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

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Abstract:

The biomarker is an indicaror 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.

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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. As screening tools,
2. To determine prognosis, and
3. To assess the adequacy of therapeutic interventions.[3-7]

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.[10-13] 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.[14]

Two publications from the same group have suggested a NT-proBNP cutoff value >395 pg/ml as having a very high specificity in detecting PAH in patients with scleroderma.[15,16] These results may have been impacted by the presence of concomitant interstitial lung disease and the fact that a number of patients were already on PAH targeted therapies at the time of NT-proBNP measurement. On the other hand, a single-center study recently reported that BNP using a cutoff value of 64 pg/ml was superior to NT-proBNP using a cutoff value of 239.4 pg/ml.[17] In a prospective study of 101 patients with scleroderma, Allanore *et al*. have reported high sensitivity (75%) and high specificity (83%) with NT-proBNP.[18] A limitation of the study was that the decision to perform RHC was based on clinical suspicion including an elevated right ventricular (RV) systolic pressure by Doppler echocardiography and a depressed diffusing capacity for carbon monoxide/alveolar volume. Therefore, only 19 patients underwent RHC and only eight were found to have PH.

Autoantibodies

Immunological biomarkers may be useful in differentiating between subtypes of scleroderma. The major cause of death in patients with anticentromere antibodies is PAH, while nucleolar antibody Th/To predisposes to both pulmonary vascular and interstitial disease.[19] Other autoantibodies such as antifibroblast antibodies and antitopoisomerase II-alpha antibodies may be useful, but have not been evaluated in large cohorts of patients. Elevated levels of several inflammatory markers including interleukins, tumor necrosis factor, and vascular endothelial growth factor have been reported among patients with PAH compared to controls,[20,21] but their role in screening, if any, remains to be defined. There are currently no data on the role of markers of inflammation in screening for PAH.

Role in Assessment of Prognosis

Accurate assessment of prognosis remains an extremely important element in caring for patients with PAH. Many studies have used "clinical worsening" or "time to clinical worsening" as surrogate end-points for this purpose. Several other markers have also been used to determine prognosis in patients with PAH.

Six-min walk test

The 6MWD is probably the most studied and widely adopted biomarker in PAH. Miyamoto *et al*. found that patients with idiopathic PAH walking <332 m had significantly lower survival compared with those walking >332 m.[22] In their study Sitbon *et al*. they found that 6MWD ≤250 m was associated with reduced survival.[23] Several multicenter trials in PAH patients have used 6MWD as the primary measure of outcome or an important component of the primary outcome.[24-31] 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.[32-34] 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).[35] 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[36] and those with connective tissue disease associated PAH.[37] 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[23,32,38-42] and cardiopulmonary exercise testing.[43,44]

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.[10-13] 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.[45] 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.[38] Furthermore, Fijalkowska *et al*. found that NT-proBNP levels correlated with 6MWD, hemodynamics and were important predictors of survival in IPAH.[46] 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.[47] A cutoff level of 1400-1500 pg/ml has been associated with poor outcomes compared to patients with lower levels.[38,47] BNP and NT-proBNP have also been used in patients with PH in the setting of chronic parenchymal lung

disease,[5,6] congenital systemic-to pulmonary shunts,[3] and in acute and chronic thromboembolic disease.[7,48,49]

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.[50] 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.[51] 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.[52]

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.[53] 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 prostacyclin therapy.[54] In a retrospective cohort study of 66 PAH patients, increased vWF levels at baseline and follow-up were associated with reduced survival.[55] 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.[56,57]

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.[58]

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.[32,59]

Several markers of inflammation, such as C-reactive protein (CRP),[60] growth differentiating factor-15,[61] and certain interleukins,[20] 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.[62-64]

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.[65-67] 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.[24-31] Later reports have confirmed that these short-term changes actually reflect improvement in outcomes.[68,69] 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,[16] whereas improvement in cardiac index[70] and CRP[60] 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).[71] Treatment related change in BNP levels did not differ significantly between the two treatment groups. In the ambrisentan study, BNP levels decreased in patients on medication and increased in patients on placebo.[72] A similar decrease in NT-proBNP levels was reported with the addition of inhaled treprostinil in PAH patients taking either bosentan or sildenafil.[73] Very 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.[74]

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.

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