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### TRANSITION FROM PROSTANOID TO COMBINATION ORAL THERAPY FOR PULMONARY ARTERIAL HYPERTENSION

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#### Abstract

**Background:** Experience with transition from parenteral prostanoid (Pgl2) to oral therapy for severe, symptomatic NYHA Functional Class (FC) III/IV pulmonary arterial hypertension (PAH) is limited. Herein, we report our experiences transitioning patients from Pgl2 therapy to oral combination therapy.

**Methods:** A retrospective review of seven PAH patients determined to be “clinically stable” while on Pgl2 during Phase I of our protocol. In Phase II, bosentan and sildenafil were added as Pgl2 was decreased during monitoring with echocardiography, six-minute walk distance, FC assessment and measurement of B-type natriuretic peptide. During Phase III, surveillance was maintained to detect clinical worsening and intervene.

**Results:** During phase I, the FC were: I(2), II(4), and III(1). At phase III’s end, the FC were: I(3) and II(4). One patient experienced right ventricular failure, resulting in requirement of subcutaneous treprostinil and return to “active UNOS listing” for lung transplant. The mean duration [±SD] for phase I: 15.9±5.1, phase II: 7±3.6, and phase III: 41.3±17.3 months. Survival during over 5 years of therapy and observation, was 86% while predicted survival for first three was 86, 80 and 74%, respectively.

**Conclusions:** Selected patients with severe, symptomatic FC III/IV PAH, may be transitioned from Pgl2 therapy to combination oral therapy.

#### Abbreviation List:

Area under the curve (AUC); B-type natriuretic peptide (BNP); Functional Class (FC); maximum peak concentration (Cmax); New York Heart Association (NYHA); parenteral prostanoid infusion (Pgl2); Pulmonary arterial hypertension (PAH); six minute walk distance (6MWD).

#### Introduction

PAH is characterized by progressive vascular remodeling.<sup>1</sup> Treatment with continuous PGI2 has been demonstrated to improve NYHA FC, pulmonary hemodynamic parameters, and afford long-term survival benefit in patients suffering from idiopathic PAH.<sup>2,3</sup> Despite the potential benefits of parenteral (either subcutaneous or intravenous) therapy, patient dissatisfaction with the complex technique as well, risk for septic complications are well recognized. Patients are often referred for consideration of lung or heart-lung transplantation when committed to such therapies.

In light of these issues, transition from continuous infusion PGI<sub>2</sub> to an oral regimen, often is entertained with trepidation, in particular when clinically stable with significant physiologic and functional improvement. Previous reports have suggested that epoprostenol could be transitioned to oral therapy in “carefully selected” and “stable” patients.<sup>4-8</sup>

Despite promising reports, patient selection and factors predictive of a successful transition are not clear. Furthermore, the optimal oral regimen for this recommendation, has not been investigated. In our series, we postulated the efficacy of a “combination oral regimen” including both bosentan and sildenafil, which would target diverse pathophysiologic mechanisms in PAH; affording potential vasodilator, anti-proliferative, and pro-apoptotic salutary properties.<sup>7</sup> In our single center retrospective pilot study, we report our experience for patients referred for consideration of lung or heart-lung transplantation who requested transition to oral therapies after initial clinical improvement associated with prostanoid infusion.

## Methods

We performed a retrospective chart review regarding subjects who had requested and consented to the transition of PGI<sub>2</sub> infusion to a combination oral therapy at our center. For each subject, a personalized time scale was developed during the course of transition. We divided this time scale into three distinct phases, and each patient spent a variable amount of time in each phase.

### **Phase I:**

In this phase, clinically improved and “stable” PAH patients receiving either epoprostenol or treprostinil by continuous infusion who declined our standard recommendation for “indefinite” continuation of prostanoid infusion, were considered appropriate and consented for transition to an oral regimen. Patients who were considered to be “clinically stable” were in NYHA FC of ≤II, 6MWD ≥ 380 m, BNP < 100 pg/ml, “stable” echocardiographic assessment of estimated RVSP and right ventricular function and without clinical evidence for decompensated right ventricular failure. Patients were excluded if they exhibited evidence for “clinical deterioration” within prior 12 months or there was future anticipated requirement for surgical intervention and general anesthesia. The retrospective review of our center’s experience in PAH has been approved by our Institutional Review Board.

### **Phase II:**

PGI<sub>2</sub> was decreased sequentially based on clinical monitoring of 6MWD, NYHA FC (I-IV), and BNP until achieving discontinuation. Reduction in PGI<sub>2</sub> dosage would be retarded for exacerbation of PAH symptoms. Concurrently, the oral vasodilator regimen was introduced with combination of bosentan and sildenafil. Bosentan was initiated at standard dosage of 62.5 mg twice daily and increased to 125 mg *b.i.d.* after 4 weeks during requisite monthly monitoring of serum aminotransferase levels. Sildenafil was initiated at 20-25 mg *t.i.d.* and was increased to 50mg *t.i.d.* in patients as indicated. Upon discontinuation of PGI<sub>2</sub>, indwelling central venous catheters were maintained for an additional two weeks in the event of potential reinitiated therapy.

### **Phase III:**

After discontinuation of PGI<sub>2</sub>, during phase III, “clinical surveillance” was maintained through clinic appointment follow-up and telephone contact to determine potential clinical deterioration. “Surveillance” entailed observation for a 10% decrement in 6MWD, increasing BNP, decline by one NYHA FC, and transthoracic echocardiographic assessment. The 6MWD test was performed according to the American Thoracic Society guidelines.<sup>9</sup> A right heart catheterization was not performed during the transition process unless clinical evidence for functional deterioration.

## **Statistical Analysis**

All quantitative variables are summarized as mean ± standard deviation (SD). The treatment effects during phase III were compared with phase II values using paired t-tests (two-sided). A p-value <0.05 was considered statistically significant. Statistical analysis was performed using SPSS 16.0 software (SPSS Inc, Chicago, IL).

## Results

### *Phase I: Baseline Characteristics*

We attempted to transition 7 subjects who had received treatment with PGI<sub>2</sub> [treprostinil (n=2) and intravenous epoprostenol (n=5)] to the combination oral therapy. These subjects experienced severe symptomatic PAH as indicated by assessment hemodynamic parameters and NYHA FC III or IV prior to initiation of PGI<sub>2</sub> treatment (table 1). Subject demographics, etiology of PAH, and type of PGI<sub>2</sub> infusion are depicted in Table 2. Subjects included idiopathic pulmonary arterial hypertension (IPAH), anorexigenic PAH, PAH concurrent with atrial septal defect and systemic lupus erythematosus which accounted for 43%, 29%, 14%, and 14% of this group, respectively.

### *Phase II: Transition*

All seven patients (F:M 5:2; age 42.0 ± 8.2 years) were successfully transitioned to oral therapy. In Table 2, depicted are: type of combination oral regimen, duration of “overlap” with oral therapy prior to discontinuation of PGI<sub>2</sub> infusion, and individual doses for Sildenafil administered as a *t.i.d.* schedule. At the time of initial PGI<sub>2</sub> dose reduction, 29% and 57% of patients were in FC I and II, respectively (figure 1). One of the patients was transitioned despite NYHA FC III symptoms, at patient’s insistence due to recurrent catheter-related sepsis. At the time PGI<sub>2</sub> was discontinued, each patient either maintained or improved their respective FC as 43% and 57% of patients were FC I and II, respectively.

### *Phase III: Follow-up data*

Total follow-up time was 41.3±17.3 months for this group of subjects. Of the seven subjects, one (female; age 35) experienced clinical worsening subsequent to oral transition. This subject required “rescue” therapy with subcutaneous treprostinil and returned to “active listing” for lung transplantation, 5 mos post-transition. At 23 mos post-transition, the patient succumbed to acute renal failure and sepsis without transplantation.

NYHA FC was maintained in six subjects during “clinical surveillance” subsequent to transition (figure 1). During phase III, the patients maintained stable or increase in median 6MWD when compared to distances achieved during phase II (420 versus 405 meters, respectively; *p*<0.05) (figure 2). The median BNP decreased insignificantly (*p*<0.05) by 3 pg/mL during phase III when compared to phase II (figure 3).

**Table 1 Clinical data and hemodynamics at baseline**

| Patient No. | NYHA baseline   | mCI baseline | mRA baseline | mPAP baseline |
|-------------|-----------------|--------------|--------------|---------------|
| 1           | III             | 2.3          | 12           | 66            |
| 2           | III             | 2.1          | 12           | 59            |
| 3           | IV              | 16           | NA           | 60            |
| 4           | IV              | 2.6          | 14           | 40            |
| 5           | III             | NA           | NA           | NA            |
| 6           | III             | NA           | NA           | NA            |
| 7           | IV              | 1.3          | 20           | 47.5          |
| Mean±SD     | III 57%, IV 43% |              | 5.6±6.9      | 14.5±3.8      |
|             |                 |              |              | 54.5±10.5     |

Abbreviations: baseline: values at the time of original diagnosis of PAH; NYHA: New York Heart Association functional class; mCI: mean cardiac index (L/min/m<sup>2</sup>); mRA: mean right atrium pressure (mmHg); mPAP: mean pulmonary artery pressure (mmHg); PCW: pulmonary capillary wedge pressure (mmHg); and NA: not available.

**Table 2 Demographics and PAH targeted therapy during Phase I and II.**

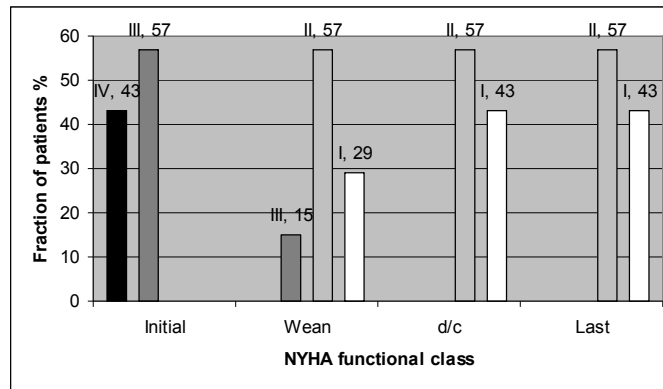
| Patient No.    | Age       | Sex     | Diagnosis | Drug d/c | PgI2 (mo)* | Max PgI2 dose | p.o. Tx | Sildenafil Dose (t.i.d.) | Oral tx <sup>†</sup> (mo) |
|----------------|-----------|---------|-----------|----------|------------|---------------|---------|--------------------------|---------------------------|
| 1              | 32        | F       | IPAH      | EPO      | 5          | 4.5           | S+B+I   | 25                       | 3                         |
| 2              | 41        | M       | IPAH      | EPO      | 17         | 18.5          | S+B     | 20                       | 14                        |
| 3              | 57        | F       | Diet      | EPO      | 18         | 10.5          | S+B     | 50                       | 6                         |
| 4 <sup>‡</sup> | 45        | F       | ASD       | TREP     | 19         | 34            | S+B     | 50                       | 9                         |
| 5              | 39        | F       | SLE       | EPO      | 14         | 20            | S+B     | 50                       | 6                         |
| 6              | 45        | M       | IPAH      | TREP     | 18         | 28            | S+B     | 50                       | 6                         |
| 7              | 35        | F       | Diet      | EPO      | 20         | 15            | S+B     | 40                       | 5                         |
| Mean±SD        | 42.0±9.8  |         |           |          |            |               |         | 15.9±5.1                 | 18.6±10.0                 |
|                | 40.7±13.0 | 7.0±3.6 |           |          |            |               |         |                          |                           |

Abbreviations: PGI2: prostanoid analogues; mo: months; p.o.: per mouth; Tx: treatment; F: female; M: male; EPO: epoprostenol ( ng/kg/min); TRE: treprostinil (ng/kg/min); S: sildenafil; B: bosentan; I: inhaled iloprost

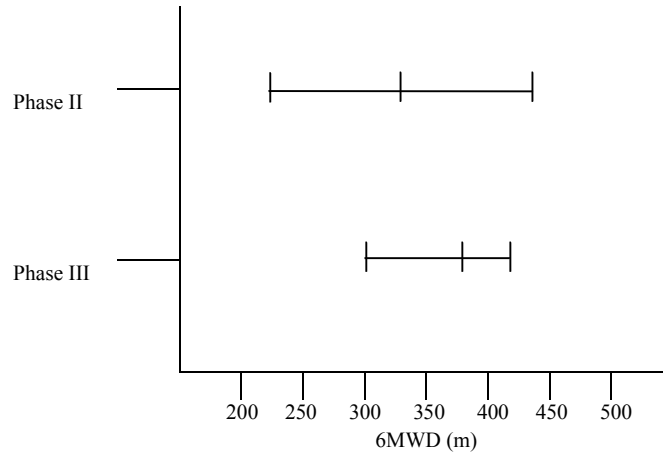
\* Total duration of prostanoid therapy prior to weaning

<sup>†</sup> Duration of oral treatment prior to discontinuation of parenteral prostanoids.

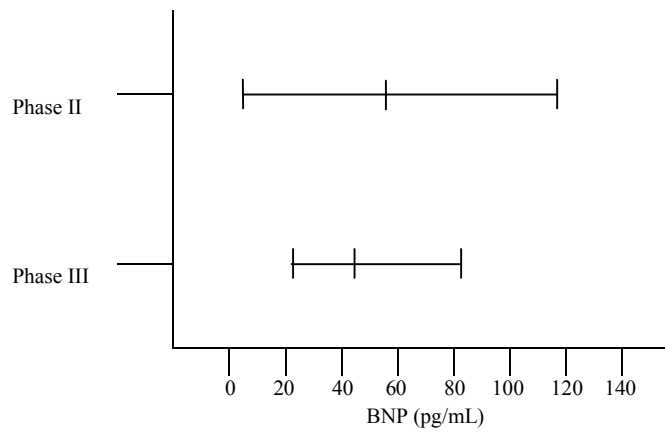
<sup>‡</sup> Patient had closure of patent foreman ovale (PFO) 12 months into PGI2 treatment.



**Figure 1:** New York Heart Association functional class (NYHA FC) at baseline (initial), weaning of PgI2



**Figure 2:** Six-Minute walk distance (6MWD) taken during Phase II (n=5) and Phase III (n=7). Data is presented as mean±5% CI.



**Figure 3:** B-type natriuretic peptide (BNP) taken during Phase II (n=5) and phase III (n=5). Data is presented as mean±95% CI.

## Discussion

In our pilot study, we have demonstrated successful transition of parenteral PGI<sub>2</sub> to a combination oral vasodilator therapy in six of seven subjects with initially severe symptomatic NYHA FC III-IV PAH. Most subjects had achieved functional improvement (i.e. baseline NYHA FC III-IV to I-II) with PGI<sub>2</sub> therapy prior to attempted transition. In addition, the mean duration of follow-up post-transition for our series was approximately 3.5 years; to our knowledge, the longest reported surveillance of subjects post-transition to oral therapy. Intriguing, the survival was 86% during the observation period, while the expected 1-yr, 2-yr, and 3-yr survival probabilities of these patients based on their baseline hemodynamic parameters were 86%, 80%, and 74%, respectively.<sup>10</sup> These observations suggest, therefore, that initial parenteral PGI<sub>2</sub> therapy with subsequent transition to a combination oral regimen, can be associated with a sustained physiologic response, potentially implicating a component of “reverse vascular modeling”.

The predictors for successful transition to oral therapies, have not yet been clarified. Prior clinical series have suggested “clinically stable” patients on PGI<sub>2</sub> therapy, NYHA FC I-II, and without evidence of right ventricular failure. However, variables such as: duration of PGI<sub>2</sub> therapy, duration of “overlapped” oral therapy prior to discontinuation of PGI<sub>2</sub>, maximum achieved PGI<sub>2</sub> dose and maximal 6MWD may further play a pivotal role in predicting success or failure in patient transition.

In our series, the duration of PGI<sub>2</sub> therapy prior to weaning was 15.9±5.1 mos. Steiner et al.<sup>4</sup> reported that a longer duration of PGI<sub>2</sub> therapy predicted transition success. Together, these results may suggest that a prolonged duration of PGI<sub>2</sub> therapy may be beneficial in allowing for “vascular reverse modeling” and hence transition to an oral regimen. Casterlain, et al. have demonstrated improvement in pressure-flow relationships of the pulmonary circulation during six weeks of PGI<sub>2</sub> therapy in IPAH.<sup>11</sup> Further, acute vasodilator response is NOT a predictor of long term response to epoprostenol, thereby suggesting a component of vascular reverse-remodeling with chronic therapy.<sup>12</sup> In contrast, Suleman et al.<sup>5</sup>, has reported that a longer duration of PGI<sub>2</sub> therapy was associated with increased risk of failure in patients being weaned off of PGI<sub>2</sub> therapy. These apparent conflicting observations may reflect differences in severity of disease between the patient groups. The duration of oral therapy “overlapping” with PGI<sub>2</sub> has varied among the available clinical reports. A small series by Kim et al.<sup>13</sup> with an average duration of 10 months for oral therapy prior to discontinuation, suggested that a longer duration was associated with higher likelihood for transitioning success. However, we as well as Johnson et al.<sup>6</sup> report success associated with an average of 7 and 4.5 months, respectively. Therefore, as with duration of PGI<sub>2</sub> therapy prior to weaning, the appropriate duration of oral therapy before transition is yet to be determined.

In preceding studies it has been suggested that an association between a lower mean PGI<sub>2</sub> dose and higher transition success was reflective of less severe disease.<sup>4,5</sup> Our study may corroborate this proposal as our maximal achieved PGI<sub>2</sub> dosage was 18.6 ng/kg/min prior to transition, while those in other studies ranged from 18-40.5 ng/kg/min. Another marker linked with pre and post transition success is 6MWD. Sitbon et al.<sup>14</sup> has reported that patients who achieved 6MWD of >380m 3 months on PGI<sub>2</sub> treatment, had a significantly better long-term survival than patients who did not reach this threshold. Although the mean 6MWD achieved by patients during phase II of our study was 347m, patients nevertheless experienced improved long-term survival compared with the NHLBI NIH Registry.<sup>10</sup> Also during phase III of our review, the mean 6MWD had achieved 405m. Similar to our series, the two studies with the highest success rate were associated with mean 6MWD of >400m.<sup>6,8</sup>

Pharmacokinetic steady-state combination of bosentan with sildenafil have significant effects on C<sub>max</sub> and AUC for drug concentration. Sildenafil effectuates a 42% increase in C<sub>max</sub> and 49.8% increase in AUC for bosentan concentration. Inversely, bosentan effects a 55.4% DECREASE in C<sub>max</sub> and 62.6% DECREASE in AUC for sildenafil pharmacokinetics.<sup>15</sup> The combination of bosentan and sildenafil in our experiences, was well tolerated and no patient required discontinuation of bosentan due to aminotransferase elevation (>3x ULN).

Clearly, this retrospective report has several inherent limitations and biases. Selection bias is likely since our patient population consisted of a cohort of subjects with severe and symptomatic PAH

who were judged to require initial Pgl<sub>2</sub> therapy and then subsequently requested transition to an oral regimen, despite our recommendations to the contrary. The rather small number of subjects studied in this context, have been a continued dilemma from our and previous reports. Our analysis is potentially also limited by virtue of a lack of invasive hemodynamic data prior to Pgl<sub>2</sub> transition, with reliance on noninvasive clinical measures alone. We speculate that further investigation with serial right heart catheterization data may serve to elucidate patients at risk for deterioration during attempted transition to an oral regimen. During our retrospective review, we were unable to identify risk factors for the observed deterioration in subject #7, based on our serial monitoring of BNP and 6MWD. At the end of Phase II the BNP was approximately 100 pg/mL while the subject had achieved 6MWD of 450 meters, thereby suggesting “clinical stability”. With these factors in mind, it is unclear if this patient would have deteriorated regardless of the transitioning protocol.

In conclusion, our experience suggests that selected patients with severe symptomatic NYHA FC III or IV PAH may ultimately be safely transitioned from long-term parenteral prostanoid infusion to a combination oral vasodilator regimen with bosentan and sildenafil. Despite this assertion, many questions yet remain. Firstly, would invasive hemodynamic measurements, both at “baseline” and subsequent to prolonged Pgl<sub>2</sub> therapy, identify patients at risk for hemodynamic and right ventricular decompensation? Secondly, what is the optimal oral or possibly, inhalational vasodilator regimen for transition? Thirdly, is there a difference in perceived “quality of life” measures for parenteral Pgl<sub>2</sub> versus an oral vasodilator regimen? Finally, should a randomized multi-center trial of pharmacologic transition therapy in PAH be further considered in order to elucidate the efficacy, safety and subgroup characteristics for this strategy?

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