

Bronchiolitis obliterans syndrome – current prophylaxis and treatment possibilities

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Abstract

Bronchiolitis obliterans syndrome (BOS) treatment remains the „Holy Grail” of lung transplantation. In this article the authors attempt to summarize the results of different immunosuppressive strategies aiming to prevent onset, delay progression and improve prognosis of BOS. Strategies discussed include switching cyclosporine (CSA) to tacrolimus (Tac), azathioprine (AZA) to mycophenolate mofetil (MMF), addition of sirolimus/rapamycin (Sir/Rapa), everolimus, azithromycin (AZI), inhaled steroids, inhaled cyclosporine, cytolytic therapy, photopheresis and total lymphoid irradiation (TLI).

Key words: lung transplantation, bronchiolitis obliterans syndrome, immunosuppression.

Streszczenie

Leczenie zespołu zarostowego zapalenia oskrzelików (ang. *bronchiolitis obliterans syndrome* – BOS) pozostaje „Świętym Graalem” dla transplantologii płuc. Autorzy tego artykułu podjęli próbę podsumowania skuteczności różnych strategii leczenia immunosupresyjnego, mającego na celu opóźnienie wystąpienia, spowolnienie procesu i poprawę rokowania w BOS. Ocenie poddano zastąpienie cyklosporyny (CSA) takrolimusem (Tac), azatiopryny (AZA) mykofenolanem mofetilu (MMF), dodanie do terapii sirolimusu/rapamycyny (Sir/Rapa), everolimusu, azytromycyny (AZI), sterydów wziewnych, surowic cytolitycznych, fotoferezy, naświetlania promieniami rentgenowskimi.

Słowa kluczowe: transplantacja płuc, *bronchiolitis obliterans syndrome*, immunosupresja.

Background

Although a relatively recent development, lung transplantation has already established its position as a viable treatment option for non-malignant end-stage pulmonary diseases and highly selected patients with advanced multifocal bronchioalveolar carcinoma [1]. It has been shown to not only impart a survival benefit (with the exception of chronic obstructive pulmonary disease patients), but also improve health related quality of life (HRQoL) to the level of the healthy population [2]. 1-year survival figures for lung transplantation are up to 90% [3]; however, the problem of chronic allograft rejection/dysfunction manifesting as bronchiolitis obliterans syndrome (BOS) remains unresolved. BOS is the major determinant of the 50% 5-year survival figure post lung transplantation and is one of the main factors resulting in decreased health-related quality of life (HRQoL) (in both physical and psychological dimensions due to depression and anxiety secondary to dyspnoea and decreased well being) in lung transplant recipients [2].

The additional costs of BOS monitoring and treatment, estimated by the Groeningen Group at an additional 25% (primarily due to the increase in hospital bed days and medication costs), should not be overlooked [4]. These costs may well be even higher in the modern era due to the costly new immunosuppressive drugs becoming available for BOS treatment.

Aim

The aim of the study is to provide an update about BOS, its prevention and treatment, mainly focusing on the immunosuppression strategies that can be employed in lung transplant recipients.

Material and methods

PubMed and Cochrane Database were searched for articles concerning immunosuppression, BOS and its treatment in lung transplantation patients.

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Definition of BOS

In 2002 the International Society for Heart and Lung Transplantation (ISHLT) updated the definition and grading algorithm for BOS (tab. I), with the aim of standardizing the terminology to allow different lung transplant programs to compare their results [5]. The term “bronchiolitis obliterans syndrome” is used as a clinical surrogate for chronic lung graft dysfunction resulting in persistent airflow obstruction and does not require histological confirmation. Obliterative bronchiolitis is in contrast the term for a histologically proven entity and is not required for the diagnosis of BOS. Standardized spirometry is used for diagnosing and estimating BOS and has been shown to be the best surrogate marker for endpoints of graft loss and mortality [6]. Absence of other potential causes of airflow obstruction such as acute rejection, infection, anastomotic stricture and bronchomalacia is required for the diagnosis of BOS.

Since regular home spirometry has been shown to detect not only acute rejection, but also to diagnose BOS up to 341 days earlier than clinic-based pulmonary function testing, it should doubtlessly be a regular component of long-term follow-up [7].

Risk factors and preventive measures

BOS is hypothesized to result from airway injury caused by a number of different mechanisms, including ischaemia-reperfusion injury, immunological mechanisms, airway infections (mostly viral) and both acid and non-acid gastroesophageal reflux [5] (tab. II). The latest can be attenuated by use of proton pump inhibitors and in resistant cases with fundoplication following lung transplantation. Other possible factors include increased risk of BOS in single lung transplantation in COPD patients [8, 9]. Bronchial hyperresponsiveness preceding the onset of BOS can be a symptom of active inflammatory process rather than its cause [8]. Although there are no studies investigating the role of non-compliance, Husain et al. have reported inadequate immunosuppression (defined as ≥ 2 whole-blood cyclosporine A (CSA) trough levels < 200 ng/ml) to be a risk factor for BOS development [10].

Tab. I. BOS classification according to ISHLT 2002 [5]

Grade	BOS classification		
	FEV1 % of baseline		FEF 25-75 % of baseline
BOS 0	>90	and	>75
BOS 0-p	81-90	and/or	≤ 75
BOS 1	66-80		
BOS 2	51-65		
BOS 3	≤ 50		

BOS – bronchiolitis obliterans syndrome; FEV1 – forced expiratory volume in 1 second; FEF 25-75 – mid-expiratory flow rate.

Influence on peritransplant risk factors

In 2005 Hadjiliadis et al. reported decreased median, 1-month, 1-year and 5-year survival in immunized lung transplant recipients (panel reactive antibodies, PRA $>25\%$) and contributed it to the effect of direct anti-HLA antibodies on the allograft [11]. The need for evaluation of pretransplantation treatment with intravenous immunoglobulin (IVIG) and plasmapheresis was suggested. In the same year Appel III J. and colleagues [12] suggested a role for peritransplant desensitization therapy with intravenous immunoglobulin (IVIG) and extracorporeal immunoabsorption (ECI). The use of this strategy in recipients with third-party or donor-directed anti-HLA antibodies resulted in a reduction in BOS incidence (to values lower than even in the non-sensitized patients) during 3-year follow-up. This could be explained by the in vitro finding of smooth muscle cells, endothelial cells and epithelial cells proliferation stimulation by polyspecific anti-HLA antibodies, or else by a significant reduction of frequency and severity of acute rejection episodes during the first 12 months in this group. IVIG is also known to reduce cytokine production by T-cells and to down-regulate antibody production. This desensitization treatment also helped to avoid primary graft dysfunction (PGD), a finding which was also seen with Perfadex in many clinical trials [13].

Although use of Perfadex for graft preservation is suggested to attenuate graft ischaemic injury most effectively during cold ischaemia time and to decrease 1-year mortality [14], it has not been shown to improve 1-year BOS-free survival [15]. None of the induction therapies OKT 3, ATG or daclizumab has been shown to be superior for BOS prophylaxis. Indeed the use of OKT3 resulted in a significantly higher incidence of infectious complications, which could potentially contribute to BOS development [16]. Long-term results with the use of basiliximab (following initial encouraging results in small numbers of patients [17]) as well as the use of alemtuzumab are awaited with interest.

Tab. II. Probable and potential risk factors for BOS development [5]

BOS probable risk factors	BOS potential risk factors
acute rejection	CMV infection
lymphocytic bronchitis/bronchiolitis	organizing pneumonia
CMV pneumonitis	bacterial/fungal/non-CMV viral infection
	recipient age
	underlying disease
	cytokine polymorphism
	donor age
	graft ischaemic time
	HLA – mismatching
	gastroesophageal reflux with aspiration

Since the use of MMF prior to lung ischaemia in an animal model has been shown to reduce lung vascular permeability indices, myeloperoxidase content and alveolar leukocyte count, without influence on nuclear factor κ B [18], it could be hypothesized that induction therapy with MMF and an NF- κ B activation affecting agent could reduce the lung ischaemia-reperfusion injury component of BOS pathogenesis. The lack of superiority of MMF over AZA in 3-year freedom from BOS in human lung transplant recipients [19, 20] could be due to lack of MMF induction prior to ischaemia or the lack of inhibition of NF- κ B activation, or else differences in molecular effects between human and rat models.

Immunosuppressive strategies for BOS prevention

Since even a solitary episode of A1 (or A2) acute rejection has been shown to be an independent risk factor for BOS [21], it would be expected that interventions reducing the rate of acute rejection would contribute to reduction of BOS occurrence. However, this has not been shown strong enough for any immunosuppression protocols as yet.

Although the Munich group has observed a trend towards BOS reduction for Tac + MMF + steroids protocol when compared with CSA + AZA + steroids, CSA + MMF + steroids or Tac + MMF + steroids in long-term observation, this has neither been shown to be significant [22] nor confirmed in other studies [23]. The main documented advantage of Tac over CSA-based immunosuppression remains the lesser propensity to cause hypertension and hyperlipidaemia [24].

Another potential method of BOS prophylaxis is the use of new immunosuppressants, which function by inhibiting signal proliferation, such as rapamycin and everolimus. The latter has been demonstrated to postpone BOS onset (and reduce acute rejection occurrence) although it has the disadvantage of potentiating CSA-induced nephrotoxicity [25].

Local anti-inflammatory treatment with inhaled steroids for prophylaxis of BOS has shown no evidence of benefit [26, 27] and this treatment has also been shown to fail to suppress cytokines involved in BOS development, such as: TNF- α , TNF- β , IL-8 or bFGF [26, 27].

The idea of using the lungs' easy accessibility to the environment for inhaled and therefore topical immunosuppression delivery has been explored again with aerosolized cyclosporine. In a randomized, double blind, placebo-controlled trial, addition of 300 mg inhaled cyclosporine to systemic immunosuppression during the first 2 years after transplantation improved survival and delayed the onset of chronic rejection. Surprisingly, it was not linked to a decrease in acute rejection incidence perhaps because only episodes of grade 2 or higher were registered [28]. Results from a longer follow-up could answer the question of how far can this regimen extend the chronic rejection-free and overall survival period.

Treatment of BOS

When BOS is diagnosed and no improvement after Solu-Medrol pulses is observed, augmentation of immunosuppression including switching cyclosporine (CSA) to tacrolimus (Tac), azathioprine (AZA) to mycophenolate mofetil (MMF) or sirolimus/rapamycin (Sir/Rapa), addition of azithromycin (AZI), methotrexate, inhaled steroids, cytolytic therapy, photopheresis and total lymphoid irradiation (TLI) can be considered.

Conversion from CSA to tacrolimus and from AZA to MMF is commonly used as a treatment strategy at the onset of BOS, although none of these drugs have been shown to improve lung function. Their main advantage remains stabilization of FEV1 [29, 30], possibly due to reduction of rejection activity mirrored by exhaled nitric oxide reduction [30].

Replacement of AZA or MMF with rapamycin has not been shown beneficial in the treatment of BOS in lung transplant patients; however, stabilization or even improvement in pulmonary function has been shown in the subpopulation with rapid decline. This observation suggests that the anti-fibrinoproliferative activity of rapamycin could be efficacious in the active BOS phase [31] and Hernandez et al. suggest that this treatment should be started in an early phase, prior to the development of fibrotic changes [32]. Groetzner and coworkers suggested the same explanation for the lack of discernible impact of conversion from CNI + MMF + steroids to Rapa + MMF + steroids on the development of BOS, and also observed beneficial effects when this switch was made early in the course of the process [33]. The ideal time point for introduction of rapamycin needs clarification as CNI-free rapamycin-based immunosuppression can result in anastomosis dehiscence in de novo lung transplant recipients [34].

Another question is toxicity in rapamycin protocols. Target concentrations of 5 to 7 ng/ml for tacrolimus and 6 to 10 μ g/ml for rapamycin when used together avoid serum creatinine deterioration and were shown to be beneficial for BOS and effective in protecting the graft from acute rejection [35]. This regimen also significantly reduced the frequency of other potential adverse effects of rapamycin, including hyperlipidaemia and leucopenia, and there were no observed episodes of rapamycin-induced interstitial pneumonitis.

Predictors of positive response to azithromycin in BOS include starting treatment earlier (for BOS diagnosed early after lung transplantation) and presence of high BAL neutrophilia and IL-8 levels [36]. The early promising findings of lung function improvement after the addition of azithromycin [37] were not confirmed in later studies; however, stabilization of lung function has been repeatedly observed [36-38]. Potential mechanisms of macrolide therapy in BOS include an anti-inflammatory effect, with reductions in neutrophils and IL-8 levels observed in the airways of BOS patients [36], as well as reductions in IL-1 β and TNF- α levels (an observation in healthy volunteers, not confirmed in lung transplant recipients) [39]. The role of antibacterial activity of azithromycin cannot be excluded, since most

participants in these studies were colonized with *Pseudomonas aeruginosa* [37, 38].

Further immunosuppression augmentation can be obtained with cytolytic therapy. Although an arrest or improvement in FEV1 is observed in fewer than 50% of patients treated with cytolytic agents, this improvement in FEV1 is sustained over the follow-up period after discontinuation of this treatment [40] and infectious complications can be avoided with administration of antimicrobial prophylaxis [41].

Data concerning use of methotrexate in BOS treatment are scant. In the most recent report it was successful in 2 of 3 BOS patients reported by Boettcher et al. [42], but concomitant acute neutropenia was observed. Lack of effect was probably caused by treatment discontinuation due to MTX-induced alveolitis and agranulocytosis. In contrast, an earlier retrospective analysis of a larger group by Dusmet et al. showed only minimal toxicity of methotrexate while significant reduction in FEV1 decline was still achieved [43].

Photopheresis using 8-methoxypsoralen results in temporary improvement in lung function, but FEV1 values subsequently decline to below pre-photopheresis levels and PTLD and infections are common complications [44]. The Vienna group also reports some benefit with photopheresis in BOS stage 1 and 2 patients, but not in BOS 3 for this treatment with an absence of complications [45].

Total lymphoid irradiation (TLI) is a nonpharmacological immunomodulatory approach to BOS treatment, which can result in stabilization of lung function in some patients. Bone marrow suppression and severe infections are the main reasons for withdrawal from TLI, but in those patients who

finish the course of TLI, a significant reduction of rate of decline in pulmonary function tests (PFTs) is observed [46].

If all other strategies fail, a definitive therapeutic option of retransplantation for BOS is possible. The Hannover group reports no difference in risk in 1- and 5-year survival between retransplantation for BOS and in first-time lung transplantation. Incidence of recurrent BOS after retransplantation for BOS did not differ between those two groups [47]. This supports earlier experience of the Clichy group, who additionally considered bronchiectases in the retained graft from the original transplant as the source of fatal infections and the cause of progressive disabling bronchorrhea after retransplantation, and hence supported replacement of the primary graft rather than contralateral implantation [48].

Discussion

We should always keep in mind the highly variable natural course of BOS post lung transplantation (ranging from a pattern of steady decline to acute drops in lung function, often followed by further periods of stability) when interpreting the results of research in this area. Together with small population numbers and short follow-up, these factors make it difficult to draw clear conclusions from published data. Experts' opinions and consensus are essential in proposing treatment standards for BOS, such as the algorithm proposed by the Toronto group [49] (tab. III).

Histopathologic assessment could shed light on the etiology of BOS, and findings of coexistent chronic vascular rejection, interstitial fibrosis or fungus infection in explan-

Tab. III. Protocols for bronchiolitis obliterans syndrome after Toronto Lung Transplantation Manual [49]

1. An FEV1 drop >10% but <20% after 6 months is not necessarily a marker of progressive change. Review the immunosuppression levels and either continue to follow them or consider an approach similar to those for changes in the FEV1 in the early post-transplantation period, or BOS stage 0-p (pre-stages BOS stage 1), which appears below.
2. In case of an FEV1 drop >10% that is sustained, BOS 0-p or a "slow" decline:
 - Review previous bronchoscopy results and immunosuppression levels.
 - Consider performing a bronchoscopy.
 - Consider using Solu-Medrol if rejection is likely or possible.
 - Consider using enhanced immunosuppression – tacrolimus for cyclosporine, or mycophenolate mofetil or sirolimus for azathioprine.
 - Consider anti-inflammatory therapy – azithromycin or inhaled steroids.
3. In case of an FEV1 decrease >20% and "rapid" decline:
 - Review the previous bronchoscopy results and immunosuppression levels and exclude infection. Consider whether a repeat bronchoscopy may be possible, depending on lung function.
 - Perform CT scanning.
 - Consider using Solu-Medrol 10 mg/kg IV for 3 days, as in acute rejection.
 - Consider cytolytic therapy (hospitalize the patient).
 - Consider enhanced immunosuppression – tacrolimus for cyclosporine, or mycophenolate mofetil or sirolimus for azathioprine.
 - Consider anti-inflammatory therapy – azithromycin or inhaled steroids.
 - Consider treatment or suppression of colonizing organisms in BOS > stage 1 – *Pseudomonas*, *Aspergillus*, or nontuberculous mycobacteria.
4. In case of a progressive loss despite the interventions in (3):
 - Consider extended therapy such as total lymphoid irradiation or photopheresis.
 - Consider whether the patient is a candidate for retransplantation.
 - Provide symptomatic or palliative care.

ted lungs with BOS could help explain differences in the response to treatment and in the natural course of the disease [50].

Use of new immunosuppression algorithms has not been shown to substantially alter the outcome of BOS; however, starting these treatments earlier, before fibrous changes appear, could result in improvement of lung function. Since BOS 0-p is a predictor of BOS development or death (81% mortality at 3 years in single lung transplant recipients) research should be focused on preventive immunosuppression augmentation in BOS 0-p stage [51]. Predictive value of BOS 0-p has also been found in double lung transplantation [52].

Untreated episodes of minimal acute rejection have been demonstrated to be an independent risk factor for subsequent BOS stage 1 [53]. This suggests that this degree of alloimmunological activity should be quickly suppressed to stop the inflammatory cascade leading to the development of irreversible changes in the airways of the transplanted lung. Hence treatment of A1 acute rejection even in the absence of clinical symptoms could perhaps postpone the onset of BOS.

Conclusions

1. No immunosuppressive prophylactic or treatment strategy is of proven benefit in the management of BOS post lung transplantation.
2. Double-blind, placebo controlled, randomized multicentre studies are needed to shed further light on the pathophysiology of BOS. Potential areas of further research include the protective value of IVIG + ECI in the early post-transplant period for increased graft tolerance, the preventive value of early treatment for minimal acute rejection and use of immunosuppression augmentation for BOS 0-p as prophylaxis against greater degrees of BOS.
3. Separate analysis of single and double lung transplant recipients should be performed to avoid the effect of native lung function improvement as described by Snell et al. [41].
4. Definition and grading of BOS according to ISHLT [5] should be used.

The authors await the results of the LARGO study, hoping that these new data will help not only to improve diagnostic accuracy but also to understand the immunological mechanisms of acute and chronic rejection in lung allografts and to find possibilities of successful intervention.

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