About the Author

Manali Mukherjee, MD

Dr. Mukherjee is an Assistant Professor in the Division of Respirology, Department of Medicine, and a translational scientist affiliated with the Research Institute of St. Joe's, Hamilton. She has demonstrated expertise in investigating inflammatory mechanisms of chronic respiratory diseases, in particular autoimmunity, response to treatment and development/validation of clinical biomarkers. Her research has identified the presence of localized autoimmune responses in the airways of patients with complex airways disease and determined their pathogenic role in driving disease severity. Recently, she has identified autoimmune responses in acute-severe COVID and linked autoimmunity with post-acute COVID-19 sequelae (or Long COVID). In the field of respiratory medicine, she published ~65 manuscripts, and in the past 5 years these have accumulated >2500 citations (*Google Scholar h-index 24, i10-index 40*). Dr. Mukherjee's research program focuses on "Lung autoimmunity and biomarkers". She is the past recipient of the Emerging Researcher Award in Allergic Asthma awarded conjointly by the Canadian Institutes of Health Research (CIHR) and the Canadian Asthma, Allergy and Immunology Foundation (CAAIF). Her lab is funded by federal and non-federal sources including CIHR-ICRH and industry. Dr. Mukherjee was recently named the AstraZeneca Chair in Respiratory Diseases (2023-2028).

Affiliations: Assistant Professor of Medicine, Division of Respirology, McMaster University (primary), Hamilton, ON
Affiliate Scientist, The Research Institute, St. Joseph's Healthcare, Hamilton, ON
Associate Member, McMaster Immunology Research Center, McMaster University, Hamilton, ON
Associate Member, Biochemistry and Biomedical Sciences, McMaster University, Hamilton, ON

Pearls from the 2024 European Respiratory Congress

Manali Mukherjee, MD

Introduction

The European Respiratory Congress 2024, held from September 7th to 11th, 2024, in Vienna, Austria, featured several presentations on airway diseases, interstitial lung diseases, bronchiectasis, and critical care, with a focus on emerging therapies, particularly on asthma and chronic obstructive pulmonary disease (COPD).

I. "*Treating eosinophilic exacerbations of asthma and COPD with benralizumab: The Acute exacerbations treated with BenRAlizumab trial (ABRA) study*" was presented in the Abstracts Leading to Evolution in Respiratory Medicine Trials (ALERT:2) session titled "*Fighting the burden of asthma and respiratory symptoms.*" The session was chaired by Drs Richard Costello and Kristin Walter. The study was presented by its senior author **Dr. Mona Bafadhel**.

More than 4 million people die of acute exacerbations of asthma and COPD worldwide every year. For the past 60 years the standard of care for acute exacerbations has remained unchanged, i.e., prednisolone, despite its well-known severe long-lasting side effects. Since eosinophilic infiltration plays a significant role in acute exacerbations of asthma and COPD, blocking the key T2 inflammatory pathway would be beneficial.[1,2] Benralizumab, a humanized monoclonal antibody against interleukin (IL)-5 receptor-α, is approved at a 30 mg subcutaneous dose. It has been shown to deplete eosinophils in blood and sputum, as well as reduce T2 cytokines.[3-6] Therefore, in the multi-centre, double-blind, double-dummy, active-comparator, placebo-controlled randomized controlled ABRA trial, the authors tested the hypothesis that a single injection of benralizumab administered during an acute eosinophilic exacerbation, either alone or in combination with prednisolone, will improve clinical outcomes compared with prednisolone, the standard of care.

Adults diagnosed with COPD/asthma at the time of acute exacerbations, with blood eosinophil counts of ≥300 cells per µL, were randomly assigned in a 1:1:1 ratio to receive acute treatment with:

Arm 1: prednisolone 30 mg once daily for 5 days and a single 100 mg benralizumab subcutaneous injection (BENRA plus PRED group)

Arm 2: placebo tablets once daily for 5 days, and a single 100 mg benralizumab subcutaneous injection (BENRA group), or

Arm 3: prednisolone 30 mg once daily for 5 days, and placebo subcutaneous injection (PRED group).

Co-primary outcomes:

Total visual analogue scale (VAS) symptoms at Day 28 and treatment failure rates (deaths, hospitalizations and retreatment) over 90 Days

Results:

A total of 158 patients were recruited, of whom 55% were diagnosed with asthma, 32% with COPD, and 12% with both. Blood eosinophil counts and fractional exhaled nitric oxide (FeNO) were raised in all 3 arms and comparable at baseline. At 90 days, treatment failures occurred in 39 (74%) of 53 participants in the PRED group (Arm 3), and 47 (45%) of 105 participants in the pooled-BENRA (Arms 1 and 2) group (OR 0.26; p=0.0005). The 28-day total VAS (mean difference of 49 mm; p=0.0065) favoured the pooled-BENRA group. Benralizumab, administered at a higher one-time administration dose of 100 mg (subcutaneous), was well tolerated, with no fatal adverse events reported, and an overall improvement in quality of life questionnaires.

Main takeaway message

1. By depleting eosinophils (and other IL-5R+ cells), benralizumab is more effective than the current standard treatment (oral corticosteroids, such as prednisolone) in the event of an exacerbation.

2. Patients receiving benralizumab had fewer treatment failures and required less additional treatment compared to those on standard steroid therapy. The number needed to treat (NNT) for benralizumab was 4. The NNT for prednisolone to prevent treatment failure in COPD is 9, and to prevent hospitalizations in asthma is approximately 8.7.

3. Potential game-changer: benralizumab could revolutionize the management of asthma and COPD exacerbations, offering a more effective and safer alternative to steroids.

The study has now been published in *The Lancet Respiratory Medicine*,[8] accompanied by an editorial from Drs Donald Sin and Clarus Leung.[9] It has received significant press and media attention given its potential impact on the clinical management of asthma and COPD exacerbations.

II. *"Depemokimab efficacy/safety in patients with asthma on medium/high-dose ICS: The Phase IIIA randomized SWIFT-1/2 studies"* was presented in the Abstracts Leading to Evolution in Respiratory Medicine Trials (ALERT:2) session titled "*Fighting the burden of asthma and respiratory symptoms.*" The session was chaired by Drs Richard Costello and Kristin Walter. The study was presented by its senior author **Dr. David Jackson.**

Type 2 inflammation is pivotal to asthma pathophysiology, supporting the current pipeline of 6 monoclonal antibodies approved for treating eosinophilic asthma. Notably, these treatments have been shown to reduce blood eosinophils, symptoms, and exacerbations.[10] IL-5 remains central to eosinophil biology. Depemokimab (GSK3511294) is a novel humanized IgG_1 anti-IL-5 monoclonal antibody, similar to its predecessor mepolizumab, which neutralizes free IL-5. However, compared to mepolizumab (monthly dosing), depemokimab has an amino acid modification (YTE modification) in its Fc region that extends its half-life, allowing for biannual dosing.[11] Dr. Jackson presented the results from the 2 parallel Phase III randomized, placebo-controlled studies, SWIFT1 and SWIFT2, which reported the efficacy of depemokimab.

Results:

In the 2 trials, 732 patients with severe eosinophilic asthma (physician diagnosis of ≥2 years) received 100 mg of depemokimab subcutaneously every 6 months over a 52-week period. Both trials met their primary endpoint, showing a statistically significant reduction in the annualized exacerbation rate by 58% in SWIFT-1 and 48% in SWIFT-2 compared to placebo (in total 54%; rate ratio 0.46; P < <0.0001) over 52 weeks. Blood eosinophil counts rapidly normalized by approximately 80% and remained suppressed for the remainder of the study, despite biannual dosing. Yet, the effect on asthma symptoms (Asthma Control Questionnaire 5 [ACQ-5], St. George's Respiratory Questionnaire [SGRQ]) or lung function (pre-bronchodilator forced expiratory volume in 1 second [FEV1]) remained unremarkable throughout the study period in both trials. The incidence and severity of treatment-emergent adverse events were similar between the depemokimab and placebo groups.

Main takeaway message

1. Depemokimab, offered a sustained inhibition of the IL-5 pathway indicated by normalized blood eosinophil counts with a convenient 6-month dosing schedule.

2. This could simplify treatment for patients with severe asthma, potentially requiring only 2 injections per year, thereby improving compliance and adherence.

3. The study is attractive to patients who are hesitant to start biologics due to a fear of needles.

The study is now published in the *New England Journal of Medicine*.[12]

The mechanistic basis for understanding the clinical effects of depemokimab was presented in another oral abstract session, titled *"Recent advances in biological treatments for asthma and chronic obstructive pulmonary disease"* chaired by Dr. Florence Schleich and me. In this session, Dr. David Jackson presented "Enhanced in vitro potency of depemokimab for interleukin-5 inhibition versus mepolizumab." This study showed that depemokimab is significantly more potent than mepolizumab in: (i) reducing IL-5-mediated proliferation of a human eosinophil cell line (TF-1) by 24.9 fold, and (ii) achieving a 31.0-fold (range

7.5–76.7) higher inhibition of IL-5-enhanced IgE-R-mediated basophil degranulation.

III. ***"Efficacy of high and low dose rilzabrutinib from a Phase II study"*** was presented in the late breaking oral presentation session titled "Airway diseases therapeutics: novel research studies." The session was chaired by Dr. Alex Mathioudakis and me. The study was presented by its senior author, **Dr. Ian Douglas Pavord.**

Rilzabrutinib (SAR444671) is an oral, reversible covalent inhibitor of Bruton's tyrosine kinase (BTK) that has shown excellent clinical benefits in treating chronic urticaria. BTK plays a key role in immune cell signalling across multiple cellular types relevant in orchestrating chronic airway inflammation, including B cells, mast cells, eosinophils, and neutrophils. It is therefore being investigated in the severe asthma domain for its clinical efficacy.[13] This was the first Phase II study in an asthma population.

The study's objective was to report the efficacy of rilzabrutinib at doses of 800 mg and 1200 mg in patients with poorly controlled moderate-to-severe asthma who were on inhaled corticosteroids (ICS)/long-acting beta-agonist (LABA) therapy (NCT05104892). In this placebo-controlled Phase II study, 196 patients were randomized 1:1 (drug and placebo) into 2 cohorts to assess the low and high doses of the drug. The study design included an initial stabilization phase (week 0 – week 4), followed by a step-wise withdrawal phase of background therapy (week 4 – week 9) and no background therapy from week 9 – week 12 (end of study). The primary endpoint was the proportion of patients who experienced level of asthma control (LOAC) events during the treatment periods. A LOAC event was defined by any one of the following: (i) ≥30% reduction in morning peak expiratory flow on 2 consecutive days; (ii) ≥6 additional reliever puffs within a 24-hour period on 2 consecutive days; (iii) an increase in ICS to ≥4 times the last prescribed dose or ≥50% of the prescribed dose if background therapy is completely withdrawn; or, (iv) an exacerbation requiring systemic steroid treatment, hospitalization or an ER visit. The secondary endpoint evaluated was a change in the ACQ-5 score from baseline.

Results:

In 32 patients on rilzabrutinib 800 mg and 32 patients on placebo over 12 weeks, LOAC events occurred in 37.5% of patients in the drug arm compared to 50% in the placebo arm (OR:0.570; 95% CI: 0.202-1.608), with a relative risk reduction (RRR) of 25%. In the high dose group (1200 mg rilzabrutinib, n=64) there was an RRR of 36.1% compared to placebo (n=68). Significant improvements in ACQ-5 scores were observed as early as week 2 with rilzabrutinib compared to placebo that were sustained up to week 12 (LS mean difference vs placebo: rilzabrutinib 800 mg: -0.59, p=0.0184; rilzabrutinib 1200 mg: -0.54, p=0.0013) despite complete ICS/LABA withdrawal. The investigational drug was safe and well-tolerated over the 12-week treatment period.

Main takeaway message

1. In a heterogenous, unselected asthma population, rilzabrutinib was associated with a reduction in LOAC events, showing clinically meaningful improvement over 12 weeks.

2. The improvement in the asthma symptoms was rapid and was observed despite the complete removal of background-controlled therapy.

3. These positive results demonstrate the potential of rilzabrutinib as a novel first-in-class oral BTK inhibitor for poorly controlled asthma, warranting further investigation in Phase 3 studies.

Honorary mentions:

Multiple interesting short abstracts were presented at the 2024 European Respiratory Society Congress, and a few are highlighted:

1. *Dupilumab reduces mucus plugging and volume*: phase 4 VESTIGE trial – presented by Dr. Celeste Porsbjerg: The VESTIGE study (NCT04400318) assessed the impact of dupilumab (anti-IL-4/IL-13 blocking monoclonal antibody) on airway mucus plugging and volume, inflammation, and lung function. The dupilumab group had reduced mucus scores and mucus volumes (voxels/mucus plugs) and were 9.8 times more likely to achieve FeNO <25 ppb and improvements in pre-bronchodilator FEV_1.

2. *Time to first moderate or severe COPD exacerbation with tezepelumab (COURSE)*- presented by Dr. Dave Singh: COURSE was a phase 2a, randomized, double-blind, placebo-controlled study that included 333 moderate-to-severe COPD patients who were randomized 1:1 to receive either tezepelumab 420 mg or placebo subcutaneously every 4 weeks for up to 52 weeks. Tezepelumab delayed the time to the first moderate or severe exacerbation compared

to placebo in the overall population (HR, 0.80 [95% CI: 0.61–1.06; median days: 253 in the tezepelumab group vs 214 in the placebo group]) irrespective of subgroups stratified by blood eosinophil counts.

3. *Safety and PK of KN-002 in subjects with moderate to severe asthma using ICS/LABA* - presented by Dave Singh: A novel lung selective potent pan-Janus kinase (JAK) inhibitor formulated as a dry powder for inhalation was well tolerated by moderate-to-severe asthma patients on ICS/LABA therapies in a Phase I study.

4. *KN-002 reduces fractional exhaled nitric oxide in moderate-to-severe asthma* - presented by Dave Singh: KN-002, an inhaled small molecule pan-JAK inhibitor. Since JAK/STAT signalling is implicated in multiple pro-inflammatory pathways of airway inflammation, its potential to reduce FeNO was evaluated. The study showed that KN-002 caused a clinically relevant FeNO reduction over 10 days, independent of baseline FeNO/blood eosinophils.

Summary

Many sessions at this year's annual congress organized by the European Respiratory Society in Vienna, Austria, highlighted promising new therapies for severe asthma and COPD, with a vision to reduce exacerbations.

Correspondence

Manali Mukherjee, MD
Email: mukherj@mcmaster.ca

Financial Disclosures

MM: Grants: Canadian Institute for Health Research and COVID-19 Immunity Task Force, Canadian Asthma, Allergy and Immunology Foundation (CAAIF), Mirimus, Methapharm Specialty Pharmaceuticals, Sanofi; **Speaking Engagement Fees (personal):** AstraZeneca, Sanofi, GSK, EAACI Knowledge Hub, and Resiplus.

References

1. Bafadhel M, McKenna S, Terry S, Mistry V, Reid C, Haldar P, et al. Acute exacerbations of chronic obstructive pulmonary disease: identification of biologic clusters and their biomarkers. Am J Respir Crit Care Med. 2011;184(6):662-671. doi:10.1164/rccm.201104-0597OC
2. Bhalla A, Zhao N, Rivas DD, Ho T, Perez de Llano L, Mukherjee M, et al. Exacerbations of severe asthma while on anti-IL-5 biologics. J Investig Allergol Clin Immunol. 2020;30(5):307-316. doi:10.18176/jiaci.0628
3. Castro M, Wenzel SE, Bleecker ER, Pizzichini E, Kuna P, Busse WW, et al. Benralizumab, an anti-interleukin 5 receptor α monoclonal antibody, versus placebo for uncontrolled eosinophilic asthma: a phase 2b randomised dose-ranging study. Lancet Respir Med. 2014;2(11):879-890. doi:10.1016/s2213-2600(14)70201-2
4. Brightling CE, Bleecker ER, Panettieri RA, Jr., Bafadhel M, She D, Ward CK, et al. Benralizumab for chronic obstructive pulmonary disease and sputum eosinophilia: a randomised, double-blind, placebo-controlled, phase 2a study. Lancet Respir Med. 2014;2(11):891-901. doi:10.1016/s2213-2600(14)70187-0
5. Mukherjee M, Huang C, Venegas-Garrido C, Zhang K, Bhalla A, Ju X, et al. Benralizumab normalizes sputum eosinophilia in severe asthma uncontrolled by Anti-IL-5 antibodies: a single-blind, placebo-controlled clinical trial. Am J Respir Crit Care Med. 2023;208(12):1330-1335. doi:10.1164/rccm.202308-1413LE
6. Sehmi R, Lim HF, Mukherjee M, Huang C, Radford K, Newbold P, et al. Benralizumab attenuates airway eosinophilia in prednisone-dependent asthma. J Allergy Clin Immunol. 2018;141(4):1529-1532.e1528. doi:10.1016/j.jaci.2018.01.008
7. Walters JA, Tan DJ, White CJ, Gibson PG, Wood-Baker R, Walters EH. Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2014;2014(9):Cd001288. doi:10.1002/14651858.CD001288.pub4
8. Ramakrishnan S, Russell REK, Mahmood HR, Krassowska K, Melhorn J, Mwasuku C, et al. Treating eosinophilic exacerbations of asthma and COPD with benralizumab (ABRA): a double-blind, double-dummy, active placebo-controlled randomised trial. Lancet Respir Med. 2024. doi:10.1016/s2213-2600(24)00299-6
9. Leung C, Sin DD. A new era in the treatment of acute exacerbations of asthma and COPD. Lancet Respir Med. 2024. doi:10.1016/s2213-2600(24)00323-0
10. Salter B, Lacy P, Mukherjee M. Biologics in asthma: a molecular perspective to precision medicine. Front Pharmacol. 2021;12:793409. doi:10.3389/fphar.2021.793409
11. Singh D, Fuhr R, Bird NP, Mole S, Hardes K, Man YL, et al. A Phase 1 study of the long-acting anti-IL-5 monoclonal antibody GSK3511294 in patients with asthma. Br J Clin Pharmacol. 2022;88(2):702-712. doi:10.1111/bcp.15002
12. Jackson DJ, Wechsler ME, Jackson DJ, Bernstein D, Korn S, Pfeffer PE, et al. Twice-yearly depemokimab in severe asthma with an eosinophilic phenotype. N Engl J Med. 2024. doi:10.1056/NEJMoa2406673
13. Tavakoli GM, Yazdanpanah N, Rezaei N. Targeting Bruton's tyrosine kinase (BTK) as a signaling pathway in immune-mediated diseases: from molecular mechanisms to leading treatments. Adv Rheumatol. 2024;64(1):61. doi:10.1186/s42358-024-00401-y