ERS/EBMT clinical practice guidelines on treatment of pulmonary chronic graft-*versus*-host disease in adults

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Shareable abstract (@ERSpublications)
Optimal management of patients with pulmonary chronic graft-*versus*-host disease is challenging. This ERS/EBMT evidence-based guideline, developed by a multidisciplinary team and patient advocates, aims to support clinicians in treating pulmonary cGvHD. https://bit.ly/48f0jgE

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Abstract

Chronic graft-*versus*-host disease (cGvHD) is a common complication after allogeneic haematopoietic stem cell transplantation, characterised by a broad disease spectrum that can affect virtually any organ. Although pulmonary cGvHD is a less common manifestation, it is of great concern due to its severity and poor prognosis. Optimal management of patients with pulmonary cGvHD is complicated and no standardised approach is available. The purpose of this joint European Respiratory Society (ERS) and European Society for Blood and Marrow Transplantation task force was to develop evidence-based recommendations regarding the treatment of pulmonary cGvHD phenotype bronchiolitis obliterans syndrome in adults. A multidisciplinary group representing specialists in haematology, respiratory medicine and methodology, as well as patient advocates, formulated eight PICO (patient, intervention, comparison, outcome) and two narrative questions. Following the ERS standardised methodology, we conducted systematic reviews to address these questions and used the Grading of Recommendations Assessment, Development and Evaluation approach to develop recommendations. The resulting guideline addresses common therapeutic options (inhalation therapy, fluticasone-azithromycin-montelukast, imatinib, ibrutinib, ruxolitinib, belumosudil, extracorporeal photopheresis and lung transplantation), as well as other aspects of general

management, such as lung functional and radiological follow-up and pulmonary rehabilitation, for adults with pulmonary cGvHD phenotype bronchiolitis obliterans syndrome. These recommendations include important advancements that could be incorporated in the management of adults with pulmonary cGvHD, primarily aimed at improving and standardising treatment and improving outcomes.

Scope and objectives

This European Respiratory Society (ERS)/European Society for Blood and Marrow Transplantation (EBMT) guideline provides evidence-based recommendations for the management of adult patients with pulmonary chronic graft-*versus*-host disease (cGvHD) after allogeneic haematopoietic stem cell transplantation (alloHSCT). It specifically focuses on patients with bronchiolitis obliterans syndrome (BOS), as defined in the National Institutes of Health (NIH) consensus document [1]. Other clinical phenotypes of pulmonary cGvHD, such as the restrictive phenotype, are not addressed in this guideline [2]. For the sake of making more homogeneous recommendations, children with pulmonary cGvHD were excluded, as were patients with BOS after lung transplantation.

This guideline does not address the clinical diagnosis of BOS, but outlines key management questions ranging from inhalation therapy to evidence on pulmonary effects of treatments used for cGvHD to lung transplantation for end-stage pulmonary cGvHD. Other aspects of general management, such as lung functional and radiological follow-up and supportive treatment, are also discussed. Table 1 provides a framework to understand the recommendations made in this document [3, 4].

The target audience for this guideline are professionals involved in adult pulmonary cGvHD care, including specialists in haematology, respiratory medicine, primary care physicians, pharmacists, specialist nurses, regulatory authorities, pharmaceutical companies and policy-makers. In addition, this guideline aims to inform patients with lung cGvHD-BOS and their carers to assist them in discussing therapeutic options with their healthcare teams and to facilitate access to appropriate care. However, a guideline document cannot address the full complexity of a disease such as lung cGvHD-BOS, and all recommendations should therefore be interpreted by considering individual clinical circumstances and perceptions, preferences and values.

Introduction

AlloHSCT is a potentially curative treatment for well-selected patients with various haematological malignancies and nonmalignant diseases [5]. Despite advances in donor and recipient selection, conditioning regimens and immunosuppressive agents, cGvHD remains a major cause of late post-transplant morbidity and mortality, occurring in 30–70% of patients [6]. It is characterised by heterogeneous disease manifestations in which virtually any organ can be affected, and in which tissue inflammation and fibrosis can result in permanent organ dysfunction [6].

Late-onset noninfectious pulmonary complications (of which pulmonary cGvHD is a frequent cause) are common after alloHSCT and develop in up to 20% of patients, mostly within the first 2 years post-transplant [7]. Pulmonary cGvHD can present with obstructive or restrictive changes, or a combination of both [8]. The obstructive phenotype BOS is the most common and best-defined late pulmonary complication and currently the only entity formally recognised as a manifestation of pulmonary

TABLE 1 Grading of Recommendations Assessment, Development and Evaluation (GRADE)-based recommendations used in this document, based on GRADE [3] and used in accordance with the European Respiratory Society methodology [4]

Target group	Strong recommendation[#] ("we recommend")	Conditional (weak) recommendation ("we suggest")
Patients	All or almost all informed people would follow the recommended advice for or against an intervention	Most informed people would choose the recommended course of action, but a substantial number would not
Clinicians	Most patients should receive the recommended course of action	The health professional should acknowledge that different choices may be appropriate for individual patients and should devote time to the process of shared decision-making by which they ensure that the informed choice reflects individual values and preferences
Policy-makers	The recommendation can be adopted as a health policy in most situations	Policy-making will require substantial debate and involvement of many stakeholders

[#]: strong recommendations based on high-quality evidence will apply to most patients for whom these recommendations are made, but they may not apply to all patients in all conditions. No recommendation can encompass all the unique features of individual patients and clinical circumstances.

cGvHD [8]. It is thought to affect 5% of patients after alloHSCT and up to 14% of patients with established cGvHD, although these numbers are probably underestimated due to suboptimal diagnosis [9]. Similar to chronic lung allograft dysfunction after lung transplantation [10], other clinical phenotypes have been identified in recent years, including a restrictive phenotype, characterised by interstitial lung disease resulting in restrictive lung function decline [2]. Clear definitions of this entity are still lacking, making its recognition in daily practice challenging. In this guideline, we focus on BOS, as this is the most common and best-described clinical phenotype.

BOS is characterised by progressive small airways disease, which often responds poorly to treatment and has a natural course of leading to respiratory insufficiency and lung failure [8]. Diagnosis is primarily based on pulmonary function testing (PFT), according to NIH criteria [1, 11]. Since PFT is often not implemented in routine clinical follow-up after alloHSCT, and respiratory symptoms only appear at an advanced disease stage and may be nonspecific, early diagnosis of BOS is often missed, precluding timely intervention [8]. The NIH consensus advocates the use of serial PFT after alloHSCT, and in asymptomatic patients [11].

Management of pulmonary cGvHD is challenging, both in terms of diagnosis and treatment. Few therapeutic options are available, some of which have been adopted from BOS after lung transplantation. There is no standard of care and conventional immunosuppression for BOS varies between centres and often consists of corticosteroids (inhaled and/or systemic), sometimes in combination with azithromycin and/or montelukast. In addition, drugs for cGvHD are used regularly. While the treatment landscape has expanded in recent years with the United States Food and Drug Administration's (FDA) approval of multiple agents for the treatment of cGvHD, little is currently known about the impact of these newer agents on BOS [12, 13]. As such, the use of these drugs often remains empirical and some are associated with significant toxicities and high failure rates, primarily because the exact underlying immunopathological mechanisms of pulmonary cGvHD are incompletely understood [6]. It is important to emphasise that pulmonary cGvHD is usually part of a broader disease spectrum, with patients already receiving immunosuppressants for other cGvHD manifestations.

Thus, there is currently no harmonised approach to manage pulmonary manifestations of cGvHD and the aim of this guideline is to provide a state-of-the-art update on available evidence and to deliver a practical guideline regarding the treatment of adults with lung cGvHD-BOS targeting 1) treatment; 2) lung functional and radiological follow-up; and 3) supportive treatment.

Methods

This guideline was developed by a joint ERS/EBMT task force chaired by R. Vos (Belgium), D. Stolz (Germany) and S. Bos (Belgium/UK) and included specialists in haematology and respiratory medicine, with recognised expertise in the management of pulmonary cGvHD and/or BOS after lung transplantation, as well as a specialist nurse, ERS methodologist, European Lung Foundation (ELF) representative and two patient representatives. The specific expertise of the panel is outlined in supplement S1. The patient representatives were actively involved in all discussions as full members of the panel, provided input into the final recommendations and will be involved in developing a lay version of the guideline. Between September 2021 and July 2023, the panel met 20 times (all videoconferences) and a smaller methodology subgroup met a further six times. In addition, regular discussions on individual topics were held *via* email.

PICO and narrative questions

Key clinical questions for both clinicians and patients about treatment of pulmonary cGvHD were discussed. Following the ERS methodology, we formulated eight questions in accordance with the PICO format (patient, intervention, comparison, outcomes) alongside two narrative questions [4]. In order to develop a meaningful and focused guideline, the panel restricted the PICO questions to agents studied specifically for lung GvHD-BOS or used for cGvHD. Since there is currently no standard of care and conventional immunosuppression used for lung cGvHD-BOS varies widely around the world, no specific comparator was chosen, also to allow inclusion of all studies available. The panel assumed that conventional immunosuppression would encompass, but not be restricted to, routinely used pharmacological treatments for cGvHD, including inhaled and/or systemic corticosteroids (PICO 1–7), possibly in combination with azithromycin and/or montelukast (PICO 3–7), and sometimes other immunosuppressants (*e.g.* calcineurin inhibitors, mycophenolate mofetil) or no immunosuppression. Often certain immunosuppressants (*e.g.* systemic corticosteroids, calcineurin inhibitors) are tapered or discontinued during the new treatment course.

The panel, including patient representatives, decided on the outcomes of interest for each PICO question, based on their relative importance to adults with lung cGvHD-BOS and clinical decision-making (supplement S1) [14]. Systematic reviews were performed to answer PICO questions. For narrative questions, systematic searches were conducted, and the evidence was reviewed in a narrative manner.

Disclosure of potential conflicts of interest

Panel members disclosed all potential conflicts of interest, as per ERS policy (supplement S1). Members with potential conflicts were asked to abstain from voting on recommendations in which there was potential conflict. The ERS methodologist, ELF representative and librarian were nonvoting members of the panel.

Systematic review

The systematic review was performed according to ERS methodology [15]. An experienced librarian designed and ran the search strategies on the electronic databases of PubMed, Embase and Cochrane Library using Medical Subject Headings terms and keywords for each clinical question. The initial searches undertaken in March 2022 were updated in March 2023. Results of the searches were sent to panel member pairs and screened independently using predefined inclusion and exclusion criteria. A detailed description of the methods and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagrams for all PICO and narrative questions can be found in supplement S1. For selective narrative questions, we conducted additional searches to seek supportive evidence from alloHSCT, general cGvHD and respiratory literature, due to a lack of data specifically addressing our questions.

Articles were summarised using the ERS framework for guideline development, including both systematic (for PICO questions) and narrative (for additional sources and narrative questions) reviews of the evidence [4].

Assessment of the level of evidence and degree of recommendations

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to assess the certainty of the evidence and the degree of recommendations [3]. Recommendations were graded as strong or conditional after considering the certainty of the evidence, balance between desirable and undesirable outcomes, assumptions about the relative importance of outcomes, implications for resource use, and acceptability and feasibility of implementation. Key considerations correlated with these gradings are summarised in table 1.

Evidence profiles and evidence-to-decision frameworks were generated for each PICO question, and evidence-to-decision frameworks were generated for narrative questions (supplements S2 and S3) [16]. Based on these formats, the panel formulated clinical recommendations and decided on their strength by consensus or voting, if required. Following the GRADE approach, strong recommendations are phrased as “we recommend”, while conditional recommendations are phrased as “we suggest”.

Results

The number of studies identified and selected for each PICO and narrative question are displayed in the PRISMA flow diagrams (supplement S1). The evidence-to-decision frameworks are summarised here, with complete versions in supplement S3, and grouped into treatment, lung functional and radiological follow-up, and supportive treatment.

Treatment

PICO question 1

In adults with lung cGvHD phenotype BOS, should inhaled corticosteroids (ICS) with or without long-acting β-agonists (LABA) be used in addition to their conventional immunosuppressive regimen?

Recommendation

- In adults with lung cGvHD phenotype BOS, we suggest using ICS with or without LABA in addition to their conventional immunosuppressive regimen. (Conditional recommendation, low certainty of evidence.)

Remarks

It is important to select the most appropriate device for a patient and train them in its use, ensuring optimal technique and taking into account patient preferences. For example, some patients will not have enough inspiratory flow to use dry powder inhalers. Consideration should also be given to environmental factors, trying to avoid pressurised metered dose inhalers where possible.

The use of ICS should be considered on a case-by-case basis in patients with a bronchiectasis phenotype.

Summary of evidence

There is one multicentre randomised controlled trial (RCT) that investigated the efficacy of ICS/LABA in 32 mild-to-moderate BOS patients [17]. It demonstrated that forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) were statistically significantly higher at 1 month compared with baseline in the budesonide/formoterol arm than in the placebo arm and remained stable at 6 months. There were no statistically significant changes in quality of life between baseline and 1 month evaluated using the St George's Respiratory Questionnaire score. Regarding undesirable effects, there was no difference in bronchial infections between both groups [17].

Certainty of the evidence was low due to downgrading for imprecision.

Other supportive evidence

Weaker supportive evidence comes from three observational studies (13–77 patients per study, 107 in total) [18–20]. One study found a mean±SD increase in FEV_1 of 534±286 mL, with all 13 patients having an improved FEV_1 of >10% predicted or ⩾200 mL [18]. BASHOURA *et al*. [20] found a statistically nonsignificant increase in median FEV_1 of +8% (p=0.057) using high-dose ICS. The third study found no difference in FEV_1, but an improvement in FVC and quality of life, assessed by the COPD Assessment Test, in 68% of patients. In addition, they found no difference in incidence of pneumonia or bronchitis symptoms requiring antibiotics 3 months before compared with 3 months after treatment [19]. Unfortunately, none of these studies provided information on the impact on oral corticosteroid dose.

This recommendation is based on four small studies, which did not compare specific types of ICS±LABA inhalers. However, in much larger RCTs of patients with another obstructive airway disease, COPD, ICS/LABA therapy has been shown to reduce death and exacerbations and improve health status and FEV_1 compared with either component alone or placebo [21, 22]. Long-term safety data in this population suggest some increase in skin bruising and oral candidiasis and a small increase in nonfatal pneumonia [23]. The benefit of combination inhalers is largely cited as being secondary to improved adherence and cost-effectiveness.

Justification of recommendation

Although the number of studies and patients included was low, one RCT showed efficacy in BOS patients with a low risk of adverse events, which was also seen in some of the observational studies. Clinicians and patient advisory group conclude that ICS±LABA offers good value as a therapeutic modality in terms of positive outcomes, especially FEV_1, without evidence of increased infection risk.

Implementation considerations

ICS±LABA inhalers are relatively widely available in countries in which alloHSCT takes place. It is important to have personnel available with experience in selecting and training how to use an inhaler. There is benefit from having a close collaboration with local respiratory department and personnel. It is also useful to have resources available on inhaler techniques (*e.g.* leaflets, online tutorials).

Monitoring/evaluation

It is important that inhaler technique and adherence are monitored and that the benefit of ICS±LABA is objectively evaluated to make decisions on continuation. The optimal duration of therapy remains unclear. Ideally, spirometry should be monitored 1 month after initiation of therapy and addition of other therapies needs consideration in case of further disease progression.

Future research

Larger studies are needed and should include RCTs of ICS/LABA for patients with severe BOS as well as combination therapy with long-acting muscarinic agonists. Given the irreversibility of BOS in most cases, the duration of inhaled therapy and need for long-term bronchodilators should also be studied.

PICO question 2

In adults with lung cGvHD phenotype BOS, should fluticasone, azithromycin and/or montelukast be used in addition to their conventional immunosuppressive regimen?

Recommendation

- In adults with lung cGvHD phenotype BOS, we suggest using fluticasone, azithromycin and/or montelukast in addition to their conventional immunosuppressive regimen. (Conditional recommendation, very low certainty of evidence.)

Remarks

Azithromycin should be used with caution in patients with a high risk of secondary malignancies or cancer predisposition syndromes (*e.g.* short telomere syndrome, Bloom syndrome, Fanconi anaemia).

Summary of evidence

Two observational studies evaluated the combination of fluticasone, azithromycin and/or montelukast (FAM) in adults with lung cGvHD-BOS [24, 25]. One prospective study, with 36 patients within 6 months of BOS diagnosis, demonstrated a statistically significant decrease in treatment failure, defined as ⩾10% FEV_1 decline at 3 months, from 40% in historical controls to 6% [25]. In contrast, a retrospective case–control study showed no significant difference in FEV_1 change at 6 months between eight patients treated with FAM and rapid steroid taper and 14 historical controls on high-dose steroids with standard taper [24]. With respect to quality-of-life outcomes, 36-item short-form survey social functioning, mental component score, and Functional Assessment of Cancer Therapies emotional wellbeing scores improved statistically significantly, as did Lee symptom score and exercise capacity [25].

The prospective study showed that prednisone dose could be reduced by ⩾50% in 48% of patients at 3 months and 71% at 6 months, although new systemic treatments were added in 31% of patients [25]. Similarly, prednisone exposure was statistically significantly lower in FAM-treated patients in the retrospective study [24]. Regarding adverse events, there was no difference in disease relapse [24] and a low incidence of respiratory tract infections (17%) and pneumonitis (3%) [25].

The certainty of the evidence was very low due to downgrading for risk of bias, inconsistency and/or imprecision.

Other supportive evidence

Two studies examined the effect of azithromycin alone [26, 27], with one RCT showing no statistically significant changes in lung function or respiratory symptoms [27], and a case series showing a 21% increase in FEV_1 and a 22% increase in FVC, as well as improvements in dyspnoea and exercise tolerance [26]. In a study examining montelukast alone, FEV_1 stabilised in all 23 patients and improved in 22% of them, with 17% achieving >50% reduction in steroid dose [28].

Use of azithromycin after alloHSCT requires caution, as it might be associated with an increased risk of relapse and neoplasm. In a retrospective study of 316 patients, azithromycin use was associated with a statistically significantly increased risk of subsequent neoplasm (hazard ratio (HR) 2.00, 95% CI 1.01–3.99), mainly squamous cell carcinoma of the skin, but there was no adjustment for prior smoking, use of azoles or prevalence of skin GvHD [29]. Another study found that prophylactic use of azithromycin early post-transplant correlated with an increased risk of haematological relapse [30]. Despite this, azithromycin has been shown to reduce the incidence of infectious exacerbations in patients with COPD [31] and non-cystic fibrosis bronchiectasis [32], and has important anti-inflammatory and immunomodulatory properties after lung transplantation [33]. Although no data are available for the BOS population, it seems fair to hypothesise that the incidence of respiratory tract infections might decrease with azithromycin therapy.

Justification of recommendation

Although the evidence is limited, the potential benefits of adding FAM to conventional immunosuppressive regimens in patients with BOS outweigh the potential risks.

Implementation considerations

FAM therapy is relatively widely available in countries in which alloHSCT is taking place, and implementation should be relatively easy, as it is a combination of inhaled and oral drugs. For inhalation therapy, it is important to have personnel experienced in selecting and training how to use an inhaler. The possible risk of haematological disease relapse and malignancy associated with azithromycin should be discussed with the patient.

Monitoring/evaluation

Patients receiving FAM therapy should be monitored regularly for symptoms, adverse events and disease progression. The optimal duration of azithromycin and montelukast therapy for BOS is not well defined and discontinuation may be considered in the absence of benefit (*e.g.* after 3–6 months). It is still unclear how to interpret the possible association between azithromycin and relapse/neoplasm risk. Screening for malignancy, particularly skin cancer, should be considered.

Future research

Future research should prioritise large RCTs to assess safety and efficacy of FAM. This includes investigating the potential risk of relapse and malignancy and the underlying mechanism of action, changes in the microbiome and metabolomics [34, 35]. Additionally, studies are needed to evaluate the safety and efficacy of using azithromycin and montelukast as standalone treatments for this patient population.

PICO question 3

In adults with lung cGvHD phenotype BOS, should imatinib be used in addition to their conventional immunosuppressive regimen?

Recommendation

- In adults with lung cGvHD phenotype BOS, we suggest either imatinib in addition to their conventional immunosuppressive regimen or conventional immunosuppression. (Conditional recommendation for either intervention or the comparison, very low certainty of evidence.)

Remarks

GvHD manifestations in other organs should be considered. For instance, imatinib might be an option in patients with sicca symptoms (*e.g.* ocular cGvHD, because of its side-effect profile, which includes peri-orbital oedema) and in patients with chronic myeloid leukaemia because of potential impact on underlying disease. It would be a less favourable option in patients with cGvHD-related myalgia, gastrointestinal symptoms and anorexia due to risk of drug-related exacerbation of these symptoms.

Summary of evidence

There were only two studies that specifically investigated the role of imatinib in BOS: a case series including two patients [36], and a prospective study with nine patients [37]. FEV_1 remained stable in most patients after starting imatinib. In the prospective study, the dose of corticosteroids could be reduced in 22% of patients and remained unchanged in the other patients [37] as well as in the two patients in the case series [36]. Risk of adverse events was low with no reports of serious adverse events [36, 37], respiratory infections [36, 37] or relapse [36].

The certainty of the evidence was very low due to downgrading for risk of bias and imprecision.

Other supportive evidence

In addition to the direct evidence, there were seven small observational studies (five prospective and two retrospective) which examined the effect of imatinib in cGvHD patients with BOS subgroup analyses (between two and 34 BOS patients per study, 120 in total). The overall response rate for BOS varied from 18% to 55%, including complete and partial responses according to NIH criteria [38–44].

Due to a lack of good cut-off and lack of control groups, the panel considered it difficult to assess treatment efficacy as trivial or small. Two studies looked at the impact on corticosteroid dose and found that it could be tapered or stopped in all patients [40, 41]. These studies also reported a low incidence of respiratory infections (9%) [40] and relapse (0–9%) [40, 41].

Justification of recommendation

A conditional recommendation for either the intervention or the alternative was selected based on a lack of good quality evidence for or against imatinib efficacy in BOS patients, in combination with a low risk of adverse events, but a risk of intolerance. Limited data come from nine small studies with variable but generally low response rates, although the steroid-sparing effect should be emphasised.

Implementation considerations

Implementation of imatinib is relatively easy as it is an oral drug and does not require any additional infrastructure or training. However, it may not be feasible everywhere due to access or resource limitations. Patients should be informed about the risk of minor side-effects requiring discontinuation (*e.g.* fluid retention, myalgia, gastrointestinal and haematological side-effects).

Monitoring/evaluation

If imatinib were to be used, patients should be monitored regularly for evolution of symptoms, side-effects and lung function over time, with a low threshold to switch to other therapies.

Future research

Large RCTs are needed to assess safety and efficacy of imatinib; although, in the opinion of the panel, future research should prioritise more promising treatment options.

PICO question 4

In adults with lung cGvHD phenotype BOS, should ibrutinib be used in addition to their conventional immunosuppressive regimen?

Recommendation

- In adults with lung cGvHD phenotype BOS, we suggest not using ibrutinib in addition to their conventional immunosuppressive regimen. (Conditional recommendation, very low certainty of evidence.)

Remarks

In general, the panel suggests against using this drug, although it might still be a valuable option in selected patients, where other options might not be possible. For example, ibrutinib might be an option in patients with cytopenia, as this is not a frequent side-effect of ibrutinib, and in patients with chronic lymphocytic leukaemia because of impact on underlying disease. It would be a less favourable option in patients with a history of frequent infectious complications, bleeding, symptoms similar to ibrutinib side-effects (*e.g.* diarrhoea, nausea, muscle cramps), and patients taking CYP3A inhibitors due to drug interactions.

Summary of evidence

There were no studies that examined the efficacy of ibrutinib in a BOS-specific population. A recently published RCT in new-onset cGvHD with 48 BOS patients showed no difference in overall response rate between both groups [45]. In addition, two observational studies (one prospective, one retrospective) of ibrutinib in cGvHD with subgroup analyses for pulmonary cGvHD were identified (six and seven BOS patients per study, 13 in total) [46, 47]. The (best) overall response rate ranged from 14% [46] to 83% [47]. In the latter study, discontinuation or significant dose reduction of corticosteroids was possible in 83% of patients; 50% of patients were alive after a median follow-up of 14 months [47].

The certainty of the evidence was very low due to downgrading for risk of bias, indirectness and/or imprecision.

Other supportive evidence

With respect to toxicity, the incidence of infections (from 55% [47] to 79% [46]), respiratory infections (pneumonia 37% [46]) and serious adverse events (58% [46]) was relatively high in the overall cGvHD cohorts. In the RCT, the incidence of serious adverse events and adverse events leading to discontinuation of ibrutinib were similar in both arms, although a higher incidence of fatal adverse events occurred in the ibrutinib arm (13% *versus* 6%) [45].

The risk of potentially fatal or debilitating adverse events is also supported by other literature [48, 49]. The risk of potentially fatal fungal or bacterial infections is of particular concern. Furthermore, the range of side-effects, based on experience in other patient populations, is wide and includes fatigue, diarrhoea, nausea, muscle spasms, cutaneous bruising, *etc*.

Justification of recommendation

Based on currently available evidence, the efficacy of ibrutinib is low. In addition, the main issues with this drug are its side-effect profile, particularly the risk of infection and bleeding. Therefore, the panel generally suggests against using this drug, although it might still be a valuable option in selected patients, based on a case-by-case discussion, where other options might not be possible.

Implementation considerations

Ibrutinib is an oral drug and does not require any additional infrastructure or training. However, the cost of the drug as well as lack of availability and/or reimbursement in some countries (*e.g.* lack of approval by the European Medicines Agency) are issues to be considered for implementation. The risk of adverse events should be thoroughly discussed with the patient.

Monitoring/evaluation

Patients should be monitored regularly for evolution of symptoms, adverse events and lung function over time. Careful follow-up of the toxicity profile is required, especially of bacterial and fungal infections. Caution is advised in patients taking anticoagulants due to the risk of bleeding.

Future research

Large RCTs are needed to assess safety and efficacy of ibrutinib; although, in the opinion of the panel, future research should rather prioritise other treatment options.

PICO question 5

In adults with lung cGvHD phenotype BOS, should ruxolitinib be used in addition to their conventional immunosuppressive regimen?

Recommendation

- In adults with lung cGvHD phenotype BOS, we suggest either ruxolitinib in addition to their conventional immunosuppressive regimen or conventional immunosuppression. (Conditional recommendation for either intervention or the comparison, very low certainty of evidence.)

Remarks

Ruxolitinib should be used with caution in patients with a history of (recurrent) infections and cytopenia. However, ruxolitinib might be an option in patients with extrapulmonary GvHD, as ruxolitinib has been demonstrated to be effective for extrapulmonary GvHD.

Summary of evidence

We identified three BOS-specific retrospective studies enrolling 43 patients [50–52]. Two studies reported an increase in FEV_1 in the majority of patients, corresponding to an overall response rate of 57% [51] and 100% [52], while the other study [50] documented stabilisation. Moreover, corticosteroids could be reduced or discontinued in all patients, and one study [52] of seven patients showed that symptoms, as assessed by the Lee symptom score, improved in all patients.

The incidence of respiratory infections was low (14%) in the study by Zhang *et al.* [52], but was 46% grade ⩾2 and 37% grade ⩾3 according to the Common Terminology Criteria for Adverse Events in another study [51]. Relapse rates were low (0–15%) [51, 52].

The certainty of the evidence was very low due to downgrading for risk of bias and imprecision.

Other supportive evidence

In addition to this direct evidence, 17 cGvHD studies with BOS subgroups were identified (between two and 141 BOS patients per study, 302 in total) [53–69]. All but one were retrospective in nature. One RCT reported a higher overall response rate at 24 weeks of 41% in patients treated with ruxolitinib compared with 25% with best available therapy (OR 2.12, 95% CI 1.01–4.45) [68]. Since the FDA considers best overall response rate rather than overall response rate at a given point in time to be representative of a clinically meaningful response, a further analysis of this study was conducted and showed a best overall response rate of 65% for ruxolitinib compared with 45% for best available therapy [70]. Response rates for BOS in the retrospective studies varied between 10% and 100%.

In the cGvHD cohort, the incidence of infectious events varied between 5% and 69% and pneumonia between 4% and 9% [53–69]. In a study by Wei *et al.* [65], 16% of patients died due to respiratory infections. However, the incidence of serious adverse events and pneumonia was similar in both groups in the RCT (37% in both groups, and 9% in ruxolitinib *versus* 10% in control group) [68]. A *post hoc* analysis of this study reported an incidence of lower and upper respiratory tract infections of 23% and 22%, respectively [70].

From data available and clinical experience, the panel concludes that ruxolitinib is generally well tolerated, but that patients and healthcare professionals should be aware of the risk of infection, especially in patients with a history of (repeated) infections and with specific attention to viral infection (*e.g.* cytomegalovirus infection).

Justification of recommendation

There is currently not enough evidence to support a recommendation with regard to the intervention. However, this recommendation places a relatively higher value on some corticosteroid dose reduction, FEV_1 stabilisation/improvement and efficacy on extrapulmonary cGvHD, and relatively lower value on some adverse events (*e.g.* infections), and therefore the panel chose a balance that does not favour either the intervention or the alternative.

Implementation considerations

Ruxolitinib is currently not available and/or reimbursed in many countries, which may complicate implementation.

Monitoring/evaluation

Patients should be monitored regularly for evolution of symptoms, side-effects and lung function over time. Specific attention should be paid to the risk of (viral) infections.

Future research

Ruxolitinib should be further tested in BOS-specific prospective studies, including RCTs, enrolling a sufficient number of BOS patients, to assess safety and efficacy as well as patient-reported outcomes. Several prospective BOS studies are ongoing (clinicaltrials.gov identifiers NCT05413356, NCT04908735, NCT03674047).

PICO question 6

In adults with lung cGvHD phenotype BOS, should belumosudil be used in addition to their conventional immunosuppressive regimen?

Recommendation

- In adults with lung cGvHD phenotype BOS, we suggest either belumosudil in addition to their conventional immunosuppressive regimen or conventional immunosuppression. (Conditional recommendation for either intervention or the comparison, very low certainty of evidence.)

Summary of evidence

Currently available evidence arises from two observational studies examining belumosudil in advanced cGvHD therapy (17–47 BOS patients per study, 64 in total) [71, 72]. While these trials included some representation of lung involvement, they were not designed to specifically address activity of this agent in BOS. Best overall response rates for BOS were 26% [71] and 28% [72]. Importantly, overall response rates were often based not only on lung function evolution, but also on improvement in symptoms. A *post hoc* analysis, performed by DeFilipp *et al*. [73] focusing on 59 BOS patients from these two studies, documented an improvement in FEV_1 of $\geqslant$5% in 39% and $\geqslant$10% in 22% of patients. Best overall response rate based on lung function was 24%, compared with 32% based on lung function and symptoms. 2-year overall survival was 82%, and 68% of patients had a clinically meaningful improvement in Lee symptom score [73].

The *post hoc* analysis supported that respiratory infections were common (53% had at least one respiratory infection) [73].

The certainty of the evidence was very low due to downgrading for indirectness and imprecision.

Justification of recommendation

Limited evidence supports that belumosudil may have activity in cGvHD patients with lung involvement. However, given the uncertainty of BOS response to belumosudil due to the limited data presented in primary trials and lack of a (randomised) comparator, the panel is of the opinion that the balance is currently probably not in favour of either the intervention or the alternative.

Implementation considerations

Access to this agent is limited, as it is only approved by the FDA and not by the European Medicines Agency at the time of writing. Cost considerations are similar to other drugs.

Monitoring/evaluation

Patients should be monitored regularly for evolution of symptoms, adverse events and lung function over time. Emerging data suggest that other immunosuppressive agents (*e.g.* tacrolimus, sirolimus) may have

altered metabolism in the setting of belumosudil co-administration; thus, enhanced monitoring and dose adjustments of these agents may be needed.

Future research

Among possible future research priorities, trials specifically focused on belumosudil therapy for BOS are needed to fully evaluate its activity in this disease. Careful study of benefit and toxicity is needed in this setting.

PICO question 7

In adults with lung cGvHD phenotype BOS, should extracorporeal photopheresis (ECP) be used in addition to their conventional immunosuppressive regimen?

Recommendation

- In adults with progressive lung cGvHD phenotype BOS, we suggest using ECP in addition to their conventional immunosuppressive regimen. (Conditional recommendation, very low certainty of evidence.)

Remarks

It might be difficult to perform ECP in every patient or at every site, given the logistical challenges. The potential need for a central line and related low risk of line infection must be considered. Patient-specific details and preferences should be considered to determine if ECP is appropriate for a given patient.

Summary of evidence

We identified four retrospective observational studies regarding the use of ECP in a BOS-specific cohort; three small studies [74–76] (between eight and 13 patients per study, 30 in total) without a comparison group and one study [77] with a comparison group (26 patients per group). In the latter study, there was no statistically significant difference in terms of FEV_1 improvement between ECP and non-ECP groups, but overall survival was higher in the ECP group (HR 0.1, 95% CI 0.01–0.3) [77]. Other studies [75, 76] reported improvement in FEV_1 1–3 months after ECP initiation, and Del Fante *et al.* [74] noted an overall response rate of 100% in 13 patients. Steroids could be tapered in the majority of patients on ECP in these studies, although it was often unclear whether steroids were being used to treat BOS or other systemic GvHD manifestations.

There was no difference in ECP and non-ECP groups regarding respiratory infections [77], and the reported incidence of relapse was low (0–17%) [74, 76].

The certainty of the evidence was very low due to downgrading for risk of bias and imprecision.

Other supportive evidence

Next to this direct evidence, we identified four prospective [78–81] and 13 retrospective [82–94] cGvHD studies with subgroup analyses for BOS (between two and 23 BOS patients per study, 151 in total). In three of the four prospective studies [78–80], overall response rate varied between 0% and 27%, while one prospective study [81] had only two BOS patients who both achieved a partial response. Stabilisation or improvement of FEV_1 was observed in the majority of patients in the retrospective studies, although some studies [87–90] showed no or a small effect. In addition, several of these studies reported that corticosteroids could be reduced or discontinued [81, 83, 84, 86, 91].

Most adverse events were mild, with infections being the most common. In one study, up to 13% withdrew ECP due to treatment-related infections, the majority of which were central line infections [88]. Other common adverse events included thrombocytopenia, anaemia, oedema and hypotension, which were often mild and reversible [79, 89].

It is important to keep in mind that ECP is very resource intensive and necessitates multiple points of contact with the healthcare facility, so the beneficial effect of ECP might also come from regular contact with healthcare providers.

Justification of recommendation

Despite some uncertainty regarding the degree of efficacy and high implementation costs, a conditional recommendation for ECP was made because several studies showed improvement or stabilisation of FEV_1,

along with dose reduction of oral corticosteroids, and only minor adverse events. In addition, a matched control study found improved overall survival in the ECP group.

Implementation considerations

Resource costs related to ECP are high and the use of ECP requires the right infrastructure, equipment and specially trained healthcare providers next to reimbursement/healthcare budget implementation. The logistics and possible central line and transfusion requirements should be explained and discussed with the patient, as well as the fact that it may take some time before the effectiveness of ECP becomes noticeable.

Monitoring/evaluation

Patients should be monitored regularly for evolution of symptoms, adverse events and lung function over time. Specific attention should be paid to line infections. The effect of treatment should be assessed at regular intervals, including the evaluation of evolution of non-lung GvHD.

Future research

Large RCTs are needed to assess the efficacy of ECP specifically for lung cGvHD-BOS. Large trials are also required to establish the optimal frequency and duration of treatment. Since ECP requires regular travel, short hospital stays and intravenous access, the panel and especially patient advocates find it important that quality-of-life parameters are included in future studies.

PICO question 8

In adults with end-stage lung cGvHD phenotype BOS, should lung transplantation be performed?

Recommendation

- In highly selected adults with end-stage lung cGvHD phenotype BOS, we suggest lung transplantation as a life-saving therapeutic option. (Conditional recommendation, very low certainty of evidence.)

Remarks

Lung transplantation might be an option for highly selected adults, taking into account other comorbidities and general eligibility criteria for lung transplantation. Specific lung transplant criteria for lung cGvHD-BOS patients should be established. Risk of haematological relapse needs to be considered based on the patient profile.

Summary of evidence

Nine observational studies (five retrospective cohort studies [95–99], four case series [100–103]) were identified that looked at lung transplantation outcomes for lung cGvHD-BOS (between two and 18 BOS patients per study, 76 in total). Overall survival was good, with reported 1-year survival of 78–90% [97–99] and 5-year survival of 75–80% [96, 97]. Other studies reported overall survival of 50%, 67% and 100% at a median follow-up of 20–24 months [99–101]. Moreover, overall survival was similar compared to matched controls [97] and the general lung transplant population [95]. Main causes of death were infection, lung graft failure/chronic lung allograft dysfunction, malignancy and haematological relapse [95–99, 101, 103].

Freedom from chronic lung allograft dysfunction was 51% at 5 years in a study by Kliman *et al.* [96] and 67–100% in other studies [95, 97, 100–102], depending on time of post-transplant follow-up. Incidence of infections varied between 11% and 50%, depending on type of infection, with cytomegalovirus and fungal infections being the most common [95–103]. Acute cellular rejection occurred in 11–43% of patients and was similar to the incidence in other lung transplant patients [95–101]. The incidence of haematological relapse and malignancy was low (0–8% and 17%, respectively) [95–103].

The certainty of the evidence was very low due to downgrading for risk of bias, inconsistency and/or imprecision.

Other supportive evidence

Nine additional studies on lung transplantation after alloHSCT also included indications other than BOS, so-called late-onset noninfectious pulmonary complications (between three and 105 patients per study, 208 in total) [104–112]. 1-year overall survival was similar to that of other lung transplant recipients [108, 112], although in one study [108], overall survival conditional on 1-year survival was lower in the BOS cohort compared with matched controls. Reported 5-year overall survival ranged from 37% to 74% [105–

108], but was comparable to matched controls in the study by Greer *et al*. [107] In addition, health-related quality of life, social reintegration and 6-min walk test improved post-transplant [110].

Relapse rates for haematological disease varied between 0% and 11% [104, 105, 107, 108, 111, 112]. Greer *et al*. [107] reported that lung transplantation within 2 years of alloHSCT increased the risk of relapse (HR 6.4, 95% CI 1.3–46.0) and 1-year mortality (HR 7.5, 95% CI 2.3–23.8). Most frequent causes of death were sepsis, malignancy and chronic lung allograft dysfunction [104, 106, 107, 109, 111, 112]. The incidence of chronic lung allograft dysfunction was similar to matched controls in a study by Riddell *et al*. [108]. However, they noted an increased risk of death due to infections compared with matched controls [108].

Justification of recommendation

Lung transplantation is the only curative, life-saving treatment in individuals with end-stage lung disease. There is good overall long-term survival for selected adults with lung cGvHD-BOS. The risk of complications, including acute cellular rejection, infections, chronic lung allograft dysfunction and malignancy, are expected undesirable outcomes and were similar to those of patients transplanted for other indications.

Implementation considerations

Resource costs related to lung transplantation are high and implementation requires the right infrastructure, equipment and specially trained healthcare providers.

It is advised that adults with end-stage lung cGvHD-BOS undergo timely referral to a lung transplant team or respiratory consultant with transplant knowledge for eligibility assessment. However, the natural course of BOS is poorly defined, and some patients remain stable at low FEV_1 for a long time. It is therefore particularly important to consider the trajectory of lung function decline, including FVC [113], exacerbations and general condition and comorbidities.

Risk factors and contraindications to be considered in the selection of lung transplant candidates are similar to those of other lung transplant candidates [114]. Specific lung transplant criteria for lung cGvHD patients need to be established. For example, attention should be paid to extrapulmonary cGvHD, especially if uncontrolled. In addition, given the possibly increased risk of relapse within 2 years of alloHSCT, caution is advised based on individual risk of relapse with respect to timing of lung transplantation.

Monitoring/evaluation

Patients should be monitored regularly post-transplant according to local lung transplant policies.

Future research

There were limited data on quality of life and levels of physical activity in the included studies. The panel and especially patient advocates find it important that these parameters are included in future studies, especially given the psychological impact a lung transplant may have after they have already undergone alloHSCT and the risk of similar symptoms if chronic lung rejection occurs. Finally, lung transplant criteria for lung cGvHD-BOS patients should be established, including specific guidelines regarding patients with extrathoracic cGvHD and optimal timing after alloHSCT.

Lung functional and radiological follow-up

Narrative question 1

How and how frequently should adults with lung cGvHD phenotype BOS be re-evaluated? 1) How often should PFT be conducted? 2) How often should imaging/chest computed tomography (CT) evaluation be conducted?

Recommendations

In adults with lung cGvHD phenotype BOS, we suggest the following evaluation. (Conditional recommendation, very low certainty of evidence stemming from narrative review of evidence.)

- We suggest spirometry at least every 3 months for follow-up.
- We suggest full PFT at the time of BOS diagnosis, annually thereafter and at the time of disease progression.
- We suggest high-resolution chest CT scan at the time of diagnosis and upon indication, for example in cases of PFT decline or respiratory symptoms, to exclude other causes.

Remarks

More frequent spirometry testing is suggested after BOS diagnosis, as some patients may have a rapid decline in FEV_1 (*e.g.* every month for the first 3 months), in patients who are clinically unstable, after the onset of new symptoms or GvHD in another organ, a respiratory infection, or a change in therapy. In patients who stabilise after treatment initiation, gradually reducing the frequency of spirometry testing to every 6–12 months may be considered based on time after transplantation and BOS diagnosis.

Summary of evidence

For PFT, one retrospective study showed that both rapid and gradual decline were possible after BOS diagnosis. In patients with a rapid decline (>25% FEV_1) in the first 3 months after diagnosis, subsequent lung function parameters and overall survival were lower [115].

With regard to chest CT imaging, Song *et al.* [116] demonstrated that disease progression occurred in 33% of BOS patients, with some patients progressing from BOS to a mixed phenotype, although this was also observed on PFT.

Other supportive evidence

Based on additional studies, an initial decline in lung function after BOS onset was often followed by stabilisation and a gradual decline thereafter, although a sudden and deep FEV_1 decline with poor prognosis was also observed [7, 113, 117–119].

The lung function trajectory gives us important information on disease progression. The panel believes the frequency of testing is likely determined by BOS severity, rate of decline and response to treatment. The panel considers it important to monitor PFT from transplantation, also to know the difference in slope before and during treatment, including a pre-transplant baseline PFT with spirometry, lung volumes by body plethysmography and diffusion capacity. Available data and the panel's clinical expertise suggest spirometry at least quarterly in BOS patients and more frequently after initial diagnosis and in cases of clinical deterioration, along with full PFT at time of diagnosis, annually thereafter and as disease progresses. These PFT monitoring recommendations are concordant with recent NIH recommendations [11].

Of note, mild and early moderate BOS may remain clinically asymptomatic requiring routine PFT screening of patients independent of pulmonary symptoms to identify BOS at earlier stages.

There are no studies that specifically study or inform the frequency of chest imaging as a monitoring modality in lung cGvHD-BOS. Findings on chest CT do not always correspond to clinical findings. For example, the value of air trapping on expiratory CT is not well known and is not predictive of BOS development or severity and may be due to other intercurrent causes (*e.g.* infection) [120, 121].

(High-resolution) chest CT scans are, in the opinion of the panel, mainly indicated at the time of diagnosis, in cases of clinical deterioration or abnormal radiography findings, and to rule out other causes of lung dysfunction. Since chest CT scans provide more detailed information than chest radiographs, the panel favours the former in these situations, if the setting allows. High-resolution chest CT scan should preferably be performed both at inspiratory and expiratory phase, to detect air trapping as a sign of small airways disease/BOS. In addition, the panel deems it useful to have a baseline chest CT scan at the time of transplantation and after the early post-transplant period (*i.e.* day 100) for later comparison [7].

In general, both PFT and chest CT scans are safe. Modern CT scan protocols require much less radiation and no contrast is needed for this indication.

Justification of recommendations

For both PFT and chest CT imaging, there is a low risk of side-effects, while important information on disease progression can be obtained. The balance favours regular PFT to assess disease progression. Chest CT scans are, in the opinion of the panel, mainly indicated at the time of diagnosis and upon indication, as explained earlier.

Implementation considerations

Although generally easily accessible, there are likely limitations to availability, accessibility and costs in some settings or countries. The need for more frequent PFT may be a logistical challenge for some lung function departments and may require more personnel and training of personnel. To reduce the burden on the lung function department and patient, home spirometry may be considered [122].

Specific attention should be paid to patients with oral GvHD, in whom it is important to exercise caution. In addition, PFT is contraindicated in patients with pneumothorax/pneumomediastinum.

Monitoring/evaluation

The technique of spirometry efforts and adherence to home spirometers should be continually assessed.

Future research

Home spirometry options should be further explored in BOS after alloHSCT as done in BOS after lung transplantation.

Supportive treatment

Narrative question 2

Should attention be paid to other healthcare interventions in adults with lung cGvHD phenotype BOS: flu, pneumococcal and coronavirus disease 2019 (COVID-19) vaccination, infection prophylaxis including immunoglobulins, pulmonary rehabilitation, smoking cessation and long-term oxygen treatment?

Recommendations

In adults with lung cGvHD phenotype BOS, we suggest paying attention to the following other interventions. (Conditional recommendation, very low quality of evidence stemming from narrative review of evidence.)

- We suggest annual influenza immunisation with an inactivated vaccine according to existing recommendations for alloHSCT patients.
- We suggest pneumococcal vaccination with four doses of the pneumococcal conjugate vaccine according to existing recommendations for cGvHD patients.
- We suggest COVID-19 vaccination with repeated booster vaccinations according to existing recommendations for alloHSCT patients and according to local policies.
- We suggest considering antimicrobial prophylaxis, targeting encapsulated organisms and *Pneumocystis* pneumonia, and antiviral and antifungal prophylaxis for the duration of immunosuppressive therapy based on individual risk factors, according to existing advice for cGvHD patients.
- We suggest considering immunoglobulins in patients with severe infections and IgG levels <400 $mg \cdot dL^{-1}$ according to existing advice for cGvHD patients.
- We suggest that physical activity, including formal pulmonary rehabilitation programmes, is encouraged in patients with functional impairment.
- We suggest using long-term oxygen therapy in case of severe chronic resting hypoxaemia, according to existing recommendations for patients with COPD.

Remarks

There is no clear evidence of the benefit of a booster influenza vaccine, although a second dose might be beneficial in cGvHD patients as they tend to respond less. Policies regarding COVID-19 vaccination may change over time due to changes in the pandemic.

Summary of evidence

There were two retrospective studies on pulmonary rehabilitation in BOS patients after HSCT. For the other interventions, no BOS-specific data were available and literature from other populations was used.

The desirable effects of good immunisation, infection prophylaxis, exercise and smoking cessation are beyond dispute, but their magnitude is not always clear. For influenza, annual vaccination is recommended by the Infectious Diseases Society of America and the European Conference on Infections in Leukaemia [123, 124]. The panel prefers the use of a tetravalent vaccine, if possible. There is no clear evidence of the benefit of a booster vaccine, although a second dose might be beneficial in cGvHD patients who tend to respond less [124]. For pneumococcal vaccination, basic vaccination with three pneumococcal conjugate vaccines 1 month apart has been recommended, followed by a fourth dose instead of the 23-valent vaccine in cases of GvHD [123, 124]. All alloHSCT patients should receive full COVID-19 vaccination with a slight preference for mRNA vaccines, as these have been mostly used in immunocompromised patients. Patients with active GvHD or ongoing immunosuppression had poorer responses and may benefit from repeat vaccinations [125, 126].

Regarding infection prophylaxis, Majhail *et al*. [127] recommended the use of antimicrobial, antiviral and antifungal prophylaxis for the duration of immunosuppressive therapy in cGvHD patients. Screening for cytomegalovirus reactivation should be based on risk factors, including intensity of immunosuppression.

The use of prophylactic immunoglobulins in the absence of infection remains controversial and supplements were mainly recommended for patients with severe or recurrent infections and IgG levels <400 mg·dL^{-1} [127].

Two BOS-specific studies on pulmonary rehabilitation demonstrated decreased dyspnoea and increased exercise tolerance and quality of life based on improvement of 6-min walk test, maximal oxygen consumption (V'_{O_2max}), respiratory muscle strength and physical function score [128, 129]. That V'_{O_2max} is a strong predictor of mortality in chronic lung disease emphasises the importance of pulmonary rehabilitation in all patients with chronic lung diseases, including BOS [128].

Smoking cessation is recommended by the World Health Organization for the general population, and cessation of exposure to tobacco and tobacco-related products is even more recommended in patients with chronic lung diseases [130–132]. Therefore, the panel considers it very important that these general measures are pursued in BOS patients.

For long-term oxygen therapy, the panel believes the same criteria can be followed as for patients with COPD and interstitial lung disease, for whom the American Thoracic Society and British Thoracic Society recommend its use for ⩾15 h·day^{-1} in case of severe chronic resting hypoxaemia [133, 134]. In addition, ambulatory oxygen use should be considered in patients with severe exertional hypoxaemia.

Other supportive evidence

Although the risk is highest in the first years post-transplant, an increased risk of infection may persist for patients with cGvHD who require extended immunosuppressive therapy. The panel believes it is important that general recommendations for patients with cGvHD are followed in BOS patients and that extra attention is needed during times of increased immunosuppression, based on the intensity and profile of the immunosuppressive agent, and patient-related risk factors.

Justification of recommendations

The certainty of the evidence is very low, as studies on pulmonary cGvHD were not available for most interventions and studies of related populations were used. However, due to the expected clinical benefit and low risk of harm, recommendations are based on assigning a higher value to low quality of evidence for clinical improvement over a low value for concerns over uncertainty of magnitude of benefit.

Implementation considerations

Most of these interventions are already in place or available in most centres, with the exception of pulmonary rehabilitation programmes, which may not be available everywhere. In addition, some countries adhere to fairly strict inclusion criteria for immunoglobulins.

Monitoring/evaluation

In patients with active GvHD, the immune response to vaccines (*e.g.* pneumococcal) might be lower and measuring of specific antibody levels before and after vaccination may be considered to determine the level of protection and need for booster immunisations [127]. Oxygen requirements should be monitored in BOS patients.

Future research

Research priorities include whether formal rehabilitation programmes are more beneficial than self-directed exercise programmes. In addition, more data are needed regarding the prevalence and impact of secondary immunodeficiency in the BOS population and the utility of immunoglobulins.

Patient values

In general, patient representatives consider overall survival, quality of life and risk of side-effects to be the most important outcomes, as one can adjust to lower lung function, and PFT data might be less relevant for some patients. In addition, they find patient-reported outcome measures and hospitalisation risk very important. Exercise capacity mainly depends on symptoms present at that time and might therefore be useful in symptomatic, more advanced disease stages. Similarly, impact on quality of life should be considered as burden of symptoms increases. As such, relevant outcomes may vary depending on the stage of the disease. While regular PFT data might be less relevant to a patient, they understand this is important from a clinician's perspective, also to detect the disease as early as possible, to intervene as soon as possible, and during treatment follow-up.

Overall, patients want to achieve the best outcome possible with as few side-effects as possible. However, values related to outcomes, including quality of life and side-effects, may vary from patient to patient and may be influenced by disease burden and personal circumstances. An open discussion about treatment with relevant information on what to expect, together with shared decision-making, should be pursued. Because quality of life and patient-reported outcome measures were often lacking in our studies, patient advocates find it important that these are included in future studies.

Conclusions

The ERS/EBMT task force recommendations for management of pulmonary cGvHD-BOS in adults are summarised in figure 1 and tables 2 and 3. In general, the use of ICS/LABA and FAM (together comprising ICS/LABA, azithromycin and montelukast) is supported in BOS patients along with ECP in progressive disease and lung transplantation for end-stage pulmonary cGvHD. More data are needed to support the use of ruxolitinib and belumosudil in BOS. Imatinib and ibrutinib are possible treatment options, but their efficacy is less convincing and the toxicity of ibrutinib should be balanced against the expected benefits. Therefore, the panel is not in favour of using the latter. The aim of this clinical guideline is to improve quality of patient care and to assist healthcare professionals in optimising pulmonary cGvHD care, to promote safe and effective treatment. Importantly, these drugs should be prescribed by physicians with expertise in their use and possible adverse events.

All recommendations in this guideline are conditional and based on very low or low certainty of evidence. The current guideline should be interpreted in light of several limitations. First, it is clear that BOS-specific studies are rare, along with the retrospective nature of most included studies and low number of BOS patients per study. Timing of BOS treatment administration was likely to be heterogeneous, *e.g.* treatment with early-phase disease *versus* established late-phase disease, which could affect treatment efficacy. Furthermore, study protocols, treatment doses, conventional immunosuppression and other transplant-related drugs, and lines of treatment differed across studies. In addition, end-points often varied and some studies used combined end-points (*i.e.* overall response rate based on symptoms and PFT data), making comparisons between studies very challenging.

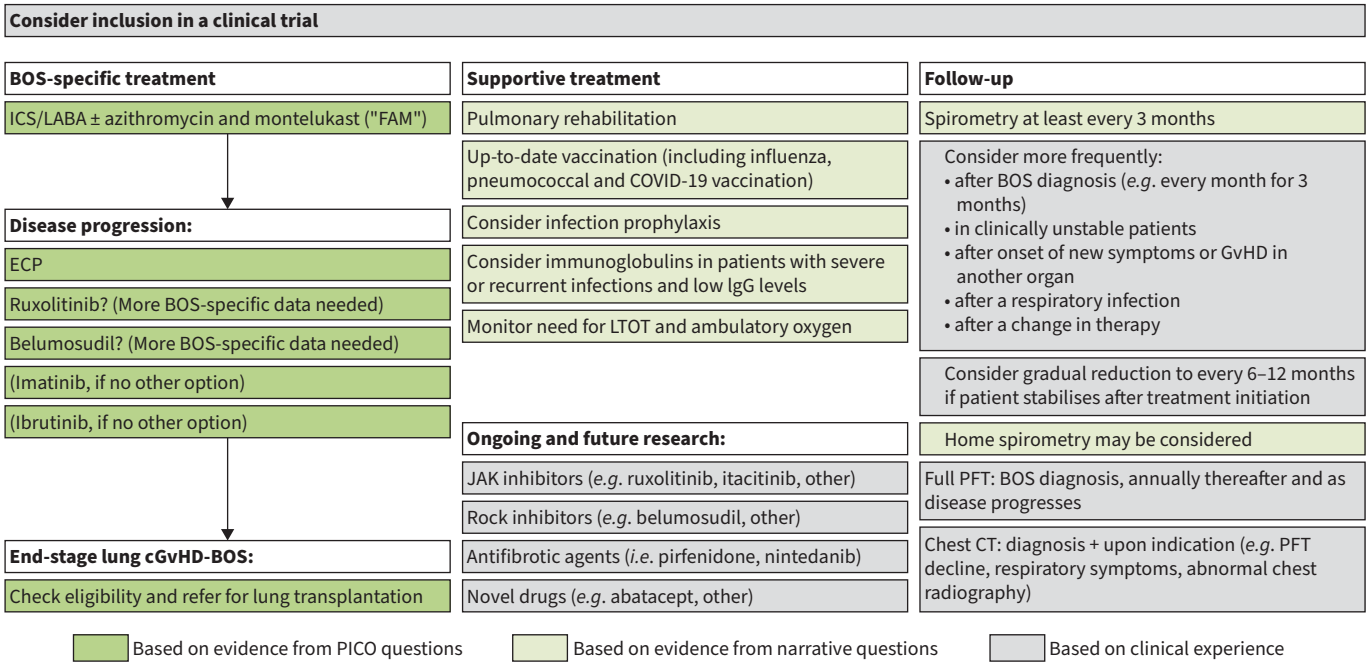

FIGURE 1 Proposed suggestions for adults with lung chronic graft-*versus*-host disease (cGvHD) bronchiolitis obliterans syndrome (BOS) with respect to BOS-specific treatment in addition to conventional immunosuppressive regimen, supportive treatment and lung functional and radiological follow-up. Full considerations can be found in the article text and the supplementary material. ICS: inhaled corticosteroid; LABA: long-acting β-agonist; FAM: fluticasone, azithromycin and/or montelukast; ECP: extracorporeal photopheresis; COVID-19: coronavirus disease 2019; LTOT: long-term oxygen therapy; JAK: Janus kinase; PFT: pulmonary function testing; CT: computed tomography; PICO: patient, intervention, comparison, outcome.

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TABLE 2 Summary of patient, intervention, comparison, outcome (PICO) questions and recommendations

	Title	Recommendation	Considerations
Question 1	In adults with lung cGvHD-BOS, should ICS±LABA be used in addition to their conventional immunosuppressive regimen?	In adults with lung cGvHD-BOS, we suggest using ICS±LABA. (Conditional recommendation, low certainty of evidence)	It is critical to select the most appropriate device for a patient and train them in its use, ensuring optimal technique and taking into account patient preferences. The use of ICS should be considered on a case-by-case basis in patients with a bronchiectasis phenotype.
Question 2	In adults with lung cGvHD-BOS, should fluticasone-azithromycin-montelukast be used in addition to their conventional immunosuppressive regimen?	In adults with lung cGvHD-BOS, we suggest using fluticasone-azithromycin-montelukast. (Conditional recommendation, very low certainty of evidence)	Azithromycin should be used with caution in patients with a high risk of secondary malignancies or cancer predisposition syndromes.
Question 3	In adults with lung cGvHD-BOS, should imatinib be used in addition to their conventional immunosuppressive regimen?	In adults with lung cGvHD-BOS, we suggest either imatinib in addition to their conventional immunosuppressive regimen or conventional immunosuppression. (Conditional recommendation for either intervention or the comparison, very low certainty of evidence)	GvHD manifestations in other organs should be considered. Imatinib might be an option in patients with sicca symptoms (*e.g.* ocular cGvHD, because of its side-effect profile which includes peri-orbital oedema) and in patients with CML because of potential impact on underlying disease. It would be a less favourable option in patients with cGvHD-related myalgia, gastrointestinal symptoms and anorexia due to risk of drug-related exacerbation of these symptoms.
Question 4	In adults with lung cGvHD-BOS, should ibrutinib be used in addition to their conventional immunosuppressive regimen?	In adults with lung cGvHD-BOS, we suggest not using ibrutinib in addition to their conventional immunosuppressive regimen. (Conditional recommendation, very low certainty of evidence)	In general, the panel suggests against using this drug, although it might still be a valuable option in selected patients, where other options might not be possible. Ibrutinib might be an option in patients with cytopenia, as this is not a frequent side-effect of ibrutinib, and in patients with CLL because of impact on underlying disease. It would be a less favourable option in patients with a history of frequent infectious complications, bleeding, symptoms similar to ibrutinib side-effects and patients taking CYP3A inhibitors, due to drug interactions.
Question 5	In adults with lung cGvHD-BOS, should ruxolitinib be used in addition to their conventional immunosuppressive regimen?	In adults with lung cGvHD-BOS, we suggest either ruxolitinib in addition to their conventional immunosuppressive regimen or conventional immunosuppression. (Conditional recommendation for either intervention or the comparison, very low certainty of evidence)	More data from BOS-specific trials are needed to fully evaluate its efficacy. Ruxolitinib should be used with caution in patients with a history of (recurrent) infections and cytopenia. Ruxolitinib might be an option in patients with extrapulmonary GvHD, as ruxolitinib has been demonstrated to be effective for extrapulmonary GvHD.
Question 6	In adults with lung cGvHD-BOS, should belumosudil be used in addition to their conventional immunosuppressive regimen?	In adults with lung GvHD-BOS, we suggest either belumosudil in addition to their conventional immunosuppressive regimen or conventional immunosuppression. (Conditional recommendation for either intervention or the comparison, very low certainty of evidence)	More data from BOS-specific trials are needed to fully evaluate its efficacy.

Continued

https://doi.org/10.1183/13993003.01727-2023

TABLE 2 Continued

	Title	Recommendation	Considerations
Question 7	In adults with lung cGvHD-BOS, should ECP be used in addition to their conventional immunosuppressive regimen?	In adults with progressive lung cGvHD-BOS, we suggest using ECP in addition to their conventional immunosuppressive regimen. (Conditional recommendation, very low certainty of evidence)	It might be difficult to perform ECP in every patient or at every site, given the logistical challenges. The need for a central line and related low risk of line infection must be considered. Patient-specific details and preferences should be taken into account to determine if ECP is appropriate for a given patient.
Question 8	In adults with end-stage lung cGvHD-BOS, should lung transplantation be performed?	In highly selected adults with end-stage lung cGvHD-BOS, we suggest lung transplantation as a life-saving therapeutic option. (Conditional recommendation, very low certainty of evidence)	Lung transplantation might be an option for highly selected adults, taking into account other comorbidities and general eligibility criteria for lung transplantation. Specific lung transplant criteria for lung cGvHD-BOS patients should be established. Risk of haematological relapse needs to be considered based on the patient profile.

cGvHD: chronic graft-*versus*-host disease; BOS: bronchiolitis obliterans syndrome; ICS: inhaled corticosteroid; LABA: long-acting β-agonist; CML: chronic myeloid leukaemia; CLL: chronic lymphocytic leukaemia; ECP: extracorporeal photopheresis.

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TABLE 3 Summary of narrative questions and recommendations

	Title	Recommendations	Considerations
Question 1	How and how frequently should adults with lung cGvHD-BOS be re-evaluated? 1) How often should PFT evaluation be conducted? 2) How often should imaging/chest CT evaluation be conducted?	In adults with lung GvHD-BOS, we suggest: • spirometry at least every 3 months for follow-up; • full PFT at the time of BOS diagnosis, annually thereafter and at the time of disease progression; • high-resolution chest CT scan at the time of diagnosis and upon indication, for example in cases of PFT decline or respiratory symptoms, to exclude other causes. (Conditional recommendation, very low quality of evidence stemming from narrative review of evidence)	More frequent spirometry testing is suggested after BOS diagnosis, as some patients may have a rapid decline in FEV_1 (*e.g.* every month for the first 3 months), in patients who are clinically unstable, after the onset of new symptoms or GvHD in another organ, a respiratory infection or a change in therapy. In patients who stabilise after treatment initiation, gradually reducing the frequency of spirometry testing to every 6–12 months may be considered based on time after transplantation and BOS diagnosis.
Question 2	Should attention be paid to other interventions in adults with lung cGvHD-BOS: flu, pneumococcal and COVID-19 vaccination, infection prophylaxis including immunoglobulins, pulmonary rehabilitation, smoking cessation, long-term oxygen treatment?	In adults with lung GvHD phenotype BOS, we suggest: • annual influenza immunisation with an inactivated vaccine according to existing recommendations for alloHSCT patients; • pneumococcal vaccination with four doses of the pneumococcal conjugate vaccine according to existing recommendations for cGvHD patients; • COVID-19 vaccination with repeated booster vaccinations according to existing recommendations for alloHSCT patients and according to local policies; • considering antimicrobial prophylaxis, targeting encapsulated organisms and *Pneumocystis* pneumonia, antiviral and antifungal prophylaxis for the duration of immunosuppressive therapy based on individual risk factors, according to existing advice for cGvHD patients; • considering immunoglobulins in patients with severe infections and IgG levels <400 $mg \cdot dL^{-1}$ according to existing advice for cGvHD patients; • physical activity, including formal pulmonary rehabilitation programmes, is encouraged in patients with functional impairment; • using long-term oxygen therapy in case of severe chronic resting hypoxaemia, according to existing recommendations for patients with COPD. (Conditional recommendation, very low quality of evidence stemming from narrative review of evidence)	There is no clear evidence of the benefit of a booster influenza vaccine, although a second dose might be beneficial in cGvHD patients as they tend to respond less. Policies regarding COVID-19 vaccination may change over time due to changes in the pandemic. Ambulatory oxygen use should be considered in patients with severe exertional hypoxaemia.

cGvHD: chronic graft-*versus*-host disease; BOS: bronchiolitis obliterans syndrome; PFT: pulmonary function testing; CT: computed tomography; FEV_1: forced expiratory volume in 1 s; COVID-19: coronavirus disease 2019; alloHSCT: allogeneic haematopoietic stem cell transplantation.

TABLE 4 Future research aims for lung chronic graft-*versus*-host disease (cGvHD) bronchiolitis obliterans syndrome (BOS)

General future research aims	• More lung cGvHD-BOS-specific studies are needed and should preferably consist of RCTs • Well-defined study end-points and treatment outcomes should be defined for lung cGvHD-BOS-specific studies, to facilitate comparison between studies • First-line treatment should be standardised across centres, even when not participating in a clinical trial • Treatment effects at different disease stages, *i.e.* mild *versus* moderate *versus* severe disease stages, should be assessed • Umbrella and platform trials may be useful to assess multiple treatments for lung cGvHD-BOS • Future research should focus on biomarkers to predict treatment response for individual patients to specific interventions • Quality of life and other patient-reported outcome measures should be systematically included in future trials
Specific future research aims	• Combination therapy of ICS, LABA and long-acting muscarinic agonists should be studied in lung cGvHD-BOS patients • The safety and efficacy of fluticasone (or equivalent other inhaled corticosteroid), azithromycin and montelukast should be assessed in RCTs to assess the potential risk of relapse and malignancy and the underlying mechanism of action, as well as the use of azithromycin and montelukast as standalone treatments for lung cGvHD-BOS • Ruxolitinib and belumosudil should be further tested in lung cGvHD-BOS-specific prospective studies, including RCTs, to assess safety and efficacy as well as patient-reported outcomes • RCTs are needed to assess the efficacy of ECP in lung cGvHD-BOS, and also to determine the optimal frequency and duration of treatment • Specific lung transplant referral and listing criteria for lung cGvHD-BOS patients should be established, including recommendations regarding patients with extrathoracic cGvHD and optimal timing after alloHSCT • Implementation of home spirometry after alloHSCT should be further explored for the diagnosis and follow-up of lung cGvHD-BOS

RCT: randomised controlled trial; ICS: inhaled corticosteroid; LABA: long-acting β-agonist; ECP: extracorporeal photopheresis; alloHSCT: allogeneic haematopoietic stem cell transplantation.

One of the outcomes of this guideline should be to promote further research on the optimal treatment of patients with pulmonary cGvHD (table 4). Larger studies are urgently needed and should preferably be randomised in nature, specifically target BOS patients and use pre-defined similar end-points. First-line treatment is best done in a clinical trial setting in experienced centres as data are lacking. The use of umbrella and platform trials to assess multiple treatments for BOS would provide valuable information, including to decide on the most appropriate immunosuppressive regimen for BOS and to create a treatment algorithm. In addition, future research should focus on biomarkers to predict treatment response for individual patients to specific interventions. Further research is very likely to have an important impact on our certainty in the effect estimate and is likely to change the estimate. As knowledge gaps and identified research priorities are addressed, these recommendations will require revision as additional data become available in the coming years.

Finally, quality-of-life parameters should be systematically included in future studies related to treatment of BOS. Treatment decisions must weigh the potential beneficial effects of the intervention against the burden of treatment and risk of adverse events and patients' values and preferences should be considered in all treatment decisions.

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The guidelines published by the European Respiratory Society (ERS) incorporate data obtained from a comprehensive and systematic literature review of the most recent studies available at the time. Health professionals are encouraged to take the guidelines into account in their clinical practice. However, the recommendations issued by this guideline may not be appropriate for use in all situations. It is the individual responsibility of health professionals to consult other sources of relevant information, to make appropriate and accurate decisions in consideration of each patient's health condition and in consultation with that patient and the patient's caregiver where appropriate and/or necessary, and to verify rules and regulations applicable to drugs and devices at the time of prescription.

A lay summary of these guidelines can be found at https://europeanlung.org/en/information-hub/guidelines/treating-pulmonary-chronic-graft-versus-host-disease-in-adults

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