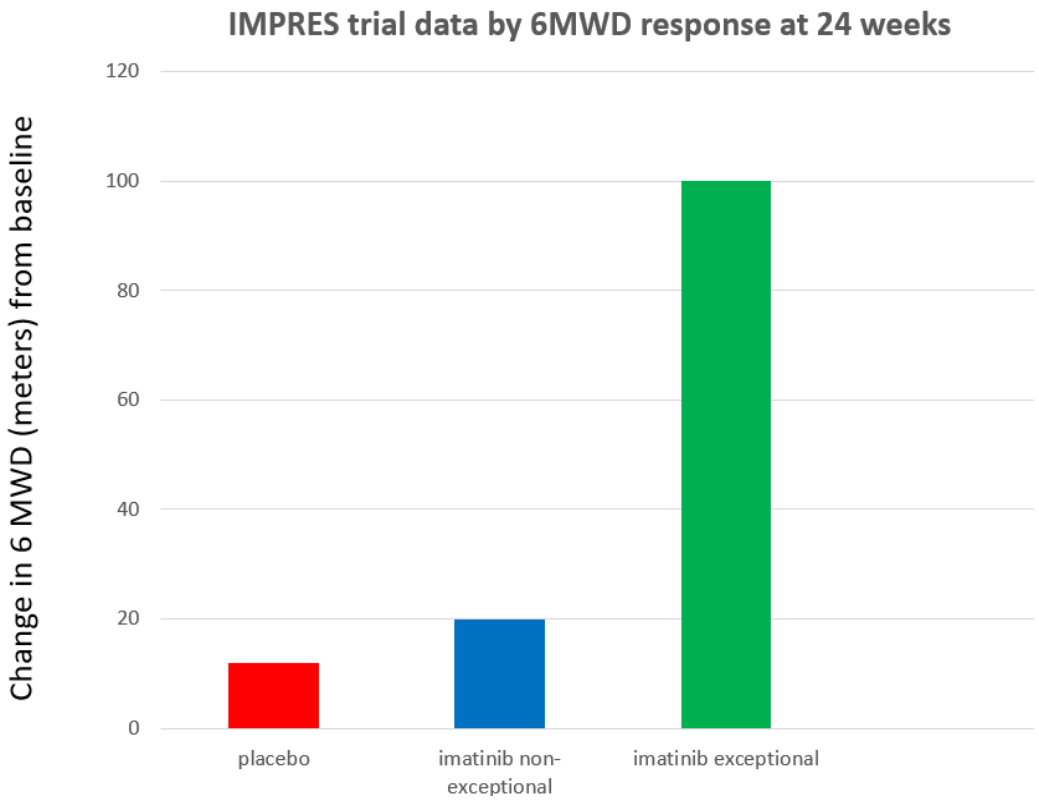
TENAX THERAPEUTICS

Oral Imatinib for Pulmonary Arterial Hypertension Has the Potential for a Treatment Effect Greater than Any Existing or Experimental Therapy

Considerable interest was created over the use of the tyrosine kinase inhibitor imatinib for PAH, as translational research continues to support the hope that it is possible to achieve a halt in the progression, and even a reversal of the disease if critical pathways that underlie the disease process are blocked. However, the withdrawal of its development after the IMPRES trial raised concerns about what role it may play in the future. There remains considerable confusion over the reported cause and number of dropouts in the trial, as well as the new observation of subdural hematomas. While some have even suggested that imatinib will never be developed for PAH, that clearly is not the case. Neither issue was the sole basis for the lack of regulatory approval, as a decision for approval of a new treatment from the FDA and EMA always considers the nature and magnitude of treatment effect against safety concerns. The Tenax Imatinib PAH Program has addressed and mitigated the regulatory concerns surrounding the high number of early dropouts and the risk of subdural hematomas. What is of equal importance, is its potential effect as an antiproliferative agent that one would hope would have greater efficacy than the existing pulmonary vasodilators.

A close review of published data on oral imatinib use in PAH reveals a much larger treatment effect on 6MWD, and a much longer duration of treatment effect, than has been achieved with any of the existing pulmonary vasodilator therapies. The magnitude of treatment effect was highlighted by a responder analysis of the patients randomized to imatinib in the IMPRES trial. [1] That revealed that 25% of the patients had an exceptional response defined as an increase in 6MWD of >50 meters, and 40% had an exceptional response defined as a reduction in PVR >30% after 24 weeks of treatment. (Figure 1). In addition, 17% of the patients had both exceptional treatment effects (combined response group). ***Equally impressive is that the mean increase in 6MWD after 24 weeks in this group was 100 meters, a change that pulmonary vasodilators, alone or in combination, have never come close to achieving***. [2]

Figure 1.

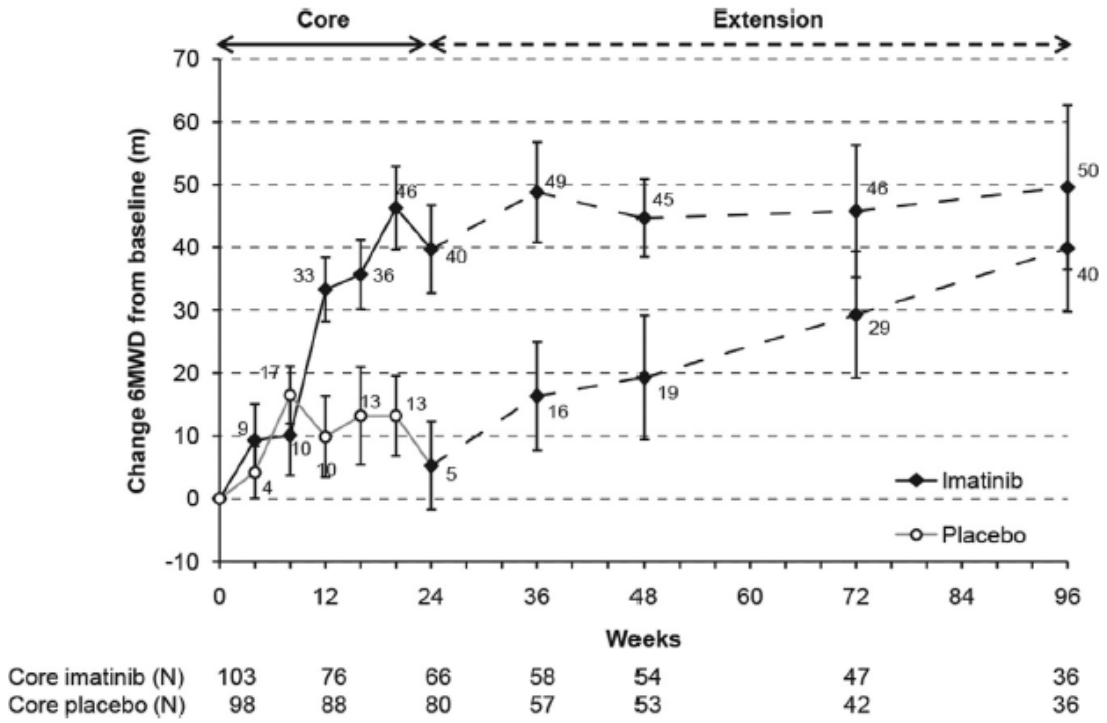


Imatinib exceptional responder patients from the IMPRES trial represents the combined response group. Imatinib non-exceptional responders represent the remaining patient randomized to active drug in IMPRES. The exceptional response group was limited to those who took oral imatinib 400 mg daily for the entire trial.

Both the phase 2 and phase 3 trials offered an open label extension to patients completing the initial randomized trial. [2,3] This allowed insight into the durability of the treatment effect. In the phase 2 pilot trial, 14 patients elected to remain in the open label extension study for long term treatment. These patients had a 55±66 meter increase in 6MWD over a period of 2-3 years of imatinib treatment. [3]

A preplanned efficacy analysis undertaken at Week 72 of the phase 3 IMPRES extension study showed that the improvements in 6MWD among the ex-imatinib patients were sustained during the extension for up to 72 weeks of the extension study (96 weeks from core baseline). After 96 weeks of imatinib treatment (Week 72 of extension), the mean improvement was 50 m (Figure 2). The mean improvement for ex-placebo patients at 72 weeks (72 weeks of imatinib) was 40 m. [4]

Figure 2.



In the combined exceptional responder group followed out to 1 year, 15 of 17 patients maintained the large increase in 6MWD with 9 patients having a treatment effect of >50 meters, and 6 patients of >75 meters. In 8/9 patients the increase in treatment effect was maintained out to 72 weeks. Although conclusions in the extension study are hampered by a high discontinuation rate, the sustained improvement in the 6MWD seen in the patients continuing drug treatment for up to180 weeks exceeds all favorable treatment effects from any pulmonary vasodilator studied either as a single therapy or in the previously reported combination studies. This suggests an ongoing effectiveness of imatinib on vascular remodeling. ***No other treatment of PAH has ever shown a treatment effect of that magnitude, or a continued increase in 6MWD beyond 48 weeks***.

In Europe, oral imatinib for PAH was made available off-label for a limited number of patients based on the encouraging results of the IMPRES study. This allows an insight into a real-world experience of imatinib for PAH. In a report from France on 2 patients with PAH, [5] one maintained their 6MWD improvement for 6 years, and the other showed continuous increasing 6MWD (>100 meters) over 4 years. A case report from Switzerland [6] showed a patient on triple pulmonary vasodilator therapy had an increase in 6MWD of 270 meters over 5 years, with normalization of the PVR. A case report from Germany [7] showed a patient with an increase in 6MWD >150 meters over 21 months. Another case series from Switzerland on 15 patients [8] showed normalization of PA pressure out to 5 years in 3 patients (Figure 3). After a median follow-up of 37 months, there was a sustained

improvement in functional class ($p = 0.032$), quality of life ($p = 0.019$), and echocardiographic parameters of right ventricular function ($p < 0.05$).

In the RCTs with pulmonary vasodilators, the increase in 6MWD tended to occur early in the trial, with a plateau after the initial 4-8 weeks of a 12 week treatment. [2] In contrast, the clinical trials in the imatinib studies were conducted over 24 weeks, to address the possibility that reverse remodeling strategies may require more time than vasodilatory approaches. However, even a treatment exposure time of 24 weeks may not reveal the full therapeutic effect. (Figure 3). Observations indicate that continued improvements of clinical status, hemodynamics, and other prognostically relevant parameters may persist far beyond 24 weeks as would be anticipated from an effective anti-proliferative approach.[8] ***Hence, the full efficacy of oral imatinib in some patients may become even more evident with extended treatment, depending on the level of underlying vascular proliferative activity.***

Figure 3.

Efficacy and Safety of Long-Term Imatinib Therapy for Pulmonary Arterial Hypertension

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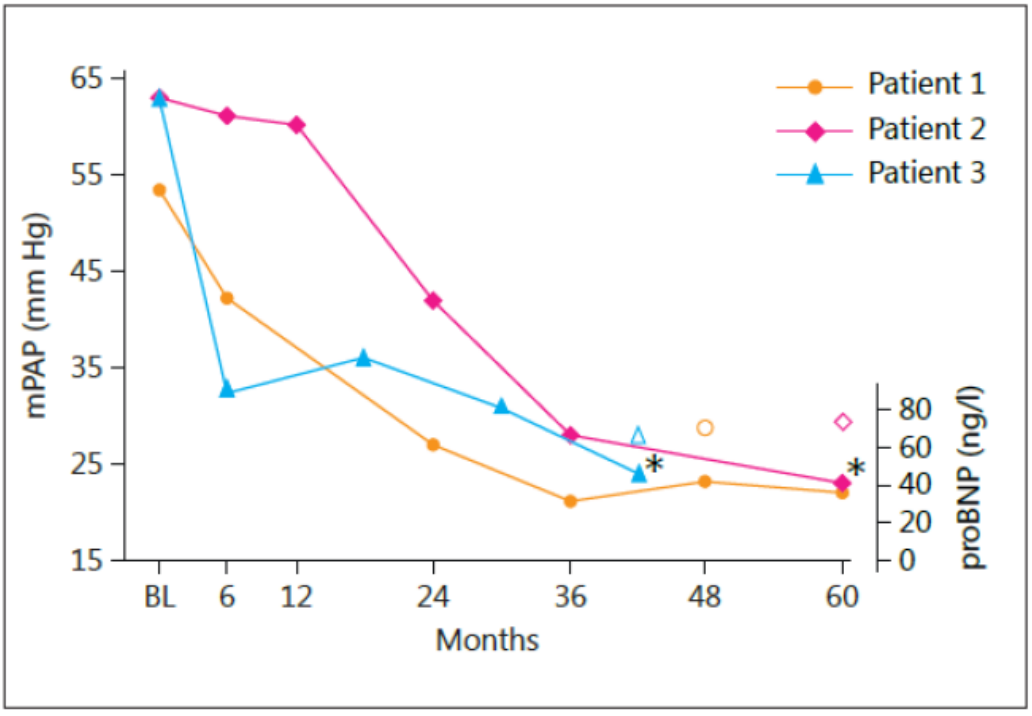
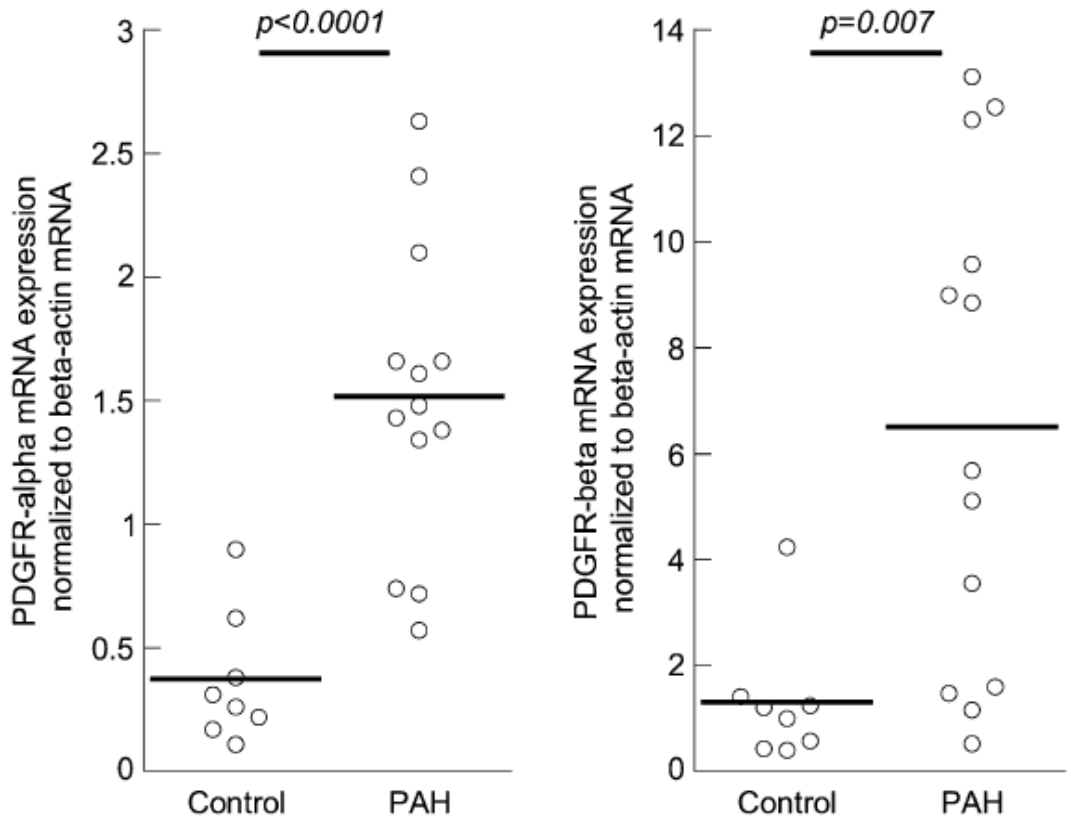


The percentage of patients with the potential to respond to oral imatinib therapy remains uncertain. Its efficacy would be expected in those patients with expression of elevated PDGF in the pulmonary arteries, and there is no way to demonstrate that in patients with PAH short of obtaining an open lung biopsy. However, there are data in human lung tissue from patients with PAH undergoing lung transplantation which showed those who had elevated PDGF expression in their pulmonary arteries. [9] In 10 of 13 patients, they had PDGFR-alpha levels, and 8 of 13 had PDGFR-beta levels that were markedly elevated compared to controls, which would support that a majority of patients with PAH stand to benefit from oral imatinib. (Figure 4).

Figure 4.



PDGF receptor (PDGFR) expression in microdissected pulmonary arteries from patients with severe pulmonary arterial hypertension (PAH) and from control subjects.

There is a wide spectrum of phenotypes and genotypes that underlie PAH. When they become better understood, it may explain why some patients have exceptional responses to imatinib whereas others do not. In addition, imatinib effects 4 different receptor tyrosine kinases which would support that it would have greater efficacy than inhibitors with a more narrow spectrum. There is data to suggest that at least 3 of those play a role in PAH, but not necessarily equally in all patients. The fact that observations have shown that some patients respond after short term exposure to imatinib, and others tend to respond after lengthy exposure, does not diminish the potential for imatinib to reverse the disease in both instances. (Figure 3)

In summary, clinical trial data show that oral imatinib is remarkably effective in improving the exercise tolerance and hemodynamics of PAH patients. In addition, a review of the published literature, and a responder analysis from the phase 3 IMPRES trial of oral imatinib for PAH show that oral imatinib produces a markedly greater treatment effect on 6MWD, with a much longer durability of treatment effect than any other available treatment, alone or in combination.

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