ELSEVIER

The Journal of Heart and Lung Transplantation

http://www.jhltonline.org

EDITORIAL

Montelukast for chronic lung allograft dysfunction: Not quite the "Full Monty"

Allan R. Glanville, MBBS, MD, FRACP

From the Lung Transplant Unit, St. Vincent's Hospital, Sydney, New South Wales, Australia.

An effective medical therapy for chronic lung allograft dysfunction (CLAD), either bronchiolitis obliterans syndrome (BOS) or restrictive allograft syndrome (RAS), is one of the greatest unmet clinical needs in lung transplantation (LTx).[1,2] One could argue that the panoply of potential therapies that has been used for CLAD (or BOS in previous literature) is a strong statement that none is universally effective[3]; hence, the need to examine alternatives, even those that may not be the complete or definitive solution (i.e., not the "Full Monty").

Montelukast (MLK) is one such alternative that has been reported previously in the bone marrow transplant (BMT) literature as a potential option for chronic graft-versus-host disease of the lung after hematopoietic cell transplantation, manifest as post-BMT "BOS," where, in combination with fluticasone and azithromycin, with or without *N*-acetylcysteine, steroid-sparing effects were observed as well as a reduction in the rate of physiologic progression, particularly in early disease.[4–6] MLK is a selective antagonist of the type-1 cysteinyl leukotriene receptor, so may be expected to ameliorate the progression of leukotriene-driven inflammatory and fibrotic processes after LTx. This hypothesis has been supported by limited experimental evidence in a rat model of BOS, where oral MLK led to a reduction in fibrosis in sub-cutaneously embedded tracheae, presumably by leukotriene B4 inhibition.[7] Sub-cutaneous tracheae, of course, do not experience the vicissitudes of airflow and are deprived of the normal mucociliary escalator, so comparisons with obliterative bronchiolitis, the dominant histopathologic determinant of BOS, must perforce be conservative.

The current report by Vos et al,[8] describing the potential role of MLK in CLAD, builds on prior work from their unit. In 2011, Verleden et al[9] reported a non-randomized, non-placebo–controlled pilot study, using a retrospective control group, in which 11 patients with BOS stage < 3, bronchoalveolar lavage neutrophilia < 15%, and current azithromycin

See Related Article, page 516

use commenced MLK at 10 mg/day. After 6 months, the rate of forced expiratory volume in 1 second (FEV_1) decline was significantly reduced. Subsequently, in 2018, Ruttens et al,[10] from the same group, reported a single-center, prospective, interventional, randomized, double-blind, placebo-controlled trial, with a 2-arm parallel group design, in 30 consecutive patients with late-onset (> 2 years after LTx) BOS. MLK had no effect on lung function decline in the overall cohort but was associated with an attenuation of the rate of FEV_1 decline in recipients with BOS stage 1. There was no additional survival benefit, although the study was underpowered.

On the basis of these results, the group performed a single-center retrospective analysis of all LTx recipients who received a transplant from July 1991 through December 2016 and who were treated for at least 3 months with MLK for progressive CLAD, despite at least 3 months of prior azithromycin therapy. The study enrolled 153 patients with CLAD (BOS, $n = 115$; RAS, $n = 38$). MLK was associated with attenuation of the rate of FEV_1 decline after 3 and 6 months, respectively (both $p < 0.0001$). Not surprisingly, patients whose FEV_1 improved or stabilized after 3 months of MLK (81%) had significantly better progression-free ($p < 0.0001$) and overall survival ($p = 0.0002$) after CLAD onset.

It is a statement attesting to the attention to detail and transparency of the group that individual patient data are presented. This is most informative and demonstrates clearly that the absolute FEV_1 improved in just over 50% of all patients at 3 months and also at 6 months. Markers of potential response included slow progression before commencing MLK and, interestingly, blood eosinophilia, a finding that bears further scrutiny. Conversely, patients with a rapid deterioration in FEV_1 before commencing MLK or a RAS phenotype were less likely to stabilize. The term stabilize is used judiciously, noting the longer-term results in particular.

Notwithstanding these potentially positive results, the natural history of airflow parameter change in CLAD needs to

Reprint requests: Allan R. Glanville, MBBS, MD, FRACP, Consultant Thoracic Physician, The Lung Transplant Unit, St. Vincent's Hospital, Sydney, NSW 2010, Australia. Telephone: +612-8382-3668. Fax: +612-8382-3084.

E-mail address: allan.glanville@svha.org.au

1053-2498/$ - see front matter
https://doi.org/10.1016/j.healun.2019.01.1312

be considered as a possible confounder. Insufficient data are presented to comment meaningfully about a potential dose-response effect, but it is important to raise the possibility of therapeutic drug monitoring for future trial analyses.

Only the passage of time will confirm whether MLK achieves a meaningful role as an adjunct to the medical treatment of CLAD or whether, like so many other therapies, will pass by the wayside. Azithromycin has utility and is commonly used but is not the panacea once hoped. Note that all patients in the current MLK study had received at least 3 months of azithromycin before commencing MLK. An adequately powered, prospective, multicenter, placebo-controlled study would provide better quality information and greater confidence in the putative role of MLK and might be achievable given the potential cost-utility vs other expensive and limited-access modalities, such as extracorporeal photopheresis and total lymphoid irradiation, with a likely more favorable risk-to-benefit ratio.[11,12] Indeed, a similar call to arms has been expressed recently in the BMT literature, calling for accessible therapies.[13]

This then is the great conundrum of contemporary LTx: Certain therapies appear to offer hope for selected patients, but the level of evidence is low. Faced with desperate situations, clinicians managing individual patients with CLAD will often trial numerous options, which confounds the way forward. At least in the current study, it is apparent that the patients reported were carefully selected and outcomes clearly delineated so we have additional evidence, but is it enough? Given the almost ubiquitous nature of CLAD, one could argue to commence MLK prophylactically in all LTx recipients knowing that the cost is acceptable, the adverse effect profile generally tolerable, and the chance of mitigating progression of CLAD reasonable. The equipoise of science and individual patient care was always thus, and the current report provides a thoughtful appraisal of a potential therapy. One anticipates that many LTx units will broaden their therapeutic armamentarium accordingly, perhaps more in hope than confidence.

Disclosure statement

The author does not have a financial relationship with a commercial entity that has an interest in the subject of the presented manuscript or other conflicts of interest to disclose.

References

1. Verleden GM, Glanville AR, Lease ED, et al. Chronic lung allograft dysfunction: definition, diagnostic criteria and approaches to treatment. A consensus report from the Pulmonary Council of the ISHLT. J Heart Lung Transplant 2019;38:493-503.
2. Glanville AR, Verleden GM, Todd JL, et al. Chronic lung allograft dysfunction: definition and update of restrictive allograft syndrome (RAS) a consensus report from the Pulmonary Council of the ISHLT. J Heart Lung Transplant 2019;38:483-92.
3. Benden C, Haughton M, Leonard S, Huber LC. Therapy options for chronic lung allograft dysfunction-bronchiolitis obliterans syndrome following first-line immunosuppressive strategies: a systematic review. J Heart Lung Transplant 2017;36:921-33.
4. Norman BC, Jacobsohn DA, Williams KM, et al. Fluticasone, azithromycin, and montelukast therapy in reducing corticosteroid exposure in bronchiolitis obliterans syndrome after allogeneic hematopoietic SCT: a case series of eight patients. Bone Marrow Transplant 2011;46:1369-73.
5. Kim SW, Rhee CK, Kim YJ, Lee S, Kim HJ, Lee JW. Therapeutic effect of budesonide/formoterol, montelukast and N-acetylcysteine for bronchiolitis obliterans syndrome after hematopoietic stem cell transplantation. Respir Res 2016;17:63.
6. Williams KM, Cheng GS, Pusic I, et al. Fluticasone, azithromycin, and montelukast treatment for new-onset bronchiolitis obliterans syndrome after hematopoietic cell transplantation. Biol Blood Marrow Transplant 2016;22:710-6.
7. Tu ZL, Zhou ZY, Xu HC, et al. LTB4 and montelukast in transplantation-related bronchiolitis obliterans in rats. J Cardiothorac Surg 2017;12:43.
8. Vos R, Vanden Eyndel R, Ruttens D, et al. Montelukast in chronic lung allograft dysfunction after lung transplantation. J Heart Lung Transplant 2019;38:516-27.
9. Verleden GM, Verleden SE, Vos R, et al. Montelukast for bronchiolitis obliterans syndrome after lung transplantation: a pilot study. Transpl Int 2011;24:651-6.
10. Ruttens D, Verleden SE, Demeyer H, et al. Montelukast for bronchiolitis obliterans syndrome after lung transplantation: a randomized controlled trial. PLoS One 2018;13:e0193564.
11. Jaksch P, Scheed A, Keplinger M, et al. A prospective interventional study on the use of extracorporeal photopheresis in patients with bronchiolitis obliterans syndrome after lung transplantation. J Heart Lung Transplant 2012;31:950-7.
12. Fisher AJ, Rutherford RM, Bozzino J, Parry G, Dark JH, Corris PA. The safety and efficacy of total lymphoid irradiation in progressive bronchiolitis obliterans syndrome after lung transplantation. Am J Transplant 2005;5:537-43.
13. Hakim A, Cooke KR, Pavletic SZ, Khalid M, Williams KM, Hashmi SK. Diagnosis and treatment of bronchiolitis obliterans syndrome accessible universally [e-pub ahead of print]. Bone Marrow Transplant. doi: 10.1038/s41409-018-0266-6. Accessed January 11, 2019