DynamicEd™ Expert Review of the Safety and Efficacy of Emerging Therapies

BACKGROUND & OVERVIEW

Chronic Obstructive Pulmonary Disease (COPD) remains a significant health challenge globally, with high rates of morbidity and mortality. Despite the availability and uptake of standard treatments, many patients continue to experience significant unmet needs.

Current COPD treatments aim to reduce symptoms, improve lung function, and prevent exacerbations but face limitations like burdensome side effects and the inability to modify disease progression significantly.

- **Bronchodilators** provide symptom relief but don't address underlying inflammation.
- **Inhaled corticosteroids** can increase pneumonia risk, especially in older adults.
- **Combination inhalers** can be challenging to adhere to.
- **Phosphodiesterase 4 inhibitors** are reserved for severe COPD with chronic bronchitis.
- **Methylxanthines** have many drug interactions, complicating management in polypharmacy patients.

Additionally, standard therapies may not consistently reduce exacerbations across all COPD phenotypes, highlighting the challenge of individualized treatment.[1]

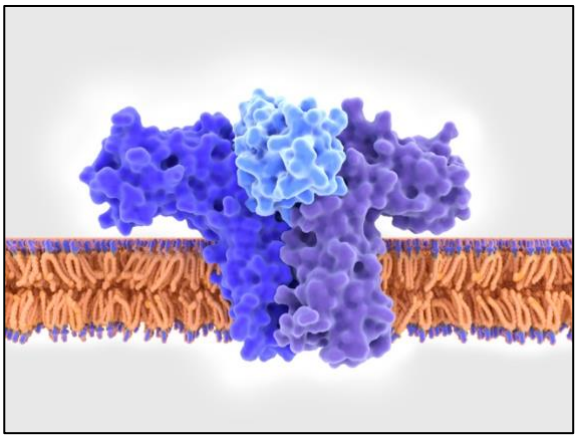
Emerging therapies, particularly biologics, offer the potential to target specific inflammatory pathways involved in COPD, providing more personalized and effective treatment options. This educational activity, in conjunction with expert **Dr. Stephanie Christenson, M.D.**, focuses on the latest clinical trials and emerging therapies for COPD.

By the end of this activity, you will better be able to:

1. Understand the safety and efficacy of new and emerging therapies for COPD.
2. Apply knowledge from recent clinical trials to improve patient outcomes.

*Disclosures: This educational activity was developed from a grant sponsored by Regeneron Pharmaceuticals.

REFRESHER: NEW BIOLOGICS TARGET KEY INFLAMMATORY PATHWAYS



COPD pathogenesis involves complex inflammatory processes, with type 2 inflammation playing a critical role in many patients. In fact, evidence of type 2 inflammation is present in 20-40% of patients with COPD and is associated with an increased risk of exacerbations.[2]

Key cytokines such as interleukins IL-4, IL-5, IL-13, type 2 innate lymphoid cells, and type 2 helper T cells are central to the type 2 inflammatory response, contributing to eosinophilia, mucus hypersecretion, and IgE class switching in B cells. The new GOLD guidelines now recognize elevated blood eosinophilia as a clinically useful biomarker in identifying COPD with type 2 inflammation.

(Figure 1)[5]: Biologics targeting type 2 inflammation pathways, such as IL-4 in the image, are potential treatment options. Several clinical trials are ongoing to explore the efficacy and safety of biologics in COPD management. *

Expert Insights by Dr. Christenson: *"Addressing type 2 inflammation in COPD represents a significant advancement in treatment. By targeting specific cytokines such as IL-4 and IL-13, biologics like Dupilumab could offer more tailored and effective options for managing COPD in clinical practice."*

* Please review our accompanying activity for more information on COPD's type 2 inflammatory pathway. “Taking a deep breath: A curriculum for current and emerging strategies for optimizing COPD treatment.”

WHAT ARE THE EMERGING THERAPIES IN COPD CARE?

Here, we discuss several biologics approved or developed for COPD treatment.

Dupixent (dupilumab)

Dupulimab is a monoclonal antibody that blocks the IL-4 receptor alpha subunit, which inhibits IL-4 and IL-13 signaling, crucial drivers of type 2 inflammation.

(Figure 2)[4]: Dupilumab has shown promise in reducing exacerbations and improving lung function in patients with COPD with elevated eosinophil counts.

HORIZONCME

Efficacy Data of Dupilumab (DUPIXENT) in COPD Treatment

Trials: **BOREAS**[2], **NOTUS**[3]
Status: FDA Priority Review as of June 03, 2024

Inclusion Criteria: In Phase 3 double-blinded randomized **BOREAS** and **NOTUS** trials, patients with COPD **40-80 years** of age diagnosed for at least 12 months before screening (with FEV1<0.70 and blood eosinophil count ≥300/µL) who were current or ex-**smokers** (≥10 pack-year history) with ≥2 moderate or ≥1 severe **exacerbation** and on **triple therapy** for >3 months were randomly assigned 1:1 to receive add-on therapy of either **dupilumab 300mg** subcutaneously or placebo.

Outcomes: **In both trials**, the primary endpoint was the annualized moderate or severe **exacerbation rate.** In the **BOREAS** trial, the exacerbation rate was significantly lower in the dupilumab group (HR 0.78, CI 0.64-0.93) compared to placebo (HR 1.1, CI 0.93-1.3). In the **NOTUS** trial, the exacerbation rate was also significantly lower in the dupilumab group (HR 0.86, CI 0.7-1.06) compared to placebo (HR 1.3, CI 0.54-0.82).

In both trials, key secondary outcomes included **improved prebronchodilator FEV1** within 2 weeks of therapy, **improvement in symptom burden** and **health-related quality of life** scores (defined using SGRQ and E-RS-COPD scores), improvement which were all observed and sustained until week 52. In the **BOREAS** trial, prebronchodilator FEV1 change was 160ml in the dupilumab group vs 77ml in the placebo group. In the **NOTUS** trial, the prebronchodilator FEV1 change was 139ml in the dupilumab group vs 57ml in the placebo group.

Clinical Takeaways:

- Improvements in COPD symptoms with dupilumab in patients with **high immune responses** confirm the significant **role of IL-4 and IL-13** in exacerbations and symptom burden among type 2 inflammatory contributors.
- The trial's **reduction in exacerbations** and **improved lung function** offer a promising solution for the high unmet needs of patients with uncontrolled COPD.
- **Safety** – Common adverse events **in both trials** included nasopharyngitis, upper respiratory tract infections, and headaches.
    - In the **BOREAS** trial, 95.1% of patients on dupilumab and 93.4% of placebo completed the 52-week period. Serious adverse events occurred in 13.6% of the dupilumab group vs 15.5% in the placebo group, with death rates of 1.5% and 1.7% respectively.
    - In the **NOTUS** trial, overall rates of adverse events were 67% for dupilumab and 66% for placebo. Adverse events leading to deaths were 2.6% for dupilumab and 1.5% for placebo.

> ***Expert Insights by Dr. Christenson:*** *The results from the BOREAS and NOTUS trials are particularly exciting. Dupilumab's significant reduction in exacerbations and improvements in lung function represents a breakthrough for patients struggling with the burdens of COPD. In my practice, I can see it becoming an essential part of our therapeutic arsenal, particularly for our subset of COPD patients who continue to experience debilitating effects despite exhausting multiple options.*

NUCALA (mepolizumab)

Mepolizumab targets IL-5, a cytokine involved in the growth and activation of eosinophils. By reducing eosinophil levels, mepolizumab aims to decrease the frequency of COPD exacerbations.

- **Trials: METREX[6], METREO[6]**
  Status: Phase III clinical trials are ongoing.

- **Inclusion Criteria:**
  - Age ≥40 years
  - **History of moderate or severe exacerbations** while on inhaled glucocorticoid-based triple-maintenance therapy
  - Patients were stratified based on blood **eosinophil** count ≥150 cells/μL at screening or ≥300 cells/μL in the previous year
  - Evaluated **mepolizumab 100mg or 300mg subcutaneously** or placebo every 4 weeks
- **Outcomes:**
  - In **METREX**, the annual rate of moderate or severe **exacerbations** was lower in the mepolizumab group (1.40 per year) compared to placebo (1.71 per year) with a rate ratio of 0.82 (95% CI, 0.68 to 0.98; P=0.04) among patients with an eosinophilic phenotype.
  - In **METREO**, the **exacerbation** rate was 1.19 per year in the 100-mg mepolizumab group, 1.27 per year in the 300-mg group, and 1.49 per year in the placebo group. The rate ratios were 0.80 (95% CI, 0.65 to 0.98; P=0.07) for the 100-mg group and 0.86 (95% CI, 0.70 to 1.05; P=0.14) for the 300-mg group.
  - **Safety:** The safety profile of mepolizumab was similar to that of placebo, with no significant differences in adverse events. Common side effects included headaches, injection site reactions, upper respiratory tract infections, back pain, fatigue, and diarrhea.
    - In the **METREX** trial, 80% of patients in the mepolizumab 100 mg group and 82% in the placebo group experienced adverse events, with serious adverse events in 28% and 31% of patients, respectively.
    - In the **METREO** trial, adverse events were reported in 86% (100 mg group), 87% (300 mg group), and 82% (placebo group), with serious adverse events in 26%, 27%, and 30% of patients, respectively, showing a similar safety profile to placebo.

Clinical Takeaways:

- Mepolizumab significantly **reduced the annual rate of moderate or severe exacerbations** in COPD patients with an eosinophilic phenotype.
- The efficacy was particularly pronounced in patients with **higher baseline blood eosinophil counts**, indicating the role of eosinophilic inflammation in COPD exacerbations.

FASENRA (benralizumab)

Benralizumab is another IL-5 inhibitor that induces apoptosis of eosinophils and basophils. It has been evaluated in smokers and ex-smokers with moderate to severe COPD.

- **Trials: GALATHEA[7], TERRANOVA[7], RESOLUTE (Ongoing)**
  Status: Phase III clinical trials recruiting and planned for completion June 2025.

- **Inclusion Criteria:**
  - Patients with moderate to very severe **COPD**
  - Frequent **exacerbations** despite receiving guideline-based inhaled treatment.
  - Stratification based on blood **eosinophil** count (≥220 cells/μL vs. <220 cells/μL)
  - Evaluated **benralizumab 30mg or 100 mg** subcutaneously vs placebo every 8 weeks

- **Outcomes:**
  - In the **GALATHEA** trials, annualized **exacerbation** rates were 1.19 per year (30 mg group), 1.03 per year (100 mg group), and 1.24 per year (placebo group). Rate ratios compared with placebo: 0.96 (30 mg, P=0.65) and 0.83 (100 mg, P=0.05)
  - In the **TERRANOVA** trials, annualized **exacerbation** rates were 0.99 per year (10 mg group), 1.21 per year (30 mg group), 1.09 per year (100 mg group), and 1.17 per year (placebo group). Rate ratios compared with placebo: 0.85 (10 mg, P=0.06), 1.04 (30 mg, P=0.66), and 0.93 (100 mg, P=0.40)
  - None of the annualized COPD exacerbation rate ratios for any dose of benralizumab reached significance in either trial.
  - **Safety:** In these trials, the most common adverse events for benralizumab were consistent with its known safety profile and included nasopharyngitis, upper respiratory tract infections, and worsening COPD. Serious adverse events occurred at similar rates in the benralizumab and placebo groups, indicating no new safety concerns. Adverse events were observed in about 75-78% of patients across both trials.

Clinical Takeaways:

- Benralizumab **did not achieve a statistically significant** reduction in the annualized rate of COPD exacerbations compared to placebo in either trial. While there was a trend towards improvement in the 100 mg dose group in the **GALATHEA** trial, this did not reach statistical significance.
- The efficacy **varied across different doses**, with the 100 mg dose showing a potential, albeit non-significant, benefit in exacerbation reduction.

- **This has led** to the initiation of the phase 3 **RESOLUTE** clinical trial, which has recruited over 600 patients with COPD and is expected to end in June 2025.

TEZSPIRE (Tezepelumab)

Tezepelumab is a monoclonal antibody targeting thymic stromal lymphopoietin (TSLP), and it has shown potential in treating moderate to very severe COPD across a broad range of blood eosinophil counts.

- **Trial:** COURSE[8]
  Status: Phase IIa clinical trial completed and presented at the American Thoracic Society on May 20, 2024.

- **Inclusion Criteria:**
  - Adults with moderate to very severe **COPD**
  - Receiving triple inhaled maintenance therapy
  - History of two or more documented COPD **exacerbations** in the 12 months prior to the trial
  - Evaluated **Tezepelumab 420mg** subcutaneously every 4 weeks vs placebo

- **Outcomes:**
  - **Overall Population:** 17% numerical reduction in the annual rate of moderate or severe COPD **exacerbations** compared to placebo (1.75 vs. 2.11 per year), which was **not statistically significant** (90% CI: -6, 36; P [1-sided] =0.1042).
  - **BEC ≥150 cells/µL:** Nominally significant **37% reduction in moderate or severe exacerbations** compared to placebo (1.52 vs. 2.40 per year).
  - **BEC ≥300 cells/µL:** 46% numerical reduction in moderate or severe exacerbations (1.20 vs. 2.24 per year).
  - **Lung Function: Improvement in FEV1** of 63 mL (BEC ≥150 cells/µL) and 146 mL (BEC ≥300 cells/µL) compared to placebo.
  - **Quality of Life**: **Improvement in SGRQ scores** by 4.2 points (BEC ≥150 cells/µL) and 9.5 points (BEC ≥300 cells/µL).

Clinical Takeaways:

- Tezepelumab demonstrated a numerical **reduction** in the rate of moderate or severe COPD **exacerbations**, with greater efficacy observed in patients with higher BEC.
- Notable improvements in **lung function** and **quality of life** were observed, particularly in patients with higher BEC.
- **Safety:** The safety and tolerability profile of tezepelumab was consistent with its use in severe asthma, showing no new safety concerns. Consistent with the approved severe asthma indication, the most frequently reported adverse events were worsening of COPD (12.1%) and COVID-19 infections (14.5%).

HORIZONCME

Itepekimab

Itepekimab is a monoclonal antibody targeting IL-33, a pro-inflammatory cytokine localized to the nuclei of different cell types and implicated in asthma and potentially in COPD. When airway epithelial cells are exposed to airborne particles, including pollutants or allergens, IL-33 is released and is proposed to imitate both type 1 and type 2 inflammation.

- **Trial:** AERIFY-1/2[9]
  Status: Phase III clinical trials are ongoing; anticipated completion is in October 2025.

- **Inclusion Criteria:**
  - Patients aged **40–75** years
  - Current or former **smokers**
  - Diagnosed with **COPD** for at least 1 year.
  - On stable triple-inhaled or double-inhaled maintenance therapy
  - Evaluated **itepekimab 300mg** subcutaneously dosed as 2 injections every 2 weeks vs placebo
- **Outcomes:**
  - The primary endpoint was the annualized rate of moderate-to-severe acute **exacerbations** of COPD. The annualized rate of acute exacerbations was 1.30 in the itepekimab group versus 1.61 in the placebo group (RR 0.81, 95% CI 0.61–1.07, p=0.13).
  - The secondary endpoint was a change in **prebronchodilator FEV1** from baseline to weeks 16–24. The least squares mean change from baseline to weeks 16–24 was 0.06 L in the itepekimab group versus 0.0 L in the placebo group (difference 0.06 L, 95% CI 0.01–0.10, p=0.024).
  - **Former Smokers: Significant reductions** in acute **exacerbations** (RR 0.58, 95% CI 0.39–0.85, p=0.0061) and FEV1 improvement (least squares mean difference 0.09 L, 95% CI 0.02–0.15, p=0.0076) compared to placebo.
  - **Current Smokers**: **No significant benefit** in exacerbations (RR 1.09, 95% CI 0.74–1.61, p=0.65) or FEV1 (least squares mean difference 0.02, 95% CI −0.05 to 0.09, p=0.54).

Clinical Takeaways:

- In phase IIa trials, Itepekimab reduced **exacerbation** rates and **improved** lung function **significantly** in former smokers with COPD, although it did not meet the primary endpoint in the overall population.
  - The subgroup analysis highlights a potential benefit for former smokers, suggesting IL-33 inhibition could be particularly effective for this group.
- **Safety:** The safety profile of itepekimab was similar to that of placebo, with common TEAEs, including respiratory infections and headaches.

Expert Insights by Dr. Christenson: *"Emerging biologics like mepolizumab, benralizumab, tezepelumab, and itepekimab offer promising COPD treatments, showing varied efficacy in reducing exacerbations and improving lung function, particularly in patients with high eosinophil counts or former smokers. These therapies, with favorable safety profiles, could significantly enhance COPD management pending further validation. With further research and potential approval on the horizon, clinicians should stay updated on these developments to enhance COPD management."*

SUMMARY

The emergence of biologics offers a promising new frontier in COPD management. By targeting specific inflammatory pathways, these therapies provide a more personalized approach, potentially reducing exacerbations and improving the quality of life for patients who do not respond adequately to traditional treatments. In several clinical trials spanning different biologic therapies in development, exacerbations, and hospitalizations were reduced in the time following the initiation of these therapies.

However, the success of these therapies hinges on identifying the right patient populations and understanding the underlying mechanisms driving their disease. Furthermore, research is still needed to guide clinicians in tapering or weaning down biological treatment and determining whether patients need inhalers.

As clinical trials continue to elucidate these biologics' efficacy and safety profiles, clinicians must stay informed and consider these options for their patients.

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