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REVIEW

Obliterative bronchiolitis following lung transplantation: from old to new concepts?

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Summary

Lung transplantation has come of age and is now considered a valid treatment for selected patients with end-stage lung disease. In recent years, survival rates have much improved, although the development of chronic rejection, characterized by a progressive and irreversible decline in FEV_1, which is clinically defined as bronchiolitis obliterans syndrome (BOS) remains the major obstacle to long-term survival. Extensive research efforts with special emphasis on innate immunity have recently led to new insights with the identification of at least two different phenotypes: on the one hand there is an azithromycin-responsive phenotype (the so-called neutrophilic reversible allograft/airways dysfunction (NRAD), on the other hand there is an azithromycin-unresponsive phenotype (the fibroproliferative form of BOS or classical obliterative bronchiolitis). The present review intends to give the scientific evidence for these two subtypes, and to clarify the role of azithromycin in the treatment of BOS.

Introduction

Lung transplantation (LTx) is nowadays accepted as the ultimate treatment for carefully selected patients with end-stage lung disease, such as emphysema, cystic fibrosis, interstitial lung diseases and pulmonary arterial hypertension. The procedure mainly intends to alleviate symptoms and to improve quality of life, although most of the patients experience an improved survival as compared with nontransplanted patients. Currently the mean actuarial 5-year survival is 55% according to the International Society for Heart and lung Transplantation database [1]. In our own lung transplant programme, the 5 year survival nowadays has increased from 50% in the initial experience to about 75% in more recent years [2]. This increase in survival rate over the last years is mainly because of a better operative and perioperative outcome, without much effect on later outcome. Indeed, obliterative bronchiolitis (OB) or its clinical correlate bronchiolitis obliterans syndrome (BOS) remains the leading cause of morbidity and death after LTx, accounting for about 30% of late mortality [1] and some 45% of patients affected by the condition 5 years after LTx [1]. Nowadays, some patients with OB/BOS can be adequately treated with azithromycin, which may explain why patients with this condition live longer. In this report, we will give an overview of newer insights into the pathophysiology of OB/BOS derived from the clinical experience with azithromycin as a treatment option.

Clinical picture and diagnosis of OB/BOS

Obliterative bronchiolitis was initially described in 1987 in a patient with a progressive decline in FEV_1 after a

Heart-LTx [3]. OB is characterized by a reduction in pulmonary function parameters, most specifically FEV_1 and $FEF_{25–75}$, attributed to irreversible airways obstruction. The onset of symptoms is mostly insidious, with progressive exertional dyspnoea, often accompanied by cough, which may be dry or productive. A respiratory tract infection (CMV or non-CMV viral infection) or an acute immunological event (acute rejection) may trigger the onset of the disease [4]. Anti-rejection treatment with high doses of intravenous steroids may but does not always improve FEV_1, which subsequently declines again and plateaus at very low volumes. This clinical presentation of OB may have a poor prognosis leading to death of the patient in a couple of months, without any medical treatment being helpful. In other patients, BOS progression is rather slow and superinfections are frequently seen and colonization of the airways with Pseudomonads and *Aspergillus fumigatus* is common. High resolution CAT scan of the thorax may reveal air trapping in the rapidly progressive patients and bronchiectasis and other signs of chronic infection in the more slowly progressive patients. Auscultation of the lungs is often normal; however, rales and squeaks may be heard. In some patients, the progression may be arrested, either spontaneously or in response to treatment [5,6].

Because of their low sensitivity (28%), and specificity (75%), OB remains difficult to prove pathologically with transbronchial biopsies (TBB) [7,8]. As a consequence, a clinical definition, called BOS was proposed [8]. This is based on pulmonary function criteria, initially FEV_1 evolution, and in a more recent revision also $FEF_{25–75}$ was incorporated [9]. In this classification, BOS is divided into 5 stages (Table 1). BOS can only be diagnosed when other clinical conditions that may confound the definition are excluded, such as infection, acute rejection, bronchial suture problems, disease recurrence, ageing, native lung hyperinflation, disease progression, and factors that induce a restrictive defect such as pleural disease, steroid myopathy, pain, etc…[9].

Table 1. The BOS classification, as percentage of the best postoperative value (adapted from 9).

BOS stage	$FEV_1/FEF_{25–75}$ (% of baseline)*
0	FEV_1 > 90% and $FEF_{25–75}$ > 75%
Potential BOS	FEV_1 81–90% and/or $FEF_{25–75}$ < 76%
1	FEV_1 66–80%
2	FEV_1 51–65%
3	FEV_1 < 50%

*Best postoperative FEV_1 and $FEF_{25–75}$ is defined as the average of two postoperative best measurements, 3–6 weeks apart.

Pathology and risk factors of OB/BOS

Obliterative bronchiolitis is the accepted pathological manifestation of chronic allograft dysfunction, and the current consensus is that chronic rejection causes or may significantly contribute to the deterioration of the pulmonary function in OB/BOS [10]. OB is essentially a scarring process affecting the small, noncartilagenous airways of the lung graft. The initial pathological process appears to be a lymphocytic infiltration of the airway submucosa and the epithelium, which is known as lymphocytic bronchiolitis [11]. Epithelial damage is common in both lymphocytic bronchiolitis and OB with epithelial cell necrosis leading to denudation and frank mucosal ulceration. This results in an inflammatory reaction with fibroblast and myofibroblast migration into the lumen, leading to the formation of intraluminal granulation tissue ending up in subtotal or total obliteration of the small airways.

Late or recurrent/refractory acute rejection ($\geq A_2$) and lymphocytic bronchitis/bronchiolitis are recognized as classical immunological risk factors, but repeated A_1 acute rejection, Human Leucocyte Antigen (HLA) mismatches at the A locus and total human leucocyte antigen mismatches, may also be involved [12,13].

Several nonimmunological risk factors have been proposed, although not yet widely accepted: cytomegalovirus (CMV) pneumonitis, ischaemia–reperfusion, early nonspecific bronchial hyper-responsiveness, donor and recipient age, graft ischaemic time, transplantation for primary pulmonary hypertension, gastro-oesophageal reflux, and bacterial/fungal/non-CMV viral infections [12,13]. Especially these nonimmunological risk factors have gained a lot of attention in recent years, and further investigation into the role of these factors has indeed led to a change in the whole pathophysiological concept of chronic allograft dysfunction, which has emerged from the experience gained with neo-macrolide antibiotics for the treatment of OB/BOS.

Pathophysiology of OB/BOS: the old concept

Obliterative bronchiolitis/BOS probably results from a primary insult (ischaemia–reperfusion injury, acute rejection, infection, …) towards the epithelium of the airways, which may be unique and severe or rather repetitive and less severe, and immunological or nonimmunological. This insult upregulates dendritic cells in the epithelium, attracting more inflammatory cells (at first lymphocytes) leading to epithelial damage and inflammation, with resulting production of chemo- and cytokines from airway structural cells such as epithelium and smooth muscle cells, macrophages and neutrophils (IL-1, -2, -4, -6, -8, -10, -12, -13, …) [9,14]. Activated neutrophils may

further increase epithelial damage via the production of reactive oxygen species and metalloproteinases [15]. After an initial inflammatory phase, a fibro-proliferative phase occurs, driven by several growth factors (PDGF, IGF, FGF, TGF-β, ET-1, …) leading to proliferation of smooth muscle cells and fibroblasts (myofibroblasts) and eventually resulting in deposition of collagen and the typical fibrous, obliterative lesions of the airways [9,13,14].

It is widely accepted now that OB/BOS is characterized by a predominantly neutrophilic airway inflammation with upregulation of airway IL-8. In fact, the first evidence for the involvement of neutrophils in OB/BOS came from a paper by DiGiovine *et al.* [16]. In that particular publication, the authors clearly showed that patients with suspected chronic rejection after LTx had significantly elevated neutrophil counts and IL-8 levels in their bronchoalveolar lavage (BAL) fluid as compared with stable patients. Furthermore, immunolocalization of IL-8 was associated with α smooth muscle actin-positive cells in the peribronchial region of OB [16]. Later on, Riise *et al.* [17] demonstrated that the BAL neutrophils were activated (because myeloperoxidase was significantly elevated in BAL of OB/BOS patients) and that the anti-oxidant status of these patients was clearly lowered. The involvement of neutrophils in the pathogenesis of OB/BOS was then corroborated by numerous groups [18,19]. Riise and others further pointed to persistent BAL neutrophilia as a possible early marker of OB/BOS [20–22]. On the other hand, differential diagnosis with infection-induced BAL neutrophilia was not always easy [23], and in fact, some authors postulated that most neutrophilia in BOS was indeed induced by infectious episodes [24].

Although an increased neutrophilic inflammation of the airways seems to be common in the BAL of OB/BOS patients, when reviewing the initial publications, it becomes clear that not all patients with OB/BOS had BAL neutrophilia. In fact, in the paper by DiGiovine *et al.* [16], several of their patients had a BAL neutrophilia less than 15%, whereas in others the percentage was as high as 95%, nonetheless, their mean BAL neutrophilia was 36%, which was significantlty higher than in the stable transplant patients (5.8%). In the Riise paper, the BAL neutrophilia in patients with OB/BOS ranged between 1% and 96.5%, again pointing to the fact that some patients with this condition had no neutrophilic airway inflammation [17]. Identical findings were published by Zheng *et al.* [18], where again some patients with OB/BOS had rather low BAL neutrophilia. Devouassoux *et al.* [21] found that neutrophilia associated to BOS stage 1 remained low, and could not be distinguished from that of stage 0. In a paper by Slebos *et al.* [25], BAL neutrophilia ranged between 0% and 97% in patients with OB/BOS, without a clear difference in percentages between the bronchiolar and the alveolar fraction of the BAL. Ward *et al.* [19] found BAL neutrophilia between 16% and 87% in OB/BOS patients and between 0.4% and 18% in stable lung transplant patients. As a consequence, although the mean % of BAL neutrophilia is increased in patients with OB/BOS, there are quite a lot of these patients without frank BAL neutrophilia, despite the fact that they seem to be in an identical clinical condition with progressive decrease of the FEV_1, compatible with BOS. Some of these different results may be explained by the technique of performing BAL in these patients, as suggested by Slebos *et al.* [25] although this may not explain all the discrepancies.

Classical treatment of OB/BOS with changes of or increased dosages of immuno-suppressives did not lead to improvement of the pulmonary function, but at best to a stabilization of the FEV_1 [26,27]. Corticosteroids, which are very effective to treat most episodes of acute rejection, do not seem to modify the classical course of the decreasing FEV_1 in OB/BOS [5,6,14]. Because of these disappointing therapeutic results, and in comparison with other known pulmonary diseases with neutrophilic inflammation, such as panbronchiolitis and cystic fibrosis (reviewed in 28), the presence of BAL neutrophilia as a common denominator for OB/BOS, led the Baltimore group to perform an open trial with azithromycin to treat this chronic allograft dysfunction. In this study, Gerhardt *et al.* [29] added azithromycin (250 mg three times a week) to the current immunosuppressive treatment in six lung transplant patients with BOS and showed a significant improvement of the FEV_1 in five patients (+17.1%, or an absolute increase of 0.5 l) after a mean follow up of 13.7 weeks. Some patients had even a complete restoration of their FEV_1. This study was further corroborated by our own group [30] and by Yates *et al.* [31], who also reported an increase in FEV_1 of about 15–18% in half of the treated patients. On the other hand, Shitritt *et al.* [32] found no improvement at all in their study with 11 patients. Recently, Porhownik *et al.* [33] found an FEV_1 improvement in two out of seven patients with BOS during treatment with azithromycin. Besides an improvement in pulmonary function, a major amelioration of bronchiectasis on CAT scan has also been demonstrated by using azithromycin in a patient with long-standing BOS [34]. The largest study up to now comes from the Hannover group and comprises 81 patients with at least BOS stage 0p who have been treated with azithromycin for a mean period of 1.3 years. In this study, 30% of the patients ($n = 24/81$) experienced an improvement of their FEV_1 [35], with some 23% of the initial responders later on again developing a progressive decrease in FEV_1, compatible with chronic rejection, while still being treated with azithromycin.

Taking all these publications together, about 35% of all patients in different stages of BOS responded to azithromycin treatment by a mean increase of their FEV_1 of about 14%. A summary of the studies with azithromycin is shown in Table 2.

These studies clearly illustrate the potential benefit of adding a neo-macrolide in the treatment of OB/BOS, but also demonstrate that not all patients are responders. Therefore, further mechanistic investigations were warranted. The possible mechanisms of action of azithromycin in OB/BOS patients were unknown, although several hypotheses have been put forward [36], such as inhibition of the transcription of quorum-sensing genes, which have indeed been detected in clinically stable lung transplant recipients without any signs of infection [37]. This may prevent production of tissue-damaging proteins. Other possibilities are: a positive effect on gastro-oesophageal reflux (macrolide antibiotics are known as motilin agonists), and an anti-inflammatory effect involving neutrophils. In favour of this latter mechanism, we recently demonstrated that azithromycin significantly reduced airway neutrophilia and IL-8 in patients with OB/BOS and that the improvement of the FEV_1 3 months after adding azithromycin to the existing immunosuppressive treatment, significantly correlated with the initial BAL neutrophilia, which enables to predict the effect of azithromycin based on neutrophil cell counts in the BAL fluid. Furthermore a BAL neutrophilia of 15% seemed essential to predict a positive response to azithromycin treatment [38]. These initial results were corroborated by Gottlieb *et al.*, who also demonstrated that only OB/BOS patients with a BAL neutrophilia of 20% or more responded to azithromycin treatment [35]. As a consequence, we proposed a new pathophysiological concept of OB/BOS in which the reversible neutrophilic inflammatory form should be differentiated from classical chronic rejection, which is largely irreversible [39].

Table 2. Published studies with azithromycin in OB/BOS patients after lung transplantation.

Reference	Number of patients	Number (%) improved	FEV_1 change (mean of all included patients)
Gerhardt *et al.* [29]	6	5	+17%
Verleden and Dupont [30]	8	4	+12%
Yates *et al.* [31]	20	10	+14%
Shitritt *et al.* [32]	11	none	stable
Verleden *et al.* [38]	14	6	+13%
Porhownik *et al.* [33]	7	2	stable
Gotlieb [34]	81	24	+17%
Total patients	147	51 (35%)	+14.6% (mean)

Pathophysiology of BOS: new concepts

From the reports by Verleden *et al.* [38] and Gottlieb [35], it can be hypothesized that at least two different BOS phenotypes can be distinguished, based on the results that have been obtained with azithromycin as additive treatment for patients with OB/BOS [28,39]. Besides the neutrophilic type, responsive to azithromycin, there is another type, without overt neutrophilic inflammation, leading to typical OB in a rather short period of time. It also appears that the neutrophilic type starts rather early after transplantation (often in the first postoperative year) [39], whereas the other type is mostly diagnosed later on. The characteristics of these two phenotypes are summarized in Table 3, although the radiological and pathological data of the two phenotypes certainly require confirmation from larger prospective studies. Typical FEV_1 evolutions of the two phenotypes are shown in Fig. 1.

How can we now explain these phenotypic differences?

For a couple of years now, there has been great interest in the possible role of IL-17 in neutrophilic inflammatory airways diseases. IL-17 is indeed recognized as an indirect neutrophil-attracting chemokine through its ability to induce IL-8 secretion from different cell types in the airways [40] and it also plays a role in the upregulation of airway metalloproteinases [41], which are indeed increased in BAL from patients with OB/BOS [15].

Table 3. Characteristics of the two phenotypes of BOS (adapted from 39).

	Neutrophilic reversible allograft/airways dysfunction (NRAD)	Fibroproliferative BOS (fBOS)
Bronchoalveolar lavage	Excess neutrophils (>15%)	Neutrophils <15%
Clinical signs	Coarse crackles, increased sputum production	No crackles, no sputum
Time of onset	Mostly early after transplantation (<1 year)	Mostly later (>1 year)
Progression of FEV_1 decrease	Slow (several years)	Rapid (<6–12 months)
Histology airway wall	Lymphocytic inflammation, ends up in fibrosis	Pure fibrosis (?)
Radiology	airway wall thickening, mucus plugging, bronchiectasis	Air trapping, consolidation
Effect of azithromycin	Improvement of FEV_1 (reversible)	No effect on FEV_1 (irreversible)

?: the initial event and pathology starting of the fBOS type is not exactly known at present.

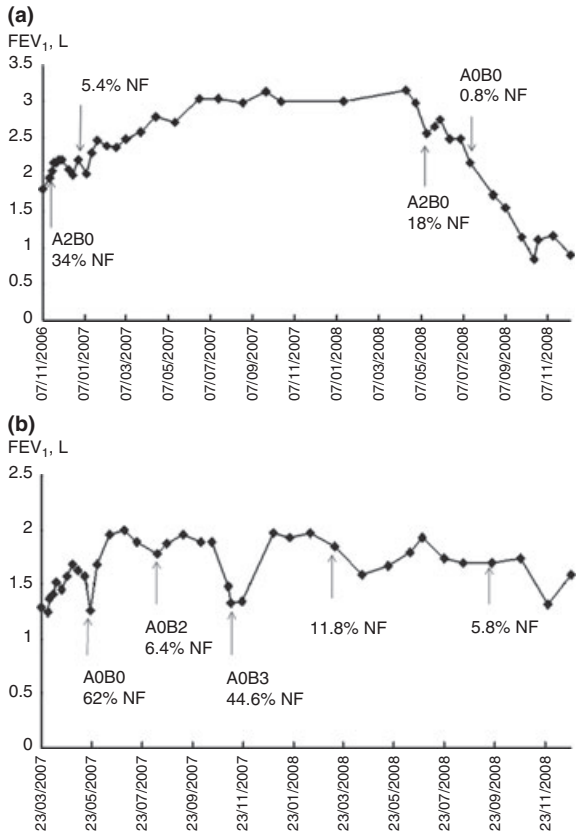

Figure 1 (a) This 22-year-old female CF patient received a double-lung transplantation in October 2006. She experienced a biopsy-proven acute rejection episode after 1 month (treated with a 3-day course of high dose intravenous steroids) and the further course was uneventful, until another A2 acute rejection was diagnosed in June 2008. High dose IV steroids only partially restored the FEV_1, which began to decline soon after this event. BAL analysis showed neutrophils, attributed to the acute rejection. All possible interventions including augmentation of steroids and tacrolimus besides association of azithromycin could not prevent further decline of the FEV_1. She is now in BOS stage 3 (fBOS). NF, neutrophils (b) This 54-year-old female patient underwent a double lung transplantation for end-stage bronchiectasis caused by agammaglobulinemia in February 2007. After 3 months, a transbronchial biopsy showed no acute rejection, but the BAL demonstrated 62% neutrophils, attributed to an infection with *Pseudomonas aeruginosa*. Upon antibiotic treatment, an increasing FEV_1. Nine months after the transplantation, she developed a progressive decline in FEV_1, considered as BOS stage 2, but characterized by BAL neutrophilia (45%, without acute alveolar rejection, although B3 on transbronchial biopsy and with negative BAL cultures). NRAD was diagnosed and she was treated by adding azithromycin to the current imunosuppressive regimen (tacrolimus and oral steroids). Within 2 months, her FEV_1 increased to the best postoperative values together with a decrease in BAL neutrophilia. NF, neutrophils.

We and others [25] demonstrated that BAL neutrophilia is also increased during acute rejection and that this may be caused by an increase in BAL IL-17 levels, which correlated with the degree of acute rejection [42]. As acute rejection is one of the major risk factors for chronic rejection, IL-17-induced neutrophilia might be a link between acute and chronic rejection. There are several lines of evidence now demonstrating the role of IL-17 in the development of chronic rejection. Burlingham *et al.* [43] published that IL-17-dependent cellular immunity to collagen type V predisposes to OB after LTx and Fukami *et al.* [44] showed in a murine model that intrabronchially administered anti-MHC class 1 antibodies induced IL-17 as well as de novo antibodies to for instance collagen V, leading to OB. Recently, our own group demonstrated the involvement of the IL-23/IL-17 axis in the pathophysiology of OB/BOS, which potentially triggers the IL-8-mediated neutrophilia. In this particular study, IL-6, IL-1beta and IL-23 seemed to be skewing cytokines and IL-2 a counteracting cytokine for T(H)17 alignment [45]. This specific involvement of T(H)17 cells may then explain the steroid-resistance in OB/BOS, as this has also been shown to be the case in experimental steroid-resistant neutrophilic asthma [46].

The increase in IL-17 in the airways of patients with BOS may indeed lead to production of IL-8 in airway smooth muscle cells [47,48] and in airway epithelial cells [49], which may then explain the BAL neutrophilia. The effect of azithromycin on neutrophilic airway inflammation in BOS may well be realized via IL-17, as we were able to show that azithromycin concentration-dependently inhibited the IL-17-induced production of IL-8 in human airway smooth muscle cells *in vitro* via inhibition of different MAP kinases and via its anti-oxidative effect [50]. The Newcastle group further showed that azithromycin also inhibits MMP-2, IL-8, granulocyte-macrophage colony stimulating factor (GMCSF) and MMP-9 levels [49] and also the LPS-induced upregulation of IL-8 and GMCSF from primary bronchial epithelial cell cultures of lung transplant patients [51].

Although the neutrophilic airways inflammation seems responsive to azithromycin, if untreated, this inflammation may indeed set off a fibroproliferative response also ending up in classical OB, but this may take several years [28,39]. This may then also explain why several authors found a persistent increase in neutrophilia to be a predictor of OB/BOS [20–22].

The major question, however now, is: what triggers that early neutrophilic airway inflammation after LTx?

It has recently been shown that transient colonization of the airways with Pseudomonads is associated with a neutrophilic inflammation of the airways [52], and that persistent colonization may well predispose to the development of OB/BOS [53–55], suggesting that chronic airway colonization after LTx, in comparison with panbronchiolitis and cystic fibrosis, may lead to a decrease in

pulmonary function. This could, however, not be demonstrated in the open studies with azithromycin in OB/BOS after LTx [29–31,33,34,39]; moreover, in the Shitritt study, nine out of the 11 patients were colonized and none improved with azithromycin [33]. In this particular study, we do not know whether the BAL of these patients was (still) neutrophilic, or the patients had already further evolved to a more proliferative form of OB/BOS. Moreover, there has been no quantification of quorum-sensing proteins in the BAL, which may be particularly sensitive to the presence of these bacteria [37].

Gastro-oesophageal reflux (GER) is nowadays also regarded as a nonimmunological risk factor for the development of OB/BOS and has been demonstrated to be a reversible cause of allograft dysfunction after LTx [56]. Fundoplication in patients after LTx, led to a significant survival difference, together with an improvement of the pulmonary function [57]. GER is indeed very frequent after LTx and can be evaluated by the detection of pepsin in BAL fluid, which is present in most of the LTx patients [58,59]. Pepsin in BAL fluid does, however, not correlate with the presence of OB/BOS but rather the presence of bile acids in BAL fluid (as a marker of nonacidic reflux) seems to correlate on the one hand with neutrophils in BAL [60] and on the other hand with the development of OB/BOS early after LTx [59,60]. As GER may also be associated with acute rejection [61] this may point to interplay between innate and adaptive immunity suggesting that GER may exert its deleterious effect through immunological as well as nonimmunological mechanisms. Bile acid aspiration is also associated with decreased BAL levels of pulmonary surfactant collectin proteins SP-A and SP-D, which is suggestive for impaired lung allograft innate immunity [62]. Recently, our group was able to show an association between Pseudomonal colonization and the presence of bile acids in BAL. Patients with colonization and bile acids had more increased BAL neutrophilia, suggesting that epithelial defects by bile acids might predispose to colonization with Pseudomonads and airway neutrophilia [63]. Whether there are still other mechanisms leading to stimulation of neutrophilic airway inflammation after LTx, remains to be elucidated.

When summarizing this new concept of OB/BOS after LTx, chronic allograft dysfunction may present as a neutrophilic airway inflammation, starting rather early after lung transplantation and triggered by GER and/or colonization. Fundoplication or treatment with azithromycin reduces the neutrophilic inflammation and may lead to an increase of the $FEV_{1.}$ The other phenotype has no neutrophilic airway inflammation, starts rather late after transplantation and does not respond to azithromycin. As a consequence, the first phenotype can no longer be considered as BOS, as this is defined as a largely irreversible and progressive airways obstruction [9]. We have therefore proposed to rename this phenotype as neutrophilic reversible allograft/airways dysfunction (NRAD), whereas the second phenotype clinically represents BOS and is pathologically characterized as OB (fBOS = fibrotic BOS) [39]. The events that set off this latter phenotype are not clearly understood, but immunological (acute rejections) and viral infections (CMV …) might certainly be involved [4]. It is accepted that the airway epithelium plays a crucial role in this process, and it was indeed recently shown that one third of BOS-patients developed antibodies reactive to epithelial cell antigen (K-alpha1 tubulin) that are distinct from HLA. Binding of these de novo-produced anti-K-alpha1 tubulin antibodies to the airway epithelial cells resulted in increased expression of transcription factors, leading to increased expression of fibrogenic growth factors, activation of cell cycle signalling, and fibroproliferation [64].

These data showing the additive value of azithromycin in the treatment of some patients with OB/BOS means that BOS can only be regarded as a manifestation of chronic rejection, once a trial with azithromycin proved ineffective (and especially when there is no neutrophilic airways inflammation) [34,39]. Whether the same holds true for fundoplication remains to be further determined. Anyway, azithromycin also reduces reflux episodes after LTx, which may allude to at least some analogies in the mechanism of action of fundoplication and azithromycin [65].

Whether early postoperative treatment with azithromycin is effective to prevent the development of neutrophilic inflammation, and hence NRAD, can only be investigated by a double-blind, placebo-controlled trial, which we are running now in our lung transplant centre. Whatever the results, this should certainly be acknowledged by a multicentre study [66]. The results of early fundoplication may indeed point into the same direction, showing a very low prevalence of BOS in the first year after LTx, although later results have not yet been published [57].

Conclusion

Although LTx has come of age, the development of chronic allograft dysfunction (OB/BOS) remains the biggest hurdle preventing long-term survival in a lot of patients. Recent new insights in the pathophysiology of OB/BOS and treatment with azithromycin have raised new hopes for patients suffering from this condition. It is our belief that these new concepts may indeed have an impact on the prevalence of OB/BOS and may improve long-term survival, although scientific proof at the present time is still lacking and is awaited by double-blind, placebo-controlled studies with azithromycin, initiated

right after the transplantation procedure in association with classical immunosuppressive treatment.

Despite these hopeful results, a lot of questions remain, such as to the dose of azithromycin, the duration of the treatment, when to start the treatment (as soon as BAL neutrophilia develops or when BOS 1 is diagnosed), what is the exact role of fundoplication ….

Perhaps the near future will bring us some more answers!

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