Saudi Guidelines on the Diagnosis and Treatment of Pulmonary Hypertension: Biomarkers in pulmonary arterial hypertension

Omar A. Minai

Abstract:
The biomarker is an indicator of a biological or pathological process. Clinical observations, measures or environmental events, or measured laboratory values can all be biomarkers in the appropriate setting. An ideal biomarker reflects the underlying biological process, predicts clinical events, is easily obtainable, is reproducible and is not prohibitively expensive. This typically requires validation in longitudinal cohort studies. Biomarkers may help understand the pathological mechanisms responsible for the disease, help as screening tools, predict disease worsening or decline, and determine adequacy of response to therapeutic interventions.

Key words:
Biomarkers, brain natriuretic peptide, heart failure, pulmonary arterial hypertension, Saudi association for pulmonary hypertension guidelines

A “biomarker” as defined by the National Institutes of Health Biomarkers Definitions Working Group refers to “a characteristic”, that is, objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention.[1,2] Clinical observations, measures or environmental events, or measured laboratory values can all be biomarkers in the appropriate setting. An ideal biomarker reflects the underlying biological process, predicts clinical events, is easily obtainable, is reproducible and is not prohibitively expensive. This typically requires validation in longitudinal cohort studies. Biomarkers may help understand the pathological mechanisms responsible for the disease, help as screening tools, predict disease worsening or decline, and determine the adequacy of response to therapeutic interventions.

Although the ideal endpoint remains survival, this may not be practical in a disease with low-prevalence and may be ethically untenable in diseases that have alternative effective therapeutic options, such as pulmonary arterial hypertension (PAH). In this instance, biomarkers may be used as surrogate endpoints to determine disease progression and response to therapy. In the field of PAH, biomarkers have predominantly been studied in three roles:

1. To assess the adequacy of any therapeutic interventions,
2. To assess the adequacy of any therapeutic interventions,
3. To assess the adequacy of any therapeutic interventions.

Studies have used measures of functional capacity (6-min walk distance [6MWD] and World Health Organization [WHO] functional class), clinical worsening (including change in therapy, hospitalization, and need for lung transplantation) and physiological parameters (e.g., cardiac index) as surrogate end-points. The best studied of these remains the 6MWD and studies have shown a significant increase in 6MWD in response to treatment in patients with PAH.[3-7] However, this has several limitations, including the potential impact of factors such as age, gender, body weight, and comorbidities as well as its potential insensitivity as a surrogate for survival.[8,9] There is a need for cheap and easily measured biomarkers that accurately reflect disease activity and are widely applicable. We will discuss the role of biomarkers in PAH in terms of their clinical utility and practical applications.

Role in Screening of Pulmonary Hypertension

The gold standard diagnostic test remains right heart catheterization (RHC). However, its invasive nature and the low disease prevalence of PAH preclude the use of RHC as a screening tool. Thus, there has been a great deal of interest in developing noninvasive markers that can help...
identify a high-risk population that could undergo more invasive testing. Unfortunately, there is currently no single marker that can reliably predict the presence of pulmonary hypertension (PH). Some of the markers that hold promise are reviewed below.

Brain natriuretic peptide and N-terminal of the prohormone brain natriuretic peptide
Plasma brain natriuretic peptide (BNP) and its N-terminal of the prohormone brain natriuretic peptide (NT-pro BNP) are secreted mainly by the ventricular myocytes in response to volume overload and increased wall stress. BNP has a plasma half-life of about 22 min, while the half-life of NT-pro BNP is nearly 2 h and both are cleared through the kidneys. There has been recent interest in using these as part of a screening strategy in a disease like scleroderma, where the prevalence of PAH may be high.

Many previous publications have used NT-proBNP rather than BNP in patients with scleroderma and even though their levels correlate, they are not interchangeable. Hesselstrand et al. showed that natriuretic peptide levels were related to the trans-tricuspid gradient in 227 consecutive patients with scleroderma, but their role in biomarkers of prognosis in patients with PAH.

RHC was based on clinical suspicion (83%) with NT-proBNP. The decision to perform RHC was based on clinical suspicion (83%) with NT-proBNP. In their study Sitbon et al. they found that 6MWD ≤250 m was associated with reduced survival. Several multicenter trials in PAH patients have used 6MWD as the primary measure of outcome or an important component of the primary outcome. Other information obtained during the 6-min walk test (6MWT) has also been found to be useful as a biomarker. Need for oxygen supplementation during the 6MWT and a lower distance saturation product have been found to be biomarkers of poor outcome in PAH. Heart rate is being looked at as an increasingly important biomarker in determining clinical worsening and prognosis. Recently, Minai et al. showed that poor heart rate recovery (HRR) at 1 min after the 6MWT (heart rate at the end of the 6MWT — heart rate after 1 min of rest after 6MWT) was a strong predictor of clinical worsening and time to clinical worsening among patients with idiopathic pulmonary arterial hypertension (IPAH). This easily measured biomarker was a better predictor of clinical worsening and time to clinical worsening compared to 6MWD and BNP even among prevalent patients with PAH already on PH specific therapy. The same group has also shown that reduced HRR after a 6MWT can predict the need for hospitalization and reduced survival among patients with IPAH and those with connective tissue disease associated PAH. These findings may reflect the presence of autonomic dysfunction among PAH patients, which has also been linked to reduced survival.

Other measures of functional capacity
Several other measures of functional capacity have also been used as biomarkers. These include modified WHO functional class and cardiopulmonary exercise testing.

Brain natriuretic peptide and N-terminal of the prohormone brain natriuretic peptide
Several studies have evaluated BNP and NT-proBNP as biomarkers of prognosis in patients with PAH. Nagaya et al. found reduced survival among patients with BNP levels >150 pg/ml at baseline or above 180 pg/ml after initiation of therapy. A recent publication from the Registry to Evaluate Early and Long-Term Registry confirmed that a BNP level above 180 pg/ml was associated with increased 1-year mortality in multivariate analysis among a cohort of predominantly prevalent patients on PH specific therapies. Furthermore, Fijalkowska et al. found that NT-proBNP levels correlated with 6MWD, hemodynamics and were important predictors of survival in IPAH. Contrasting results were reported by Mathai et al. who found that NT-pro BNP were predictive of survival in patients with scleroderma but not in patients with IPAH. A cutoff level of 1400-1500 pg/ml has been associated with poor outcomes compared to patients with lower levels. BNP and NT-proBNP have also been used in patients with PH in the setting of chronic parenchymal lung
Other circulating markers

Endothelial dysfunction is considered to be a significant early phenomenon in PAH; therefore, markers of endothelial dysfunction are of great interest in this condition. Endothelin-1 (ET-1) is a potent vasoconstrictor, and is mainly produced by endothelial cells into the pulmonary circulation. ET-1 has shown some promise as a biomarker for PAH. A small study of 16 PAH patients reported that active ET-1 and its precursor, big ET-1 correlated with cardiopulmonary hemodynamics and 6MWD and were strong prognostic markers for patients with IPAH. In a recent study of PAH patients, Montani et al. found that the ET-1/ET-3 ratio had a strong correlation with right atrial pressure, mixed venous oxygen saturation, WHO functional class, and 6MWD.

Shitrit et al. enrolled 14 patients with PAH and showed that D-dimer is elevated in patients with IPAH compared with the controls and was associated with disease severity and 1-year survival. Synthesized mainly in endothelial cells, plasma von Willebrand factor (vWF) plays a role in platelet aggregation and adhesion at sites of vascular injury. In a small study (N = 10), vWF was found to be elevated in severe PAH and paralleled improvements in hemodynamics on prostanycin therapy. In a retrospective cohort study of 66 PAH patients, increased vWF levels at baseline and follow-up were associated with reduced survival. Elevated plasma vWF antigen (vWF:Ag) has also been found in PAH and baseline vWF:Ag correlated with the risk of death in the subsequent year.

Serum uric acid (UA) is a marker of impaired oxidative metabolism and is elevated in several chronic conditions such as heart failure and chronic obstructive pulmonary disease. In a study of 99 IPAH patients and age-matched controls, Nagaya et al. showed that serum UA levels were elevated, correlated with pulmonary hemodynamics, had a strong association with long-term mortality, and decreased with vasodilator therapy.

Decreased renal function as measured by elevated blood urea nitrogen levels or increased serum creatinine and decreased glomerular filtration have been shown to be associated with a worse hemodynamic profile and were independent predictors of mortality in patients with PAH.

Several markers of inflammation, such as C-reactive protein (CRP), growth differentiating factor-15 and certain interleukins, have been shown to have potential for prognostic information as well; however, these biomarkers require further study and validation.

Cardiac troponin-T is a sensitive and specific marker for myocardial injury and can be detected in the setting of acute RV failure from acute pulmonary embolism. Preliminary studies suggest that detection of cardiac troponins may be markers of poor prognosis in patients PAH.

Quality of life questionnaires

The patients’ own assessment of wellbeing may also be considered a biomarker indicative of disease severity and progression. The Cambridge Pulmonary Hypertension Outcome Review is used for this purpose. It consists of three separate scales that are specific to PH: Symptoms, functioning, and quality of life and may be a useful measure in clinical practice.

Role in Assessment of Therapeutic Response

Changes in clinically assessed biomarkers, such as 6MWD and WHO functional class, have been reported from several large PAH clinical trials. Later reports have confirmed that these short-term changes actually reflect improvement in outcomes. There is very little experience with using blood biomarkers to assess response to therapy in PAH. In uncontrolled studies, an increase in NT-pro BNP was associated with reduced survival whereas improvement in cardiac index and CRP levels were associated with improved survival. Although most recent clinical trials studying new therapies in PAH included serial measurements of BNP or NT-proBNP, there is little data on their utility regarding response to therapy in clinical practice. In a small randomized controlled trial comparing bosentan and sildenafil in 26 modified WHO functional class III patients with PAH, compared to baseline levels, BNP levels fell significantly among sildenafil patients (P = 0.014). Treatment related change in BNP levels did not differ significantly between the two treatment groups. In the ambisentan study, BNP levels decreased in patients on medication and increased in patients on placebo. A similar decrease in NT-proBNP levels was reported with the addition of inhaled treprostinil in PAH patients taking either bosentan or sildenafil.

Little information is available regarding changes in other biomarkers in response to therapy. A more recent study showed an improvement in levels of angiopoietin 2, matrix metalloproteinase 9, and vascular endothelial growth factor with the addition of intravenous treprostinil.

Conclusions

Biomarkers are reproducible and quantifiable measures of the disease that can aid in its diagnosis and management. Most of the candidate biomarkers discussed in this monograph are in early stages of development and require further evaluation in longitudinal studies and clinical trials to prove their validity.

References

1. Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework. Clin Pharmacol Ther 2001;69:89-95.
2. Snow JL, Kawut SM. Surrogate end points in pulmonary arterial hypertension: Assessing the response to therapy. Clin Chest Med 2007;28:75-89, viii.
3. Nagaya N, Nishikimi T, Uematsu M, Kyotani S, Satoh T, Nakanishi N, et al. Secretion patterns of brain natriuretic peptide and atrial natriuretic peptide in patients with or without pulmonary hypertension complicating atrial septal defect. Am Heart J 1998;136:297-301.
4. Elstein D, Nir A, Klutstein M, Rudensky B, Zimran A. C-reactive protein and NT-proBNP as surrogate markers for pulmonary hypertension in Gaucher disease. Blood Cells Mol Dis 2005;34:201-5.
5. Bozkanat E, Tozkoparan E, Baysan O, Deniz O, Ciftci F, Yokusoglu M. The significance of elevated brain natriuretic peptide levels in chronic obstructive pulmonary disease. J Int Med Res 2005;33:537-44.

6. Leuchte HH, Neurohr C, Baumgartner R, Holzapfel M, Giehl W, Vogeser M, et al. Brain natriuretic peptide and exercise capacity in lung fibrosis and pulmonary hypertension. Am J Respir Crit Care Med 2004;170:360-5.

7. Kucher N, Printzen G, Goldhaber SZ. Prognostic role of brain natriuretic peptide in acute pulmonary embolism. Circulation 2003;107:2545-7.

8. Rich S. The current treatment of pulmonary arterial hypertension: Time to redefine success. Chest 2006;130:1198-202.

9. Macchia A, Marchioli R, Marfisi R, Scarano M, Levantesi G, Tavazzi L, et al. A meta-analysis of trials of pulmonary hypertension: A clinical condition looking for drugs and research methodology. Am Heart J 2007;153:1037-47.

10. Nagaya N, Nishikimi T, Okano Y, Uematsu M, Satoh T, Kyotani S, et al. Plasma brain natriuretic peptide levels increase in proportion to the extent of right ventricular dysfunction in pulmonary hypertension. J Am Coll Cardiol 1998;31:202-8.

11. McNairy M, Gardetto N, Clopton P, Garcia A, Krishnaswamy P, Kazanegra R, et al. Stability of B-type natriuretic peptide levels during exercise in patients with congestive heart failure: Implications for outpatient monitoring with B-type natriuretic peptide. Am Heart J 2002;143:406-11.

12. Lubien E, DeMaria A, Krishnaswamy P, Clopton P, Koon J, Kazanegra R, et al. Utility of B-natriuretic peptide in detecting diastolic dysfunction: Comparison with Doppler velocity recordings. Circulation 2002;105:595-601.

13. Yandle TG. Biochemistry of natriuretic peptides. J Intern Med 1994;235:561-76.

14. Hesselstrand R, Ekman R, Eskilsson J, Isaksson A, Scheja A, Ohlin AK, et al. Screening for pulmonary hypertension in systemic sclerosis: The longitudinal development of tricuspid gradient in 227 consecutive patients, 1992-2001. Rheumatology (Oxford) 2005;44:366-71.

15. Mukerjee D, Yap LB, Holmes AM, Nair D, Ayerton P, Black CM, et al. Significance of plasma N-terminal pro-brain natriuretic peptide in patients with systemic sclerosis-related pulmonary arterial hypertension. Respir Med 2003;97:1230-6.

16. Williams MH, Handler CE, Akram R, Smith CJ, Das C, Sme J, et al. Role of N-terminal brain natriuretic peptide (N-TproBNP) in scleroderma-associated pulmonary arterial hypertension. Eur Heart J 2006;27:1485-94.

17. Cavagna L, Caporali R, Klersy C, Ghio S, Albertini R, Scelsi L, et al. Comparison of brain natriuretic peptide (BNP) and NT-proBNP in screening for pulmonary arterial hypertension in patients with systemic sclerosis. J Rheumatol 2010;37:2064-7.

18. Allameh Y, Borderie D, Avouac J, Zerkak D, Meune C, Hachulla E, et al. High N-terminal pro-brain natriuretic peptide levels and low diffusing capacity for carbon monoxide as independent predictors of the occurrence of precapillary pulmonary arterial hypertension in patients with systemic sclerosis. Arthritis Rheum 2008;58:284-91.

19. Steen VD. Autoantibodies in systemic sclerosis. Semin Arthritis Rheum 2005;35:35-42.

20. Soon E, Holmes AM, Treacy CM, Doughty NJ, Southgate L, Machado RD, et al. Elevated levels of inflammatory cytokines predict survival in idiopathic and familial pulmonary arterial hypertension. Circulation 2010;122:920-7.

21. Selimovic N, Bergh CH, Andersson B, Sakiniene E, Carlsten H, Rundqvist B. Growth factors and interleukin-6 across the lung circulation in pulmonary hypertension. Eur Respir J 2009;34:662-8.

22. Miyamoto S, Nagaya N, Satoh T, Kyotani S, Sakamaki F, Fujita M, et al. Clinical correlates and prognostic significance of six-minute walk test in patients with primary pulmonary hypertension. Comparison with cardiopulmonary exercise testing. Am J Respir Crit Care Med 2000;161:487-92.

23. Sitbon O, Humbert M, Nunes H, Parent F, Garcia G, Hervé P, et al. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: Prognostic factors and survival. J Am Coll Cardiol 2002;40:780-8.

24. Barst RJ, Rubin LJ, Long WA, McGoon MD, Rich S, Badesch DB, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. N Engl J Med 1996;334:296-301.

25. Channick RN, Simonneau G, Sitbon O, Robbins IM, Frost A, Tapon VF, et al. Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: A randomised placebo-controlled study. Lancet 2001;358:1119-23.

26. Simonneau G, Barst RJ, Galie N, Naefle R, Bourge RC, et al. Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension: A double-blind, randomized, placebo-controlled trial. Am J Respir Crit Care Med 2002;165:800-4.

27. Rubin LJ, Badesch DB, Barst RJ, Galie N, Black CM, Keogh A, et al. Bosentan therapy for pulmonary arterial hypertension. N Engl J Med 2002;346:896-903.

28. Galie N, Badesch D, Oudiz R, Simonneau G, McGoon MD, Keogh AM, et al. Ambrisentan therapy for pulmonary arterial hypertension. J Am Coll Cardiol 2005;46:529-35.

29. Galie N, Ghofrani HA, Torbicki A, Barst RJ, Rubin LJ, Badesch D, et al. Sildenafil citrate therapy for pulmonary arterial hypertension. N Engl J Med 2005;353:2148-57.

30. Barst RJ, Langleben D, Badesch D, Frost A, Lawrence EC, Shapiro S, et al. Treatment of pulmonary arterial hypertension with the selective endothelin-A receptor antagonist sitaxsentan. J Am Coll Cardiol 2006;47:2049-56.

31. Galie N, Olschewski H, Oudiz RJ, Ambrisentan in Pulmonary Arterial Hypertension, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Efficacy Studies (ARIES) Group, et al. Ambrisentan for the treatment of pulmonary arterial hypertension: Results of the ambrisentan in pulmonary arterial hypertension, randomized, double-blind, placebo-controlled, multicenter, efficacy (ARIES) study 1 and 2. Circulation 2008;117:3010-9.

32. Batal O, Khatib OF, Dweik RA, Hammel JP, McCarthy K, Minai OA. Comparison of baseline predictors of prognosis in pulmonary arterial hypertension in patients surviving ≤2 years and those surviving ≥5 years after baseline right-sided cardiac catheterization. Am J Cardiol 2012;109:1514-20.

33. Paciocco G, Martinez FJ, Bosson E, Pielsicker E, Gillespie B, Rubenfire M. Oxygen desaturation on the six-minute walk test and mortality in untreated primary pulmonary hypertension. Eur Respir J 2001;17:647-52.

34. Al Ameri HF. Six minute walk test in respiratory diseases: A university hospital experience. Ann Thorac Med 2006;1:16-9.

35. Minai OA, Gudavalli R, Mummadi S, Liu X, McCarthy K, Foreman AJ, Coffey CS, et al. Predicting survival in pulmonary arterial hypertension: Insights from the registry to evaluate early and long-term pulmonary arterial hypertension disease management (REVEAL). Circulation 2010;122:164-72.
39. D’Alonso GE, Barst RJ, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, et al. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. Ann Intern Med 1991;115:343-9.

40. Kuhn KP, Byrne DW, Arbogast PG, Doyle TP, Loyd JE, Robbins IM. Outcome in 91 consecutive patients with pulmonary arterial hypertension receiving epoprostenol. Am J Respir Crit Care Med 2003;167:580-6.

41. McLaughlin VV, Shillington A, Rich S. Survival in primary pulmonary hypertension: The impact of epoprostenol therapy. Circulation 2002;106:1477-82.

42. McLaughlin VV, Sitbon O, Badesch DB, Barst RJ, Black C, Galí N, et al. Survival with first-line bosentan in patients with primary pulmonary hypertension. Eur Respir J 2005;25:244-9.

43. Wensel R, Opitz CF, Anker SD, Winkler J, Höpfken G, Kleber FX, et al. Assessment of survival in patients with primary pulmonary hypertension: Importance of cardiopulmonary exercise testing. Circulation 2002;106:319-24.

44. Oudiz RJ, Barst RJ, Hansen JE, Sun XG, Garofano R, Wu X, et al. Cardiopulmonary exercise testing and six-minute walk correlations in pulmonary arterial hypertension. Am J Cardiol 2006;97:123-6.

45. Nagaya N, Nishikimi T, Uematsu M, Satoh T, Kyotani S, Sakamaki F, et al. Plasma brain natriuretic peptide as a prognostic indicator in patients with primary pulmonary hypertension. Circulation 2000;102:865-70.

46. Fijalkowska A, Kurzyna M, Torbicki A, Szewczyk G, Florczyk M, Pruszczczyk P, et al. Serum N-terminal brain natriuretic peptide as a prognostic parameter in patients with pulmonary hypertension. Chest 2006;129:1313-21.

47. Mathai SC, Bueno M, Hummers NK, Boyce D, Lechtzin N, Le Page J, et al. Disproportionate elevation of N-terminal brain natriuretic peptide in scleroderma-related pulmonary hypertension. Eur Respir J 2010;35:95-104.

48. Nagaya N, Ando M, Oya H, Ohkita Y, Kyotani S, Sakamaki F, et al. Plasma brain natriuretic peptide as a noninvasive marker for efficacy of pulmonary thromboendarterectomy. Ann Thorac Surg 2002;74:180-4.

49. Nagaya N, Sasaki N, Ando M, Ogino H, Sakamaki F, Kyotani S, et al. Prostacyclin therapy before pulmonary thromboendarterectomy in patients with chronic thromboembolic pulmonary hypertension. Chest 2003;123:383-48.

50. Giaid A, Yanagisawa M, Langleben D, Michel RP, Levy R, Shennib H, et al. Expression of endothelin-1 in the lungs of patients with pulmonary hypertension. N Engl J Med 1993;328:1732-9.

51. Rubens C, Ewert R, Halank M, Wensel R, Orzechowski HD, Schultheiss HP, et al. Big endothelin-1 and endothelin-1 plasma levels are correlated with the severity of primary pulmonary hypertension. Chest 2001;120:1562-9.

52. Montani D, Souza R, Binkert C, Fischli W, Simonneau G, Clozel M, et al. Endothelin-1/endothelin-3 ratio: A potential prognostic factor of pulmonary arterial hypertension. Chest 2007;131:101-8.

53. Shitrit D, Bendayan D, Bar-Gil-Shitrit A, Huerta M, Rudensky B, Fink G, et al. Significance of a plasma D-dimer test in patients with primary pulmonary hypertension. Chest 2002;122:1674-8.

54. Veyradier A, Nishikubo T, Humbert M, Wolf M, Sitbon O, Simonneau G, et al. Improvement of von Willebrand factor proteolysis after prostacyclin infusion in severe pulmonary arterial hypertension. Circulation 2000;102:2460-2.

55. Kawut SM, Horn EM, Berekashvili KK, Widlitz AC, Rosenzweig EB, Barst RJ. von Willebrand factor independently predicts long-term survival in patients with pulmonary arterial hypertension. Circulation 2005;112:2555-62.

56. Friedman R, Mears JG, Barst RJ. Continuous infusion of prostacyclin normalizes plasma markers of endothelial cell injury and platelet aggregation in primary pulmonary hypertension. Circulation 1997;96:2782-4.
74. Hiremath J, Thanikachalam S, Parikh K, Shanmugasundaram S, Bangera S, Shapiro L, et al. Exercise improvement and plasma biomarker changes with intravenous treprostinil therapy for pulmonary arterial hypertension: A placebo-controlled trial. J Heart Lung Transplant 2010;29:137-49.

How to cite this article: Minai OA. Saudi Guidelines on the Diagnosis and Treatment of Pulmonary Hypertension: Biomarkers in pulmonary arterial hypertension. Ann Thorac Med 2014;9:S92-7.

Source of Support: Nil, Conflict of Interest: None declared.