers.[9,10]

Many conditions mimic and/or coexist with asthma and should be evaluated, and validated questionnaires can help save exam time.[59] Cardiovascular disease and other obstructive lung disorders (eg bronchiectasis) can be assessed with exercise tests and high-resolution CT scans.[10,13,29,36,41] Up to

50% of asthmatics could have vocal cord dysfunction/inducible laryngeal obstruction, best confirmed with direct laryngoscopic methods as questionnaires are inconclusive.[13,36,42] Symptomatic GERD, another common comorbidity (46% to 63%), can be managed with a 3-month trial of medications with simultaneous tracking of asthma symptoms, or with an impedance probe.[10,2129,42] Asthma patients also have a high prevalence (39%) of obstructive sleep apnea (OSA), confusing night-waking with asthma, initially assessed with a validated questionnaire (eg Berlin Questionnaire) and/or referral for somnography with follow-up treatment.[13,36,42]

Obesity (BMI ≥30 kg/m^2) causes independent breathing problems and is also a contributing factor in 21% to 48% of adult-onset severe asthma patients.[20,21,34,36,41,42] Anxiety and depression often coexist with severe asthma (81% and 31%, respectively) and may be assessed with questionnaires. Panic attacks may also cause dysfunctional breathing and may mimic asthma exacerbations.[36,42] Medication lists should be inspected as possible extrinsic sources of symptoms (eg ACE-Inhibitors, aspirin, NSAIDs, ß-blockers).[1,8,21,36]

Given that about 40% of moderate-to-severe asthma patients do not stabilize with ICS/LABA combinations, even when a LAMA is added, particularly with this phenotypic group, Jane clearly needs specialty care.[9,21] A trial of azithromycin could be initiated before bronchial thermoplasty.

Weight loss combined with exercise training offer clinically significant improvements in asthma control and quality of life.[42] Shared decision-making is once again important in choosing the best course.

> **Treatment plan for Jane:** She and her clinician elect bronchial thermoplasty, 3 sessions over 3 months. Additionally, she is following a moderate dietary plan, which limits calories, and has begun an exercise plan.
>
> **Result:** Through regular follow-up, nutrition and emotional support, and slow but steady weight loss, her breathing symptoms improve. At 1-year follow-up she has lost significant weight (BMI=32 kg/m^2) and her ACT=21.

Follow-up and assessment

It is vital that throughout the treatment process the patient is repeatedly checked for compliance, inhaler technique, and signs of suboptimal control. Additionally, GINA strategies advocate for decreasing medications to the minimum effective dose to avoid side-effect risks.[1] A recent U.K. analysis shows that dose reductions contributed to health care cost savings without adversely affecting outcomes.[60] Advances in biologic therapy contribute toward decreasing steroid exposure and offer an even brighter future as we explore novel treatments and fresh targets for immune modulation (**Table 2**).

TABLE 2: Stratifying severe asthma in adults

	Atopic T2-High	Non-Atopic T2-High	T2-Low
Phenotypic characteristics[4,9,20,39]	Early-onset Allergic rhinitis African American + ICS response	Late-onset Nasal polyps +ICS response Some COPD overlap	Mid-age women Obesity Smoking history Overlap w/COPD
IgE[9,24]	>100-300 IU/mL	<100-300 IU/mL	<30 IU/mL
FeNO[9,24]	High (30-50ppb)	Very High (>50ppb)	Low (<25ppb)
Eos (blood)[9,24]	>150 cells/µL	>300 cells/µL	<100 cells/µL
Add-on to ICS/LABA[1,28]	Anti-IgEs Anti-IL4/13 Cromolyn, LTRAs, LAMAs Immune therapy	LAMAs Azithromycin Anti-IL5s Anti-IL4/13	LAMAs Azithromycin Bronchial Thermoplasty
Investigational	Quilizumab, ligelizumab (anti-IgEs)[9] Tezepelumab (anti-TSLP)[28,61]	GATA-3[16,28] Tezepelumab (anti-TSLP)[28,61] Ekotimab (anti-IL33)[28,62]	Lipoxin A4 (LXA4) analogs[4] Anti-IL17s[39] Tezepelumab (anti-TSLP)[28,61]

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As add-on maintenance treatment for patients (12+ years) with moderate-to-severe asthma with an eosinophilic phenotype, or with OCS-dependent asthma regardless of phenotype

ONLY DUPIXENT
REDUCED OR ELIMINATED OCS USE WHILE SIMULTANEOUSLY IMPROVING ASTHMA CONTROL[1,a-c]

99.9% OF INSURANCE PLANS REQUIRE NO BIOMARKER TESTING FOR OCS-DEPENDENT ASTHMA PATIENTS ON DUPIXENT[2]

[a] 86% of patients reduced or eliminated their OCS dose while maintaining asthma control from baseline at Week 24 with DUPIXENT 300 mg + SOC (n=103) vs 68% with placebo + SOC (n=107) (Trial 3, ITT population).[3]

[b] 59% reduction in annualized rate of severe exacerbations while reducing OCS dose at Week 24 with DUPIXENT 300 mg + SOC (n=103) vs placebo + SOC (n=107) (0.65 vs 1.60; rate ratio: 0.41 [95% CI: 0.26, 0.63]) (Trial 3, ITT population, secondary endpoint).[1]

[c] 220 mL improvement in pre-bronchodilator FEV_1 while reducing OCS dose at Week 24 with DUPIXENT 300 mg + SOC (n=103) vs 10 mL with placebo + SOC (n=107) (LSM difference: 220 mL [95% CI: 90, 340 mL]) (Trial 3, ITT population, secondary endpoint).[1,3]

INDICATION

DUPIXENT is indicated as an add-on maintenance treatment in patients with moderate-to-severe asthma aged 12 years and older with an eosinophilic phenotype or with oral corticosteroid dependent asthma.

LIMITATION OF USE

DUPIXENT is not indicated for the relief of acute bronchospasm or status asthmaticus.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATION: DUPIXENT is contraindicated in patients with known hypersensitivity to dupilumab or any of its excipients.

EOS, eosinophils; FEV_1, forced expiratory volume in 1 second; ITT, intention-to-treat; LSM, least squares mean; OCS, oral corticosteroid; SOC, standard of care.

Please see additional Important Safety Information throughout and brief summary of full Prescribing Information on the following pages.

Learn more at *DupixentAsthmaHCP.com*

DUPIXENT® (dupilumab) Injection
200mg · 300mg

DUPIXENT HELPED ASTHMA PATIENTS REDUCE OR ELIMINATE THEIR OCS DOSE

86%

OF PATIENTS REDUCED OR ELIMINATED THEIR OCS DOSE

while maintaining asthma control from baseline at Week 24 with DUPIXENT 300 mg + SOC (n=103) vs **68%** with placebo + SOC (n=107) (Trial 3, ITT population)[3,a,b]

DUPIXENT IS THE ONLY BIOLOGIC INDICATED FOR OCS-DEPENDENT ASTHMA PATIENTS[1]

TRIAL 3: 24-WEEK STUDY–210 subjects (≥12 years) with asthma who required daily OCS in addition to regular use of standard of care of high-dose ICS plus an additional controller medication were randomized to either DUPIXENT 300 mg Q2W[c] + SOC + OCS (n=103) or placebo + SOC + OCS (n=107). Subjects with baseline blood eosinophil levels >1500 cells/µL (<1.3%) were excluded. **Primary endpoint:** Percent reduction from baseline in OCS dose at Week 24, while maintaining asthma control, in the overall population. **Secondary endpoints:** Annualized rate of severe exacerbation events during the 24-week treatment period and mean change from baseline to Week 24 in FEV_1. **Selected baseline demographics:** Mean age: 51 years; female: 61%; white: 94%; mean duration of asthma: 20 years; mean exacerbations in previous year: 2.1; high-dose ICS use: 89%; pre-dose FEV_1 at baseline: 1.58 L; mean FeNO: 38 ppb; mean total IgE: 431 IU/mL; and mean baseline blood eosinophil count: 350 cells/µL.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hypersensitivity: Hypersensitivity reactions, including generalized urticaria, rash, erythema nodosum, anaphylaxis and serum sickness or serum sickness-like reactions, were reported in <1% of subjects who received DUPIXENT in clinical trials. If a clinically significant hypersensitivity reaction occurs, institute appropriate therapy and discontinue DUPIXENT.

Eosinophilic Conditions: Patients being treated for asthma may present with serious systemic eosinophilia sometimes presenting with clinical features of eosinophilic pneumonia or vasculitis consistent with eosinophilic granulomatosis with polyangiitis (EGPA), conditions which are often treated with systemic corticosteroid therapy. These events may be associated with the reduction of oral corticosteroid therapy. Physicians should be alert to vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients with eosinophilia. Cases of eosinophilic pneumonia were reported in adult patients who participated in the asthma development program and cases of vasculitis consistent with EGPA have been reported with DUPIXENT in adult patients who participated in the asthma development program as well as in adult patients with co-morbid asthma in the chronic rhinosinusitis with nasal polyposis development program. A causal association between DUPIXENT and these conditions has not been established.

Acute Asthma Symptoms or Deteriorating Disease: Do not use DUPIXENT to treat acute asthma symptoms, acute exacerbations, acute bronchospasm or status asthmaticus. Patients should seek medical advice if their asthma remains uncontrolled or worsens after initiation of DUPIXENT.

FeNO, fractional exhaled nitric oxide; ICS, inhaled corticosteroid; Q2W, once every 2 weeks.

Please see additional Important Safety Information throughout and brief summary of full Prescribing Information on the following pages.

DUPIXENT® (dupilumab) Injection
200mg · 300mg

DUPIXENT IMPROVED ASTHMA CONTROL IN OCS-DEPENDENT ASTHMA PATIENTS WHILE REDUCING THEIR OCS DOSE

59%

REDUCTION IN ANNUALIZED RATE OF SEVERE EXACERBATIONS

while reducing OCS dose at Week 24 with DUPIXENT 300 mg + SOC (n=103) vs placebo + SOC (n=107) (0.65 vs 1.60; rate ratio: 0.41 [95% CI: 0.26, 0.63]) (Trial 3, ITT population, secondary endpoint)[1,a,b,d]

220 mL

IMPROVEMENT IN PRE-BRONCHODILATOR FEV_1

while reducing OCS dose at Week 24 with DUPIXENT 300 mg + SOC (n=103) vs **10 mL** with placebo + SOC (n=107) (LSM difference: 220 mL [95% CI: 90, 340 mL]) (Trial 3, ITT population, secondary endpoint)[1,3,a,b]

- Effects on lung function and on oral steroid and exacerbation reduction were similar irrespective of baseline blood eosinophil levels[1]

70% reduction in OCS dose (median 100%) from baseline at Week 24 with DUPIXENT 300 mg + SOC (n=103) (95% CI: 60%, 80%) vs 42% (median 50%) with placebo + SOC (n=107) (Trial 3, primary endpoint).[1]

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont'd)

Reduction of Corticosteroid Dosage: Do not discontinue systemic, topical, or inhaled corticosteroids abruptly upon initiation with DUPIXENT. Reductions in corticosteroid dose, if appropriate, should be gradual and performed under the direct supervision of a physician. Reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy.

[a] ITT population was unrestricted by minimum baseline eosinophils or other Type 2 biomarkers (eg, FeNO or IgE).[3]
[b] The baseline mean OCS dose was 12 mg in the placebo group and 11 mg in the group receiving DUPIXENT.[1]
[c] With 600 mg loading dose.
[d] Asthma exacerbation was defined as a temporary increase in OCS dose for at least 3 days.

Learn more at *DupixentAsthmaHCP.com*

99.9%

OF INSURANCE PLANS REQUIRE NO BIOMARKER TESTING FOR OCS-DEPENDENT ASTHMA PATIENTS ON DUPIXENT[2]

Learn more at *DupixentAsthmaHCP.com*

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont'd)

Parasitic (Helminth) Infections: It is unknown if DUPIXENT will influence the immune response against helminth infections. Treat patients with pre-existing helminth infections before initiating therapy with DUPIXENT. If patients become infected while receiving treatment with DUPIXENT and do not respond to anti-helminth treatment, discontinue treatment with DUPIXENT until the infection resolves.

ADVERSE REACTIONS: The most common adverse reactions (incidence ≥1%) in patients with asthma are injection site reactions, oropharyngeal pain, and eosinophilia.

DRUG INTERACTIONS: Avoid use of live vaccines in patients treated with DUPIXENT.

USE IN SPECIFIC POPULATIONS

- **Pregnancy:** There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to DUPIXENT during pregnancy. Healthcare providers and patients may call 1-877-311-8972 or go to https://mothertobaby.org/ongoing-study/dupixent/ to enroll in or obtain information about the registry. Available data from case reports and case series with DUPIXENT use in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Human IgG antibodies are known to cross the placental barrier; therefore, DUPIXENT may be transmitted from the mother to the developing fetus.
- **Lactation:** There are no data on the presence of DUPIXENT in human milk, the effects on the breastfed infant, or the effects on milk production. Maternal IgG is known to be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for DUPIXENT and any potential adverse effects on the breastfed child from DUPIXENT or from the underlying maternal condition.

References: 1. DUPIXENT Prescribing Information. **2.** UnitedHealthcare. *UnitedHealthcare Pharmacy Clinical Pharmacy Programs.* 2019. **3.** Rabe KF, Nair P, Brusselle G, et al. Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. *N Engl J Med.* 2018;378(26):2475-2485.

Please see brief summary of full Prescribing Information on the following pages.

DUPIXENT® (dupilumab) Injection
200mg · 300mg

SANOFI GENZYME

REGENERON

DUP.20.07.0632 09/2020

DUPIXENT® (dupilumab) injection, for subcutaneous use Rx Only
Brief Summary of Prescribing Information

1 INDICATIONS AND USAGE

1.1 Asthma

DUPIXENT is indicated as an add-on maintenance treatment in patients with moderate-to-severe asthma aged 12 years and older with an eosinophilic phenotype or with oral corticosteroid dependent asthma.

Limitation of Use

DUPIXENT is not indicated for the relief of acute bronchospasm or status asthmaticus.

4 CONTRAINDICATIONS

DUPIXENT is contraindicated in patients who have known hypersensitivity to dupilumab or any of its excipients *[see Warnings and Precautions (5.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity

Hypersensitivity reactions, including generalized urticaria, rash, erythema nodosum and serum sickness or serum sickness-like reactions, were reported in less than 1% of subjects who received DUPIXENT in clinical trials. Two subjects in the atopic dermatitis development program experienced serum sickness or serum sickness-like reactions that were associated with high titers of antibodies to dupilumab. One subject in the asthma development program experienced anaphylaxis *[see Adverse Reactions (6.2)]*. If a clinically significant hypersensitivity reaction occurs, institute appropriate therapy and discontinue DUPIXENT *[see Adverse Reactions (6.1, 6.2)]*.

5.3 Eosinophilic Conditions

Patients being treated for asthma may present with serious systemic eosinophilia sometimes presenting with clinical features of eosinophilic pneumonia or vasculitis consistent with eosinophilic granulomatosis with polyangiitis, conditions which are often treated with systemic corticosteroid therapy. These events may be associated with the reduction of oral corticosteroid therapy. Physicians should be alert to vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients with eosinophilia. Cases of eosinophilic pneumonia were reported in adult patients who participated in the asthma development program and cases of vasculitis consistent with eosinophilic granulomatosis with polyangiitis have been reported with DUPIXENT in adult patients who participated in the asthma development program, as well as in adult patients with comorbid asthma in the CRSwNP development program. A causal association between DUPIXENT and these conditions has not been established.

5.4 Acute Asthma Symptoms or Deteriorating Disease

DUPIXENT should not be used to treat acute asthma symptoms or acute exacerbations. Do not use DUPIXENT to treat acute bronchospasm or status asthmaticus. Patients should seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment with DUPIXENT.

5.5 Reduction of Corticosteroid Dosage

Do not discontinue systemic, topical, or inhaled corticosteroids abruptly upon initiation of therapy with DUPIXENT. Reductions in corticosteroid dose, if appropriate, should be gradual and performed under the direct supervision of a physician. Reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy.

5.7 Parasitic (Helminth) Infections

Patients with known helminth infections were excluded from participation in clinical studies. It is unknown if DUPIXENT will influence the immune response against helminth infections. Treat patients with pre-existing helminth infections before initiating therapy with DUPIXENT. If patients become infected while receiving treatment with DUPIXENT and do not respond to antihelminth treatment, discontinue treatment with DUPIXENT until the infection resolves.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail elsewhere in the labeling:

- Hypersensitivity *[see Warnings and Precautions (5.1)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Asthma

A total of 2888 adult and adolescent subjects with moderate-to-severe asthma (AS) were evaluated in 3 randomized, placebo-controlled, multicenter trials of 24 to 52 weeks duration (AS Trials 1, 2, and 3). Of these, 2678 had a history of 1 or more severe exacerbations in the year prior to enrollment despite regular use of medium- to high-dose inhaled corticosteroids plus an additional controller(s) (AS Trials 1 and 2). A total of 210 subjects with oral corticosteroid-dependent asthma receiving high-dose inhaled corticosteroids plus up to two additional controllers were enrolled (AS Trial 3). The safety population (AS Trials 1 and 2) was 12-87 years of age, of which 63% were female and 82% were white. DUPIXENT 200 mg or 300 mg was administered subcutaneously Q2W, following an initial dose of 400 mg or 600 mg, respectively.

In AS Trials 1 and 2, the proportion of subjects who discontinued treatment due to adverse events was 4% of the placebo group, 3% of the DUPIXENT 200 mg Q2W group, and 6% of the DUPIXENT 300 mg Q2W group.

Table 3 summarizes the adverse reactions that occurred at a rate of at least 1% in subjects treated with DUPIXENT and at a higher rate than in their respective comparator groups in Asthma Trials 1 and 2.

Table 3: Adverse Reactions Occurring in ≥1% of the DUPIXENT Groups in Asthma Trials 1 and 2 and Greater than Placebo (6-Month Safety Pool)

Adverse Reaction	AS Trials 1 and 2		
	DUPIXENT 200 mg Q2W N=779 n (%)	DUPIXENT 300 mg Q2W N=788 n (%)	Placebo N=792 n (%)
Injection site reactions[a]	111 (14%)	144 (18%)	50 (6%)
Oropharyngeal pain	13 (2%)	19 (2%)	7 (1%)
Eosinophilia[b]	17 (2%)	16 (2%)	2 (<1%)

[a] Injection site reactions cluster includes erythema, edema, pruritus, pain, and inflammation.

[b] Eosinophilia = blood eosinophils ≥3,000 cells/mcL, or deemed by the investigator to be an adverse event. None met the criteria for serious eosinophilic conditions *[see Section 5.3 Warnings and Precautions]*.

Injection site reactions were most common with the loading (initial) dose. The safety profile of DUPIXENT through Week 52 was generally consistent with the safety profile observed at Week 24.

Specific Adverse Reactions:

Hypersensitivity Reactions

Hypersensitivity reactions were reported in <1% of DUPIXENT-treated subjects. These included serum sickness reaction, serum sickness-like reaction, generalized urticaria, rash, erythema nodosum, and anaphylaxis *[see Contraindications (4), Warnings and Precautions (5.1), and Adverse Reactions (6.2)]*.

Eosinophils

DUPIXENT-treated subjects had a greater initial increase from baseline in blood eosinophil count compared to subjects treated with placebo. In subjects with atopic dermatitis, the mean and median increases in blood eosinophils from baseline to Week 4 were 100 and 0 cells/mcL, respectively. In subjects with asthma, the mean and median increases in blood eosinophils from baseline to Week 4 were 130 and 10 cells/mcL, respectively. The incidence of treatment-emergent eosinophilia (≥500 cells/mcL) was similar in DUPIXENT and placebo groups. Treatment-emergent eosinophilia (≥5,000 cells/mcL) was reported in <2% of DUPIXENT-treated patients and <0.5% in placebo-treated patients. Blood eosinophil counts declined to near baseline levels during study treatment *[see Warnings and Precautions (5.3)]*.

Cardiovascular (CV)

In the 1-year placebo-controlled trial in subjects with asthma (AS Trial 2), CV thromboembolic events (CV deaths, nonfatal myocardial infarctions [MI], and nonfatal strokes) were reported in 1 (0.2%) of the DUPIXENT 200 mg Q2W group, 4 (0.6%) of the DUPIXENT 300 mg Q2W group, and 2 (0.3%) of the placebo group.

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to dupilumab in the studies described that follow, with the incidence of antibodies in other studies or to other products, may be misleading. Approximately 5% of subjects with atopic dermatitis, asthma, or CRSwNP who received DUPIXENT 300 mg Q2W for 52 weeks developed antibodies to dupilumab; ~2% exhibited persistent ADA responses, and ~2% had neutralizing antibodies. Approximately 9% of subjects with asthma who received DUPIXENT 200 mg Q2W for 52 weeks developed antibodies to dupilumab; ~4% exhibited persistent ADA responses, and ~4% had neutralizing antibodies.

Approximately 4% of subjects in the placebo groups in the 52-week studies were positive for antibodies to DUPIXENT; approximately 2% exhibited persistent ADA responses, and approximately 1% had

neutralizing antibodies.

Approximately 16% of adolescent subjects with atopic dermatitis who received DUPIXENT 300 mg or 200 mg Q2W for 16 weeks developed antibodies to dupilumab; approximately 3% exhibited persistent ADA responses, and approximately 5% had neutralizing antibodies.

Approximately 4% of adolescent subjects with atopic dermatitis in the placebo group were positive for antibodies to DUPIXENT; approximately 1% exhibited persistent ADA responses, and approximately 1% had neutralizing antibodies.

The antibody titers detected in both DUPIXENT and placebo subjects were mostly low. In subjects who received DUPIXENT, development of high titer antibodies to dupilumab was associated with lower serum dupilumab concentrations *[see Clinical Pharmacology (12.3) in the full prescribing information]*.

Two subjects who experienced high titer antibody responses developed serum sickness or serum sickness-like reactions during DUPIXENT therapy *[see Warnings and Precautions (5.1)]*.

7 DRUG INTERACTIONS

7.1 Live Vaccines

Avoid use of live vaccines in patients treated with DUPIXENT.

7.2 Non-Live Vaccines

Immune responses to vaccination were assessed in a study in which subjects with atopic dermatitis were treated once weekly for 16 weeks with 300 mg of dupilumab (twice the recommended dosing frequency). After 12 weeks of DUPIXENT administration, subjects were vaccinated with a Tdap vaccine (Adacel®) and a meningococcal polysaccharide vaccine (Menomune®). Antibody responses to tetanus toxoid and serogroup C meningococcal polysaccharide were assessed 4 weeks later. Antibody responses to both tetanus vaccine and meningococcal polysaccharide vaccine were similar in dupilumab-treated and placebo-treated subjects. Immune responses to the other active components of the Adacel and Menomune vaccines were not assessed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to DUPIXENT during pregnancy. Please call 1-877-311-8972 or go to https://mothertobaby.org/ongoing-study/dupixent/ to enroll in or to obtain information about the registry.

Risk Summary

Available data from case reports and case series with DUPIXENT use in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Human IgG antibodies are known to cross the placental barrier; therefore, DUPIXENT may be transmitted from the mother to the developing fetus. There are adverse effects on maternal and fetal outcomes associated with asthma in pregnancy *(see Clinical Considerations)*. In an enhanced pre- and post-natal developmental study, no adverse developmental effects were observed in offspring born to pregnant monkeys after subcutaneous administration of a homologous antibody against interleukin-4-receptor alpha (IL-4Rα) during organogenesis through parturition at doses up to 10 times the maximum recommended human dose (MRHD) *(see Data)*. The estimated background risk of major birth defects and miscarriage for the indicated populations are unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo-fetal Risk

In women with poorly or moderately controlled asthma, evidence demonstrates that there is an increased risk of preeclampsia in the mother and prematurity, low birth weight, and small for gestational age in the neonate. The level of asthma control should be closely monitored in pregnant women and treatment adjusted as necessary to maintain optimal control.

Data

Animal Data

In an enhanced pre- and post-natal development toxicity study, pregnant cynomolgus monkeys were administered weekly subcutaneous doses of homologous antibody against IL-4Rα up to 10 times the MRHD (on a mg/kg basis of 100 mg/kg/week) from the beginning of organogenesis to parturition. No treatment-related adverse effects on embryo-fetal toxicity or malformations, or on morphological, functional, or immunological development were observed in the infants from birth through 6 months of age.

8.2 Lactation

Risk Summary

There are no data on the presence of dupilumab in human milk, the effects on the breastfed infant, or the effects on milk production. Maternal IgG is known to be present in human milk. The effects of local gastrointestinal and limited systemic exposure to dupilumab on the breastfed infant are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for DUPIXENT and any potential adverse effects on the breastfed child from DUPIXENT or from the underlying maternal condition.

8.4 Pediatric Use

Asthma

A total of 107 adolescents aged 12 to 17 years with moderate-to-severe asthma were enrolled in AS Trial 2 and received either 200 mg (N=21) or 300 mg (N=18) DUPIXENT (or matching placebo either 200 mg [N=34] or 300 mg [N=34]) Q2W. Asthma exacerbations and lung function were assessed in both adolescents and adults. For both the 200 mg and 300 mg Q2W doses, improvements in FEV_1 (LS mean change from baseline at Week 12) were observed (0.36 L and 0.27 L, respectively). For the 200 mg Q2W dose, subjects had a reduction in the rate of severe exacerbations that was consistent with adults. Safety and efficacy in pediatric patients (<12 years of age) with asthma have not been established. Dupilumab exposure was higher in adolescent patients than that in adults at the respective dose level, which was mainly accounted for by difference in body weight *[see Clinical Pharmacology (12.3) in the full prescribing information]*.

The adverse event profile in adolescents was generally similar to the adults *[see Adverse Reactions (6.1)]*.

8.5 Geriatric Use

Of the 1977 subjects with asthma exposed to DUPIXENT, a total of 240 subjects were 65 years or older. Efficacy and safety in this age group was similar to the overall study population.

10 OVERDOSE

There is no specific treatment for DUPIXENT overdose. In the event of overdosage, monitor the patient for any signs or symptoms of adverse reactions and institute appropriate symptomatic treatment immediately.

17 PATIENT COUNSELING INFORMATION

Advise the patients and/or caregivers to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Pregnancy Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to DUPIXENT during pregnancy. Encourage participation in the registry *[see Use in Specific Populations (8.1)]*.

Administration Instructions

Provide proper training to patients and/or caregivers on proper subcutaneous injection technique, including aseptic technique, and the preparation and administration of DUPIXENT prior to use. Advise patients to follow sharps disposal recommendations.

Hypersensitivity

Advise patients to discontinue DUPIXENT and to seek immediate medical attention if they experience any symptoms of systemic hypersensitivity reactions *[see Warnings and Precautions (5.1)]*.

Eosinophilic Conditions

Advise patients to notify their healthcare provider if they present with clinical features of eosinophilic pneumonia or vasculitis consistent with eosinophilic granulomatosis with polyangiitis *[see Warnings and Precautions (5.3)]*.

Not for Acute Asthma Symptoms or Deteriorating Disease

Inform patients that DUPIXENT does not treat acute asthma symptoms or acute exacerbations. Inform patients to seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment with DUPIXENT *[see Warnings and Precautions (5.4)]*.

Reduction in Corticosteroid Dosage

Inform patients to not discontinue systemic or inhaled corticosteroids except under the direct supervision of a physician. Inform patients that reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy *[see Warnings and Precautions (5.5)]*.

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