

## New Developments in Pulmonary Arterial Hypertension

a report by

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The pace of progress in the field of pulmonary arterial hypertension (PAH) continues to be breathtaking. In the past couple of years two new oral agents have been granted licences. Fourteen major international drug trials are underway, many evaluating the role of combination therapies, and at least three agents (simvastatin, imatinib and aviptadil) are undergoing proof of concept studies in humans. Basic science has moved on, suggesting a role for platelet-derived growth factor (PDGF), in controlling cellular proliferative responses in PAH. Finally, as we now have combinations of agents that can deliver real reductions in the haemodynamic strain faced by the right ventricle, evidence is beginning to accumulate in favour of pressure reduction or goal-directed therapy.

Since the discovery of bone morphogenetic protein receptor-2 (BMPR-2) mutations as the genetic basis for most familial (F)PAH, many groups have worked to understand how dysregulation of BMPR leads to elevated pulmonary pressures. BMPR-2 mutations have been shown to lead to pulmonary endothelial cell apoptosis,<sup>1</sup> exposing pulmonary artery smooth muscle cells (PASMC) to mitogenic serum factors. BMPR-2 deficiency induced dysregulation of the Smad signalling system in small pulmonary arteries has been shown to inhibit their ability to regulate proliferation and apoptosis,<sup>2</sup> possibly in part through relative upregulation of TGF- $\beta$  signalling pathways.<sup>3</sup> This construct may be of relevance to more than just FPAH, as BMPR-2 signalling pathways have also been shown to be down-regulated in idiopathic (I)PAH<sup>2</sup> and some animal models of PH,<sup>4,5</sup> and a closely associated pathway (BMPR1A) is down-regulated in some forms of associated PAH.<sup>6</sup> Systemic sclerosis (SSc) is recognised as a condition in which dysregulation of TGF- $\beta$  signalling is pivotal<sup>7</sup> and is the connective tissue disease most strongly associated with PAH. It has been shown that TGF- $\beta$  increases the expression of PDGF, especially in SSc.<sup>8</sup> Imatinib, a PDGF inhibitor, is now undergoing proof of concept trials in humans, if successful this may be the first example of a new therapeutic avenue opened up by our increasing understanding of the intracellular perturbations leading to various forms of PAH.

Another area of progress has been further characterisation of associated conditions that lead to PAH. Portal hypertension has long been associated with PAH; however, evaluation of transplant populations has shown the strength of this association, around 4% of patients referred for liver transplantation are now known to have PAH<sup>9</sup> and the prevalence is significantly higher in those with porto-systemic shunts. Screening for PAH is now essential as part of the transplant work-up. In addition we now recognise chronic haemolytic conditions (sickle cell disease and thalassemia) as causes of pulmonary hypertension.<sup>10</sup> A recent echo-base study has suggested that up to 30% of adults with SCD may have PAH, and that even minor elevations of pulmonary pressure is associated with a very adverse prognosis in this population.<sup>11</sup> The ASSET trials are already investigating the potential role of bosentan in this population and other trials are planned.

The publication of the first double blind randomised trial of bosentan in patients with Eisenmenger's syndrome is another landmark in the treatment of this condition. This study has not only demonstrated the safety of treatment of PAH associated with shunting, but has also shown that significant clinical benefit can be achieved and maintained for at least 40 weeks.<sup>12</sup> There has also been progress in the field of connective tissue disease associated PAH, with the publication of the first study showing evidence of substantial improvement in prognosis in scleroderma patients given first-line endothelin receptor antagonist therapy.<sup>13</sup>

To date the evidence base, and consequently published guidelines, have been limited to advocating monotherapy, yet clinical practice has moved on as over one-third of patients fail to improve on any single therapy, and the mortality in these patients remains high. The proven measures of therapeutic response remain rather crude (NYHA grade, absolute as opposed to change in six minute walking distance and invasive haemodynamics). A substantial body of evidence now supports serial natriuretic peptide measurement as a valid monitoring tool. A brain natriuretic peptide (BNP)

level of  $<180\text{pg/ml}^{14}$  or N-terminal pro-BNP level of less than  $1,400\text{pg/ml}^{15}$  is associated with a good prognosis in iPAH, while a 10-fold change in Nt-pro-BNP level has been shown to predict a four-fold change in prognosis in patients with systemic sclerosis associated PAH.<sup>16</sup> Magnetic resonance imaging (MRI) also shows promise: delayed contrast imaging shows abnormalities of the right ventricle insertion points extending into the septum as the condition progresses,<sup>17</sup> and contractility can now be assessed using pressure volume loops.<sup>18</sup>

While there is still some controversy surrounding the importance of resting pulmonary haemodynamics as a treatment goal, evidence is gradually accumulating in favour of this end-point. Data from lung transplant<sup>19</sup> and thrombectomy<sup>20</sup> populations have

confirmed that reverse remodelling of the right ventricle occurs in these patients, in addition it is known that in patients responding to calcium channel blockers (CCBs) with near normalisation of pulmonary pressures the long-term outlook is excellent.<sup>21</sup> Finally, we know that in patients managed with prostanoids<sup>22</sup> or combination therapy,<sup>23</sup> achieving a substantial reduction of pulmonary vascular resistance is the key to long-term survival. Taken together these data provide a rational basis for goal-directed therapies, which will be formally tested over the next few years.

In conclusion, the field of PAH continues to develop apace, and the next few years promise to bring many further improvements in patient management, for this previously untreatable condition. ■

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