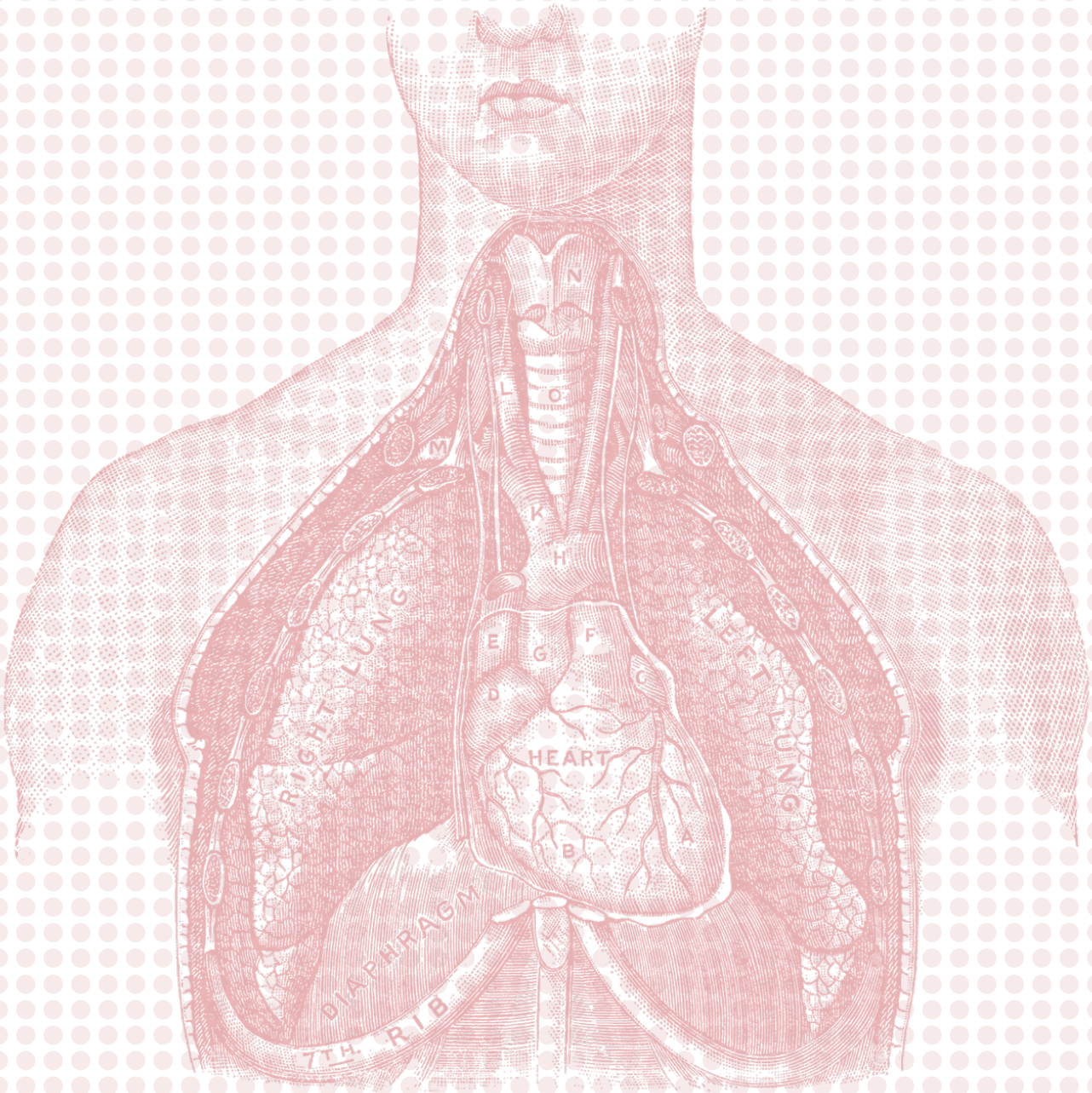
SEVERE ASTHMA FORUM

7TH INTERNATIONAL SOUTHEAST MEETING ON SEVERE ASTHMA

4. - 5. April 2025, Bled



SAF2025

Združenje pnevmologov Slovenije
Slovenian Respiratory Society

SEVERE ASTHMA FORUM

7TH INTERNATIONAL SOUTHEAST MEETING ON SEVERE ASTHMA

SPOMLADANSKO STROKOVNO SREČANJE ZDRUŽENJA PNEVMOLOGOV SLOVENIJE

Proceedings of Scientific Congress

4. – 5. April 2025, Bled

Organiser: ***Slovenian Respiratory Society***
Organising committee: ***Mitja Košnik, Robert Marčun, Sabina Škrgat***
Scientific Committee: ***Sabina Škrgat, Peter Korošec, Ramesh Kurukulaaratchy, Stefano Del Giacco, Marina Lampalo, Sanja Hromiš, Peter Kopač, Natalija Edelbaher, Katja Mohorčič***
Editors and reviewers: ***Mitja Košnik, Sabina Škrgat***

Electronic edition

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SPOMLADANSKO STROKOVNO SREČANJE ZDRUŽENJA PNEVMOLOGOV SLOVENIJE

Organizer: Slovenian Respiratory Society
Date: 4-5 April 2025
Location: Hotel Rikli Balance Bled

Amgen

AstraZeneca

Berlin Chemie

MSD

Sanofi

Boehringer Ingelheim
Chiesi
IRIS
Medis
Pliva Teva
Roche

SCIENTIFIC PROGRAMME

FRIDAY 5TH OF APRIL, 2025

08.30-08.40: Introduction (Sabina Škrgat, Mitja Košnik)

08.40-09.45: Basic science in severe asthma: what is new (Peter Korošec, Ramesh Kurukulaaratchy)

08.40-09.05: Peter Korošec: Basic science in severe asthma: Pathophysiology and mechanisms (Invited plenary lecture)

09.05-09.30: Matija Rijavec: Basic science in severe asthma: Biomarkers and genetics (Invited plenary lecture)

09.30-09.45: Discussion

09.45-11.15: Problematic case reports with discussion/workshop-1 st part (Ramesh Kurukulaaratchy, Sabina Škrgat)

9.45-10.05: Saša Rink: Development of Allergic Bronchopulmonary Mycosis During Benralizumab Treatment

10.05-10.25: Žiga Piletič: Steroid burden in asthma – a case report

10.25-10.45: Anamarija Štajduhar, Marina Lampalo: Complicated asthma in an obese patient

10.45-11.05: Ivan Čekerevac: Hypereosinophilia and severe asthma

11.05-11.15: Additional discussion time (if needed)

11.15-11.35: Coffee break

11.35-13.20: Perspectives and clinical outcomes in severe asthma (Stefano Del Giacco, Mihaela Zidarn)

11.35-12.05: Ramesh Kurukulaaratchy: Comorbidities and Multimorbidity – Important New Perspectives in Severe Asthma (Invited plenary lecture)

12.05-12.30: Stefano Del Giacco: Remission in asthma (Invited plenary lecture)

12.30-12.55: Sabina Škrgat: Outcomes and challenges in severe asthma with fungal senzitisation (Invited plenary lecture)

12.55-13.20: Discussion

13.20- 13.40: Satellite symposium AstraZeneca Stefano Del Giacco, Unlocking Airways: Benralizumab's Pioneering Role in Severe Asthma Management

13.40-14.30: Lunch

14.30-16.30: Reports from clinics and real life studies (Peter Kopač, Branislava Milenković)

14.30-14.45: Sanja Hromiš: Weight-adjusted biologic therapy – are there some benefits? (Invited lecture)

14.45-15.00: Mirna Vergles: A new rhythm in severe asthma management: extending the intervals for biologics? (Invited lecture)

15.00-15.15: Irena Šarc: Biologic Therapy in eosinophil COPD: Insights from Our Clinical Experience. (Invited lecture)

15.15-15.30: Peter Kopač: The Significance of Eosinophil Location in Severe Asthma: Insights from Induced Sputum (Invited lecture)

15.30-15.45: Luka Kunej, Škrgat Sabina: Clinical and molecular response to dupilumab treatment in patients with eosinophilic asthma (Invited lecture)

15.45-16.15: Discussion

16.15-16.35: Satellite symposium AstraZeneca Mark Kačar, Saša Rink, Natalija Edelbaher: TSLP - This Special Little Protein, what it does and how it can help us.

16.30-17.00 Coffee break

Parallel section I

17.00-18.15 Problematic case reports with discussion-2nd part. (Ivan Čekerevac, Željko Vrbica)

17.00-17.20: Marija Gomerčić Palčić: Patient with Severe Eosinophilic Asthma and CRSwNP Who Developed EGPA While Being Treated with Benralizumab

17.20-17.40: Jasmina Bošnjić: Asthma and pulmonary embolism

17.40-18.00: Špela Kosi: The Importance of Diagnosing and Treating OSA in Patients with Severe Asthma

18.00-18.15 Additional discussion time (if needed)

18:15-19:05 Satellite symposium Sanofi. From Clinical Trials to Real Life: How Dupilumab is Changing Practice (Jure Urbančič)

Jure Urbančič: Introduction: T2I is the common denominator

Mirna Vergles: Severe asthma: Can clinical remission be achieved?

Mihkel Plaas. Is precision medicine possible for CRSwNP?

Panel discussion

Parallel section II

17:00-19:10 DROBOCELIČNI RAK (Katja Mohorčič, Zala Leštan Ramovš)

17:00 Duška Vidovič: Drobnocelični rak pljuč: kje smo in kam gremo ? (Invited lecture)

17:10 Katja Adamič: Urgentna stanja pri bolnikih z rakom pljuč (Invited lecture)

17:25 Dimitrij Kuhelj: Vstavitev opornice v zgornjo votlo veno (Invited lecture)

17:40 Eva Ćirić: Ali je drobnocelični rak pljuč lahko ozdravljiva bolezen? (Invited lecture)

17:55 Loredana Mrak: Kaj je novega v sistemski terapiji drobnoceličnega raka pljuč? (Invited lecture)

18:10 Razprava

18:30 SATELITSKI SIMPOZIJ ASTRAZENECA Marina Čakš: Izkušnje zdravljenja z imunoterapijo pri slovenskih bolnikih z drobnoceličnim rakom pljuč

18:50 SATELITSKI SIMPOZIJ MSD Urška Janžič: Neželeni učinki imunoterapije

20.00: Dinner

SATURDAY 05.04.2025

Comorbidities in severe asthma and MDT approach

Part 1 (Matevž Harlander, Natalija Edelbeher)

8.15-8.35: Miodrag Janić: Diabetes/obesity/severe asthma (Invited lecture)

8.35-8.55 Hočevar Alojzija: EGPA from reumatologist perspective (Invited lecture)

8.55-9.15 Urbančič Jure: EIT specialist in severe asthma patient (Invited lecture)

9.15-9.35 Ana Komlenić : Psychologist- Basic personality traits of severe asthma patients and their impact on treatment outcomes (Invited lecture)

9.35-9.50 Discussion: part 1

9:50 Satellite symposium Berlin-Chemie Peter Kopač: Airway Remodeling in Asthma and the Effects of Mepolizumab Treatment

Part 2: (Ramesh Kurukulaaratchy, Sanja Hromiš)

10.05-10.30 Ziherl Kristina: The Challenge of Comorbid OSA in Patients with Severe and Difficult-to-Treat Asthma (Invited plenary lecture)

10.30-10.55 Matjaž Fležar: Functional algorithm for severe airway disease; from diagnosis to follow-up and fenotipization (Invited plenary lecture)

10.55-11.15 Discussion: part 2

11.15 End of the conference and closing remarks (Sabina Škrgat)

Farewell cocktail

KAZALO

INVITED PLENARY LECTURE

BASIC SCIENCE IN SEVERE ASTHMA: PATHOPHYSIOLOGY AND MECHANISMS

Peter Korosec. University Clinic of Respiratory and Allergic Diseases, Golnik; Faculty of Pharmacy, University of Ljubljana

BACKGROUND

Type 2 immunity is a pattern of immunity characterized by the activation of TH2 cells and group 2 innate lymphoid cells (ILC2s) that produce the type 2 cytokines IL-4, IL-5, IL-9, and IL-13, with the inclusion of eosinophils and /or mast cells and is primarily known for its detrimental roles in type 2 (T2) asthma. On the other hand, non-T2 asthma involves the activation of various pathways in multiple types of immune cells, including activation of and the possible release of cytokines and chemokines from macrophages, neutrophils, dendritic cells, and especially epithelial cells.

METHODS

To describe several novel mechanisms of regulation and function of T2 immune cells in asthma, focusing on ILC2s, TH2, mast cells, and neuroimmunology. To describe novel mechanisms pivotal in initiating and amplifying the inflammatory response, ultimately contributing to the development and progression of non-T2 asthma.

RESULTS

The development of chronic allergic airway pathology is attributed to the epigenetic acquisition of memory by ILC2s, the infiltration of mucosal tissues by stemlike memory TH2 cells, and tissue-resident memory TH2 cells. Further, mast cells can be regulated by lipids and are not just the sources but also the targets of lipids. There seem to be interactions between type 2 immune cells and peripheral neurons, including neuronal control of immune homeostasis in the lung and multisynaptic neuronal pathways for airway constriction in asthma. Novel molecular mechanisms of non-T2 asthma include inflammasome activation, type I, II, and III IFN response upon respiratory viral infection, IL-6 signaling pathway, and alarmins and epithelial-derived cytokines, like TSLP and IL-33, which, in addition to driving T2 inflammation in asthma, may also contribute to non-T2 asthma.

CONCLUSIONS

The use of advanced technologies, single-cell RNA sequencing, and ILC experimental genetic models has fueled these mechanistic developments, which are significant for novel discoveries in clinical medicine, including further drug development for severe asthma.

INVITED PLENARY LECTURE

BASIC SCIENCE IN SEVERE ASTHMA: BIOMARKERS AND GENETICS

Matija Rijavec
University Clinic of Respiratory and Allergic Diseases Golnik, Slovenia
Biotechnical Faculty, University of Ljubljana, Ljubljana, Slovenia

Severe asthma remains a significant clinical challenge, impacting morbidity, mortality, and healthcare resource utilization, despite accounting for a small proportion of overall asthma prevalence. Asthma is a complex, highly heterogeneous disease with multiple phenotypes and endotypes, and current diagnostic tools often fall short of fully addressing its variability. This highlights the increasing need for new diagnostic, predictive, and prognostic biomarkers to enable more personalized treatment strategies. Recent advances in the understanding of asthma's heterogeneity and immunopathogenesis have facilitated the identification of precise disease pathways, which, in turn, support the development of targeted therapies.

Biomarkers can improve early diagnosis of asthma, allowing for prompt intervention that can prevent disease progression, reduce complications, and improve long-term outcomes. Reliable biomarkers also aid in monitoring disease activity and treatment efficacy in real-time, enabling better disease management. This approach can ultimately reduce hospitalizations, emergency visits, and the overall healthcare costs associated with poorly controlled asthma.

For patients with severe asthma, who often fail to respond to standard therapies, the identification of novel biomarkers is crucial for guiding the development of specialized treatments. Biomarkers are being investigated across various levels, from clinical presentations and patient characteristics to biochemical, immunologic, genetic, and epigenetic factors (such as DNA methylation and microRNAs). Some biomarkers are already clinically available, albeit the majority are still candidate biomarkers. Understanding the molecular mechanisms underlying different asthma endotypes—such as eosinophilic versus neutrophilic asthma—has provided insights into the variable response to treatments and is key to more precise management. Biomarkers linked to frequent exacerbations and severe asthma (e.g., IL-6, IL-1β, specific miRNAs, and genetic variants) have the potential to significantly enhance patient management.

Biologic therapies, guided by these biomarkers, represent a promising shift towards personalized treatment, improving patient outcomes, reducing exacerbations, and enhancing quality of life. For example, biomarkers associated with T2-high asthma (e.g., FeNO, eosinophils, total IgE, IL-4, IL-5, IL-13, periostin) can help tailor therapies aimed at reducing eosinophilic inflammation. Conversely, biomarkers associated with T2-low asthma (e.g., Th17 cells, neutrophils, YKL-40) can guide the use of treatments targeting neutrophilic or Th17-driven inflammation. Ongoing research is focused on refining existing biomarkers and discovering new ones, with the goal of further optimizing treatment precision. However, challenges remain in accurately predicting responses due to the complexity of asthma's pathophysiology. Continued research into biomarkers and genetic factors is essential for realizing the full potential of biological treatments and optimizing care for patients with severe asthma.

DEVELOPMENT OF ALLERGIC BRONCHOPULMONARY MYCOSIS DURING BENRALIZUMAB TREATMENT

Saša Rink. Department of Pulmonary Diseases and Allergy, University Medical Centre Ljubljana

INTRODUCTION

Allergic bronchopulmonary mycosis (ABPM) is an umbrella term for hypersensitivity reactions to various fungal species, with *Aspergillus fumigatus* being the most common cause in allergic bronchopulmonary aspergillosis (ABPA). ABPA is well-defined by elevated blood eosinophils (BEC >500 × 10^6/L), increased total serum IgE (>500 IU/mL), and specific IgE/IgG to *Aspergillus* (1).

CASE HISTORY

A 69-year-old woman with severe asthma was evaluated for biologic therapy due to frequent exacerbations and lung function decline. She had chronic sinusitis without nasal polyposis and a history of ABPA in long-term remission, with blood eosinophil count (BEC 500x10^6), negative specific IgE/IgG for *Aspergillus* and *Candida*, normal total IgE (150 IU/mL), and FEV1 1580 ml (62%). HRCT showed mild bronchiectasis and mucus plugging without active ABPA.

Benralizumab was initiated, leading to symptom improvement, no exacerbations, a rise in FEV1 2560 ml (105%), and a BEC of 0. However, after six months, she developed productive cough, gradual decline of FEV1 2370 ml (96%), and increasing total IgE (316 IU/mL), though sputum analysis showed no fungal or bacterial growth. HRCT revealed worsening bronchiectasis and new bronchoceles indicatin possible ABPA flare up.

At one year, despite well-controlled asthma and BEC 0, total IgE had increased significantly (3160 IU/mL), with sensitization to both *Aspergillus* and *Candida*. Fleeting opacities appeared on HRCT, and bronchoscopy revealed thick mucus and *Schizophyllum* growth. She later disclosed significant mold exposure at her holiday home. Itraconazole was added to her asthma treatment.

CONCLUSION

Systemic corticosteroids remain the mainstay of ABPM treatment, with antifungal therapy recommended for refractory cases. Biologic therapies, particularly anti IL-5 agents, offer a steroid-sparing option (2,3). Despite benralizumab treatment and absent peripheral eosinophilia, our patient developed ABPM caused by *Schizophyllum commune* - a fungus found in decaying wood that has the ability to trigger IgE-mediated immune responses, often cross-reacting with other fungal species like *Aspergillus (4)*. This case highlights the complexity ABPM and the need for tailored management strategies.

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STEROID BURDEN IN ASTHMA – A CASE REPORT

Žiga Piletič. Department of pneumology, Novo mesto General Hospital

BACKGROUND

Steroids are the cornerstone of asthma treatment. Inhaled glucocorticoids (ICS) have the primary role in controlling symptoms, reducing airway inflammation and exacerbation risk while oral glucocorticoids (OCS) are used either to treat exacerbations or to maintain disease control when other interventions have failed (1,2). While awareness of both short- and long-term OCS therapy burden is rising with experts suggesting minimising exposure to OCS and active screening for possible side-effects (1,3–5), knowledge of systemic side effects of ICS is sparser. Evidence is emerging of not only adrenal gland suppression (6,7) but also major adverse cardiovascular events, pneumonia and pulmonary embolism risk being increased, especially with higher doses or longer time of ICS use (8). Using high doses (500-1000 mcg of fluticasone propionate or equivalent (1,9)) of ICS corresponds to systemic effects of approximately 2-4 mg prednisolone daily (10), which confers a high cumulative steroid burden with longer exposure. Initiating biological therapy in severe asthma patients has been shown as an effective steroid-sparing intervention (1,11)

CASE REPORT

I present a 69-year-old female, never smoker, retired asthma nurse, with childhood onset asthma, arterial hypertension and celiac disease. Asthma has been treated with oral prednisolone for 29 years and later 20 years with medium to high-dose ICS. Last 30 years asthma has been prone to exacerbations with frequent bouts of OCS. Prolonged OCS treatment was needed in recent years for Covid pneumonia and later Pneumocystis jirovecii infection. As a result, she has developed adrenal insufficiency, steroid diabetes, osteoporosis, obesity. Mild positional obstructive sleep apnoea and treatment-resistant atrial fibrillation were discovered. Her eosinophil count was perpetually low, no fungal sensitization or allergies were discovered, inhalation technique and adherence were always good. Even on highest doses of inhaled medications exacerbations were frequent and stabilised only on OCS. In April 2024 anti-TSLP therapy was initiated. Asthma has been stable since then.

DIRECTIONS FOR FUTURE RESEARCH

More data is needed on systemic effects of ICS treatments, especially high-dose, which are often used to avoid maintenance OCS prescription. Guidelines should be updated accordingly and focus also on high-dose ICS sparing interventions. Awareness should also be raised with other specialists to recognise and promptly refer severe asthma patients with OCS use and frequent exacerbation history to a specialised centre.

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COMPLICATED ASTHMA IN AN OBESE PATIENT - A CASE REPORT

Anamarija Štajduhar. Marina Lampalo. Ena Tolić.
Clinic for Pulmonary Diseases Jordanovac, Clinical Hospital Center Zagreb

Obesity represents a global health issue. Adipose tissue is a metabolically active organ, and obese patients with asthma have greater everyday impairment than lean asthma patients.
Here, we present a case of an obese female patient with severe asthma and a challenge that poses a treatment of such patient.

A 51-year-old patient who was diagnosed with non-allergic eosinophilic asthma at the age of 14. She is a professional cleaner, a lifelong non-smoker, and was hospitalized several times for asthma in childhood and at least 1 to 2 times a year in adulthood. Comorbidities include Cushing's syndrome, osteoporosis, arterial hypertension, adiposity, and type 2 diabetes. The highest recorded blood eosinophil values were 1800 cells/mcL, and she tested negative for allergies.
Her symptoms include dry cough and exercise intolerance. She is dependent on the use of oral corticosteroids as well as high doses of inhaled corticosteroids. Over the years, BMI has varied from 28 kg/m2 to 42 kg/m2. Pulmonary function is severely impaired – FVC 47% (1.52 L), FEV1 19% (0.49 L), FEV1/FVC 0.32 with normal diffusion capacity for CO and FeNO values. Chest CT scan showed diffuse bilateral small peribronchial infiltrates in the lung parenchyma with deformed bronchi with thickened walls. Echocardiographic findings were nonsignificant.

Pulmonary rehabilitation was performed several times. Ultimately, a multidisciplinary team decided to start treatment with mepolizumab. After 70 cycles of mepolizumab, the number of eosinophils in the blood normalized (10 cells/mcL), but with further need for prednisone, annual asthma exacerbations and permanently reduced lung function (FVC 51%, FEV1 25%, FEV1/FVC 0.40). The therapy was switched to tezepelumab in 2024. The patient's condition has been improving (ACT 25), she has started to lose weight, but due to sleep hypopnea (AHI 10) and long-term oxyhemoglobin desaturation (SpO2 <80% 40 min), BIPAP was introduced along with home oxygen therapy. The patient is currently without exacerbations, in a stable asthma phase, and an attempt to discontinue oral corticosteroids is imminent.

In conclusion, obesity-related changes in the respiratory system aggravate asthma, causing frequent and severe exacerbations and worse quality of life. It is an issue that needs to be promptly addressed as part of the everyday care of asthma patients.

HYPEREOSINOPHILIA AND SEVERE ASTHMA

Ivan Čekerevac. Faculty of Medical Sciences University of Kragujevac; Clinic for pulmonology, University Clinical Center Kragujevac

INTRODUCTION

Hypereosinophilia is defined as an absolute peripheral blood eosinophil count that is >1,500 cells/μL on two occasions, at least 1 month apart, or in the presence of significant tissue eosinophilia. Hypereosinophilic syndrome (HES) be reserved for cases that fulfil the definition of HE and have otherwise unexplained organ dysfunction/damage. HES may be classified into primary (neoplastic) and secondary (reactive).
Sometimes in patients with T2 high severe asthma and hypereosinophilia we have suspicion or red flags for other diseases.

CASE REPORT:

A 47-year-old woman with a background of asthma for about 4 years consulted an allergist because of eosinophils up to 1000/ μL. She was on a regular therapy Fluticasone/Vilanterol 92/22mcg and SAMA/SABA as needed and had partially controlled asthma. Laboratory tests related to tumor markers, immunology including ANCA and stool examination for parasites were negative. Specific IgE to inhaled allergens, as well as the rhino-provocation test, were also negative. In the next few months, the dose of the same inhaler was increased to a high. We saw the patient for the first time in January 2025 with a history that she had two moderate exacerbations of asthma in the last three months treated with systemic corticosteroids. She mentioned having a severe cough and audible wheezes but no associated upper respiratory tract symptoms. Laboratory examination revealed increased peripheral blood eosinophil numbers (2300 /μL). The fraction of exhaled nitric oxide (FeNO) was elevated (62 ppb). Pulmonary function test showed obstructive pulmonary dysfunction (FEV1 69% ,FEV1/FVC 68%). We admitted her to the hospital and repeated eosinophils were 1800/ μL , IgE total 183, ANCA were negative. Chest CT scans showed crazy paving consolidation dominant subpleural/the appearance of ground-glass opacities with thickening of the wall of segmental bronchi. Flexible bronchoscopy with transbronchial biopsy was performed for diagnostic purposes. Histological finding included epithelium with dominated by goblet cells and smooth muscle hypertrophy/hyperplasia. CT of the sinuses showed signs of pansinusitis (all paranasal cavities filled with thick contents), without nasal polyposis. A bone marrow biopsy was performed with findings in support of reactive eosinophilia (up to 20%). An EMG was performed without signs of sensorimotor peripheral neuropathy or mononeuritis multiplex. We decided to administer Reslizumab (3mg/kg) per month and two months later her asthma was under control, spirometry was normal, blood eosinophils 140/ μL and no significant infiltration on chest x-ray.

Conclusion: Identification of a comprehensive set of red flags (lung infiltrates etc.) in patients with severe asthma and hypereosinophilia can be used to raise the suspicion of other diseases, primarily EGPA and HES. Pulmonologists should maintain high awareness to the disease with patients presenting with asthma, especially when they are uncontrolled or severe and have high BECs.

Key words: hyperosinophilia, severe asthma

INVITED PLENARY LECTURE

COMORBIDITIES AND MULTIMORBIDITY - IMPORTANT NEW PERSPECTIVES IN SEVERE ASTHMA

Prof Ramesh J Kurukulaaratchy. University of Southampton, United Kingdom

BACKGROUND

There is increasing awareness that comorbidities are frequently present in patients with difficult-to-treat/ severe asthma. However their impacts on asthma patients remain poorly understood as does the concept of how they combine in the form of multimorbidity.

AIMS

The aims of this talk are to:

1: Understand the nature and impacts of comorbidities associated with difficult-to-treat/severe asthma.

2: Consider comorbidities as treatable traits in difficult-to-treat/ severe asthma.

3: Recognise multimorbidity profiles/ phenotypes in difficult-to-treat/ severe asthma.

4: Consider the concept of a multimorbidity index to improve understanding of asthma impacts.

5: Appreciate impacts of multimodal approaches to multimorbidity in difficult-to-treat/ severe asthma.

FINDINGS

Comorbidities are commonplace in patients with difficult-to-treat/severe asthma. They (both individually and collectively) show detrimental impacts on asthma outcomes including maintenance oral steroid need, asthma exacerbation, lung function and asthma control. They may negatively influence long-term asthma control, impair biologic remission, negatively impact quality of life and impose significant health economic burden. In parallel, recognition of comorbidities in asthma care is suboptimal. However, many comorbidities can be regarded as “treatable super traits” that detrimentally impact patients with asthma, but which can be addressed to help improve patient outcomes. A new concept is the recognition that comorbidities in asthma usually occur in combination within a framework of multimorbidity. Recent work in the Severe Heterogeneous Asthma Research Collaboration: Patient-Centred (SHARP) has identified multimorbidity clusters and categories in severe asthma patients that show different clinical manifestations. There is also emerging evidence of the ability of a multimorbidity index to provide an alternative holistic perspective that highlights worse asthma outcome risk in severe asthma patients. Furthermore, studies have shown the benefits of addressing comorbidities/ multimorbidity within a comprehensive treatable traits approach in patients with severe asthma.

CONCLUSIONS:

Look for comorbidities in difficult-to-treat/ severe asthma and you will find them; find and you should address them, address them and you will improve your patients' outcomes.

INVITED PLENARY LECTURE

OUTCOMES AND CHALLENGES IN SEVERE ASTHMA WITH FUNGAL SENZITISATION

Sabina Škrgat. Department of Pulmonary Diseases and Allergy, University Medical Centre, Ljubljana
Medical Faculty, University of Ljubljana

BACKGROUND

Fungal sensitization is common in asthma, with prevalence varying across studies. It appears to be higher in severe asthma than in mild asthma, with reported rates ranging from 35% to 75% (1).

Sensitization to Aspergillus fumigatus is associated with a spectrum of conditions (2):

- A. fumigatus sensitization (AFS) is defined by increased IgE levels or a positive skin prick test for A. fumigatus.
- A. fumigatus-associated asthma (AFAA) refers to allergic sensitization to A. fumigatus in patients with mild to moderate asthma.
- Allergic bronchopulmonary aspergillosis/mycosis (ABPA/M) encompasses severe allergic reactions to Aspergillus spp. or other fungi in patients with severe asthma and bronchiectasis. ABPA is diagnosed based on a combination of clinical, radiological, and immunological criteria.
- Severe asthma with fungal sensitization (SAFS) is identified in patients with severe asthma and elevated fungus-specific IgE who do not meet the criteria for ABPA or ABPM.
- Allergic fungal airway disease (AFAD) is an umbrella term that includes fungal asthma, fungal bronchitis, AFAA, SAFS, ABPA, ABPM, and fungal allergies in patients with chronic obstructive pulmonary disease (COPD) (2).

According to the most recent ISHAM-ABPA guidelines (3), the diagnostic algorithm incorporates radiological features and recommends subclassifying ABPA into:

- Serological ABPA
- ABPA with bronchiectasis
- ABPA with mucus plugging
- ABPA with high-attenuation mucus
- ABPA with chronic pleuropulmonary fibrosis

CLINICAL EVIDENCE

Patients with IgE sensitization to *Aspergillus fumigatus* (AFS) are at risk of lung damage (4). Kurukulaaratchy et al. (5) reported that AFS in patients with difficult-to-treat asthma is associated with a more severe disease phenotype, characterized by older age, male sex, longer disease duration, lung function impairment, bronchiectasis, higher inflammatory markers, greater treatment needs, but fewer psychophysiological comorbidities.

In a small, single-center Slovenian SHARP cohort, a higher prevalence of bronchiectasis in severe asthma patients with AFS was observed, confirming previous findings. However, this association was not seen with FEV1 decline or maintenance oral corticosteroid use (6).

DIRECTIONS FOR FUTURE RESEARCH

Real-world clinical data on AFS remain limited, highlighting the need for larger multinational studies to better understand this under-recognized comorbidity. Early screening for AFS in asthma patients may serve as a preventive measure against progression of airway damage.

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INVITED LECTURE

WEIGHT-ADJUSTED BIOLOGIC THERAPY – ARE THERE SOME BENEFITS?

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ABSTRACT

Weight-adjusted biologic therapy – are there some benefits?

Severe asthma patients with predominant eosinophilic inflammation require anti-IL-5 therapy due to key roles of IL-5 in the differentiation, maturation, recruitment, and activation of eosinophils. Among currently available anti-IL-5 biologics (mepolizumab, reslizumab and benralizumab), meta-analyses and real-world studies have shown comparable efficacy.

Reslizumab is the only biologic administered in a weight-adjusted dose through intravenous infusion (IV) requiring more healthcare resources but potentially offering advantages. A suboptimal response to biologics may be linked to dosing regiments and administration routes. Studies suggest that higher doses and IV administration of anti-IL-5 drugs are associated with better suppression of eosinophilic inflammation in the airways leading to greater clinical improvements. This may be especially relevant for patients with late-onset, corticosteroid dependent asthma. In certain cases, using a fixed dose of subcutaneous mepolizumab may result in insufficient neutralization of IL-5, especially in patients with higher local inflammation. Experimental studies suggest that this could lead to the formation of immune complexes (high molecular weight IL-5 bound complexes) and subsequently activation of the complement system contributing to increased inflammation. This risk appears to be significantly lower in patients treated with weight-adjusted reslizumab. Additionally, auto-IgG antibodies against eosinophil peroxidase (EPX) have been identified in some patients with an airway autoimmune response and their presence is associated with a reduced response to biologics. Notably, a reduction in sputum anti-EPX IgG has been observed in reslizumab treated patients in clinical studies. Furthermore, mepolizumab, as an IgG1 molecule may have the potential to activate complement and form hetero-immune complexes, although evidence supporting these effects in clinical settings is limited. In contrast, reslizumab and benralizumab, being IgG4 molecules, are unlikely to bind complement and instead inhibit complement-mediated lysis. Lastly, some reports suggest that benralizumab may carry a slightly higher risk of exacerbations due to viral or bacterial infections compared to mepolizumab or reslizumab, possibly related to a reduction in NK cell number or function, though further investigation is required.

Therefore, weight-adjusted reslizumab may be a valuable therapeutic option, particularly for patients with late onset, corticosteroid-dependent asthma, and uncontrolled airway inflammation as well as those with frequent infectious exacerbations. Further research is needed to refine patient selection criteria and optimize individualized treatment strategies.

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INVITED LECTURE

A NEW RHYTHM IN SEVERE ASTHMA MANAGEMENT: EXTENDING THE INTERVALS FOR BIOLOGICS?

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BACKGROUND

Severe eosinophilic asthma (SEA) remains a therapeutic challenge despite advances in biologic treatments. Clinical remission has recently been recognized as a potential treatment goal in SEA management. Despite promising outcomes with biologics, key questions remain unanswered, particularly regarding the possibility of safely discontinuing therapy in patients who have attained remission. The randomized clinical study **OPTIMAL**, conducted in Denmark, addressed this question by titrating anti-IL-5 therapy through prolonged dosing intervals. The study concluded that titration of anti-IL-5 biologics is possible in patients who have become stable on treatment. Further studies on the long-term prognosis of titration and adjustments to the OPTIMAL titration algorithm are warranted.

METHODS

A similar observational study was conducted at **University Hospital Dubrava** on **31 SEA patients** treated with anti-IL-5 biologics (mepolizumab and benralizumab) from **January 2024**. All patients had to meet the criteria for a **four-component clinical remission (CR)** to be eligible for dose titration. The dosing interval was increased by **25%** over a period of six months. Evaluation at six months included spirometry (FEV1), fractional exhaled nitric oxide (FeNO), asthma control test (ACT), and blood eosinophil count (BEC). The loss of any remission component resulted in the patient being reverted to the original dosing interval.

RESULTS

Among the 31 SEA patients included, the majority were female. No significant differences were observed in age, sex, or comorbidity index. There were no recorded acute exacerbations or need for systemic corticosteroids during the study period. FEV1, FeNO, ACT, and BEC showed no statistically significant changes at six months compared with baseline.

CONCLUSION

Gradual titration of anti-IL-5 biologics by extending dosing intervals at **25% increments** every six months appears to be a safe and feasible strategy for SEA patients in remission. The absence of acute exacerbations and stable clinical parameters during the study period **indicates** the potential for dose titration in well-controlled SEA. Further long-term studies are warranted to confirm these findings and refine titration protocols.

INVITED LECTURE

BIOLOGIC THERAPY IN EOSINOPHILIC COPD: INSIGHTS FROM OUR CLINICAL EXPERIENCE

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ABSTRACT

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) with an eosinophilic phenotype is associated with frequent exacerbations and increased systemic corticosteroid (CS) use. Mepolizumab, an anti-IL-5 monoclonal antibody, has shown efficacy in reducing exacerbations in eosinophilic airway diseases. This study evaluated the effectiveness of mepolizumab in COPD patients with eosinophilic inflammation and emphysema in a real-life setting.

METHODS

This monocentric study included 12 COPD patients initiated with mepolizumab (100 mg subcutaneously every four weeks) from 2020 to 2022 and followed for 2 years. Patients required at least two exacerbations in the previous year requiring systemic CS treatment or maintenance oral corticosteroids (OCS) and a blood eosinophil count >300 cells/µL.

RESULTS

Mepolizumab treatment led to a significant reduction in exacerbation rates. The mean annualized rate of moderate or severe exacerbations decreased from 5.75 to 1.42 per year (rate ratio [RR] = 0.25, 95% confidence interval [CI] 0.14–0.42, p = 0.011). Hospitalization-related exacerbations were significantly reduced from 2.58 to 0.17 per year (RR = 0.06, 95% CI 0.02–0.27, p = 0.007). Moderate exacerbations requiring systemic CS decreased from 3.17 to 1.25 per year, but this reduction was not statistically significant (RR = 0.39, 95% CI 0.22–0.72, p = 0.138). Among seven patients who continued treatment for the second year, the exacerbation rate showed a trend toward further reduction (1.42 to 0.58 per year, RR = 0.47, 95% CI 0.19–1.14, p = 0.074). OCS maintenance therapy was discontinued in two of four patients (50%) after the first year (Fisher's exact p = 0.640).

CONCLUSIONS

Mepolizumab significantly reduced exacerbation rates in this highly selected cohort of COPD patients with an eosinophilic phenotype and frequent exacerbations, with 66% of patients responding and an overall 75% reduction in exacerbation rates. Among responders, the reduction was sustained into the second year of treatment. These findings suggest that mepolizumab may be a valuable treatment option for a subset of COPD patients, particularly those with a high exacerbation burden and corticosteroid dependence.

KEYWORDS: COPD, anti-IL-5, mepolizumab, eosinophilic COPD, exacerbations, biologic therapy, precision medicine

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a progressive lung condition, primarily caused by long-term cigarette smoking, characterized by persistent airflow limitation, chronic inflammation, and recurrent exacerbations (1). Acute exacerbations contribute to disease progression, increased healthcare utilization, and higher morbidity and mortality rates. While infections are a major trigger, some exacerbations are intrinsic and associated with elevated blood and sputum eosinophils (2,3).

Current guidelines recommend triple inhaled therapy—combining inhaled corticosteroids (ICS), long-acting β2-agonists (LABAs), and long-acting muscarinic antagonists (LAMAs) - for COPD patients with frequent exacerbations and elevated blood eosinophils (4). However, despite this regimen, 30–40% of patients continue to experience moderate to severe exacerbations.

COPD is a heterogeneous disease with multiple clinical phenotypes and inflammatory endotypes (5). Eosinophilic COPD, defined by blood eosinophil counts ≥150–200 cells/µL, is associated with a higher exacerbation risk but shows a better response to corticosteroid therapy (3). Given its pathophysiological similarities to eosinophilic asthma, targeted anti-IL-5 therapy has been investigated for COPD . Mepolizumab, a humanized monoclonal antibody against interleukin-5 (IL-5), reduces blood and tissue eosinophils by blocking IL-5 signaling. In severe eosinophilic asthma, it has significantly lowered exacerbation rates and improved quality of life (6). However, its role in COPD remains less clear. Two randomized controlled trials (METREX and METREO) assessed mepolizumab in COPD patients with moderate-to-severe exacerbations. A significant reduction in annual exacerbation rates was observed in METREX ($p=0.04$), particularly in patients with higher baseline eosinophil counts (7). Similar findings were reported for benralizumab, another anti-IL-5 biologic, in the GALATHEA and TERRANOVA trials, although statistical significance was not reached for overall exacerbation reduction (8).

Recent trials have explored dupilumab, a monoclonal antibody targeting interleukin-4 (IL-4) and interleukin-13 (IL-13), which are key drivers of Type 2 inflammation. The BOREAS trial demonstrated that dupilumab significantly reduced moderate-to-severe COPD exacerbations (rate ratio 0.70; $p<0.001$) in patients with eosinophilic COPD (≥300 eosinophils/µL), alongside improvements in lung function and quality of life. The NOTUS trial further confirmed these findings, showing a 34% reduction in exacerbation risk ($p<0.001$), with sustained FEV1 improvements at weeks 12 and 52 (9). These findings reinforce the role of Type 2 inflammation in COPD pathophysiology. However, optimal patient selection criteria remain a challenge.

This study aims to evaluate the efficacy of mepolizumab in a highly selected cohort of COPD patients with eosinophilic inflammation and a high exacerbation burden, providing further insight into its role in exacerbation reduction and overall clinical benefit.

METHODS

SUBJECTS

This monocentric study was conducted at the University Clinic for Respiratory and Allergic Disease Golnik from 2020 to the end of 2022. During this period, thirteen COPD patients were initiated on mepolizumab.

Eligibility for mepolizumab treatment was based on the following criteria:

- Clinical instability: At least two exacerbations in the previous year requiring systemic corticosteroid (CS) treatment or maintenance oral corticosteroid (OCS) therapy for disease stability despite a high-dose inhaled corticosteroid (ICS) regimen for at least six months.
- Eosinophilic fenotype: A blood eosinophil count of >300 cells/µL in the last year.
- Case review and approval by a multidisciplinary team (MDT) specializing in obstructive lung diseases before mepolizumab initiation.

Eligibility for study inclusion required additional criteria:

- A history of smoking ≥20 pack-years.
- The presence of emphysema on high-resolution computed tomography (HRCT) of the lungs.

STUDY PROTOCOL

Patients received mepolizumab (100 mg sc every four weeks) while continuing their standard COPD treatment, including inhaled bronchodilators and corticosteroids, as indicated.

Patients were regularly followed up at each application visit and underwent additional comprehensive assessments every six months. Clinical evaluations at one year and two years post-treatment initiation included exacerbation frequency (number of moderate/severe exacerbations per year, focused on those requiring systemic corticosteroids) and oral glucocorticoid use (requirement for maintenance therapy).

Patients were classified as responders if their annual exacerbation frequency or OCS maintenance dose decreased by at least 50%. One patient was excluded from the final analysis due to a short treatment duration and insufficient data. The study was approved by the National Medical Ethics Committee.

Data Analysis

Continuous variables were expressed as medians and interquartile ranges (IQRs), while categorical variables were summarized as percentages. Exacerbation rates before and after treatment were compared using the Wilcoxon signed-rank test for paired data. A two-tailed p-value <0.05 was considered statistically significant.

RESULTS

Baseline patient characteristics

The study included 12 patients with a mean age of 67.8 ± 5.1 years, of whom 66.7% were female. The mean BMI was 27.0 ± 4.5 kg/m², and the mean smoking history was 41.7 ± 20.0 pack-years. All patients were ex-smokers at baseline. Baseline blood eosinophil levels had a mean of 230.0 ± 194.4 cells/µL, with a historical maximum of 805.8 ± 335.7 cells/µL in the previous three years. On average, FeNO and total IgE levels were increased, with means of 78.6 ± 29.8 ppb and 214.0 ± 195.4 IU/mL, respectively. At six months, eosinophil counts had decreased to a mean of 55.8 ± 46.2 cells/µL (p = .002). Lung function also showed a significant improvement, with an increase in FEV1% predicted (p=0.032). Detailed baseline characteristics are presented in Table 1.

All patients had HRCT performed within one year before treatment initiation. Imaging revealed emphysema in all patients. All patients had varying degrees of mucus plugging. Bronchiectasis was present in at least a minimal form in 7 of 12 patients, and excessive dynamic airway collapse (EDAC) was observed in 5 patients.

Table 1: Baseline patient characteristics

Characteristic	Value
Number of pts.	12
Age (years)	67.8 ± 5.1
Gender, female	8 (66.7%)
BMI (kg/m²)	27.0 ± 4.5
Smoking history (pack-years)	41.7 ± 20.0
BEC max (cells/µL)	805.8 ± 335.7
BEC baseline (cells/µL)	230.0 ± 194.4
BEC baseline (%)	2.0 ± 1.6

FVC (mL)	2681.7 ± 1123.2
FVC% (%)	84.2 ± 24.6
FEV1 (mL)	1018.3 ± 459.0
FEV1 % (%)	41.7 ± 15.4
Ti %	38.5 ± 9.3
FeNO (ppb)	78.6 ± 29.8
Total IgE (IU/mL)	214.0 ± 195.4
Atopy, n	1 (8.3%)
ICS fluticasone equivalent (µg/day)	1110 ± 161
FVC at 6 M (mL)	2953.3 ± 1195.8
FVC at 6 M (%)	92.8 ± 24.6
FEV1 at 6 M (mL)	1114.2 ± 507.0
FEV1 % at 6 M (%)	45.8 ± 16.7
BEC at 6 M (cells/µL)	55.8 ± 46.2
BEC at 6 M (%)	0.55 ± 0.43

Data are number of participants (%), mean ± SD; BMI – body mass index; BEC – blood eosinophil count; FVC – forced vital capacity; FEV1 – forced expiratory volume in 1 second; FeNO – fractional exhaled nitric oxide; ICS – inhaled corticosteroid; at 6 M – values measured at 6 months.

EXACERBATIONS AND TREATMENT RESPONSE

Based on predefined criteria of a 50% reduction in exacerbations or a decrease in maintenance OCS dose within the first year of treatment, 8 patients (66%) were classified as responders, while 4 patients (33%) were classified as non-responders. Three patients died in the first year of treatment: two non-responders due to COPD and one responder due to an unrelated cause. Furthermore, two patients discontinued treatment in the first year due to a lack of benefit.

Treatment with mepolizumab led to a statistically significant reduction in exacerbation rates. In the analysis of moderate and severe AE, the mean annualized rate of moderate or severe exacerbations before treatment was 5.75 per year, as compared with 1.42 per year after one year of treatment (RR = 0.25, 95% CI [0.14, 0.42], p = 0.011). The reduction in hospitalization-related exacerbations was significant. The mean annual rate before treatment was 2.58 per year, as compared with 0.17 per year after one year of treatment (RR = 0.06, 95% CI [0.02, 0.27], p = 0.007). For moderate exacerbations requiring systemic corticosteroids, the mean annualized rate was 3.17 per year before treatment, as compared with 1.25 per year after one year (RR = 0.39, 95% CI [0.22, 0.72], p = 0.138).

Among patients who remained on treatment for the second year (7 patients), the annualized exacerbation rate was 1.42 per year in Year 1, as compared with 0.58 per year in Year 2 (RR = 0.47, 95% CI [0.19, 1.14], p = 0.074).

The difference in OCS maintenance use between pre-treatment and post-treatment was also analyzed. Before treatment, 4 of 12 patients (33%) were receiving chronic OCS maintenance therapy; after the first year, 2 of these patients (50%) had discontinued OCS maintenance (Fisher's exact p = 0.640).

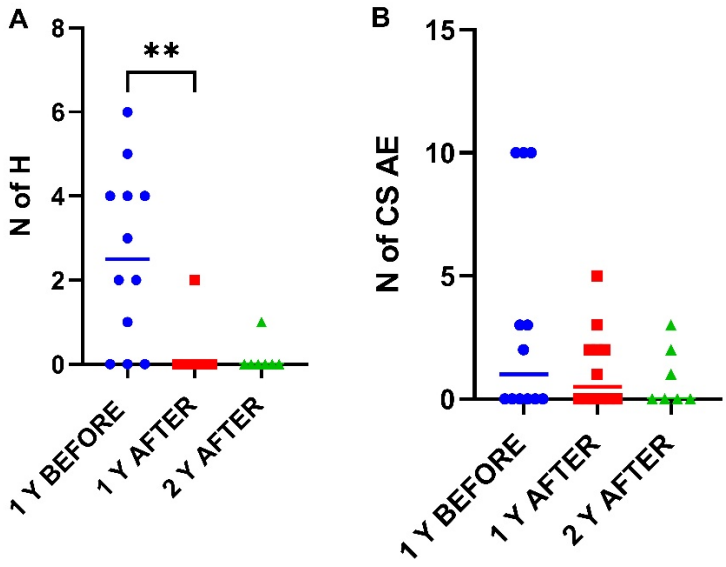

Figure 1: Acute Exacerbation numbers over time. A: AE hospitalisation over time; B: CS treated moderate AE over time

DISCUSSION

Our study demonstrated a significant reduction in moderate exacerbations and exacerbations requiring hospitalization in a small cohort of patients with severe eosinophilic COPD treated with mepolizumab in a real-world clinical setting, with 66% of patients responding to treatment in the first year. These findings provide valuable insight into the effectiveness of mepolizumab in this high-risk population, highlighting its potential role in reducing the exacerbation burden in patients with frequent, corticosteroid-dependent exacerbations.

Our study adds to the growing body of knowledge on the role of anti-IL-5 therapies in eosinophilic COPD. In the METREX trial, mepolizumab reduced the annualized exacerbation rate from 1.71 to 1.40 per year (RR = 0.82, 95% confidence interval [CI] 0.68–0.98, p = 0.04), while the METREO trial reported a decrease from 1.49 to 1.19 per year (RR = 0.80, 95% CI 0.65–0.98, p = 0.07) (7). The GALATHEA study of benralizumab reported an AE rate reduction from 2.33 to 1.19 per year, but without statistical significance (RR = 0.96, 95% CI 0.65–1.36, p = 0.65). Similarly, the TERRANOVA trial showed a decrease from 2.28 to 1.21 per year (RR = 0.85, 95% CI 0.06–1.37, p = 0.06) (8). While both mepolizumab and benralizumab were associated with numerical reductions in exacerbations, only the METREX trial demonstrated a statistically significant effect, highlighting the complexity of anti-IL-5 therapy in COPD and the need for a more refined approach to patient selection.

Our study population differed from those in these randomized trials in several important ways. In all studies, spirometric measures of disease severity, as assessed by FEV1, were similar and comparable to those in our cohort. However, our pre-treatment exacerbation rate was substantially higher, with a baseline annualized rate of 5.75 per year, compared to 2.6 per year in METREX, 2.7 in METRO, and 2.3 in both GALATHEA and TERRANOVA, suggesting that our cohort represented a more severe disease phenotype (7,8). After one year of mepolizumab treatment, exacerbations in our study were reduced to 1.42 per year, reflecting an overall 75% reduction. This magnitude of reduction exceeds that observed in clinical trials, reinforcing the importance of patient selection, particularly in those with a history of high eosinophil counts, and very frequent exacerbations requiring systemic corticosteroid treatment.

Furthermore, our study focused specifically on exacerbations requiring systemic corticosteroids, whereas randomized trials often include exacerbations treated with antibiotics or increased inhaled therapy. This likely further improved the selection precision of patients with the greatest benefit potential. A post hoc analysis of the METREX and METREO studies has already suggested that patients with higher blood eosinophil counts and those with exacerbations requiring systemic corticosteroids benefited the most from mepolizumab, which is consistent with our findings (7).

In contrast to mepolizumab, the GALATHEA and TERRANOVA trials evaluating benralizumab in patients with ≥220 eosinophils/µL failed to meet their primary endpoints for exacerbation reduction, despite high baseline BEC levels (8). This raises questions about the reliability of BEC as a predictive biomarker for anti-IL-5 response in COPD. Meanwhile, therapies targeting a broader spectrum of type 2 inflammation, such as IL-4 and IL-13 inhibition with dupilumab, have shown promising results in COPD patients with elevated eosinophils and/or FeNO. The BOREAS and NOTUS trials demonstrated both exacerbation reduction and lung function improvement in this broader inflammatory phenotype (9,10). In our study, patients had very high historical BEC levels, which, combined with frequent exacerbations, may reflect transient eosinophil surges during exacerbations. This suggests that historical BEC, rather than stable-state BEC, could serve as a more refined biomarker for identifying patients most likely to benefit from anti-IL-5 therapy. This concept is further supported by a recent study demonstrating that benralizumab successfully reduced treatment failure in eosinophilic asthma and COPD exacerbations when administered at the time of an exacerbation (11).

In our study, we also observed an improvement in lung function, a finding not reported in previous trials, suggesting that anti-IL-5 therapy may provide additional benefits beyond exacerbation reduction. This improvement may indicate that when anti-IL-5 treatment effectively reduces exacerbations, it can also positively impact other disease parameters. The observed reduction in BEC reflects a decrease in eosinophilic airway inflammation, a key pathophysiological mechanism in a subset of COPD patients. This reduction likely contributes not only to a lower exacerbation frequency but also to potential improvements in lung function.

A key strength of our study is the extended follow-up beyond one year, allowing for the assessment of longer-term treatment effects. The observed trend toward a further reduction in exacerbation rates in the second year among patients who continued with mepolizumab is an important finding. Although the small sample size limits the statistical power of this observation, it suggests that the benefits of treatment may not only persist but potentially increase over time in a carefully selected population of patients with severe eosinophilic COPD.

Despite the limitations of a small sample size and the absence of a control group, our study provides valuable real-world evidence on the effectiveness of mepolizumab in a distinct subgroup of eosinophilic COPD patients with high exacerbation and corticosteroid burden. It reinforces findings from larger clinical trials and contributes to a better understanding of patient selection for mepolizumab treatment. Future larger prospective studies are needed to confirm our findings, further assess the long-term impact of mepolizumab in this population, and compare its efficacy with other emerging biologic therapies targeting type 2 inflammation.

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INVITED LECTURE

THE SIGNIFICANCE OF EOSINOPHIL LOCATION IN SEVERE ASTHMA: INSIGHTS FROM INDUCED SPUTUM

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Eosinophils, originating in the bone marrow, are regulated by cytokines such as IL-3, GM-CSF, and IL-5, which influence their expansion and migration. In asthma, elevated eosinophil counts are observed in both blood and sputum. The use of biologic therapies targeting IL-5 and IL-13 has revolutionized treatment for eosinophilic asthma, yet the optimal biomarker for evaluating therapeutic response remains unclear.

While increased eosinophil levels in blood are often associated with asthma severity, they lack specificity, as other allergic conditions can also elevate eosinophil counts. Furthermore, eosinophil levels may primarily reflect Th2-driven inflammation rather than direct airway pathology. Although eosinophil counts are commonly used to predict responses to anti-Th2 biologics, they may not reliably indicate airway inflammation. In contrast, induced sputum analysis provides a more direct assessment of airway eosinophilia and helps differentiate eosinophilic from non-eosinophilic exacerbations. However, sputum eosinophilia is not exclusive to airway diseases and exhibits variability, limiting its reproducibility.

In severe asthma, a baseline eosinophil count above 300/µL may predict a favorable response to anti-Th2 therapies. However, even low eosinophil counts in patients on anti-IL-5 monoclonal antibodies (mAbs) may correlate with poor asthma control and persistent sputum eosinophilia. Conversely, elevated eosinophil counts in patients receiving anti-IL-4R mAbs may be associated with improved asthma control. Discrepancies between and sputum eosinophil levels, particularly in patients on systemic corticosteroids, suggest local eosinophilopoiesis driven by unneutralized IL-5 in the airways. Thus, eosinophil monitoring may not always reflect airway inflammation or treatment response.
Despite the availability of multiple biologic therapies, 10%-20% of patients switch treatments due to suboptimal response. Persistent airway eosinophilia despite anti-IL-5 therapy indicates the necessity of targeting local eosinophil production for better asthma control. Benralizumab has demonstrated superior efficacy in suppressing sputum eosinophilia compared to mepolizumab or reslizumab, making sputum eosinophils a key consideration in treatment adjustments. Additionally, factors such as sinus disease and mucus plugging may contribute to persistent symptoms.

Severe asthma is a heterogeneous disease requiring individualized, targeted therapies for optimal disease management. A comprehensive approach considering both systemic and local eosinophil activity is essential for improving clinical outcomes.

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INVITED LECTURE

IMMUNOLOGICAL PATHWAYS IN SEVERE T2 ASTHMA PATIENTS DURING DUPILUMAB TREATMENT

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BACKGROUND

Patients with severe asthma (SA) may present with type 2 (T2) inflammatory disease as shown by elevated exhaled nitric oxide (FeNO), total circulating IgE (cIgE) and peripheral eosinophilia (1,2). Dupilumab is a human monoclonal antibody targeting IL-4 and IL-13, which both play an important role in promoting T2 inflammation in SA.

IMMUNOLOGICAL EVIDENCE

By blocking IL-4 and IL-13 receptors dupilumab impacts several clinical and molecular pathways in SA.

- IL-13 suppression mitigates bronchoconstriction and mucus secretion (1), thus resulting in improved lung function parameters, such as FEV 1 (%).
- NO production takes place in airway epithelium and is stimulated by IL-13. Reduced FeNO levels are a biomarker of less intense T2 inflammation and a predictor of lower exacerbation rates. (3)
- IL-4 pathway promotes differentiation of Th2 cells, which are important mediators of T2 inflammation, and class switching of plasm cells into production of IgE (4). Reduced levels of cIgE have been observed in dupilumab treated patients.
- Eosinophils from peripheral blood are one of the main drivers of T2 airway inflammation in SA. IL-4 and IL-13 both stimulate recruitment of eosinophils through chemokine production and higher prevalence of adhesion molecules on the endothelium surface (5). Dupilumab treatment can lead to peripheral eosinophilia, if eosinophils cannot migrate to airway tissue and remain in peripheral blood.
- 19 adult SA patients treated at University Medical Centre Ljubljana from November 2021 to December 2023 were included in a prospective real-life study. Clinical, inflammatory and immunological parameters were measured at baseline before dupilumab introduction and after 12 months of follow up. Dupilumab treatment significantly improved FEV 1 % (p=0,0085), reduced asthma oral corticosteroids (OCS) related exacerbations (p=0,0051) and reduced levels of total IgE (p=0,0386). There was no significant difference in peripheral eosinophilia (p=0,1327) and FeNO (p=0,0555) (6).

CONCLUSION AND FUTURE GOALS

Introduction of dupilumab to severe T2 asthma patients broadly supresses T2 inflammation biomarkers and concomitantly improves lung function parameters. Patients experience fewer OCS-related SA exacerbations and have reduced levels of cIge. Further research is needed to clarify whether IL-4 pathway blockage is associated with the reduction of specific IgE in patients with specific atopies and their clinical outcomes.

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PATIENT WITH SEVERE EOSINOPHILIC ASTHMA AND CRSWNP WHO DEVELOPED EGPA WHILE BEING TREATED WITH BENRALIZUMAB

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We report the case of a 58-year-old obese woman who developed EGPA during treatment with benralizumab for severe eosinophilic asthma. The patient was diagnosed with eosinophilic asthma, CRSwNP, and AERD at the age of 35 and had undergone two surgeries for nasal polyps. In 2021, treatment was initiated with mepolizumab, but she was a non-responder. Therefore, after six months, her treatment was switched to benralizumab. Following this change, her quality of life, number of exacerbations, ACT score, and lung function improved. Occasionally, she required OCS due to nasal polyps (1-2 times per year), without the need for surgery. Over a four-year period, she experienced two asthma exacerbations that required OCS due to viral infections.

At the start of 2025, the patient noticed a lump in the corner of her left eye. A CT scan of the paranasal sinuses revealed a large dacryocyst. An extensive biopsy was performed, showing eosinophilic inflammation and raising suspicion for EGPA or IgG4-related disease. ANCA antibodies were negative, and eosinophil levels in peripheral blood were zero. To confirm the diagnosis and address the patient's symptoms, an ENT specialist and maxillofacial surgeon collaborated on a more extensive procedure. Pathology excluded IgG4-related disease, but EGPA could not be definitively ruled out.

CT scans revealed bilateral ground-glass opacities (GGO) in the upper lung lobes, a few small mucoid impactions, and slightly enlarged mediastinal lymph nodes. The patient declined a bronchoscopy at this time due to her recent surgery but planned to undergo the procedure after recovery. A rheumatologist was consulted, and based on all available data, a diagnosis of EGPA was made. It was decided to shorten the interval between benralizumab doses to 4 weeks, and a continuous dose of prednisone 0.5 mg/kg body weight was introduced with two 1 g/iv rituximab infusiones separated by two weeks as part of the treatment plan.

Clinicians should remain vigilant for the development of EGPA in patients with severe asthma and eosinophilia, despite benralizumab treatment, especially during the peroid of OCS withdrawal.

ASTHMA AND PULMONARY EMBOLISM: CASE REPORT

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ABSTRACT

The association between severe asthma and pulmonary embolism is still unclear. Pulmonary embolism is one of the most frequent cardiovascular diseases, with a high risk of adverse clinical outcomes. A significant number of patients at increased risk of pulmonary embolism is still not recognized in routine clinical practice. Asthma is chronic inflammatory diseases associated with procoagulants and antifibrinolytic activities in the airways. Here we present a case of severe asthma associated with pulmonary embolism, presented with shortness of breath and chest discomfort, complicated by submassive thrombosis on computed tomography angiography, successfully treated with conventional anticoagulant therapy. This case report suggests that asthma and pulmonary embolism can present with overlapping symptoms, and distinguishing between these two conditions can be challenging in clinical practice. Physicians should keep in mind that patients with asthma are at considerable risk of pulmonary embolism. Severe asthma can be associated with various comorbidities and complications, and the right identification of these risk factors is necessary to reduce the risk.

KEYWORDS: severe asthma, pulmonary embolism, inflammation, coagulopathy

THE IMPORTANCE OF DIAGNOSING AND TREATING OSA IN PATIENTS WITH SEVERE ASTHMA

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KEY WORDS: severe asthma, obstructive sleep apnea, biological therapy, CPAP

BACKGROUND

Asthma and obstructive sleep apnea (OSA) are common respiratory diseases that frequently coexist and share common risk factors, such as rhinitis, obesity, and gastroesophageal reflux disease. Estimated prevalence of OSA in asthmatic patients ranges from 38% to 70%, with asthma severity associated with a higher risk of OSA (2, 3). Conversely, asthma itself may contribute to OSA development (4). We present three patients with adult-onset severe eosinophilic asthma and clinically significant OSA. With continuous positive airway pressure (CPAP) and biologic therapy, one achieved remission, and all showed marked improvement.

CASE REPORTS

Case 1: A 59-year-old female with eosinophilic asthma and a strong psychological component experienced frequent exacerbations requiring systemic corticosteroids. We confirmed moderate OSA and initiated CPAP therapy. As inhaled corticosteroids were insufficient, benralizumab was introduced, resulting in disease remission and improved lung function.

Case 2: A 62-year-old male with asthma had six exacerbations in the past year. He had a prior diagnosis of severe OSA, for which CPAP therapy was initiated. The introduction of benralizumab led to less exacerbations.

Case 3: A 75-year-old female with severe asthma-chronic obstructive pulmonary disease overlap syndrome features, obesity, and long-term home oxygen therapy was diagnosed with moderate OSA. CPAP therapy improved symptoms, but compliance remained an issue. Mepolizumab was introduced, eliminating further need for systemic corticosteroid therapy and hospitalization.

CONCLUSION

With increasing evidence of the connection between asthma and OSA, it is important for healthcare providers to consider OSA in patients with severe or difficult-to-treat asthma. Early detection and the initiation of CPAP therapy, combined with appropriate asthma management, improved outcomes of presented patients. Further trials in this area are needed.

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INVITED LECTURE

ROLE OF OTORHINOLARYNGOLOGIST IN SEVERE ASTHMA PATIENT

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ABSTRACT

Brief statement of the purpose of the study: Upper airways have a significant role in asthma management. Therefore, the collaborative role of the otorhinolaryngologist and pulmonologist provides comprehensive care and ensures accurate diagnosis and effective treatment plans(1). With the advent of progressive research in asthma, common airways, and chronic rhinosinusitis, more overlapping molecular mechanisms have been found(2). The new knowledge has opened new opportunities for mutual collaboration to help otorhinolaryngologists overcome the legacy role in managing allergic rhinitis, chronic rhinosinusitis (CRS), and laryngopharyngeal reflux(3). The new role is to be an equal member of the multidisciplinary board for the common airways to help better diagnose and treat many illnesses of the upper and lower airways, including severe asthma.

THE METHOD USED

The Pulmonology and Department of Otorhinolaryngology and Cervicofacial Surgery at UMC Ljubljana founded a separate Multidisciplinary board for common airways (MDBCA) in the autumn of 2024. Competencies and the overall field of expertise were set by trying to establish an institutional consulting body for patients with complex upper and lower airway disease. The expert committee, frequency of sessions, and the hybrid type of meeting were chosen. The main goals were the more elaborate presentation of cases and a crossectional transfer of knowledge and expertise. The measured outcome was a number of presented patients, as well as diagnostics and treatment efficacy in terms of availability of definite care.

THE RESULT OBSERVED

From December 2024 to March 2025, MDBCA had four hybrid meetings using MS Teams. 15 patients were presented from different institutions. The mean length of sessions was 40.25 minutes. Most were for assessing the introduction of the biologicals for CRS with asthma. Three were severe asthma patients with leading lower airway disease. All but one with a positive result had therapy within three weeks of the board meeting.

THE CONCLUSIONS BASED UPON RESULTS

Collaboration in pulmonology and otorhinolaryngology has been established priorly, including mutual work with University Clinic Golnik. However, at the MDBCA level, this joint effort is preferable since the main results are available in real-time. Patients also benefit from a lack of delay in referring.

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INVITED LECTURE

EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS – A RHEUMATOLOGICAL PERSPECTIVE

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BACKGROUND

Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare small vessel vasculitis, classified according to Chapel Hill Consensus Conference among ANCA vasculitides (1). The clinically heterogeneous disease is characterized by asthma, marked upper and lower respiratory tract involvement, and necrotising vasculitis of small to medium-sized vessels. Tissue and peripheral eosinophilia are additional hallmarks of EGPA (2). Not infrequently clinical and laboratory features overlap with hypereosinophilic syndromes. Recently, the therapeutic recommendations for EGPA have been updated (3).

OBJECTIVE

the aim of our observational study was to analyse the cohort of EGPA patients diagnosed and followed at Department of Rheumatology, UMC Ljubljana and to estimate the incidence rate of EGPA in Ljubljana region.

METHODS

we prospectively collected patients, diagnosed with EGPA for the first time in the period between January 2010 and December 2024. The diagnosis of EGPA was clinical, based on the combination of clinical features, functional tests, laboratory, imaging and histological findings. Disease manifestations at diagnosis and treatment were analysed. The disease activity and severity were assessed by five factor score (4), and Birmingham vasculitis activity score (BVAS) (5). In addition, the fulfilment of ACR/EULAR 2022 EGPA classification criteria (6) was determined. Descriptive statistic was used. Results were expressed as medians and interquartile ranges (IQRs) for non-normally distributed variables, and as means with standard deviations (SD) for normally distributed metric variables. Categorical variables were expressed as absolute numbers and percentages. Finally, the incidence rate of EGPA was estimated.

RESULTS

During the 15-year observation period we diagnosed 36 patients with EGPA, 20 of them being residents of Ljubljana region. There were 18 males (50%), and the median (IQR) age at diagnosis was 60 (51; 70) years. Symptom duration time (excluding asthma) before diagnosis was 2 (2; 7) months. At diagnosis 31 (86%) of patients had known asthma and 3 additional patients were diagnosed with asthma during follow up. The average (SD) duration of asthma was 9.6 (10.2) years. The inflammation of upper respiratory tract was present in 22 patients (61%). The median (IQR) number of organ involvement was 4 (3; 4). Lungs were the most commonly affected organ (26 cases; 72%), followed by peripheral nervous system (20 cases; 56%) and skin (18 patients; 51%). Cardiac and renal involvement were detected in 13 (36%) and 11 (31%) patients, respectively. Median (IQR) BVAS score was 18 (15; 21). Five factor score of 0, 1 and 2 or more was found in 17 (47%), 12 (33%) and 7 (20%) patients, respectively. ANCA were detected in 47% patients. Thirty-four patients (94.4%) fulfilled ACR/ELAR 2022 classification criteria for EGPA. Regarding treatment, all patients except one received systemic glucocorticoids. Six patients were treated only with glucocorticoids. As an

induction therapy 19 patients (53%) received cyclophosphamide, 11 (31%) rituximab and 1 (3%) azathioprine.
The estimated average incidence rate (95% CI) of EGPA during the 15-year observation period was 2.4 (1.5; 3.8) per million inhabitants.

CONCLUSION

This study represents the first analysis of EGPA patients managed in our centre. Compared to literature data, the proportion of ANCA positive cases was higher in our cohort. In addition, for the first time ever, we have estimated the incidence rate of EGPA in Ljubljana region. Since Slovenian population is homogeneous, the numbers could be generalized for entire country.

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INVITED LECTURE

DIABETES/OBESITY/SEVERE ASTHMA

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Asthma is often related to allergies and non-allergic problems such as obesity, insulin resistance, and type 2 diabetes. These metabolic comorbidities lead more frequently to severe asthma with worse control, increased symptoms, increased use of medications, more emergency visits and hospitalisations, and poorer quality of life. Overweight or obese people have 1.5 to 2.5 times higher risk of developing asthma than lean individuals, while those with diabetes face a 2.2 times higher risk.

The management of asthma, obesity, and insulin resistance/diabetes requires a comprehensive approach. Asthma treatments include inhaled glucocorticoids, long-acting beta agonists, leukotriene receptor antagonists, long-acting antimuscarinic agents, and biologic therapies, especially for high-T2-resistant asthma. There is still a treatment gap, as some patients still have poorly controlled asthma despite advanced therapies. In those with asthma, along with obesity and insulin resistance/diabetes, the non-T helper cell 2 (Th2) phenotype is more common and generally resistant to therapies. GLP-1 and GIP/GLP-1 receptor agonists may help fill this void. Evidence suggests that GLP-1 and potentially GIP/GLP-1 receptor agonists have the ability to improve asthma outcomes indirectly by effectuating weight reduction and directly by decreasing airway inflammation and mucus production, attenuating Th2 and non-Th2 inflammation signalling, reducing interleukins 4, 5, 13, 33, as well as 1β, 6 and 17 among other mediators, lowering mast cell activity, improving surfactant production, and smooth muscle relaxation. This phenomenon has been corroborated on a broader scale, as exemplified in a study in which asthma exacerbations decreased significantly in people with moderate to severe asthma who started therapy with the GLP-1 receptor agonist compared to other drug users, six months after starting GLP-1 receptor therapy. The same trend was observed regarding asthma symptoms, and the findings remain consistent even after adjustment for variations in body mass index and glucose control, indicating that these associations and benefits are not solely dependent on weight or glucose management.

However, prospective studies are still required to rigorously evaluate the effects of GLP-1 and GIP/GLP-1 receptor agonists on primary endpoints related to lung outcomes, especially within a subset of patients characterised by uncontrolled non-Th2 asthma among obese individuals.

INVITED LECTURE

BASIC PERSONALITY TRAITS OF SEVERE ASTHMA PATIENTS AND THEIR IMPACT ON TREATMENT OUTCOME

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INDTRODUCTION

The Five-Factor Personality Model has broad usage in describing the basic personality traits related to asthma. Model was designed with the goal of categorizing observed behaviors into constructs that are relatively stable over time, and in the Serbian population, it includes Neuroticism, Extraversion, Aggressiveness, Conscientiousness, Openness, Positive and Negative Valence. The aim of the research is to examine the impact of the basic personality traits of severe asthma patients and their influence on treatment outcome measured with asthma control. Previous studies link high neuroticism with the current diagnosis of asthma and duration of symptoms.

Methods: The study was conducted in March at the Institute for Pulmonary Diseases of Vojvodina, with a total of 265 participants, including 106 individuals receiving treatment for severe asthma with biological therapy and 159 individuals not receiving treatment for severe asthma. Asthma control was measured using the Asthma Control Test and Asthma Control Questionnaire, while the basic personality dimensions were measured using the VP+2 questionnaire. The study had a correlational design, and the data were processed using SPSS 24.

THE RESULTS

Neuroticism (on entire sample) is significantly associated with poor asthma control ($r = .222$, $n = 265$, $p = .000$, $p < .01$). The correlation between neuroticism and asthma control is significant but effect is smaller in participants receiving biological therapy ($r = .236$, $n = 106$, $p = .015$, $p < .05$). We further found that neuroticism was significantly higher in participants with poorly controlled asthma in the overall sample ($p < 0.05$, $F (2, 252) = 6.159$, $p = .002$), which was not the case in patients receiving biological therapy, where such differences were marginal.

A significant correlation was also found between low conscientiousness and poorer disease control in participants on biological therapy ($r = –.213$, $n = 108$, $p = .028$, $p < .05$), as well as in the overall sample, with the lowest conscientiousness observed in participants with poorly controlled asthma ($F (2, 252) = 4.178$, $p = .02$, $p < 0.05$).

CONCLUSION

Basic personality dimensions are associated with disease control, but the influence of neuroticism is neutralized by biological therapy and psychological treatments aimed at reducing neuroticism and increasing conscientiousness.

INVITED PLENARY LECTURE

THE CHALLENGE OF COMORBID OSA IN PATIENTS WITH DIFFICULT-TO-TREAT ASTHMA

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ABSTRACT

INTRODUCTION

Obstructive sleep apnoea (OSA) and asthma are common chronic respiratory disorders with overlapping risk factors, including obesity, rhinitis, and gastroesophageal reflux disease (GERD). Their bidirectional interaction can worsen symptom control, particularly in difficult-to-treat asthma, where OSA prevalence remains unclear. Both conditions contribute to sleep disturbances, fragmented sleep, and excessive daytime sleepiness (EDS), making it challenging to differentiate symptoms. This study aimed to assess OSA prevalence in patients with difficult-to-treat asthma, nighttime symptoms, and their impact on asthma control.

METHODS

A prospective study was conducted at the University Clinic Golnik, enrolling 108 patients with difficult-to-treat asthma between August 2022 and October 2023. Patients underwent multidisciplinary evaluation, including polysomnography, asthma control assessments, and sleep questionnaires.

RESULTS

Polysomnography identified sleep-disordered breathing (SDB) in 59 patients (55%). OSA was diagnosed in 53 (49%) patients (3 [3%] with mild OSA and Epworth Sleepiness Scale [ESS] >10, 25 [23%] with moderate OSA, and 25 [23%] with severe OSA), while six had central sleep apnoea. Polysomnography results revealed that 76 (70%) had prolonged sleep latency, 87 (81%) experienced prolonged wake after sleep onset, 82 (76%) had suboptimal sleep efficiency, 62 (58%) exhibited an arousal index >15/h, and 49 (46%) had a periodic leg movement index >15/h. Patients reported a range of sleep problems, including snoring (32%), breathing pauses during sleep (28%), night awakenings (59%), night cough (42%), nocturia (70%), symptoms of restless leg syndrome (43%), restless sleep (36%), unrefreshed sleep (37%), and morning headaches (18%). Asthma control (Asthma Control Test [ACT] score <20) was significantly worse in patients experiencing breathing pauses (39% vs. 16%, p=0.007), night awakenings (71% vs. 45%, p=0.007), night cough (60% vs. 23%, p<0.001), restless sleep (51% vs. 21%, p=0.002), and unrefreshed sleep (50% vs. 23%, p=0.005).

CONCLUSIONS

Patients with difficult-to-treat asthma frequently exhibit symptoms of disrupted sleep and demonstrate poor sleep quality. Clinically significant OSA is present in half of these patients. Patients presenting with breathing pauses, night awakenings, night cough, restless sleep, and unrefreshed sleep demonstrate poorer asthma control.

KEY WORDS: obstructive sleep apnoea (OSA), difficult-to-treat asthma, polysomnography

INTRODUCTION

Obstructive sleep apnoea (OSA) and asthma are among the most common chronic respiratory disorders. The estimated global prevalence of clinically significant OSA is 10%, affecting approximately 425 million people aged 30–69 years worldwide (1). In contrast, asthma has an estimated prevalence of 4.4% (2). OSA is characterized by repetitive episodes of complete (apnoea) or partial (hypopnoea) collapse of the upper airway during sleep, occurring at the level of the soft palate, tongue, and/or epiglottis (3). Asthma, on the other hand, is defined by variable expiratory flow limitation, accompanied by symptoms such as wheezing, shortness of breath, chest tightness, and cough (4).

OSA and asthma share common risk factors, including obesity, rhinitis, and gastroesophageal reflux disease (GERD). There is a bidirectional interaction between these diseases, where one condition can influence the severity of the other (5). Difficult-to-treat asthma is characterized by inadequate symptom control despite treatment with medium- or high-dose inhaled corticosteroids combined with a second controller or maintenance oral corticosteroids. It also includes cases requiring high-dose treatment to maintain good symptom control and minimize exacerbations. Approximately 17% of asthma patients have difficult-to-treat asthma, and OSA is a potential contributing factor to poor symptom control in this group. Therefore, patients with difficult-to-treat asthma should be evaluated for comorbid OSA (4), but the prevalence of OSA in this group of patients is not known.

Both OSA and asthma can lead to fragmented sleep, poorer sleep and excessive daytime sleepiness (EDS). Recurrent coughing and dyspnoea during sleep contribute to EDS in asthma. Both conditions involve frequent awakenings due to airflow limitation, increased respiratory effort, and oxygen desaturation during sleep. (6) It is often challenging to distinguish which symptoms belong to which disease.

The aim of this study was to evaluate the prevalence of OSA in patients with difficult-to-treat asthma, the occurrence of nighttime symptoms and their influence on asthma control.

METHODS

SUBJECTS

This prospective monocentric study was conducted at the University Clinic for Respiratory and Allergic Disorders Golnik. Patients were recruited from the outpatient clinic using a multidisciplinary team (MDT) approach designed for the evaluation of difficult-to-treat asthma. All consecutive patients attending the clinic from August 2022 to October 2023 were invited to participate. The study was approved by the National Medical Ethics Committee.

All patients had been referred to the MDT outpatient clinic by secondary care pulmonologists. Clinical history was obtained, and patients underwent chest X-rays, pulmonary function tests, skin prick testing for inhalant allergens, and a six-minute walk test (6MWT). Blood samples were collected for biochemical analysis. Additionally, a pharmacist evaluated each patient's medication regimen, adherence, and inhalation technique.

STUDY PROTOCOL

Patients who consented to a sleep study were evaluated at the Laboratory for Sleep-Related Breathing Disorders. The study was conducted during a period of relative clinical stability. Patients completed sleep-related symptom questionnaires and the Epworth Sleepiness Scale (ESS). Anthropometric measurements (height, weight, neck circumference, and waist circumference) were also recorded.

Full attended diagnostic polysomnography was performed using the Alice 5 (Philips Respironics, USA) or NoxA1 (Nox Medical, Iceland) device. The recordings were manually scored by a certified European sleep expert, using American Academy of Sleep Medicine (AASM) second edition scoring rules (7).
Sleep-disordered breathing was defined based on the apnoea-hypopnoea index (AHI):

- No sleep-disordered breathing: AHI <5/h
- Mild: AHI 5 to <15/h
- Moderate: AHI 15 to <30/h
- Severe: AHI >30/h

OSA and central sleep apnoea (CSA) were classified based on the predominance of events (>50% obstructive events for OSA, >50% central events for CSA). Excessive daytime sleepiness was defined as an ESS score >10. Clinically relevant sleep-disordered breathing was defined as either AHI >15/h or AHI >5/h with ESS >10.

DATA ANALYSIS

Data were analysed using SPSS version 26.0. Results are presented as either the number of participants (%) or mean (standard deviation, SD). Categorical variables were compared using Pearson's chi-square test, while continuous variables were analyzed using an independent-sample t-test.

RESULTS

Between August 2022 and October 2023 108 patients with difficult-to-treat asthma consent to undergo in laboratory diagnostic polysomnography; 55 men (51%), 57.9 ±12.6 years old, 42 (39%) were classified as obese. Comparing men and women, men more often had comorbid arterial hypertension and coronary artery disease. Table 1 presents the basic demographical and clinical characteristics of patients included.

	Overall (N=108)	**Men (N=55)**	**Women (N=53)**	**p-value**
Age (years)	57.9 ±12.6	57.1±12.6	58.8±12.6	0.486
BMI (kg/m^2)	28.9 ± 5.5	29.2±5.1	29.7±5.9	0.640
VC (%predicted)	97.6 ± 15.4	95.1±15.5	100.3±15.0	0.077
FEV1 (% predicted)	78.4 ± 20.0	75.6±30.3	81.2±19.5	0.143
TI (% predicted)	62.8 ± 12.9	61.6±13.5	64.0±12.2	0.339
Allergic rhinitis	42 (39%)	18 (33%)	24 (45%)	0.181
Atopic status	52 (48%)	24 (44%)	28 (53%)	0.339
Arterial hypertension	43 (40%)	27 (49%)	16 (30%)	**0.045**
Coronary artery disease	4 (4%)	4 (7%)	0 (0%)	**0.045**
Diabetes mellitus II	15 (14%)	10 (18%)	5 (9%)	0.176
Hypothyroidism	9 (8%)	2(4%)	7(13%)	0.072
GERD	35 (32%)	16 (29%)	19 (36%)	0.453

Table 1: Basic characteristics of patients included, divided by gender. Data are number of participants (%), mean ± SD, BMI = body mass index, GERD = gastroesophageal reflux disease

Patients often complained of sleep problems – Table 2, most common symptoms were nocturia, night awakenings, night cough, and restless leg symptoms. Women more often experienced night cough, restless leg symptoms and unrefreshed sleep, while men more often had nocturia.

	Overall (N=108)	Men (N=55)	Women (N=53)	p-value
Snoring	34 (31%)	18 (33%)	16(30%)	0.727
Breathing pauses	30 (28%)	14 (25%)	16 (30%)	0.583
Night awakenings	63 (58%)	32 (58%)	31 (58%)	0.936
Night cough	45 (42%)	17 (31%)	28 (53%)	**0.021**
Nocturia	76 (70%)	45 (82%)	31 (58%)	**0.008**
Restless leg symptoms	46 (43%)	18 (33%)	28 (53%)	**0.035**
Unrefreshed sleep	40 (37%)	15 (27%)	25 (47%)	**0.032**

Table 2: Nighttime symptoms in patients with difficult-to-treat asthma

Asthma control (Asthma Control Test [ACT] score <20) was significantly worse in patients experiencing breathing pauses (39% vs. 16%, p=0.007), night awakenings (71% vs. 45%, p=0.007), night cough (60% vs. 23%, p<0.001), restless sleep (51% vs. 21%, p=0.002), and unrefreshed sleep (50% vs. 23%, p=0.005).

Sleep-disordered breathing (SDB) was confirmed in 59 patients (55%), including 3 patients (3%) with mild sleep apnoea and an ESS >10, 29 (27%) with moderate sleep apnoea, and 27 (25%) with severe sleep apnoea. Among them, 53 were diagnosed with OSA, while 6 had central sleep apnoea, with none in the latter group experiencing severe sleep apnoea.

Polysomnography revealed disturbed sleep in most patients, despite no reported difficulty falling asleep—76 patients (70%) had a sleep latency of less than 30 minutes. However, 87 patients (81%) experienced wake after sleep onset (WASO) exceeding 30 minutes, and sleep efficiency (SE) was below 85% in 82 patients (76%). Additionally, 23 patients (21%) had an arousal index greater than 15/h.

Patients with SDB had higher BMI (30.5 +/- 5.5 vs. 27.0 +/- 4.9, p=0.001), more often had arterial hypertension (31 (52%) vs. 12 (25%), p=0.003), and more often reported breathing pauses (22 (37%) vs. 8 (16%), p=0.015).

DISCUSSION

The present study confirms high prevalence of clinically significant OSA in population of patients with difficult-to-treat asthma and underscores the significant comorbidity between asthma and OSA. It is well-established that OSA is more prevalent in individuals with asthma compared to the general population, and this co-occurrence can have substantial implications for asthma management. (8) Our findings align with the notion that clinicians should consider screening for OSA in asthma patients, particularly those with poorly controlled symptoms, especially nocturnal manifestations.

Two studies have examined the relationship between severe/difficult-to-treat asthma and OSA prevalence. Julien et al. found that OSA was present in 50% of patients with severe asthma, 23% with moderate asthma, and 12% in the control group. The prevalence was significantly higher in severe asthma compared to both moderate asthma (p = 0.044) and controls (p = 0.003), but the difference between moderate asthma and controls was not statistically significant (p = 0.303). (9) Similarly, Yigla et al. conducted a study on 22 patients with difficult-to-treat asthma and reported an exceptionally high OSA prevalence of 95.5%. (10) It is important to acknowledge that not all studies have found a significant association between asthma severity and OSA risk. (11) Variations in the reported prevalence of OSA in asthma may be attributed to the diagnostic methods employed, with PSG generally yielding higher prevalence rates compared to validated questionnaires.

The concept of a bidirectional relationship between asthma and OSA is supported by the literature. Shaker et al. suggested a bidirectional relationship where the frequency of OSA increased with increasing asthma severity. (12) This implies a complex interplay between the two conditions, where each may influence the other. Potential pathophysiological mechanisms underlying this comorbidity likely involve both systemic and local airway inflammation. (13)

In our study, patients frequently reported sleep disturbances, which were confirmed by polysomnography. This aligns with the findings of Alanazi et al., where 66% of asthmatic patients experienced poor sleep quality, particularly those with suboptimal asthma control. (14)
Several other studies corroborate the impact of OSA on asthma control. Teodorescu et al. reported that a high risk of OSA was linked to nearly three times higher odds of poorly controlled asthma. (15) Tay et al. observed that asthmatics with OSA had worse Asthma Control Test (ACT) scores in univariate analysis. (16) In our cohort, patients experiencing night symptoms had more often poorly control asthma.

CONCLUSIONS

Patients with difficult-to-treat asthma frequently exhibit symptoms of disrupted sleep and demonstrate poor sleep quality. Clinically significant OSA is present in half of these patients. Patients presenting with breathing pauses, night awakenings, night cough, restless sleep, and unrefreshed sleep demonstrate poorer asthma control.
Our findings reinforce the clinical significance of recognizing and managing the co-occurrence of OSA in patients with asthma, especially those with poorly controlled disease.

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INVITED PLENARY LECTURE

FUNCTIONAL ALGORITHM FOR SEVERE AIRWAY DISEASE: FROM DIAGNOSIS TO FOLLOW-UP AND PHENOTYPING

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BACKGROUND

Lung function measurements are a cornerstone of asthma diagnosis and follow-up. Since in physiological terms, asthma is disease of airways with variable and reversible obstruction, tests of airway function are used in regular follow up and treatment.

This review focuses on airway development (trajectories of lung growth), respiratory infection burden in asthma development and effects of treatments of asthma on lung function outcomes.

METHODS

We have used PubMed search for relevant topics described in background using the filters of systematic review and metanalysis. We presented samples of most prevalent lung function trajectories for patients on biologic therapy and practical guidelines for lung function testing in follow-up and in patients with comorbidities.

RESULTS

25 studies linked to asthma development, influence of infections and effects of asthma treatment were chosen for analysis. We have shown that there are at least three different lung growth trajectories from childhood till adult age with predictors such as childhood asthma, atopy, early childhood wheezing, lower respiratory tract infections, particulate matter exposition, etc. There is a genetic background of early onset childhood wheeze and predisposition to develop T2 response to rhinovirus infection. Effect of biologics in severe asthma is least seen on improvement of lung function indexes, disease modifying potential of these drugs extends to remodelling reversibility and lung function improvement that can be permanent. Relationship to success on treatment is related more to Pre BD FEV1 than Post BD FEV1. Overall, the response of lung function to biologics is in general very unpredictable and the best parameter to access is the rate of variability of obstruction over subsequent visits.

CONCLUSION

We still have to monitor lung function changes in asthma, since remodelling and development of fixed airway obstruction is still an unmet need for future treatments of asthma.

CO-USE OF DUAL BIOLOGIC THERAPIES IN PATIENT WITH SEVERE ASTHMA AND ANKYLOSING SPONDYLITIS: SAFETY PROFILE

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BACKGROUND

Severe asthma and ankylosing spondylitis are chronic inflammatory diseases that require different biologic therapies. Benralizumab, an IL-5 receptor antagonist, and infliximab, a TNF-α inhibitor, have been used independently for these conditions, but limited data exist on their combined use in patients with comorbidities.

CASE PRESENTATION

A 61-year-old female with a 10-year history of asthma and ankylosing spondylitis presented to the pulmonology clinic for ongoing disease management. The patient had a significant history of poorly controlled asthma, characterized by frequent exacerbations, reliance on oral corticosteroids, and a high level of eosinophils in her blood (eosinophil count >500 cells/μL). Her asthma remained inadequately controlled despite high-dose inhaled corticosteroids (ICS) and long-acting beta-agonists (LABAs). Additionally, the patient had ankylosing spondylitis, initially treated with NSAIDs and physical therapy. Over time, she developed significant axial and peripheral joint involvement, anterior uveitis, as well as frequent morning stiffness and pain, leading to decreased quality of life and functional impairment. Benralizumab was initiated two years ago after the patient failed to achieve sufficient control with inhaled therapies and oral corticosteroids. She reported significant improvement in asthma symptoms and a reduction in exacerbations. Infliximab was introduced eight months ago after an inadequate response to NSAIDs and conventional therapy.

METHODS

The patient was closely monitored with regular clinical assessments, including asthma control tests, lung function tests, disease activity scores for ankylosing spondylitis, and laboratory tests to evaluate inflammation markers and potential side effects of combined therapy.

RESULTS

After six months of dual therapy, the patient demonstrated significant improvement in asthma control, with reduced exacerbations and improved lung function. Disease activity in ankylosing spondylitis also decreased, with reduced inflammatory markers and improved mobility. No major adverse events were noted, although mild injection site reactions were observed.

CONCLUSION

This case suggests that dual biologic therapy with benralizumab and infliximab may be a feasible and effective option for patients with both severe asthma and ankylosing spondylitis, though careful monitoring for safety is essential. Further studies are needed to better understand the long-term safety of this treatment combination.

DROBNOCELIČNI RAK PLJUČ: KJE SMO IN KAM GREMO?

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UVOD

Pljučni rak predstavlja resen zdravstveni problem, saj je najpogostejši vzrok za umrljivost in zbolevnost zaradi raka v svetu in pri nas. Razvrščamo ga v dve veliki skupini: drobnocelični rak pljuč (DRP) in nedrobnocelični rak pljuč (NDRP)

DRP predstavlja približno 15 % vseh pljučnih rakov in je ena najbolj smrtonosnih malignih bolezni z izrazito slabim petletnim preživetjem, manj kot 7 %. Je najpogostejši nevroendokrini tumor v pljučih in z drugimi (karcinoidi, velikocelični nevroendokrini tumorji) predstavlja 13% vse pljučnih tumorjev. Večina bolnikov z DRP so trenutni ali bivši težki kadilci.

DRP je prvi opisal Bernard leta 1926. Terapevtske možnosti so bile v tistem obdobju neznatne. Napredek pri zdravljenju je bilo zaznati šele s pojavom kemoterapije (KT) in radioterapije (RT) v obdobju od šestdesetih do osemdesetih let prejšnjega stoletja.

Kemoterapija (KT) na osnovi platine v kombinaciji z etopozidom in/ali radioterapijo (RT) ostaja osnovno zdravljenje DRP že zadnjih 40 let. V tem času se je petletno preživetje le malo izboljšalo iz 3,6% na slabih 7%.

Zdravljenje z operacijo je zaradi hitrega podvojitvenega časa tumorja in nagnjenosti k zasevanju le redko možno. Poskusi zgodnjega odkrivanja DRP se niso obnesli niti v populaciji z visokim tveganjem.

SIMPTOMI, DIAGNOSTIKA IN PROGNOZA

Večina bolnikov je ob postavitvi diagnoze simptomatskih. Simptomi se običajno pojavijo manj kot 3 mesece pred postavitvijo diagnoze in približno 75% bolnikov potrebuje hospitalizacijo v prvih treh mesecih po postavitvi diagnoze. Ob odkritju je rak pri 70% bolnikov že razširjen. Do sedaj opravljene študije niso pokazale dobrobiti presejalnih programov za DRP. Z letnim spremljanjem z nizkodoznim CT se ni zmanjšal niti odstotek razširjene bolezni niti se ni izboljšalo preživetje.

Simptomi kot so kašelj, sprememba značaja kašlja, hemoptiza, monofoni piski, dispneja, hripavost, bolečina, sindrom zgornje vene kave in disfagija so posledica prizadetosti pljuč in drugih organov v prsnem košu zaradi pritiska, vraščanja ali zasevanja v sosednje organe (mediastinalne bezgavke, požiralnik, srce, perikard, plevro in prsno steno). Simptomi, ki so posledica oddaljenih zasevkov, so lahko splošni, kot so neješčnost, hujšanje, utrujenost in oslabelost, zasevki v kosteh, jetrih, nadledvičnih žlezah in drugih organih pa lahko povzročajo bolečine, krvavitve, zapore organov in patološke zlome kosti, nevrološka simptomatika se pojavi ob zasevanju v CŽS. Več različnih simptomov in znakov je posledica sistemskih hormonskih učinkov tumorja, ki povzročajo različne paraneoplastične sindrome (sindrom neustreznega izločanja ADH, Cushingov sindrom, hiperparatireodizem, hiponatriemija, hiperkalciemija, nefrotski sindrom, motnje v koagulaciji in presnovi glukoze).

Ob sumu na pljučni rak opravimo najprej slikovno diagnostiko CT trojček (prsni koš, trebuh in glavo), pri omejeni bolezni tudi PET/CT in MR glave. Vzorce za patohistološko analizo in ev. sekvencioniranje naslednje generacije - NGS (pri nekadilcih z DRP) pridobimo iz najbolj dostopne spremembe bodisi iz primarnega tumorja v pljučih z bronhoskopijo bodisi s punkcijo najdostopnejšega zasevka.

Slab izid zdravljenja in nizko stopnjo preživetja napovedujejo negativni prognostični dejavniki: obsežna bolezen, slabo splošno stanje, hujšanje, kaheksija, visok LDH v serumu. K ugodnejšemu poteku bolezni poleg omejene oblike pripomore dobro splošno stanje, ženski spol, starost pod 70 let, normalna LDH in kreatinin v serumu, manjše število zasevkov pri obsežni bolezni in opustitev kajenja.

KJE SMO IN KAM GREMO?

Zaradi vse boljšega razumevanja DRP in intenzivnega razvoja novih zdravil je v zadnjem času nekaj več upanja tudi za bolnike z DRP. Čeprav do danes še nimamo zanesljivih markerjev, ki bi napovedovali odziv na zaviralce imunskih kontrolnih točk (ZIKT) pri DRP, je odobritev atezolizumaba, pembrolizumaba in nivolumaba v kombinaciji s KT doprinesla k kliničnemu napredku pri zdravljenju.

Zaradi genomske nestabilnost in skoraj popolne inaktivacije genov TP53 in RB1 je za DRP značilna dobra vaskularizacija tumorja, hitra rast in zgodnje zasevanje. Posledično ima večina bolnikov z DRP že ob postavitvi diagnoze zasevke tudi zunaj prsnega koša. Odzivnost na začetno zdravljenje je sicer dobro, vendar se bolezen pogosto ponovi. Po enem letu se rak ponovi pri več kot 88% bolnikov. Ko se rak ponovi, je bolj odporen na zdravljenje in popolna ozdravitev je izredno redka.

V zadnjem desetletju pojavnost DRP upada, predvsem zaradi zmanjšane incidence pri moških. Zdi se da PET/CT izboljša natančnost zamejitve in načrtovanja zdravljenja. Omejeni stadij (limited disease - LD) je potencialno ozdravljiva bolezen, z dolgoročnim preživetjem približno 20 % pri zdravljenju s kemoterapijo na osnovi platine in sočasnim obsevanjem prsnega koša. Hiperfrakcionirano obsevanje prsnega koša in profilaktično obsevanje glave (PCI) lahko znatno izboljšata splošno preživetje pri izbranih bolnikih z omejeno boleznijo. Pri bolnikih z obsežno boleznijo (extended disease - ED) se lahko preživetje poveča s kombinirano kemoterapijo, vendar bolezen ostaja neozdravljiva, dolgoročno preživetje je redko. Uporaba PCI lahko dodatno izboljša splošno preživetje pri razširjeni bolezni. Več novejših citotoksičnih učinkovin ima obetavno učinkovitost v zgodnjih kliničnih preskušanjih. Čeprav je bilo v predkliničnih študijah za DRP ugotovljenih veliko potencialnih molekularnih tarč, molekularno usmerjena terapija v kliničnih preskušanjih še ni pokazala bistvene učinkovitosti. Kljub temu bo prihodnji napredek pri tej bolezni nedvomno odvisen od izboljšav v našem razumevanju molekularnih mehanizmov, ki poganjajo proliferacijo in preživetje celic DRP.

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INVITED LECTURE

URGENTNA STANJA V DIAGNOSTIKI PLJUČNEGA RAKA

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UVOD

Bolniki s pljučnim rakom so pogosti obiskovalci urgentnih ambulant, že na začetku diagnostike in kasneje v procesu zdravljenja ter paliativne oskrbe.

Glavni razlogi za obiske v urgentnih ambulantah pri bolnikih, ki jim je bil kasneje ugotovljen pljučni rak, so bile nevrološke težave, plevralni izliv, pljučnice, perikardialni izliv, hemoptize in elektrolitske motnje. Zdravniki v urgentnih ambulantah bi morali biti pri kadilcih z omenjenimi težavami pozorni na možnost pojava pljučnega raka.

Pravih urgentnih stanj, ki so zahtevala takojšnje ukrepanje ali ukrepanje v 24 urah, je bilo malo (< 5 %). V literaturi zasledimo dve stopnji nujnosti. Prva stopnja nujnosti se nanaša na stanja, ki bolnika neposredno ogrožajo z okvaro organa ali življenja. Druga stopnja nujnosti so stanja, kjer je potrebno hitro, vendar ne takojšnje ukrepanje. Določena manj urgentna stanja lahko že v nekaj urah preidejo v ogrožajoča. Za pravilno ukrepanje sta največkrat odločilna klinična presoja in opazovanje bolnika.

PARANEOPLASTIČNI SINDROMI

Paraneoplastični sindromi (PNS) so skupina nepravilnosti, ki se lahko pojavijo pri bolnikih z različnimi, običajno malignimi neoplazmami. So posledica izločanja hormonov ali funkcionalnih peptidov (encimi, rastni dejavniki, citokini) iz tumorskih celic ali posledica navzkrižne imunske reakcije med tumorskim in gostiteljskim, to je bolnikovim tkivom. Ocenjujejo, da ima 10–20% bolnikov z maligno boleznijo tudi PNS. PNS so pri teh bolnikih drugi najpogostejši neposredni vzrok smrti, takoj za maligno boleznijo. Večino PNS razložita dva mehanizma: imunološki, ki je verjetno pogostejši, in neimunološki. Nosilci neimunološkega mehanizma so hormoni ali njim podobne snovi, funkcionalne beljakovine ali citokini, ki jih lahko izdelujejo nekatere tumorske celice. Ti lahko povzročajo elektrolitske in/ali presnovne nepravilnosti, npr. hiponatremijo zaradi prekomernega izločanja antidiuretičnega hormona (ADH) ali hiperkalcemijo zaradi prekomernega izločanja paratiroidnemu hormonu podobnega peptida. Nekateri PNS lahko resno ogrozijo bolnikovo življenje, so nujna stanja in zahtevajo prednostno ukrepanje. Ključno zdravljenje je učinkovito zdravljenje osnovne, maligne bolezni. Vse druge oblike zdravljenja so simptomatske, kar pomeni, da PNS ne zdravijo, ampak lahko le ublažijo njihove simptome in zmanjšajo ali preprečijo nastanek nepopravljivih okvar. Sem sodi imunosupresivno zdravljenje in plazmaferezo. Med imunosupresivnimi zdravili so prva izbira kortikosteroidi, redkeje imunoglobulini in ciklosporin.

HIPERKALCEMIJA

Hiperkalcemija je najpogostejša elektrolitska motnja pri bolnikih z malignimi boleznimi. Povezana je lahko s kostnim zasevki ali pa gre za paraneoplastično hiperkalcemijo, ki je lahko posledica ektopičnega izločanja PTH-rP, 1,25-dihidroksiholekalciferola (1,25-OHD; vitamin D) ali druge aktivne substance, ki se vpleta v presnovo kosti oz. homeostazo kalcija. PTH-rP po strukturi in delovanju posnema paratiroidni hormon (PTH). Spodbuja resorbcijo kosti in ledvično izgubo fosfata. To vodi v hiperkalcemijo in hipofosfatemijo, vrednosti intaktnega PTH (iPTH) je ob tem normalna ali znižana. V laboratorijskih izvidih izstopa visoka vrednost serumskega kalcija in ob tem zmanjšana kalciurija. Klinična slika bolnika je zelo odvisna od hitrosti nastanka hiperkalcemije in višine kalcija v serumu. Bolniki tožijo o slabosti, suhih ustih, žeji, poliuriji, zaprtju, splošni oslabelosti. Če ti simptomi niso prepoznani, sledi dehidracija, ledvična okvara, nevrološki simptomi,

kot je hipertonija, mišični krči, psihična spremenjenost, hipertenzija, življenjsko nevarne aritmije. Potrebna je izdatna hidracija bolnika z infuzijami fiziološke raztopine in stimulacija kalciurije. Ključno simptomatsko zdravilo so bisfosfonati. Zdravljenje s kalcitoninom ima manjši pomen. Vrednost serumskega kalcija po uporabi kalcitonina običajno hitro pade, vendar je učinek le kratkotrajen.

HIPONATRIEMIJA KOT POSLEDICA SIADH

SIADH (Sindrom neustreznega izločanja antidiuretičnega hormona) je najpogostejši paraneoplastični endokrini sindrom povezan z drobnoceličnim rakom pljuč. Vzrok je neregulirana proizvodnja ADH, kar povzroči hiponatremijo, nizko osmolarnost, povečano izločanje natrija v urinu ter visoko osmolarnost urina v primerjavi s plazemsko osmolarnostjo. Zdravljenje SIADH, ki je posledica PNS, vključuje zdravljenje osnovnega malignoma. Hiponatremijo pa simptomastsko zdravimo z omejitvijo vnosa tekočin na 1 liter dnevno, dodajanjem soli v prehrano ali infuzijo 3% NaCl v primeru simptomatske hiponatremije. Druge možnosti zdravljenja so antagonisti receptorjev za vazopresin, ki jih je treba uporabljati previdno, da se prepreči prekomerna korekcija hiponatremije. Hitrost korekcije natrija je pomembna, da se prepreči nevrološke poškodbe, kot je osmozna demielinizacija. Pri bolnikih z akutno hiponatremijo je korekcija 1–2 mmol/L/h varna in zadostna. Pri bolnikih s kronično hiponatremijo naj bi bila hitrost korekcije 0,5–1 mmol/L/h, brez preseganja 10–12 mEq natrija v prvih 24 urah.

PARANEOPLASTIČNI NEVROLOŠKI SINDROMI

Nevrološki PNS so redki. Natančna pojavnost ni poznana, ocenjujejo, da je 1–5-%,vendar je verjetno podcenjena, saj so zaradi redkosti in kompleksnosti številni PNS neprepoznani. Prizadet je lahko kateri koli del živčnega sistema: osrednje živčevje, živčno-mišični stik, periferno živčevje ali več nivojev sočasno. Skladno s tem je klinična slika odvisna od nivoja, na katerem je patološko dogajanje. Patogeneza je verjetno raznolika in pogosto ni pojasnjena. Za nekatere je poznan imunsko posredovan mehanizem, to je navzkrižna reakcija med antigeni tumorskih celic in njim podobnimi antigeni živčnega sistema (onkonevralni antigeni), ki jo izzovejo t. i. onkonevralna protitelesa. Prisotnost nekaterih protiteles je povezana z različnimi nevrološkimi sindromi. Prav tako je pri nekem nevrološkem sindromu lahko prisotnih več različnih protiteles. Zelo pomembna je zgodnja prepoznava, saj onkonevralna protitelesa lahko povzročijo trajno poškodbo živčnega sistema, ki vodi v trajno zmanjšano kakovost življenja bolnika. Diagnostični postopki so pogosto zahtevni in vključujejo
klinični pregled, slikovne (MR, FDG-PET/CT), serološke, elektrofiziološke preiskave elektroencefalografija, elektromiografija, analizo likvorja in drugo. Pomembna preiskava je določanje onkonevralnih protiteles v likvorju in serumu. Slabost te diagnostične metode je nizka občutljivost in specifičnost. Do 30% bolnikov nima zaznavnih protiteles v serumu ali likvorju, zaznamo pa jih tudi pri posameznikih brez znakov in simptomov in brez znane maligne bolezni.

Primer PNS na živčno mišičnem stiku je Lambert-Eatonov miastenični sindrom (LAMS). Klinična slika spominja na miastenijo gravis. Bolnik toži o šibkosti proksimalnih mišic, predvsem spodnjih okončin. Težave ima pri osnovnih dejavnostih,kot so hoja po stopnicah in vstajanje s stola. Večkratna ponovitev določenega giba težave zmanjša. Zgodaj se lahko razvijejo tudi simptomi prizadetosti avtonomnega živčevja: suha usta, zmanjšano znojenje, zaprtje, erektilna disfunkcija.

Miastenija gravis je periferni nevropatski sindrom. Patološki proces je značilen in povzročen s prisotnostjo onkonevralnih protiteles, protiteles proti acetilholinu (anti-Ach), ki delujejo na ravni nevromišične sinapse. Klinično se kaže z utrujenostjo in šibkostjo mišic, ki vključuje prostovoljne in neprostovoljne mišične

skupine. Mišična šibkost se poslabša skozi dan in z ponovljenim naporom. Ta šibkost je še posebej izrazita v proksimalnih mišicah okončin. Očesna in bulbarna prizadetost sta prav tako pogostejši kot pri LEMS. Vključenost diafragmatskih mišic je prisotna pri hudih primerih miastenije gravis.
Limbični encefalitis se kaže kot akuten ali subakuten klinični sindrom. Bolniki imajo anterogradno amnezijo, spremembe razpoloženja, halucinacije in epileptične napade.
Opsoklonus-mioklonus-ataxija je redka nevrološka motnja, ki združuje tri glavne simptome: opsoklonus: hitri, neprostovoljni in neurejeni gibi oči; mioklonus: kratki, neprostovoljni trzaji mišic ali skupin mišic; ataksija: motnje ravnotežja in koordinacije, kar lahko vodi v pogoste padce.
Paraneoplastična cerebelarna degeneracija je redka nevrološka motnja, ki je povezana z različnimi vrstami tumorjev, vključno z rakom pljuč. Simptomi se pogosto začnejo nenadoma in lahko vključujejo težave z hojo, izgubo koordinacije okončin, težave z govorom (dizartrija), težave s požiranjem (disfagija), nistagmus (nenadzorovana gibanja oči) in omotico. Včasih se lahko pojavijo tudi predhodni simptomi, kot so povišana telesna temperatura, slabo počutje, slabost in bruhanje.
Subakutna senzorna nevropatija je stanje, pri katerem pride do postopnega pojava senzoričnih motenj, kot so bolečine, parestezije ali zmanjšana občutljivost, običajno na rokah in nogah. Pogosto je povezana z avtoimunskimi ali paraneoplastičnimi ganglionopatijami zadnjega korena hrbteničnega živca.

POVIŠANA TELESNA TEMPERATURA

Bolnik toži o splošnem slabem počutju, ima zagone porasta telesne temperature, splošno propada, ima slab apetit, izgublja telesno težo. Vzrok so verjetno pirogeni citokini ali njim podobne substance, ki jih proizvajajo tumorske celice, kot so interlevkin- 1 (IL-1), tumorje nekrotizirajoči dejavnik (angl. *tumor necrosis factor*, TNF), IL-6 itd. Najprej je treba izključiti vnetni (infektivni) vzrok za povišano telesno temperaturo. Diagnoza paraneoplastične vročine je izključitvena. Spremlja lahko številne maligne bolezni, najpogostejša je pri limfoproliferativnih boleznih, pojavlja pa se tudi pri nekaterih solidnih rakih. Specifično zdravljenje je zdravljenje osnovne bolezni, simptomatsko vključuje nesteroidne antirevmatike.

OBILNA KRVAVITEV IZ DIHAL

Življenjsko nevarna ali masivna hemoptiza je opredeljena kot večja količina krvi, medtem ko je klinična nestabilnost bolj ustrezna opredelitev. Količina krvi za masivno hemoptizo se giblje med 100 in 1000 mL v 24 h. Pomembnost krvavitve temelji na njenih kliničnih posledicah, ki lahko vključujejo: obstrukcijo dihalnih poti, hipoksemijo, intubacijo, hipotenzijo, potrebo po transfuziji, enostransko pljučno ventilacijo in smrt. Pri malignih obolenjih obstajajo številni mehanizmi hemoptize, ki vplivajo na količino in hitrost krvavitve. Vzroki za hemoptize so: neovaskularizacija znotraj tumorja in v njegovi okolici, razjedanje tumorske površine, vraščanje tumorja v dihalne poti okoliške žilne strukture ter iatrogene krvavitve po posegih na dihalnih poteh. Manjša hemoptiza je veliko pogostejša kot masivna hemoptiza, ki je razmeroma redka. Določanje klinične stabilnosti bolnika je na prvem mestu. Čas nastanka, ocenjena količina izkašljane krvi in hitrost krvavitve pomagajo pri oceni tveganja. Lokacija tumorja prav tako pripomore k opredelitvi tveganja za krvavitev. CT angiografija žilja v prsnem koša z omogoča podrobno oceno mesta krvavitve. Začetni pristop k masivni hemoptizi se mora vedno začeti z obvladovanjem dihalne poti in hemodinamske stabilizacije bolnika. Ko je bolnik stabiliziran, je ključnega pomena lokalizacija strani krvavitve, da zaščitimo nekrvaveče pljučno krilo. Pri hemoptizi, povezani z maligno boleznijo, je poznavanje mesta primarnega tumorja bistveno, saj je to najverjetnejši vir krvavitve. Metastatska bolezen z obojestransko prizadetostjo pljuč pa lahko predstavlja večji izziv, saj je lahko več možnih mest krvavitve. Ko je določena stran krvavitve, je pomembno bolnika namestiti v lateralni dekubitus položaj s krvavečo stranjo navzdol. Ta položaj uporablja gravitacijo, da prepreči razlitje ali aspiracijo krvi v nepoškodovano pljučno krilo. Prisotnost obojestranskih

intraalveolarnih infiltratov lahko nakazuje razlitje krvi v kontralateralno, nekrvaveče pljučno krilo in lahko pomeni bližajočo se respiratorno odpoved. Pomembna dispneja, nezmožnost obvladovanja količine krvi ali izločkov, slabša izmenjava plinov in/ali poslabšanje hipoksemije, hemodinamska nestabilnost ali hitro napredujoča hemoptiza so vsi indikacije za intubacijo. Velikost tubusa naj bo ≥8 mm. Večji notranji premer omogoča uporabo terapevtskega bronhoskopa in drugih pripomočkov, kot so bronhialni blokatorji. Pri intubiranem bolniku se priporoča takojšnjo bronhoskopijo za odstranitev strdkov iz dihalnih poti. Terapevtski endobronhialni postopki so: bronhialni blokatorji, endobronhialna uporaba ledene fiziološke raztopine in vazokonstriktorjev, koagulacija z argon plazmo, z elektrokavterjem, laserjem, endobronhialno radioterapijo, vstavitev stentov. Konzervativno zdravljenje masivne hemoptize naj bi zagotavljalo le začasni terapevtski učinek, saj brez bolj definitivnih ukrepov obstaja 50–100-odstotna stopnja ponovitve. Bronhialna arterijska embolizacija je danes široko uporabljena kot prva in učinkovita terapija za obvladovanje masive hemoptize. Postopek vključuje arteriogram, običajno izveden z kanulacijo femoralne arterije, in embolizacijo prizadete bronhialne arterije. S kirurško resekcijo dela pljuč odstranimo vzrok krvavitve. V akutni fazi jo napravimo takrat, kadar BAE ni bila uspešna in pri krvavitvah iz velikih žil. Z odloženimi resekcijami preprečimo ponovitev krvavitve po sicer uspešni BAE.

Traneksamska kislina (TK) deluje kot antifibrinolitik. Njeno delovanje temelji na inhibiciji pretvorbe plazminogena v plazmin, kar zmanjšuje raztapljanje fibrinskih strdkov in s tem zmanjšuje krvavitve. V nekaterih primerih hemoptize je lahko peroralna ali nebulizirana uporaba TK učinkovita pri obvladovanju krvavitev. Čeprav večina raziskav obravnava hemoptizo, ki ni povezana z rakom, so nekatere manjše serije primerov pokazale pomemben učinek inhalirane in intravenske TK pri hemoptizi, povezani z malignimi obolenji.

SINDROM ZGORNJE VOTLE VENE

Tumorji zgornjega mediastinuma lahko pritisnejo na zgornjo votlo veno in posledično povzročijo moten odtok krvi v srce. Najpogostejši simptomi sindroma zgornje votle vene (SZVV) so otekanje obraza, vratu in rok. Čeprav sami po sebi niso nevarni, so lahko pokazatelj potencialno nevarnega edema drugje v telesu. Otekanje v grlo lahko povzroči dispnejo, stridor, kašelj ali disfagijo. Cerebralni edem lahko vodi do glavobola, zmedenosti in v najslabšem primeru do smrti zaradi cerebralne herniacije. Simptomi se pogosto poslabšajo pri ležanju ali sklanjanju naprej. Vidne so napolnjene vene vratu in zgornjega dela prsnega koša (kolateralni obtok). Najpogosteje vidimo SZVV pri drobnoceličnem raku pljuč. Pri tem podtipu raka je enako uspešno hitro specifično zdravljenje s kemoterapijo ali obsevanjem, pri ostalih vrstah je bolj uspešno obsevanje. V primerih akutnega SZVV s hudimi simptomi so začetni koraki zdravljenja ključni. Na srečo se v manj kot 15 % primerov SZVV pojavijo hudi simptomi. Dvig vzglavja postelje in dodatek kisika sta preprosta ukrepa za ublažitev simptomov. Intubacija je potrebna, če je prisoten znaten laringealni edem. Steroidi lahko zmanjšajo velikost tumorjev, odvisno od vrste. V literaturi ni podpore za uporabo diuretikov. Če bolnik potrebuje nujno zdravljenje venskih obstrukcij, kot so akutna obstrukcija osrednjih dihalnih poti, huda oteklina grla ali koma zaradi cerebralnega edema, je potrebno razmisliti o neposrednem odprtju ovire z endovaskularnim stentiranjem in angioplastiko s trombolizo. Takšen pristop lahko takoj lajša simptome, preden se uvedejo specifične terapije za raka, in je lahko primeren kot standardno zdravljenje za takojšnje simptomatsko obvladovanje. Endovaskularno stentiranje je prednostno v primerjavi z drugimi načini zdravljenja, saj hitreje olajša simptome SZVV v primerjavi s kemoterapijo in obsevanjem. Prav tako je stentiranje indicirano pri blagih simptomih, ki vztrajajo ali se ponovijo po sistemskem zdravljenju.

OBSEŽEN MALIGNI PLEVRALNI IZLIV

Maligni plevralni izliv je lahko prvi znak pljučnega raka ali pa nastane kot posledica zasevanja drugih malignomov. Bolnik dražeče kašlja, navaja dušenje in bolečino v prsnem košu. Pogosto potoži, da lahko leži oz. spi brez težav le na tisti strani, kjer je plevralni izliv. neslišno dihanje. Na rentgenski sliki pljuč obsežen izliv potiska mediastinum in srce na zdravo stran. Pri kliničnem pregledu ugotavljamo tahipnejo, perkutorno zamolklino in oslabljeno dihanje. Priporočeno je odstraniti največjo možno varno količino izliva, saj s tem zagotovimo maksimalno olajšanje dispneje, pridobimo podatke o zmožnosti razpenjanja pljuč in čimbolj podaljšamo čas do ponovne razbremenilne punkcije. Večina priporočil priporoča odstranjevanje do 1500ml tekom ene torakocenteze, pomembna je prekinitev razbremenjevanja v primeru pojava bolečine ali tiščanja v prsnem košu. Ob sočasnem merjenju plevralnih tlakov, s katero tekom plevralne punkcije merimo plevralne tlake in njihovo dinamiko upada, lahko varno odstranimo tudi do 5000ml, poleg tega pa nam krivulje upada tlakov z odstranjenim volumnom razkrijejo ujeta pljuča. V primeru ustreznega razpenjana pljuč in dobrega kliničnega stanja bolnika izvedemo plevrodezo s talkom, ki jo izvajamo med torakoskopijo ali preko torakalnega drena. Če ima bolnik ujeta pljuča in se plevralni izliv hitro nabira ter so potrebne pogoste izpraznitvene punkcije, bolniku vstavimo trajni drenažni plevralni kateter. Na ta način velikokrat dosežemo mehansko plevrodezo in kateter kasneje odstranimo.

MALIGNI PERIKARDIALNI IZLIV S TAMPONADO SRCA

Pljučni rak je najpogostejši primarni tumor, ki prizadane perikard, s prevalenco do 50 %. Maligni perikardialni izliv s tamponado srca predstavlja nabiranje tekočine v perikardu. Nastane, ko sta zaradi zasevkov v perikardu ali razraščanja tumorja v mediastinumu ovirani limfatična in venska drenaža. Bolniki z majhnim perikardialnim izlivom večinoma nimajo težav. Večji izlivi, ki povzročajo motnje diastolične polnitve srca in posledični padec utripnega volumna srca, pa vodijo v hipotenzijo in tamponado srca. Bolniki navajajo topo bolečino v prsnem košu, dušenje, hiter ali nereden srčni utrip, utrujenost in vrtoglavico. Pri bolniku ugotavljamo nabrekle vratne vene, tahikardijo, tihe srčne tone, pri tamponadi pa tudi paradoksni utrip – zmanjšanje sistoličnega tlaka v inspiriju za več kot 10 mmHg. Za diagnozo je treba narediti ultrazvočno preiskavo srca in izmeriti velikost izliva. Pod ultrazvočno vodeno punkcijo v enoti intenzivne terapije, ob skrbnem monitoringu bolnika, izpraznimo perikardialni izliv preko katetra, ki ga vstavimo v perikardialni prostor.

OBSTRUKCIJA DIHALNIH POTI

Obstrukcijo zgornjih dihalnih poti pri raku pljuč zasledimo redko, do nje lahko pride zaradi zunanjega pritiska tumorja ali zasevkov na sapnik ali primarnega tumorja traheje, ki pa je redek. Obstrukcija spodnjih dihal je pri bolnikih z rakom pogostejša, vendar večinoma ni življenjsko ogrožajoča. Bolniki se dušijo, kašljajo, lahko se pojavi stridor, hemoptize, avskultatorno slišimo piske. Obstrukcijo večjih dihalnih poti (pogosto že poobstrukcijski pnevmonitis) pokaže rentgensko slikanje pljuč, manjše pa pogosto vidimo le na CT slikah. Za hitro lajšanje težav dajemo bolniku kortikosteroide in kisik ter bronhodilatatorje. Bolnik mora čim prej opraviti endoskopski pregled dihalnih poti, ki je istočasno lahko že terapevtski (mehanska odstranitev tumorja s kleščicami, krioterapijo, z laserjem ali endobronialna opornica pri pritisku od zunaj).

KOMPRESIJA HRBTENJAČE

Kompresija hrbtenjače ni življenjsko ogrožajoče stanje, lahko pa vodi v hudo invalidnost. Do nje pride, če zasevek pljučnega raka raste v spinalni kanal. Običajno gre za mehko tkivno tumorsko maso, ki raste paravertebralno in najde pot skozi intervertebralne foramne, ali pa zasevek povzroči destrukcijo in posledično sesedanje vretenca, ki nato pritisne navzad na hrbtenjačo. Običajno so bolnikove prve težave

bolečine, ki jim sledijo nevrološki simptomi, kot so motnje senzibilitete, retenca urina in blata ter motnje motorike. Rentgenska preiskava lahko prikaže samo skeletne spremembe, ne pa tudi mehko tkivnih tumorskih mas. Pri razviti parezi je potrebno ukrepanje v 24 urah. Bolnika naj pregleda nevrolog, ki določi nivo okvare hrbtenjače. Na osnovi tega pregleda naredimo MR hrbtenice, v primeru kontraindikacij pa CT. Možnosti zdravljenja so: operacija (dekompresija in stabilizacija) in obsevanje ali samo obsevanje. Zasevke v skelet kot prvi znak pljučnega raka opisujejo v 2 % primerov. Če histološko rak še ni potrjen, je med operacijo nujno odvzeti tkivo za patološke preiskave. Bolnik naj miruje, predpišemo mu protibolečinsko terapijo in antiedematozno terapijo s kortikosteroidi.

ZVIŠAN INTRAKRANIALNI TLAK

Možgani so pogosto mesto zasevkov pljučnega raka. Zaradi omejene možnosti širjenja struktur znotraj lobanje ob tumorski rasti in edemu nastanejo znaki zvišanega znotrajlobanjskega pritiska. Pojavi se glavobol, slabost, bruhanje, zmedenost, vrtoglavica, v najhujših primerih otrplost tilnika, edem papile, hipertenzija in bradikardija. Drugi znaki, ki so pogosteje znaki same lege zasevkov, pa so zanašanje pri hoji, afazija, hemiplegija, motnje vida. CT glave nam razkrije zasevke, njihovo število in velikost. Bolj natančna pa je preiskava z MR, ki je potrebna, če je na CT viden le en zasevek, saj je v primeru solitarnega zasevka najuspešnejša njegova operativna odstranitev. Če zasevek ni večji od 3 cm, se ga lahko enako uspešno stereotaktično obseva. V primeru številnih zasevkov obsevamo celotne možgane. Pri obsežnem edemu uspešno blažimo simptome s kortikosteroidi v visokih odmerkih in z infuzijami manitola. V primeru epileptičnih napadov uvedemo še antiepileptike.

ZAKLJUČEK

Urgentna stanja pri bolniku, ki je v diagnostiki pljučnega raka, nastanejo kot posledica invazivne rasti tumorja, izločanja aktivnih substanc iz tumorja ali pa so posledica invazivne diagnostike. Gre za raznolika klinična stanja, ki pogosto zahtevajo multidisciplinarno obravnavo. Ker gre pogosto za neposredno ogrožujoče življenjsko stanje, moramo ukrepati hitro in je prav, da jih pozna vsak zdravnik, ki dela v urgentni ambulanti.

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INVITED LECTURE

VSTAVITEV OPORNICE V ZGORNJO VOTLO VENO

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UVOD

Sindrom zgornje votle vene (SZV) povzroči zožitev ali zapora zgornje votle vene in/ali njenih vej. Klinično se najpogosteje kaže kot zatekanje glave in vratu ter zgornjih okončin ter je lahko enostransko ali obojestransko. Lahko se kaže tudi z ortopnejo, vrtoglavico ali zamegljenim vidom, znaki so najbolj izraženi zjutraj. SZV lahko celo ogroža življenje bolnika, če nastane edem možgan ali dihalnih poti(1).

Vzrokov za nastanek SZV je več, najpogostejši je maligen, ki ga povzročita drobnocelični rak pljuč ali limfom. Vse pogosteje srečujemo SZV tudi pri pacientih z vstavljenimi različnimi katetri (bolniki na dializi, tisti s srčnimi spodbujevalci…).
Diagnoza je klinična, s slikovnimi preiskavami le potrdimo vzrok za nastalo oteklino in/ali razširjene obvodne vene. Navadno uporabimo CT venografijo, redkeje MR venografijo. Kateterski prikaz zgornje votle vene je namenjen zdravljenju in se redko uporablja kot diagnostična metoda.

Zdravimo izključno paciente, ki imajo simptome- preventivno zdravljenje slikovno odkritih sprememb ni smiselno, saj lahko do klinične manifestacije SZV sploh ne pride.
V primeru življenje-ogrožujočega SZV je potrebno čim prejšnje znotrajžilno zdravljenje. Pri bolnikih, ki so manj prizadeti, je oblika zdravljenja odvisna od etiologije- sama balonska širitev vene je navadno malo učinkovita, vstavitev opornice pa predstavlja trajen tujek v organizmu, zato znotrajžilno zdravljenje brez ustrezne opredelitve spremembe navadno ni smiselno.
Pri drobnoceličnem raku pljuč in simptomatskem SZV je znotrajžilno zdravljenje navadno prvo zdravljenje, saj je radioterapevtsko in zdravljenje s kemoterapijo zdravljenje učinkovito v 3-30 dneh (2). Pogosto je znotrajžilno zdravljenje tudi prvo pri benignih vzrokih SZV, tako da ostaja kirurško zdravljenje omejeno le v primeru, ko znotrajžilno zdravljenje ni uspešno ali izvedljivo.

IZVEDBA POSEGA

Poseg je enostaven, pričakovanih zapletov je malo. Priprava bolnika zahteva, da je tešč ter da ima ustrezne vrednosti strjevanja krvi. Najpogosteje ga izvedemo v lokalni anesteziji, splošna anestezija je občasno potrebna zaradi bolnikovega splošnega stanja ali zaradi bolečin, ki nastanejo pri širjenju vene, predvsem v primeru benignih zožitev zaradi fibroze.
Pristopimo skozi skupno femoralno veno, punkcijo izvedemo pod UZ kontrolo. Uvedemo žilno uvajalo ter poizkusimo preiti zožitev ali zaporo v zgornji votli veni. V primeru, da nam to ne uspe, navadno pristopimo še z druge strani, skozi kubitalno ali jugularno veno.
Po prehodu zožitve ali zapore prikažemo njen obseg in premer pretočne zgornje votle vene. Apliciramo 5000 IE heparina. Glede na meritve izberemo ustrezno žilno opornico. Navadno uporabimo samoraztezne žilne opornice z visoko radialno silo. V zgornjo votlo veno postavimo navadno opornico premera od 20-40 mm. Če zajema sprememba tudi vene, ki se vlivajo v zgornjo votlo veno, moramo navadno dodati opornice tudi tja (Y konfiguracija), ki so premera do 14-20 mm. V primeru, da je vena v celoti zaprta, jo lahko najprej razširimo z balonskim katetrom, saj brez tega ni možno uvesti opornice. Samo širjenje ven z balonskim katetrom navadno ni uspešno, saj se po širjenju vena najpogosteje zapre nazaj. Balonske katetre vedno

uporabimo za širitev opornice po njeni postavitvi. Ker je širjenje boleče in se bojimo raztrganja vene, se navadno odločimo za postopno širjenje z balonskimi katetri naraščajočega premera. Cilj posega je doseči dober pretok ter navadno vsaj 50% normalnega premera vene. V primeru ponovnih simptomov je mogoče poseg tudi ponoviti.

Alternativa opornicam so pokrite žilne opornice. Njihova prednost je v tem, da zmanjšajo možnost raztrganja vene, vraščanja tumorja v opornico ter njeno ponovno zaporo. Pokrite žilne opornice so vsaj dva krat dražje od navadnih ter izključijo obvodnice, ki so lahko pomembne, če nastane ponovna zapora.

Pri benignih spremembah navadno uporabljamo balonske katetre z zdravili, ki zavirajo hiperplazijo intime in verjetno omogočajo dolgoročnejšo prehodnost vene.

Občasno veno zaprejo strdki, ki jih je v veliki meri možno odstraniti z različnimi pripomočki, ki jih uporabljamo v intervencijski radiologiji. Ob tem ne moremo v celoti izključiti distalnih embolij, v tem primeru pljučne embolije, ki pa je najpogosteje subklinična ter jo pacient niti ne občuti.

Po posegu izvršimo ročno kompresijo vbodnega mesta, zaradi nizkih takov v venskem sistemu ne pričakujemo večjih zapletov. Pacient lahko vstane čez 6-12 ur, glede na velikost žilnega uvajala.

ZAPLETI

V literaturi navajajo do 9% zapletov, resnih pa 1-2% (1). Najresnejši zaplet je verjetno raztrganje votle vene, ki pa navadno ni hemodinamsko pomembno in lahko poteka subklinično, posebno pri raztrganju z žico. Metaanaliza, ki je vključila več kot 2000 bolnikov z malignimi in benignimi vzroki je pokazala uspešnost metode okrog 90% in da povrnitev simptomov v manj kot 10% bolnikov v prvem letu (3).

ZDRAVILA PO POSEGU

Priporočajo oralne antikoagulanse 3-6 mesecev po posegu za bolnike z malignimi vzroki SZV ter tiste z akutno ali subakutno trombozo. Na izbiro medikamentozne terapije bi verjetno moral vplivati tudi pretok skozi zgornjo votlo veno, ki ga dosežemo s posegom. V primeru tehnično relativno slabega rezultata bi moralo biti medikamentozno zdravljenje bolj agresivno.

ZAKLJUČEK

Vstavitev opornice v zgornjo votlo veno je enostaven postopek, ki takoj Izboljša kakovost življenja bolnikov s simptomatskim sindromom zgornje votle vene. Pri malignih vzrokih sindroma je možna kombinacija tako s kemo kot radioterapijo, ki delujeta tudi sistemsko in odpravljata vzrok zapore. Izbira vrste zdravljenja je odvisna od bolnikovega stanja, pri edemu dihalnih poti in pri možganskem edemu je znotrajžilno zdravljenje prva izbira.

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INVITED LECTURE

ALI JE DROBNOCELIČNI RAK PLJUČ LAHKO OZDRAVLJIVA BOLEZEN?

Eva Ćirić

UVOD

Drobnocelični rak predstavlja okrog 15 odstotkov vseh rakov pljuč. Gre za biološko agresivno oblika raka, za katero je značilno hitro napredovanje in zgodnje zasevanje. Bolezen je tako pri več kot dveh tretjinah bolnikov odkrita v razširjenem stadiju, ki ni več ozdravljiv. Petletno preživetje bolnikov z drobnoceličnim rakom pljuč je manj kot 7%.

Čeprav tudi pri drobnoceličnem raku pljuč (DRP) za določanje stadija uporabljamo TNM klasifikacijo, se v klinični praksi in raziskavah pogosteje uporablja delitev na omejeno in razširjeno obliko bolezni. Omejena oblika je definirana kot bolezen brez oddaljenih zasevkov omejena na prsni koš do obsega, ki ga je mogoče zajeti v radikalno obsevalno polje. Pri nekaterih od teh bolnikov lahko s kombinacijo kemo- in radioterapije ter profilaktičnega obsevanja možganov dosežemo ozdravitev. Petletno preživetje po tovrstnem zdravljenju je okrog 30 odstotkov. Nedavno objavljeni rezultati raziskave ADRIATIC pa kažejo tudi na vlogo imunoterapije oz. zaviralcev imunskih kontrolnih točk pri zdravljenju omejene oblike drobnoceličnega raka. V pričujočem prispevku bom tako osvetlila osnovne principe radikalnega zdravljenja omejene oblike DRP, katerega primarni cilj je vedno ozdravitev.

DIAGNOSTIČNE PREISKAVE ZA DOBRO ZAMEJITEV BOLEZNI

Glede na visok metastatski potencial je poleg CT glave, prsnega koša in trebuha za zamejitev bolezni priporočena PET/CT preiskava, ki pri 19 odstotkih bolnikov z omejeno obliko po CT preiskavah stadij zviša v razširjenega, pri 8 odstotkih pa iz razširjene oblike zniža v omejeno. Ob diagnozi drobnoceličnega raka pljuč ima 10 do 15 odstotkov bolnikov možganske zasevke, zato je priporočena tudi MR glave. Ker DRP hitro napreduje, naj dodatne zamejitvene preiskave ne bi podaljšale časa do pričetka zdravljenja za več kot teden dni, zato je dobro načrtovanje diagnostike brez nepotrebnega izgubljanja časa izjemno pomembno. Kadar bi dodatne diagnostične preiskave (PET/CT, MR glave) pomembno podaljšale čas do pričetka zdravljenja ali pa je bolnik močno simptomatski, zdravljenje pričnemo brez njih.

ZDRAVLJENJE LOKALNO OMEJENE OBLIKE BOLEZNI (STADIJ I DO IIA)

Bolniki, pri katerih je bolezen odkrita zelo zgodaj, to je preden zaseva v bezgavke (N0), so zelo redki. Takšnih je manj kot 5 odstotkov. Če so medicinsko operabilni in je mogoča operacija do obsega lobektomije, je to metoda, s katero začnemo zdravljenje. Po operaciji je ne glede na majhnost tumorja indicirana dopolnilna kemoterapija, v primeru pato-histološkega N2 stadija pa tudi pooperativno obsevanje. S takšnim pristopom poročajo o do 60 odstotnem 5-letnem preživetju, brez dopolnilne kemoterapije pa so preživetja precej slabša.

Bolnike z N0 boleznijo, ki niso operabilni, zdravimo s sočasno kemoradioterapijo ali pa v zadnjem času, kadar je mogoče, s stereotaktičnim obsevanjem in dopolnilno kemoterapijo. Retrospektivna analiza na veliki skupini bolnikov ni pokazala razlik v preživetju med obema pristopoma, brez kemoterapije pa je tudi pri tej skupini bolnikov preživetje bistveno slabše.

Dobrobit profilaktičnega obsevanja možganov (PCI) je pri tako zgodnjih stadijih nejasna, zato odločitev sprejmemo po pogovoru z bolnikom. V kolikor se bolnik za PCI ne odloči, se priporoča redno sledenje z MR glave na 3 do 4 mesecev prvi dve leti po zdravljenju.

ZDRAVLJENJE LOKALNO NAPREDOVALE OBLIKE BOLEZNI

Večina bolnikov z omejeno obliko bolezni ima ob diagnozi močno lokoregionalno razširjeno bolezen s pogosto obsežnimi zasevki v hilusnih in mediastinalnih bezgavkah. Zdravljenje izbora za to skupino predstavlja sočasna kemoradioterapija. Bolniki prejmejo štiri do šest krogov kemoterapije po shemi etopozid + cisplatin oz. karboplatin ter obsevanje z radikalno dozo 45 Gy v 30-ih frakcijah danih 2 krat dnevno oz. z dozo 60 do 66 Gy v 30 do 33-ih frakcijah danih 1 krat dnevno. Druga možnost je logistično precej lažje izvedljiva in se zato v našem prostoru uporablja bistveno pogosteje. Rezultati velike randomizirane raziskave CONVERT kažejo na podobno preživetje in toksičnost pri obeh režimih. Kar nekaj podatkov iz kliničnih raziskav kaže tudi na pomen čim prejšnjega pričetka z radioterapijo, saj je zgodnejši pričetek z obsevanjem in krajše celokupno trajanje zdravljenja povezano z boljšim izhodom. Obsevanje tako, če je le mogoče, priključimo že k prvemu oz. drugemu krogu kemoterapije. Kasnejši pričetek ali celo zaporedni režim, ko z obsevanjem pričnemo po zaključeni kemoterapiji, ki zmanjša obseg tumorskih sprememb v prsnem košu ter s tem obsevalno polje, pa je primeren za šibkejše bolnike in tiste z velikim obsegom bolezni. Najpogostejši neželeni učinki zdravljenja s kemoradioterapijo so poleg alopecije še hematološka toksičnost, radioezofagitis in radiopnevmonitis.

Po zaključeni kemoradioterapiji je pri vseh bolnikih na mestu presoja glede profilaktičnega obsevanja možganov (več o tem spodaj).

Opisani pristop je vrsto let predstavljal standardno zdravljenje omejene oblike DRP, ki se v zadnjih treh desetletjih pravzaprav ni bistveno spremenilo. Z njim smo dosegali 5 letno preživetje okrog 30 odstotkov. Šele lansko leto objavljeni rezultati raziskave ADRIATIC končno kažejo tudi napredek pri zdravljenju teh bolnikov. Izkazalo se je, da, podobno kot pri nedrobnoceličnem raku pljuč, dopolnilno zdravljenje z zaviralcem imunskih kontrolnih točk, durvalumabom, ki ga bolniki prejemajo 2 leti po zaključeni kemoradioterapiji ± PCI, podaljša čas do progresa bolezni in celokupno preživetje teh bolnikov. Razlika v 2-letnem preživetju je bila 10% (68 % v roki z durvalumabom in 58 % v roki s placebom). Takšen pristop bo tako v kratkem predstavljal novo standardno zdravljenje. Tudi Sloveniji zato prvi bolniki z omejeno obliko DRP, ki so nedavno zaključili z radikalno kemoradioterapijo, že pričenjajo dopolnilno zdravljenje z durvalumabom.

PROFILAKTIČNO OBSEVANJE MOŽGANOV

Pri DRP se v poteku bolezni možganski zasevki (MZ) razvijejo kar pri 50 odstotkih bolnikov. Več starejših randomiziranih raziskav je pokazalo, da profilaktično obsevanje celotnih možganov pomembno zmanjša incidenco MZ tako pri omejeni kot pri razširjeni obliki DRP. Metaanaliza randomiziranih raziskav na 987 bolnikih z omejeno ali razširjeno DRP objavljena že leta 1999 je potrdila pomembno znižanje incidence MZ (HR 0.45, $p < 0{,}001$) in pokazala za dobrih 5 odstotkov izboljšano 3-letno preživetje s PCI (HR 0.84, $p = 0.01$). V večini teh raziskav sicer CT ali MR slikanje možganov ni bilo zahtevano, zato ni povsem jasno, ali bi dobrobit v preživetju obstajala tudi ob dobri slikovni zamejitvi pred PCI. Randomizirana japonska raziskava na bolnikih z razširjenim DRP na primer, ki so pred PCI imeli negativen MR glave, dobrobiti v preživetju s PCI ni pokazala, čeprav je bila incidenca MZ s PCI signifikantno manjša. So pa imeli vsi bolniki v tej raziskavi redno sledenje z MR glave na 3 mesece in je bil progres v možganih hitro razpoznan. Podobna randomizirana raziskava z MR sledenjem na bolnikih z omejeno obliko DRP je v teku in nam bo dala odgovor glede resnične dobrobiti PCI v preživetju tudi pri tej skupini.

Zaenkrat PCI ponudimo vsem bolnikom z omejeno obliko DRP z odgovorom na kemoradioterapijo, ki so v dobrem stanju zmogljivosti. Ob tem podamo znane podatke glede dobrobiti in glede neželenih učinkov, ki lahko predvsem pri starejših bolnikih in tistih z obstoječimi nevrološkimi okvarami pomembno vplivajo na

kvaliteto življenja. Pri tej skupini bolnikov je namreč možnost kroničnih nevrokognitivnih okvar po PCI relativno visoka. Ni še povsem jasno, ali obsevalna tehnika s ščitenjem hipokampalnih regij zmanjša stopnjo nevrokognitivnh okvar, jo pa bolniku, ki se za PCI odloči, lahko ponudimo. Obsevalna doza, ki jo predpišemo za PCI, je nekoliko nižja kot pri paliativnem obsevanju celotnih možganov in je 25 Gy v 10-ih frakcijah. Kadar se bolnik za PCI ne odloči, opravljamo redno sledenje z MR glave prvi dve leti po zdravljenju.

ZAKLJUČEK

DRP je agresivna maligna bolezen, ki se pogosto, kljub dobrim začetnim odgovorom na zdravljenje, ponovi. Vseeno je ozdravitev pri nemajhnem deležu bolnikov z omejeno obliko DRP mogoča z uporabo multimodalnega pristopa, ki vključuje kemoterapijo, obsevanje, v zelo začetnih oblikah tudi operacijo in glede na podatke nedavno objavljene raziskave sedaj še imunoterapijo. Prav je, da bolniki ob prvem soočenju s to težko diagnozo slišijo takšno sporočilo.

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INVITED LECTURE

KAJ JE NOVEGA V SISTEMSKI TERAPIJI DROBNOCELIČNEGA RAKA PLJUČ?

Avtorica: Loredana Mrak

Drobnocelični rak pljuč (DRP), ki predstavlja približno 15 % vseh pljučnih rakov, že več desetletij ni doživel pomembnih napredkov v zdravljenju. Osnova terapije pri omejeni in razširjeni obliki bolezni ostaja kemoterapija na osnovi platine, pri zgodnjih oblikah pa se uporablja tudi sočasno obsevanje ali, pri zelo zgodnjih oblikah, kirurško zdravljenje. Dolgoročni izhodi zdravljenja teh bolnikov zaenkrat ostajajo slabi (5 – letno preživetje napredovale oblike < 5%).

Manjši napredek v preživetju bolnikov z metastatskim DRP je pred nekaj leti prinesla uvedba imunoterapije (atezolizumab ali durvalumab) v kombinaciji s standardno kemoterapijo na osnovi platine ter nadaljnje vzdrževalno zdravljenje z imunoterapijo z zaviralci imunskih nadzornih točk. Ta pristop je izboljšal srednje celokupno preživetje za približno dva meseca (iz 10 na 12 mesecev), vendar večini bolnikov ni prinesel pričakovanih koristi imunoterapije. Kljub temu ta terapija glede na podatke iz raziskave omogoča približno 12-odstotno 5-letno preživetje.

Leta 2024 so bili objavljeni še obetavnejši podatki o uporabi imunoterapije z zaviralci imunskih nadzornih točk po zaključku kemoradioterapije pri zgodnjem DRP. Vzdrževalno zdravljenje z durvalumabom je v primerjavi s placebom izboljšalo celokupno preživetje za 22,5 meseca (55,9 proti 33,4 meseca), kar pomeni pomemben napredek v dolgoročnih izidih zdravljenja za te bolnike.

Večina DRP slabo odgovori na zdravljenje z imunoterapijo, saj gre za t. i. »imunsko-hladne« tumorje z motnjo v predstavitvi antigenov imunskemu sistemu. Zato se je razvoj terapije pri DRP usmeril v bispecifične T-celične povezovalce. Ti se na eni strani vežejo na T-limfocit, na drugi pa na rakavo celico, s čimer vzpostavijo citolitično sinapso, ki omogoča uničenje rakave celice neodvisno od predstavitve antigena preko molekule glavnega kompleksa histokompatibilnosti I (MHC I).

Eno izmed najdlje preizkušanih zdravil iz te skupine je tarlatamab, ki je že pridobilo odobritev ameriškega Urada za hrano in zdravila (FDA) za uporabo v drugi liniji zdravljenja napredovalega DRP. Tarlatamab je bispecifični T-celični povezovalec (monoklonsko protitelo), ki se veže na molekulo CD3 na citotoksičnih T-limfocitih in na DLL3 (delta-like ligand 3) na rakavih celicah DRP. DLL3 je protein vključen v NOTCH signalno pot, ki je pri DRP spremenjena. Pri zdravih celicah se DLL3 nahaja znotrajcelično, medtem ko se pri DRP v približno 85–94 % primerih nepravilno izraža na površini rakavih celic in predstavlja tarčo za ciljano zdravljenje.

Zdravilo tarlatamab je bilo v ZDA odobreno na podlagi študije faze II DeLLphi-301, ki je preučevala njegovo učinkovitost pri bolnikih z napredovalim DRP v drugi ali naslednji liniji zdravljenja. Testirana sta bila dva odmerka zdravila, in sicer 10 mg in 100 mg, pri čemer je bila za nadaljnje raziskave izbrana doza 10 mg zaradi primerljive učinkovitosti in boljšega varnostnega profila. Podatki podaljšanega spremljanja bolnikov, zdravljenih s tarlatamabom v odmerku 10 mg, kažejo 40-odstotno stopnjo odgovora na zdravljenje, srednji čas do napredovanja bolezni 4,3 meseca in srednje celokupno preživetje 15,2 meseca. Še posebej spodbudno je dejstvo, da je pri večini bolnikov, ki so se odzvali na zdravljenje (31 od 40), ta odziv trajal več

kot 6 mesecev. Učinkovitost tarlatamaba se sedaj preučuje v študiji faze III (DeLLphi-304), kjer ga primerjajo s standardno kemoterapijo v drugi liniji zdravljenja napredovalega DRP.

Zdravljenje z bispecifičnimi T-celičnimi povezovalci prinaša tudi specifične neželene učinke, predvsem sindrom sproščanja citokinov (CRS) in nevrotoksičnost (ICANS, ki je kratica za immune effector cell-associated neurotoxicity syndrome, ki sta bila doslej bolj poznana pri CAR-T terapijah.

CRS se pojavi pri približno polovici bolnikov, najpogosteje po prvi (43 %) ali drugi dozi (29 %) zdravila, običajno v blagi do zmerni obliki s srednjim časom do nastopa simptomov 13,5 ur po aplikaciji tarlatamaba. Najpogostejši simptomi s katerimi se CRS kaže so: vročina ≥ 38 stopinj C, hipotenzija in hipoksija. Blagi primeri se obvladujejo simptomatsko z npr. paracetamolom za zbijanje vročine, občasno je potrebna tudi uporaba intravenske hidracije in aplikacija kortikosteroida. Pri zmernih in hujših primerih pa je potrebno že navedenim ukrepom pridružiti še zdravljenje s kisikom, vazopresorji in tocilizumabom.

Patofiziologija ICANS še ni dobro poznana. Povečana produkcija vnetnih citokinov lahko povzroči aktivacijo endotelijskih celic, povečano prepustnost krvno-možganske pregrade in zvišane ravni citokinov v likvorju. ICANS se pojavi pri okoli 10% bolnikov zdravljenih s tarlatamabom v odmerku 10 mg, večinoma v blagi do zmerni obliki, redkeje v težji obliki. Simptomi vključujejo zmedenost, motnje pozornosti, afazijo, tremor in mišično oslabelost. Pojavi se povprečno 30 dni po začetku zdravljenja. Gre za izključitveno diagnozo, saj so simptomi lahko podobni hudim okužbam ali sepsi, možganski kapi, elektrolitskim motnjam (hiponatremija), neželenim učinkom ob uporabi analgetikov ali napredovanju bolezni v osrednjem živčevju. V terapiji se pri blažjih primerih uporablja podporna terapija in kortikosteroidi, pri hujših pa je lahko potrebna dihalna podpora in zdravljenje epileptičnega statusa.

Zaradi teh tveganj je pri prvih dveh odmerkih zdravljenja s tarlatamabom priporočeno 24 urno bolnišnično spremljanje, pričetek zdravljenja z znižanim začetnim odmerkom ter premedikacija s kortikosteroidi in intravensko hidracijo. Zaenkrat ni zanesljivih markerjev, ki bi napovedali, kdo bo razvil CRS ali ICANS, bolj pa naj bi bili ogroženi bolniki z visokim tumorskim bremenom, številnimi predhodnimi zdravljenji in pomembnimi pridruženimi boleznimi.

V prihodnjih letih lahko poleg bispecifičnih T-celičnih povezovalcev pričakujemo tudi razvoj konjugatov protitelo-zdravilo pri zdravljenju DRP. Gre za ciljno usmerjeno terapijo, in sicer monoklonsko protitelo z vezanim s citotoksičnim zdravilom (kemoterapevtikom) prek posebne povezovalne molekule. Protitelo prepozna specifične tarčne beljakovine na površini rakavih celic in se nanje veže. Po vezavi se kompleks vnese v celico, kjer se povezovalni element razgradi in sprosti kemoterapevtik, ki nato uniči celico. Celice DRP izražajo več potencialnih tarčnih beljakovin, ki so v središču razvoja teh zdravil, med drugim B7-H3 [CD276], SEZ6 90 [seizure-related homolog 6], TROP2 [tumor-associated calcium signal transducer 2] in nenazadnje tudi DLL3. Prve klinične raziskave so pokazale obetavne rezultate, saj so ta zdravila pri bolnikih s ponovitvijo DRP bolezni dosegla visoke stopnje odgovora na zdravljenje (42–73 %).

Čeprav DRP trenutno obravnavamo kot enotno bolezen, se to v prihodnosti morda spremeni. Na podlagi ekspresije specifičnih transkripcijskih faktorjev se namreč pojavljajo delitve DRP na štiri podtipe, odvisno od prevladujočega transkripcijskega faktorja. Ta razvrstitev bi lahko v prihodnje omogočila bolj personaliziran pristop k zdravljenju in izboljšala terapevtske možnosti za bolnike.

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BIOLOGIC TREATMENT WITH RESLIZUMAB IN SEVERE ASTHMA WITH FUNGAL SENSITIZATION: A CASE REPORT OF CLINICAL RESPONSE

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INTRODUCTION

Severe asthma with fungal sensitization (SAFS) is an allergic, immune-mediated disorder that lies between nonsensitized asthma and allergic bronchopulmonary aspergillosis (ABPA). Both thermotolerant and non-thermotolerant fungi can trigger allergic sensitization in humans.

AIM

To present the case of poorly controlled asthma, despite guideline-based (GINA step 4) treatment. The patient was found to be sensitized to both thermotolerant and non-thermotolerant fungi, which led to the initiation of biologic therapy.

CASE PRESENTATION

A 47-year-old male with a 20-year history of asthma presented with worsening symptoms. He reported increased symptoms indoors, in the presence of mold. Despite treatment with inhaled corticosteroids, long-acting β-2 agonists, theophylline, and antileukotrienes, his asthma remained poorly controlled, with an Asthma Control Test (ACT) score of 10/25 and an Asthma Control Questionnaire (ACQ) score of 3.33. The patient had frequent exacerbations, requiring systemic corticosteroids more than five times in the past year. Spirometry showed moderately severe obstruction (FEV1 52%, FEV1/FVC 0.55). Although skin prick tests for Aspergillus and mold mixtures were negative, specific IgE levels for *A. alternata* (3.34 IU/ml) and *P. notatum* (12.96 IU/ml) were elevated. Total IgE was also elevated (128 IU/ml), as well as blood eosinophils (670 cells/µl). *A. fumigatus*-specific IgG was increased (83.75 U/ml), IgM was borderline (52.84 U/ml), but Aspergillus galactomannan Ag was negative. Sputum culture was also negative. Chest radiography was normal. Based on clinical evaluation, the patient met the criteria for SAFS—uncontrolled severe asthma despite conventional treatment and fungal sensitization in the absence of ABPA. As a result, biologic treatment was initiated. Commonly used biologics include omalizumab. Given the patient's eosinophilia, anti-IL5 biologics were also considered. Reslizumab was administered. After one year of treatment, the patient showed clinical and subjective improvement. Over the year, he experienced only two exacerbations, which required short-term corticosteroid use. The ACT improved to 19, and the ACQ score reduced to 2.5. Spirometry revealed improved lung function (FEV1 70%, FEV1/FVC 0.63). The eosinophil count reduced to 0 cells/µl.

CONCLUSION

The treatment approach for SAFS should be similar to other forms of severe asthma. In this case, biologics, specifically reslizumab, were effective in improving asthma control and reducing exacerbations.

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