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REVIEW

Research Progress and Comparative Evaluation of Three Cutting-Edge Chronic Obstructive Pulmonary Disease Treatment Strategies: Biologics, Bronchoscopic Lung Volume Reduction, and Stem Cell Therapies

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Abstract: Chronic obstructive pulmonary disease (COPD) is characterized by persistent airflow limitation, and traditional treatment regimens struggle to curb the progressive deterioration of lung function. Inspired by the principles of precision medicine, novel treatment strategies targeting specific disease phenotypes or key pathophysiological processes have opened new avenues for the management of COPD. This article comprehensively reviews and compares three classes of cutting-edge therapies with potential disease-modifying effects—targeted biologics, bronchoscopic lung volume reduction (BLVR), and stem cell therapy. It covers their mechanisms of action, clinical research evidence, patient selection criteria, efficacy and safety profiles, and health economic considerations. As a narrative review, this article synthesizes findings from key clinical trials and pivotal studies to provide a comparative perspective. By elucidating the advantages, limitations, and future directions of each therapy, this article aims to offer valuable guidance for treatment decisions and future research in clinical practice.

Keywords: COPD, targeted biologics, bronchoscopic lung volume reduction, stem cell therapy, precision medicine, comparative analysis

Introduction

Chronic obstructive pulmonary disease (COPD) poses a significant public health challenge globally, leading to high morbidity and mortality rates.[1] Its complex pathophysiological processes involve chronic airway inflammation, imbalance of proteases and anti-proteases, oxidative stress responses, and destruction of lung parenchyma, among multiple interconnected aspects.[2] Although inhaled bronchodilators and corticosteroids form the cornerstone of current COPD management, these methods cannot fundamentally alter the natural progression of the disease.[3] Long-term regular use of inhaled corticosteroids (ICS) can alleviate symptoms and reduce the frequency of acute exacerbations to some extent, but their impact on disease progression is limited and may be accompanied by adverse reactions such as increased risks of pneumonia and fractures.[4] More critically, data from many studies indicate that long-term adherence to inhalation devices among COPD patients is generally suboptimal,[5–9] further limiting the expected outcomes of standard treatment regimens.

The significant heterogeneity of COPD is reflected in its diverse clinical subtypes, differentiated pathophysiological mechanisms, and varying responses to treatment.[10] This heterogeneity arises from the complex interactions between genetic backgrounds and environmental exposures,[11] making the implementation of individualized precision treatment a significant challenge. Studies have shown that in COPD patients who continue to smoke, the function of corticosteroid receptors may be altered due to exposure to tobacco smoke, leading to reduced sensitivity to ICS.[4] Moreover, ICS may

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interfere with type I interferon signaling pathways, thereby enhancing the replication capacity of rhinoviruses, which partly explains why ICS cannot effectively prevent acute exacerbations induced by viral infections.[12] The limitations of the aforementioned standard therapies have prompted researchers to turn their attention to novel treatment strategies with greater disease-modifying potential.

In recent years, three categories of advanced therapies have demonstrated significant therapeutic potential. The first category encompasses biologics, exemplified by monoclonal antibodies, designed to precisely interrupt and modulate pivotal inflammatory signaling cascades.[13,14] Given the profound inflammatory heterogeneity inherent in COPD, these agents address distinct endotypes: type 2 (eosinophilic) inflammation driven by IL-5 and the IL-4/IL-13 axis, in contrast to non-type 2 pathways characterized by neutrophilic infiltration and mediated by IL-17 and tumor necrosis factor-alpha (TNF-α). For instance, Tezepelumab, an anti-TSLP monoclonal antibody, inhibits downstream type 2 inflammatory cascades by neutralizing TSLP, an "alarmin" secreted by airway epithelial cells.[15,16] The second category comprises bronchoscopic lung volume reduction (BLVR), which employs minimally invasive strategies, such as unidirectional endobronchial valves, to induce collapse of hyperinflated, functionally compromised lung parenchyma. This approach directly counteracts the mechanical sequelae of emphysema—namely, severe hyperinflation, loss of elastic recoil, ventilation/perfusion mismatch, and diaphragmatic dysfunction—thereby restoring pulmonary mechanics and gas exchange efficiency.[17] The third category involves stem cell therapies, which exert their effects through immune modulation, potent anti-inflammatory activity, and the capacity for tissue repair and regeneration. These interventions aim to mitigate the impaired tissue repair, chronic inflammatory microenvironment, and cellular senescence that define the pathophysiology of COPD.[18] Furthermore, emerging avenues, including nanodrug delivery systems, exosome-based therapeutics, and anti-senescence strategies (eg, senolytics), offer novel opportunities for COPD management.[19,20] This article examines these three cutting-edge therapeutic modalities, systematically evaluating their mechanisms of action and clinical utility. Additionally, it discusses their clinical positioning, current challenges, and future trajectories within the framework of personalized COPD treatment.

Biologic Therapy: Targeting Inflammatory Pathways

Mechanisms of Action and Target Selection

The inflammatory phenotype of COPD exhibits significant heterogeneity, providing a theoretical basis for the development of targeted therapeutic strategies. However, this heterogeneity also poses challenges for precise intervention.[10,21] Approximately 20% to 40% of COPD patients exhibit type 2 inflammation characterized by eosinophilia and increased levels of type 2 cytokines (including IL-4, IL-5, IL-13). Biologic agents can target key molecules in the inflammatory pathway (including IL-5, IL-4/IL-13, TSLP) with high selectivity, thereby specifically inhibiting the inflammatory response.[22] Current research on biologics primarily focuses on type 2 inflammatory responses, with the core therapeutic strategy targeting IL-5 or its receptor (IL-5R). Anti-IL-5 antibodies (such as mepolizumab and reslizumab) and anti-IL-5Rα antibodies (benralizumab) effectively inhibit the differentiation, activation, and survival of eosinophils by neutralizing IL-5 or blocking its receptor, thereby reducing eosinophil levels in peripheral blood and sputum, ultimately decreasing the risk of acute exacerbations.[13,23] A meta-analysis demonstrates that anti-interleukin-5 (IL-5) therapy is associated with a lower risk of acute exacerbations in COPD (rate ratio 0.92, 95% CI 0.86–0.97); however, this effect may depend on baseline eosinophil levels.[24] Another important therapeutic target is the IL-4/IL-13 pathway, exemplified by dupilumab, which specifically binds to the IL-4 receptor alpha subunit (IL-4Rα). This subunit is a common component of both the IL-4 and IL-13 signaling pathways. By antagonizing IL-4Rα, dupilumab simultaneously inhibits the signaling of these two key type 2 inflammatory cytokines, reducing inflammatory cell recruitment and activation, decreasing mucus hypersecretion, and delaying airway remodeling.[14] The latest Phase III clinical trials (such as the NOTUS and BOREAS trial) have further demonstrated that dupilumab significantly reduces acute exacerbations and improves lung function in COPD patients with blood eosinophil counts (BEC) ≥300 cells/μL.[14,25,26] Clinical research evidence indicates that elevated peripheral BEC predict better therapeutic responses to interventions targeting type 2 inflammation.[27]

However, the inflammatory mechanisms of COPD extend far beyond type 2 inflammation. Exploratory studies targeting inflammatory mediators such as TNF-α, IL-1β, and IL-6 have mostly failed to reach primary clinical endpoints,[2,28] highlighting the insufficient research on non-eosinophilic (ie, T2-low) type COPD and the current lack of effective targeted treatment options.

Clinical Efficacy Evidence and Patient Selection

The clinical efficacy of biologics depends heavily on precise patient selection, with peripheral BEC serving as a key biomarker. For COPD patients with an eosinophilic phenotype (eg, BEC ≥300 cells/μL, or BEC ≥150 cells/μL with a history of acute exacerbation), anti-IL-5/IL-5R therapies have demonstrated a reduction of approximately 20–25% in the annual rate of moderate to severe acute exacerbations in multiple phase III clinical trials. However, such therapies have limited and inconsistent effects on lung function indicators (such as forced expiratory volume in one second, FEV1).[13,23] Similarly, dupilumab has also confirmed its efficacy in reducing acute exacerbations in COPD patients with eosinophilia.[14] Currently, dupilumab and mepolizumab have been included in the treatment recommendations of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines. The use of other biologics in COPD treatment remains investigational and is currently only regarded as an individualized therapeutic option for specific patient subgroups, rather than a recommended first-line regimen.[29] In terms of patient selection, in addition to BEC, a comprehensive assessment considering clinical indicators such as asthma history and frequent acute exacerbation history is also necessary.[30,31] Patients lacking clear type 2 inflammatory biomarkers (ie, low BEC levels) are unlikely to benefit from biologic therapy.[32,33] Future research directions include exploring combinations of sputum cell classification and multi-cytokine profiles as biomarkers to further optimize patient selection strategies.[34,35]

Safety, Limitations, and Future Prospects

Overall, targeted biologics for type 2 inflammation are generally well-tolerated, with common adverse events such as headache and injection site reactions, while anaphylaxis is relatively rare, which indicates a favorable safety profile. However, long-term safety data continue to be accumulated.[36] These therapies also have significant limitations: (1) Their efficacy is limited to specific inflammatory phenotype patients, with a narrow coverage of the population; (2) The high cost of treatment places a certain burden on healthcare resources; (3) They cannot reverse already established structural lung changes such as emphysema or pulmonary fibrosis.[37] Future research should focus on exploring new targets for neutrophilic inflammation (eg, CXCR2 antagonists) and evaluating treatment strategies that combine biologics with interventional therapies such as BLVR.

BLVR: Reshaping Pulmonary Mechanics

Technical Principles and Procedure Selection

BLVR is a safe and effective treatment strategy for patients with advanced emphysema, indicated for patients who continue to experience severe dyspnea despite adequate pharmacological treatment.[29,38,39] Its core mechanism involves the use of bronchoscopic intervention techniques to induce collapse of overinflated, non-functional target lung lobes, thereby reducing total lung volume, enhancing diaphragm function and the elastic recoil of the remaining lung tissue, ultimately alleviating dyspnea.[40,41] Emphysema causes irreversible reductions in lung compliance, resulting in gas trapping, while BLVR aims to optimize lung function and control clinical symptoms by reducing overinflation.[17,42]

Current technical approaches mainly include the following: (1) unidirectional valve implantation: this technique allows gas to escape from the target lung lobe while preventing its inhalation, thereby inducing lobar atelectasis, primarily suitable for patients with heterogeneous emphysema and intact fissures;[40,41] (2) thermal vapor ablation: this technique induces local inflammatory responses and fibrosis by delivering high-temperature water vapor, requiring relatively low integrity of fissures and suitable for both homogeneous and heterogeneous emphysema;[43,44] (3) coil implantation or polymer lung volume reduction: this technique achieves lung volume reduction through the mechanical wrinkling effect produced by the implants.[17,42] The ongoing development of these technologies aims to provide an

effective treatment option for patients with severe COPD that falls between pharmacological treatment and surgical intervention.[38,41]

Clinical Efficacy and Patient Selection

Multiple clinical studies have confirmed that carefully selected patients with severe emphysema experience significant and sustained improvements in lung function indicators (such as FEV1 and residual volume, RV), exercise tolerance (assessed by the 6-minute walk distance, 6MWD), and quality of life (measured by the St. George's Respiratory Questionnaire, SGRQ) after undergoing BLVR (especially unidirectional valve and thermal vapor ablation) treatment, with effects lasting for several years.[39,41,42,45–48] The key to successful treatment lies in precise patient selection, a process that typically requires a multidisciplinary emphysema diagnostic and treatment team for comprehensive evaluation.[49]

Core selection criteria include: (1) diagnosis of severe emphysema (FEV1 percentage of predicted value 15%-45%, RV exceeding the predicted value by 175%); (2) persistent severe dyspnea symptoms despite adequate pharmacological treatment; (3) high-resolution computed tomography (HRCT) confirming heterogeneous distribution of emphysema with intact fissures (particularly important for valve treatment); (4) smoking cessation for more than 4 months; (5) absence of severe comorbidities.[50] Retrospective analyses indicate that only about 19% of referred patients meet the criteria for BLVR, with the main exclusion reasons being lack of suitable target lobes, mismatched emphysema phenotype, or insufficient degree of overinflation.[50] Notably, patients who meet the selection criteria and receive treatment have significantly longer survival than those who are not selected,[49,50] suggesting that a successful patient selection process may itself be an important prognostic predictor.

Complications, Cost-Effectiveness, and Research Progress

Although BLVR is a minimally invasive interventional treatment, it still carries certain risks of complications, primarily including chronic obstructive pneumonia (more common after valve implantation but usually controllable), pneumothorax, hemoptysis, and acute exacerbations of COPD.[38] Among these, the incidence of pneumothorax can be as high as 34.3%, with most cases requiring chest tube drainage.[49] However, at experienced medical centers, the incidence of serious complications is relatively low.[51] In terms of cost-effectiveness, the upfront treatment costs of BLVR are high, but it may achieve long-term savings in healthcare costs by significantly reducing hospitalizations due to acute exacerbations of COPD.[42] The GOLD guidelines recommend BLVR based on level A evidence, and more than 25,000 procedures have been performed globally.[29,38,42] Current technical advancements include developing new treatment models for patients with collateral ventilation,[52] a bilateral BLVR strategy combining surgical fissure completion followed by valve placement,[53] and further optimizing patient selection criteria using imaging techniques such as quantitative CT and lung perfusion scans, which are also current research hotspots.[42,49]

Stem Cell and Cell Therapy: Repairing and Modulating Function

Cell Types and Their Mechanisms of Action

Stem cell therapy opens new possibilities for the treatment of COPD. Its core mechanism of action does not involve direct differentiation into functional lung cells, but rather relies primarily on paracrine effects, releasing exosomes, various growth factors, and anti-inflammatory cytokines, thereby achieving multiple biological effects.[54] This paracrine mechanism involves the continuous release of exosomes, vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), and various other growth factors, as well as anti-inflammatory cytokines; these molecules operate as a sophisticated regulatory network, synergistically mediating multiple biological effects such as inhibiting the inflammatory storm, promoting tissue repair, and regulating immune responses.[54] Mesenchymal stem cells (MSCs) are currently the most widely studied cell type and can be sourced from bone marrow, adipose tissue, umbilical cord, and other tissues.[55,56]

MSCs primarily exert their effects through the following pathways: (1) immune modulation: inhibiting the excessive activation of T lymphocytes and macrophages, thereby alleviating chronic inflammatory responses in the lungs;[57] (2) anti-fibrotic and anti-apoptotic effects: delaying the progression of lung tissue fibrosis and promoting endogenous repair

mechanisms;[58,59] (3) promoting angiogenesis: improving pulmonary vascular remodeling and related pulmonary hypertension. Additionally, endothelial progenitor cells (EPCs) are believed to be involved in the repair process of pulmonary vascular endothelium.[60,61] Specific cell types derived from induced pluripotent stem cells (iPSCs) are still in preclinical research stages.[62] Although iPSCs possess nearly unlimited self-renewal and multi-directional differentiation potential, their clinical application faces critical challenges including insufficient cell maturity and effective integration in vivo.[62] MSCs therapy, as a cutting-edge regenerative medicine strategy, demonstrates unique potential in the treatment of COPD.[63]

Current Clinical Research Status and Challenges

Currently, most related clinical studies are in Phase I or II trials, primarily aimed at assessing safety and preliminary efficacy.[60] Commonly used administration routes include intravenous infusion and bronchial instillation.[56,64] Existing small-scale clinical data indicate that MSC treatment is generally safe, with no reported serious treatment-related adverse events or tumorigenic risks.[65] However, evidence regarding its efficacy remains inconsistent: some studies indicate that post-treatment, patients show trends of improvement in inflammatory markers (such as C-reactive protein, CRP), quality of life scores (eg, SGRQ), and 6MWD.[66] A meta-analysis including 11 studies and a total of 371 patients found that stem cell therapy significantly increased patients' 6MWD (average increase of 52 meters), and FEV1 also showed a positive trend of improvement (average increase of 71 milliliters).[66] Nevertheless, there is still a lack of large-scale, rigorously designed phase III randomized controlled trials to confirm its clinical efficacy.[62]

Key challenges in this field include: (1) non-standardized treatment protocols: the optimal cell source, treatment dosage, administration route, and frequency have not been clearly defined;[55] (2) lack of efficacy predictive biomarkers: currently, there are no reliable biomarkers to predict which patients may benefit from treatment;[65] (3) low cell survival and homing efficiency: MSCs have limited ability to home to diseased lung tissue in vivo, and their survival rate post-transplantation is low;[67] (4) regulatory and production standardization issues: there is a need to establish unified quality control standards to regulate the production and oversight of cell products.[68]

Future Prospects

Future Research Directions May Focus on the Following Aspects

Acellular Therapies

Research on acellular therapies focuses on thoroughly analyzing exosomes derived from MSCs and their key effector molecules, such as microRNAs and proteins, aiming to develop acellular therapeutic products based on these components.[69] Notably, exosomes are recognized as key carriers mediating the therapeutic effects of MSCs.[54] These nanoscale vesicles are internalized by target cells, facilitating the transmission of repair signals and the modulation of immune responses. Furthermore, due to their low immunogenicity and low risk of tumorigenesis, these vesicles are regarded as therapeutic tools with superior therapeutic potential compared to traditional live cell therapies.[70,71]

Genetic Engineering Modifications

Genetic engineering strategies involve modifying MSCs to enhance their therapeutic properties. For instance, MSCs overexpressing Wnt3a demonstrated stronger homing and differentiation capabilities in COPD animal models, thereby more effectively alleviating disease symptoms.[72]

Integration of Nanotechnology

Utilizing nanocarriers to deliver the stem cell secretome (ie, all active factors released by stem cells) to address the issue of low targeted delivery efficiency.[73]

Personalized Treatment Strategies

Since different phenotypes of COPD (such as chronic bronchitis type and emphysema type) may have varying responses to MSCs treatment,[74] it is essential to deeply explore personalized therapy strategies based on the patient's COPD phenotype.

Comparative Treatment Paradigms of the Three Therapies

In the absence of direct head-to-head comparative trials, the analysis presented herein relies on a theoretical synthesis of existing indirect evidence, therapeutic mechanisms, and clinical applications.

Differences in Action Targets and Treatment Goals

Biologics

Biologics utilize an "anti-inflammatory and stabilizing" strategy, with well-defined action targets, focusing on specific inflammatory signaling pathways (such as IL-5, IL-4/IL-13). The treatment goal is to control chronic inflammation and reduce the frequency of acute exacerbations. Long-term maintenance treatment is typically required, but it cannot reverse structural damage already formed in lung tissue. They are primarily suitable for patient subgroups with specific biomarkers (such as elevated eosinophil counts) who frequently experience acute exacerbations.[75]

BLVR

BLVR belongs to the category of "mechanical remodeling" strategies, directly targeting the physical and mechanical abnormalities caused by emphysema. By folding non-functional, overexpanded lung tissue via BLVR, the mechanical properties of the lungs (such as elastic recoil) can be immediately improved, and patient symptoms can be alleviated. Its efficacy is typically observed within weeks after the interventional procedure and may last for 3 to 5 years. It is suitable for patients with well-defined anatomical targets (such as heterogeneous emphysema), significant pulmonary hyperinflation, and an inadequate response to optimized drug therapy.[45,76]

Stem Cell Therapy

It embodies a "biological modulation and repair" strategy, featuring multi-target characteristics, focusing on immune modulation and potential tissue repair. Its goal is to modulate the imbalanced pulmonary immune microenvironment and slow disease progression. The onset time, effect intensity, and duration are still uncertain, and repeated dosing may be needed to maintain effects.[69] Additionally, the screening criteria for applicable populations have yet to be established.[62]

Similarities and Differences in Applicable Populations and Screening Criteria in Table 1

Efficacy Characteristics, Onset Speed, and Durability

Biologics

Biologics typically show efficacy within weeks to months, primarily aimed at reducing the frequency of acute exacerbations,[14] and typically require long-term maintenance therapy. Efficacy may diminish after treatment interruption, with a potential risk of developing anti-drug antibodies.[77]

Table 1 Applicable Populations and Screening Criteria for the Three Therapeutic Methods

Screening Dimension	Biologic Agents	Bronchoscopic Lung Volume Reduction	Stem Cell Therapy
Core Criteria	Blood biomarker (BEC≥150–300 cells/μL) + history of frequent exacerbations	Imaging anatomical features (heterogeneity of emphysema, integrity of interlobar fissures) + pulmonary function parameters (RV>175% predicted value)	No clear universal standards, early studies included moderate to severe COPD patients
Key Technologies	Eosinophil count, asthma history	High-resolution CT, quantitative CT analysis, perfusion scanning	Potential biomarkers: cytokine profiles, immune cell subpopulations, exosome contents
Screening Results	Only 21.7% of patients in the real world meet the criteria	Only 19% of referred patients were ultimately selected	Awaiting large-scale studies to establish stratification models

BLVR

BLVR has a rapid onset (within weeks post-surgery) and a long duration of effect (usually over 3–5 years),[38,78] providing structural and functional long-term benefits. It is classified as a one-time or limited intervention.

Stem Cell Therapy

Its effects may present slow and sustained characteristics, with specific mechanisms not fully elucidated.[60] Improvements in some clinical indicators can be observed within months after a single infusion; however, it remains unclear whether this improvement signifies a long-term change in disease progression, and future repeated dosing may be needed to maintain efficacy.[69]

Safety, Accessibility, and Health Economic Considerations

Safety Risk Profiles

Biologics

Main risks are related to the immune system, including theoretically increased risks of infections and allergic reactions, but overall risk is manageable.[79] Elderly patients (>70 years) typically show good tolerance,[13,14,80] and no significant adverse effects have been observed during pregnancy.[81]

BLVR

Minimally invasive surgical procedures are characterized by an inherent safety profile. BLVR primarily comprises techniques including valve implantation and thermal steam ablation. Despite being minimally invasive, these interventions carry risks associated with general surgical complications.[82] Specifically, the main risks of valve implantation include postoperative pneumonia and pneumothorax.[51] Thermal steam ablation uses thermal energy to induce fibrosis in the targeted lung tissue, posing postoperative risks that primarily include inflammatory reactions and hemoptysis.[83] Although the incidence of these serious complications is reported to be low in experienced centers, the procedure itself is technically demanding, highlighting the necessity of a collaborative multidisciplinary team (including respiratory medicine, thoracic surgery, imaging, and anesthesiology doctors) to jointly complete patient assessment, surgical procedures, and postoperative management.[84] Therefore, the safety of BLVR depends not only on the technology itself but also on the expertise of the clinical team and the strict screening of indications.

Stem Cell Therapy

Theoretical risks include infusion-related reactions, pulmonary embolism, abnormal cell differentiation, or potential tumorigenicity, but to date, no such serious adverse events have been reported in ongoing clinical studies.[65,85] The lack of long-term safety data is a key issue limiting its development.[86]

Costs, Accessibility, and Clinical Implementation

Biologics

Annual treatment costs are extremely high and depend on cold chain logistics and regular dosing, limiting widespread application due to healthcare insurance coverage.[87,88] In real-world applications, challenges include insufficient biomarker testing and a low proportion of patients meeting strict treatment criteria (only about 21.7%).[89]

BLVR

While the upfront cost of a single therapy is substantial, it may reduce overall medical expenditures in the long run.[90] The implementation of this technology has high barriers, requiring advanced bronchoscopy skills, precise imaging assessments, and support from multidisciplinary collaborative teams.[91] Artificial Intelligence (AI)-assisted CT quantitative analysis technology helps optimize patient selection.[92]

Stem Cell Therapy

The preparation process is complex, with current costs unknown and expected to be extremely high.[93] Its future accessibility will be constrained by production capacity, quality control systems, regulatory approval processes, and final pricing strategies.[93,94]

Current Clinical Guidelines Positioning and Real-World Applications

Recommendations From Domestic and International Guidelines

Biologics

Although the GOLD 2024 guidelines initially referenced biological agents, they were not formally recommended in that iteration. Currently, dupilumab and mepolizumab have been officially included in the treatment recommendations of the GOLD guidelines, with dupilumab recommended for specific COPD patient populations based on Grade A evidence.[29] In contrast to asthma management, biological therapy for COPD has not yet established a systematic and standardized treatment regimen.[95]

BLVR

The GOLD guidelines recommend EBV-BLVR based on Grade A evidence for carefully selected patients with severe emphysema, while LVRC-BLVR and BTVA-BLVR are supported by Grade B evidence.[29] Numerous clinical studies have also confirmed that EBV-BLVR can significantly improve lung function, exercise tolerance, and quality of life.[38,41,45,76]

Stem Cell Therapy

Currently, no major international guidelines recommend its routine clinical use for COPD,[66,86] and it is limited to evaluation in well-designed, strictly regulated clinical trials.

Challenges and Optimization Strategies in Real-World Applications

Biologics

The primary barrier is the low uptake of biomarker testing. Optimization strategies include enhancing clinical physician education and establishing patient stratification management processes based on BEC.[96]

BLVR

Challenges mainly arise from the complexity of the patient selection process. Optimization strategies include establishing regional emphysema diagnosis and referral centers, ensuring the accuracy of patient selection and treatment safety through comprehensive assessments by multidisciplinary teams.[91]

Stem Cell Therapy

Future challenges include rigorous validation of efficacy (requiring Phase III randomized controlled trials), standardization of the treatment process (involving cell source, preparation processes, dosing regimens, etc), and approval from regulatory agencies (which requires long-term safety data support).[97]

Evolution Directions of Various Therapies

Biologics

Progressing towards enhanced precision, utilizing multi-omics technologies to define more refined disease subtypes. The development of bispecific antibodies or drugs targeting novel sites (such as CXCR2 antagonists) to cover a broader range of inflammatory mechanisms.[98,99]

BLVR

As an effective treatment for severe emphysema, BLVR have become well-established. Future efforts should focus on optimizing patient selection strategies to maximize clinical benefits and minimize associated risks. Future research should concentrate on improving the accuracy of patient screening, particularly regarding the assessment of emphysema

distribution homogeneity.[100] Although BLVR, such as endobronchial valve placement, is primarily suitable for patients with heterogeneous emphysema and intact interlobar fissures, the efficacy and safety of alternative techniques, such as coils, polymer sealants, or thermal ablation, in the broader population of patients with homogeneous emphysema still require more robust evidence.[100] In clinical practice, it is essential to integrate quantitative imaging metrics with clinical symptoms (such as the COPD Assessment Test score) and pulmonary function parameters to establish a comprehensive and reliable preoperative evaluation system.[101]

Stem Cell Therapy

Evolving from cell products to acellular products (such as exosomes, conditioned media).[69] Developing "ready-to-use" universal products (such as induced pluripotent stem cell-derived cells) to overcome batch-to-batch variability issues of autologous cell sources.[62]

Conclusion

The treatment landscape for COPD is undergoing a profound paradigm shift from the traditional "one-size-fits-all" model to individualized precision medicine. Biologics, BLVR, and stem cell therapy provide unprecedented treatment possibilities for patients with different disease phenotypes from the perspectives of molecular immunity, anatomical mechanics, and tissue regeneration repair.

According to expert strategic assessments, the successful application of biologics marks the entry of COPD into the era of "biomarker-driven" treatment. Monoclonal antibodies targeting pathways such as IL-5 and IL-4/IL-13 constitute precise approaches to targeted anti-inflammatory therapy, particularly suitable for patients with specific types of inflammation like eosinophilic inflammation. Data from the BOREAS and NOTUS trials demonstrated that dupilumab reduced the annual rate of moderate-to-severe acute exacerbations by 31% and improved FEV1 in patients with COPD exhibiting the specific phenotype; similarly, Phase III clinical data from the MATINEE study showed that mepolizumab reduced the annual incidence of moderate-to-severe acute exacerbations by 21% and the risk of emergency department visits or hospitalizations by 35% in patients with COPD. However, the widespread application of biologics remains limited by an incomplete understanding of COPD inflammation types, the lack of stable and reliable biomarkers, and insufficient long-term efficacy and safety data. Additionally, biologics cannot reverse structural damage. High-quality clinical studies, such as LIBERATE and STEP-UP, have confirmed that BLVR offers clear and durable efficacy in improving lung function, exercise tolerance, and quality of life for patients with severe heterogeneous emphysema, thereby solidifying its clinical role. The key to its success lies in precise patient selection (eg, assessing lesion heterogeneity and target areas through CT and perfusion scans) and continuous technological optimization. BLVR and biologics form a complementary "anti-inflammatory-remodeling" relationship, reinforcing the concept that treatment must match pathophysiological mechanisms. In contrast, stem cell therapy points to the ultimate vision of tissue repair, with the potential to reverse or delay the destruction of lung parenchyma. However, this field is still in the preclinical and early clinical exploration stages, with core scientific challenges such as its exact in vivo mechanisms of action, optimal cell sources and delivery methods, long-term safety, and reproducible efficacy evidence urgently needing to be addressed.

When balancing the perspectives of different studies, it is essential to recognize that these three strategies differ significantly in terms of target populations, mechanisms of action, levels of evidence, safety profiles, and health economic burdens. The future management of COPD is by no means about choosing one of the three but about constructing an integrated treatment strategy based on multidimensional phenotypic assessment. Clinical decision-making should begin with a comprehensive assessment: BEC guides the application of biologics; high-resolution CT and pulmonary function tests identify candidates suitable for BLVR; meanwhile, eligible patients should be enrolled in clinical trials of cell therapy. Looking ahead, the framework for personalized COPD treatment will be further refined on this basis. Research directions should focus on: first, using multi-omics technologies to deepen endotype classification of the disease and discover biomarkers that can predict the efficacy of biologics, achieving "the right drug for the right person"; second, continuously optimizing patient selection criteria and technical details for BLVR (such as new valves and next-generation coils) to expand its beneficiary population and improve safety; third, elucidating the mechanisms of action of stem cell therapies through rigorous basic research and conducting well-designed, standardized phase II/III

clinical trials to verify their efficacy and safety. Particularly promising is exploring the combined application of the above different strategies (for example, BLVR improving mechanics followed by combined anti-inflammatory therapy to maintain efficacy, or attempting combined repair therapies at specific stages), which may produce synergistic effects and provide comprehensive, breakthrough therapeutic alternatives for patients with complex, refractory COPD who currently have limited options. This comprehensive precision medicine framework, integrating interventional techniques, targeted drugs, and regenerative medicine, holds the potential to truly alter the disease course of COPD and improve patients' long-term prognosis, thereby propelling the diagnosis and treatment of COPD into a new era that is patient-centered, evidence-based, and precision-oriented.

Abbreviations

COPD, Chronic Obstructive Pulmonary Disease; BLVR, Bronchoscopic Lung Volume Reduction; ICS, Inhaled Corticosteroids; BEC, Blood Eosinophil Count; FEV1, Forced Expiratory Volume in One Second; MSCs, Mesenchymal Stem Cells; 6MWD, 6-Minute Walk Distance.

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