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Therapy options for chronic lung allograft dysfunction–bronchiolitis obliterans syndrome following first-line immunosuppressive strategies: A systematic review

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BACKGROUND: Long-term success of lung transplantation is limited by the development of chronic lung allograft dysfunction (CLAD), of which bronchiolitis obliterans syndrome (BOS) is the most common form. This systematic review sought to identify the current evidence base for CLAD-BOS therapies after initial immunosuppressive treatment strategies.

METHODS: The MEDLINE, Embase, and Cochrane Library databases from inception to May 3, 2016, were searched using keywords relating to CLAD-BOS, study designs, and treatments of interest, including extracorporeal photopheresis (ECP), aerosolized cyclosporine, total lymphoid irradiation (TLI), alemtuzumab, and montelukast. Titles, abstracts, and full texts were screened by 2 independent reviewers to identify studies of CLAD-BOS second-line therapy in adult lung transplant patients. Quality was assessed according to the Downs and Black checklist.

RESULTS: Of the 936 individual citations identified, 47 reports of 40 studies met inclusion criteria, including 17 full publications, 11 recent (2015–2016), and 12 older (pre-2015) congress proceedings. Most of the full publications and recent abstracts investigated ECP ($n = 11$), TLI ($n = 5$), alemtuzumab ($n = 4$), and montelukast ($n = 2$). Most studies were uncontrolled and retrospective. Compared with standard therapy alone, improved lung function and survival was reported for ECP in 2 studies without randomization, with lower-quality evidence for improved lung function for TLI, montelukast, and aerosolized cyclosporine.

CONCLUSIONS: Because most identified studies were of retrospective and uncontrolled design, comparison of treatment effects was limited. Available evidence suggests stabilized lung function after ECP in combination with established immunosuppressive regimens in late-line CLAD-BOS treatment, with fewer data for TLI, montelukast, and aerosolized cyclosporine.

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Lung transplantation is an established therapeutic option for selected patients with end-stage lung disease.[1] However, according to international registry figures, the median overall survival of lung transplant recipients is only 5.7 years.[1] The long-term success of lung transplantation

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is limited by the development of chronic lung allograft dysfunction (CLAD), an umbrella term used to define a persistent (≥ 3 weeks) decline in pulmonary function (forced expiratory volume in 1 second [FEV_1], with or without a decline in forced vital capacity) of ≥ 10% from baseline.[2] Bronchiolitis obliterans syndrome (BOS) is the most common form of CLAD, with a prevalence ranging from 50% after 5 years to 76% after 10 years among surviving lung transplantation recipients.[1] Overall, BOS is the most common cause of death beyond the first year after lung transplantation.[1]

Bronchiolitis obliterans, a histologic diagnosis, involves abnormal remodeling of the terminal bronchioles, caused by fibrosis-induced scarring, which results in airflow limitation.[3] BOS, the physiologic correlate of bronchiolitis obliterans, is defined by persistent lung function decline (decline in FEV_1 of > 20% from baseline in absence of infection) and presents with severe airway obstruction, dyspnea, exercise limitation, and, eventually, death caused by respiratory insufficiency.[2,4]

Lung transplant recipients typically receive immunosuppressive regimens after transplantation, most commonly consisting of a calcineurin inhibitor (cyclosporine/tacrolimus) combined with an anti-proliferative agent (azathioprine, mycophenolate, sirolimus, everolimus) and a corticosteroid.[5] Initial treatment of BOS consists of modification of this maintenance immunosuppression, including the switch from cyclosporine to tacrolimus or vice versa.[6] In addition, the International Society for Heart and Lung Transplantation (ISHLT)/American Thoracic Society/European Respiratory Society clinical practice guidelines recommend a trial of azithromycin therapy—unless contraindicated—as part of immunomodulation for a minimum of 3 months in all lung transplant recipients who develop a decline in lung function consistent with the onset of BOS.[7] If lung function continues to decline, patients progress to second-line or "salvage" therapy, where evidence is limited.[2,7]

To our knowledge, no systematic review of salvage therapy studies in CLAD-BOS has been published. The purpose of this review is to systematically identify the current evidence base, including randomized controlled trials (RCTs), interventional non-RCTs, and observational studies, for the efficacy and safety of CLAD-BOS second-line/salvage therapy.

Methods

Search strategy and selection of studies

The systematic literature review (SLR) was performed in accordance with the methodologic principles of systematic review conduct, as detailed in the University of York Centre for Reviews and Dissemination's "Guidance for Undertaking Reviews in Health Care."[8] The computerized search covered MEDLINE/MEDLINE In-Process, Embase, and Cochrane Library databases (Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Database of Abstracts of Reviews of Effectiveness), from database inception to May 3, 2016, and was conducted using keywords relating to CLAD-BOS, study designs, and therapies of interest (Supplementary Material A, available online at www.jhltonline.org).

For pragmatic reasons, the searches included terms for the following treatments: extracorporeal photopheresis (ECP), antithymocyte globulin (ATG), cyclophosphamide, etanercept, inhaled/aerosolized cyclosporine (CSA), methotrexate, pirfenidone, total lymphoid irradiation (TLI), muromonab-CD3, alemtuzumab, mesenchymal stem cells, nintedanib, and montelukast. Treatments of interest were identified through consensus between the authors.

To be eligible for inclusion, publications had to describe an RCT, interventional non-RCT, or an observational study reporting efficacy or safety data for an intervention of interest for the treatment of adult lung transplant patients with BOS unresponsive to modifying the immunosuppression regimen with azithromycin, tacrolimus, cyclosporine, azathioprine, montelukast, or everolimus. Case studies and case reports were excluded. The search was limited to studies published in English.

Two reviewers (M.H. and a trained SLR analyst) independently screened titles and abstracts of search results from indexed databases using the pre-specified inclusion criteria. Full-text articles selected were retrieved and independently reviewed for inclusion by the 2 reviewers. Disagreements were resolved by consensus.

In addition, to better understand current research in the field, the 2015–2016 conference proceedings from key congresses (ISHLT Annual Meeting, International Congress on Lung Transplantation, American Transplant Congress, World Transplant Congress, and European Respiratory Society International Congress) and the reference lists of all included publications were reviewed to identify any additional publications relevant to the study question.

Data extraction and analysis

Study characteristics and treatment outcomes related to the efficacy and safety of salvage therapy for CLAD-BOS were extracted using a predefined extraction grid (Supplemental Material B, online) by 1 reviewer and independently checked by a second reviewer. Where our search identified both interim and final published results, only final results were extracted. The quality of the included studies was assessed according to the York Centre for Reviews and Dissemination checklist for RCTs[8] (RCTs only) and the Downs and Black checklist (non-RCT interventional and observational studies).[9] Records deemed potentially relevant to the study question were categorized as full publications, congress abstracts presented pre-2015 with no follow up publications, and recent (2015–2016) congress abstracts.

Results

Study selection

After removing duplicates, the literature search identified 936 individual citations (Figure 1). We rejected 835 references after screening of titles and abstracts, and a further 54 were rejected based on full-text review (Figure 1; Supplemental Material C, online). The remaining 47 reports were reviewed and found to report results from 40 unique studies. Overall, 17 studies (43%) had been published as a full-length article, with 11 recent (2015–2016) and 12 older (pre-2015) congress abstracts meeting inclusion criteria