Pulmonary Circulation

Targeting inflammation and immunity in pulmonary arterial hypertension: any easier after the CANTOS proof-of-concept that anti-inflammation cuts cardiovascular events?

Pulmonary Circulation 2018; 8(1) 1–3
DOI: 10.1177/2045893218754855

Pulmonary arterial hypertension (PAH) is characterized by progressive obliteration of the pulmonary vascular bed leading to increased right ventricular afterload, right heart failure, and death.[1]

PAH is now regarded as a disease caused mainly by pulmonary vascular remodeling rather than by abnormal pulmonary vasoconstriction. Histopathological hallmarks are proliferation of endothelial cells, abnormal intimal cells, and vascular smooth muscle cells leading to vessel narrowing and complete occlusion with exuberant collateralizations. Experimental and clinical studies point to the bone morphogenic protein receptor 2 (BMPR2) signaling pathway on the background of an impaired metabolic and chronic inflammatory state in the vessel wall as underlying causes.[1] The strong association of PAH with dysregulated immunity and inflammation has been long established and substantiated by a concurrence of PAH with auto-immune diseases, most prominently scleroderma. Recent data suggest a failure to resolve inflammation based on altered immune processes as a central mechanism of all subsets of PAH.[1] It is very logical that next-step therapeutic targets for PAH today include the pulmonary vascular remodeling process, rather than simply optimizing vasodilation to save the right ventricle.

One of the most robust observations across multiple cohorts of PAH has been an increase in interleukin 6 (IL-6), both in the lung and systemically. Recently, a mast cell–B cell axis driven by IL-6 as a critical immune pathway has been implicated in the pathophysiology of pulmonary hypertension (PH).[2] IL-6 is secreted by T cells and macrophages in response to specific microbial agents, referred to as pathogen-associated molecular patterns (PAMPs) to stimulate immune responses, e.g. during infection and mechanical trauma. PAMPs bind to an important group of signature molecules of the innate immune system, called pattern recognition receptors (PRRs), including Toll-like receptors (TLRs). These are present on the cell surface and intracellular compartments and induce intracellular signaling cascades that give rise to inflammatory cytokine production. IL-6 is responsible for stimulating acute phase protein synthesis, as well as the production of neutrophils in the bone marrow. It supports the growth of B cells and is antagonistic to regulatory T cells. IL-6 is an important mediator of fever and of the acute phase response during infectious disease. It is capable of crossing the blood–brain barrier and initiating synthesis of PGE_2 in the hypothalamus, thereby changing the body's temperature set point.

Anti-IL-6 therapy was initially developed for treatment of autoimmune diseases, but IL-6 blockade was later also evaluated for cancer treatment. The first anti-IL-6 agent was tocilizumab, which has been approved for rheumatoid arthritis, systemic juvenile idiopathic arthritis, and Castleman's disease, a benign B-cell tumor. Tocilizumab is used for the treatment of moderate to severe rheumatoid arthritis, applied alone or in combination with methotrexate. Treatment is able to slow down the progression of rheumatoid arthritis and can improve physical function of patients.[3] Whether a vasculo-protective function of methotrexate[4] is contributory has not as yet been clarified.

TRANSFORM-UK is an open label study of intravenous (IV) tocilizumab in patients with group 1 PAH. The co-primary outcome measures will be safety and the change in resting pulmonary vascular resistance (PVR). Clinically relevant secondary outcome measurements include 6-minute walk distance, World Health Organization (WHO) functional class, quality of life score, and N-terminal pro-brain natriuretic peptide (NT-proBNP). If the data support a potentially useful therapeutic effect with an acceptable risk profile, the study is intended to be used to power a Phase III study to properly address efficacy.

Data suggest that inflammation is playing a role in the pathogenesis of PAH,[1] but it is unclear whether inflammation is primary or secondary to other mechanisms, and whether anti-inflammatory treatments are sufficient to treat the disease once the diagnosis is made. This is where CANTOS, a trial of more than 10,000 patients that validated the inflammatory pathogenesis of atherosclerosis, helps to carry hope for TRANSFORM- UK, as it set the

stage for a new chapter in therapeutic targeting. CANTOS demonstrated that IL-1β inhibition by canakinumab reduced the incidence of repetitive atherothrombotic events in patients with post-myocardial infarction on optimal medical therapy.[5]

While the absolute anti-atherothrombotic effect size of canakinumab administration appears small as 189 patients had to be treated over one year to prevent one myocardial infarction episode, CANTOS delivered the proof that inflammatory vascular disease responds to anti-inflammatory treatments. The magnitude of such an effect seen in CANTOS raises the question of whether any effect can be possibly seen in 21 patients with group 1 PAH receiving an antagonist to a mediator downstream of IL-1β, particularly if one considers the number of vessels that would have to be reverse-remodeled to change PVR by 30%. Based on our experience during balloon pulmonary angioplasty of patients with chronic thromboembolic pulmonary hypertension (CTEPH), patency of at least one entire segment of one lung would have to be functionally restored to cause such a change.

As said, compared with CANTOS, TRANSFORM-UK is a tiny study. However, in rare disease, sample sizes are always rather small. Nevertheless, TRANSFORM-UK is even smaller than other recent phase II studies in PAH.[6,7] A formidable group to start a more formal trial would have been PAH subgroups in which the underlying cause was an inflammatory process such as systemic lupus erythematosus, mixed connective tissue disease (MCTD), and Castleman's disease, as there have been case reports demonstrating regression of PAH with tocilizumab. Authors defend their choices to exclude this group of PAH in particular, yet an alternative design deserves some thought. Likewise, authors may have been better off restricting their group 1 inclusions to idiopathic, heritable, and drug-toxin-induced PAH, rather than permitting scleroderma PAH which represents a diverse and inhomogeneous subset of PH.

Treatment with canakinumab was associated with a mild increase in the incidence of serious adverse events with $\sim$1 in 750 patients intervened during one year developing a fatal infection or sepsis.[5] Fatal infection or sepsis may be a side-effect of tocilizumab, and even mild infection in a patient with PAH may be deadly, which provokes concerns whether immunosuppression with tocilizumab in patients who are lacking an indication in the absence of rheumatic disease is an easy ethical decision.

Another PAH trial targeted at reverse remodeling of pulmonary vessels was IMPRES, a randomized, double-blind, placebo-controlled 24-week trial evaluating the tyrosine-kinase inhibitor imatinib in patients with PVR $\geq$ 800 dynes $\times$ s $\times$ cm^{-5} symptomatic on $\geq$ 2 PAH therapies. While the trial was formally positive by improving exercise capacity and hemodynamics in patients with advanced PAH, drug side effects and drug–drug interactions put a halt to the development of imatinib for PAH. The most serious of those were subdural hematomas due to a poorly explicable interaction of imatinib treatment with chronic oral intake of vitamin K antagonists. This observation raises the question of whether all potential drug–drug interactions can be foreseen under treatment with IV tocilizumab, such as, for example, liver enzyme elevations in patients on concomitant treatments with endothelin receptor antagonists, and other side effects such as effects on endogenous retroviruses.[8] One of the tocilizumab side effects is hypertension, which must be closely monitored because whenever there is a rise in systemic pressures there is a rise in pulmonary pressures.

Of course, CANTOS was a large multicenter, multinational trial with a randomized, controlled, double-blind design, and based on C-reactive protein as a prognostic biomarker, and on 1400 events within five years to be assessed by a formal evaluation with adjustments for multiple comparisons in a closed testing procedure. This observation raises the question of whether reverse vascular remodeling of pulmonary vessels is possibly happening within six months? Data from reverse remodeling after treating pulmonary vascular obstruction in CTEPH point to a minimal timeframe of six months.[9] If authors are lucky, robust changes may just be seen at the end of the trial. Furthermore, is NT-proBNP a biomarker that safely permits classifying disease severities (in the inclusion criteria NYHA functional classes II–IV) of PH?

In their manuscript,[10] Hernandez et al. try to overcome some of the limitations as discussed above, with sophisticated statistics, and provide a thorough and expanded explanation. But is particular statistical testing principally able to overcome inherent limitations of a trial?

The Bayesian statistical view assumes that a probability is a measure of subjective degree of belief and that such probabilities apply to parameters as well as random variables. Bayesians take the view that a random variable has a probability distribution depending on another parameter and this parameter has a probability distribution depending at least in part on observed values of random variables. To find this probability distribution two measures are required:

1. "Prior" distribution of the parameter: applied before the experiment is performed and derived from previous knowledge, experience or subjective belief.
2. Experimental data: the probability derived from experimental data is used to modify the prior distribution of the parameter in order to produce the "posterior" distribution. This is obtained according to the rule: posterior distribution = prior distribution $\times$ probability of the data.

The posterior distribution obtained using this approach is used to make inductive statements about the parameter. These might be statements of estimation or statements giving an interval within which the parameter lies with certain probability. TRANSFORM-UK authors employ Bayesian analysis with flat priors.

The Bayesian approach does not assume unlimited repeatability of random experiments. Therefore, the

advantage of Bayesian statistics is their applicability to data derived from small sample sizes. Still, it takes religious belief even among statisticians to commit to the Bayesian approach for this small study targeting inflammation and immunity in PAH.

Strong beliefs and religious indulgence have always been part of real science, even after CANTOS.

Conflict of interest

CG received compensation for scientific symposia from AOPOrphan Pharmaceuticals AG, Actelion, and GlaxoSmithKline, and received an educational grant from Bayer (Grant no. 15662). IML has relationships with drug companies including AOPOrphan Pharmaceuticals, Actelion, Bayer-Schering, Astra-Zeneca, Servier, Cordis, Medtronic, GSK, Novartis, Pfizer, and United Therapeutics. In addition to being investigator in trials involving these companies, relationships include consultancy service, research grants, and membership of scientific advisory boards.

References

1. Rabinovitch M, Guignabert C, Humbert M, et al. Inflammation and immunity in the pathogenesis of pulmonary arterial hypertension. *Circ Res* 2014; 115: 165–175.
2. Breitling S, Hui Z, Zabini D, et al. The mast cell-B cell axis in lung vascular remodeling and pulmonary hypertension. *Am J Physiol Lung Cell Mol Physiol* 2017; 312: L710–721.
3. Fleischmann RM, Halland AM, Brzosko M, et al. Tocilizumab inhibits structural joint damage and improves physical function in patients with rheumatoid arthritis and inadequate responses to methotrexate: LITHE study 2-year results. *J Rheumatol* 2013; 40: 113–126.
4. Thornton CC, Al-Rashed F, Calay D, et al. Methotrexate-mediated activation of an AMPK-CREB-dependent pathway: a novel mechanism for vascular protection in chronic systemic inflammation. *Ann Rheum Dis* 2016; 75: 439–448.
5. Ridker PM, Everett BM, Thuren T, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med* 2017; 377: 1119–1131.
6. Simonneau G, Torbicki A, Hoeper MM, et al. Selexipag: an oral, selective prostacyclin receptor agonist for the treatment of pulmonary arterial hypertension. *Eur Respir J* 2012; 40: 874–880.
7. Ghofrani HA, Hoeper MM, Halank M, et al. Riociguat for chronic thromboembolic pulmonary hypertension and pulmonary arterial hypertension: a phase II study. *Eur Respir J* 2010; 36: 792–799.
8. Saito T, Miyagawa K, Chen SY, et al. Upregulation of Human Endogenous Retrovirus-K is linked to immunity and inflammation in pulmonary arterial hypertension. *Circulation* 2017; 136: 1920–1935.
9. Skoro-Sajer N, Marta G, Gerges C, et al. Surgical specimens, haemodynamics and long-term outcomes after pulmonary endarterectomy. *Thorax* 2014; 69: 116–122.
10. Hernandez-Sanchez J, Harlow L, Church C, et al. Clinical trial protocol for TRANSFORM-UK: A therapeutic open-label study of tocilizumab in the treatment of pulmonary arterial hypertension. *Pulm Circ* 2018; 8: 2045893217735820.

Christian Gerges and Irene Lang
Department of Internal Medicine II, Division of Cardiology, Vienna General Hospital, Medical University of Vienna, Vienna, Austria

Corresponding author: Irene Lang, Department of Internal Medicine II, Division of Cardiology, Medical University of Vienna, Währinger Gürtel 18-20, 1090 Vienna, Austria.
Email: irene.lang@meduniwien.ac.at