Intravenous Treatment (Three Times a Week) with PBI-Compound Corrects Anemia, and Reduces Kidney and Heart Fibrosis in 5/6-Nephrectomized (NX) Rats

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#SU438

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Introduction and Aim

PBI-Compound is a first-in-class novel orally active molecule that promotes the production of erythrocytes by a mechanism of action distinct from erythropoietin (EPO). This mechanism involves differentiation of earlier progenitor stem cells (CFU-GEMM) than those stimulated by EPO (BFU-E, CFU-E). Furthermore, PBI-Compound induces sufficient erythropoiesis to raise the red blood cell (RBC) level and hemoglobin (Hb) in chemotherapy-induced anemia (CIA) patients, resulting in the reduction of blood transfusion.

The aim of this study was to determine the effect of PBI-Compound on RBC and Hb levels in 5/6-nephrectomized (NX) rats, a model of chronic kidney disease/end-stage renal disease.

Methods

Six-week old Sprague-Dawley rats were subjected to 5/6-NX or sham operations. Two-thirds of the left kidney was removed on day 0, followed by the removal of the right kidney on day 7. A catheter was implanted via the femoral vein on day 7. Sham operated rats underwent exposition of the kidneys and removal of the perirenal fat, were treated with vehicle, and used as controls. On day 21, rats were randomized based on glomerular filtration rate (GFR) results, and treated with an intravenous administration (three times a week) of saline or PBI-Compound (10 or 30 mg/kg). Animals were treated from day 21 to 104 and were sacrificed on day 105.

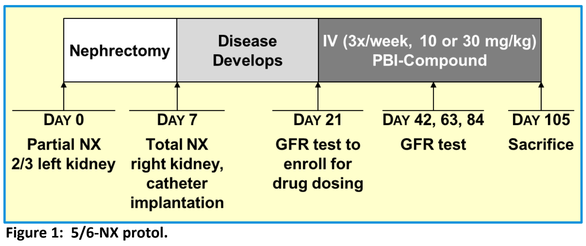

Figure 1: 5/6-NX protol.

Results

A. IV administration (30 mg/kg, TIW) of PBI-Compound corrects anemia

The anemia induced by the 5/6-NX (red line) slightly increased the reticulocyte counts. Intravenous administration of PBI-Compound (30 mg/kg) (blue line) induced a significant increase of reticulocyte counts from day 28 to day 56, followed by a return to reticulocyte count values observed in the untreated animals.

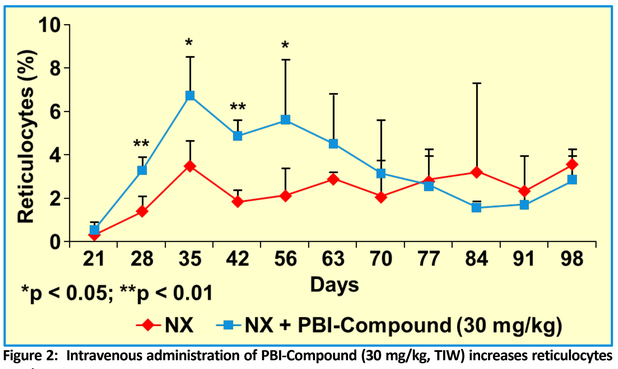

Figure 2: Intravenous administration of PBI-Compound (30 mg/kg, TIW) increases reticulocytes in 5/6-NX rats.

While RBC count decreased drastically in 5/6-NX rats from day 35 to day 42 and remained at a low level for the remaining of the experiment, intravenous treatment with 30 mg/kg of PBI-Compound maintained a relatively stable level of RBC counts throughout the period of treatment. It is interesting to note that changes in RBC counts appeared subsequently to the increase of reticulocyte counts.

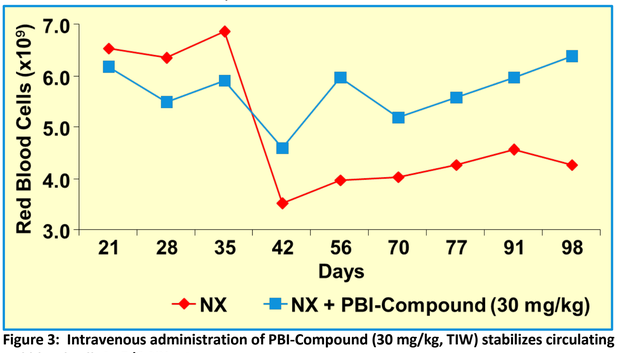

Figure 3: Intravenous administration of PBI-Compound (30 mg/kg, TIW) stabilizes circulating red blood cells in 5/6-NX rats.

Rats randomized to the PBI-Compound-treated group were more anemic (lower Hb and RBC) than those included to the control nephrectomized group. However, treatment with intravenous administration of PBI-Compound resulted in an increase of Hb from day 70 to day 98 compared to control (between 1.4 and 1.6 g/dl).

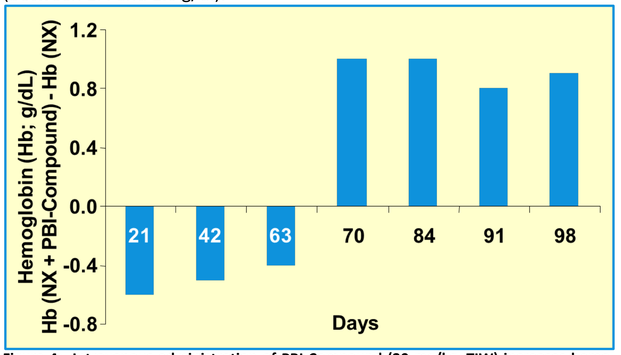

Figure 4: Intravenous administration of PBI-Compound (30 mg/kg, TIW) increases hemoglobin level.

B. IV administration (10 mg/kg) of PBI-Compound reduces fibrosis kidney

Histological examination of the remaining renal tissue from 5/6-NX animals revealed interesting differences. Kidneys from PBI-Compound-treated animals showed a significant reduction of interstitial and glomerular fibrosis/sclerosis (HPE and Masson's Trichrome staining).

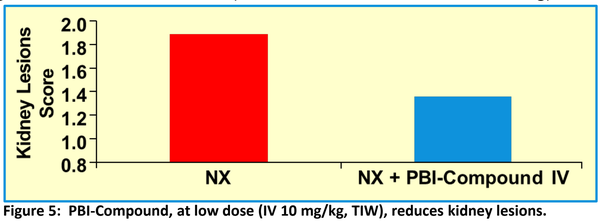

Figure 5: PBI-Compound, at low dose (IV 10 mg/kg, TIW), reduces kidney lesions.

The mRNA expression of the key mediator of fibrosis Connective Tissue Growth Factor (CTGF) was reduced in the remnant kidney of PBI-Compound-treated rats compared to 5/6-NX controls.

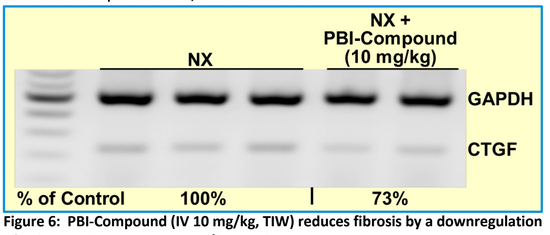

Figure 6: PBI-Compound (IV 10 mg/kg, TIW) reduces fibrosis by a downregulation of kidney CTGF expression in 5/6-NX rats.

C. IV administration (10 mg/kg) of PBI-Compound reduces heart fibrosis

Photomicrographs of heart from PBI-Compound-treated animal showed a significant reduction of interstitial fibrosis by reduction of collagen deposition (Masson's Trichrome staining). IV administration of PBI-Compound reduces total lesions score (inflammation, necrosis and collagen deposition) in the heart at day 105.

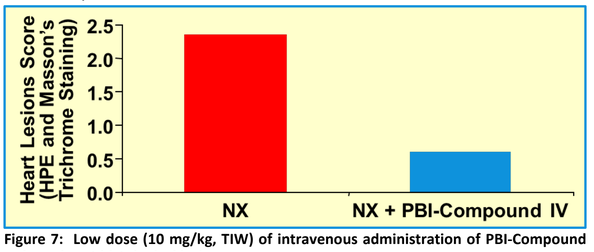

Figure 7: Low dose (10 mg/kg, TIW) of intravenous administration of PBI-Compound reduces heart histological lesions.

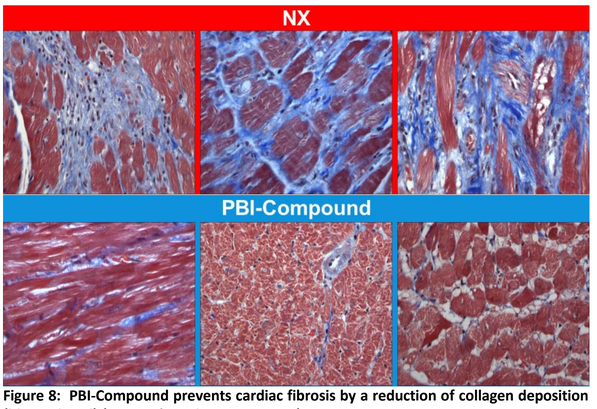

Figure 8: PBI-Compound prevents cardiac fibrosis by a reduction of collagen deposition (blue-colored) (Masson's trichrome staining).

Conclusions

PBI-Compound offers the potential as a novel therapy by correcting anemia, and preventing or reducing kidney and heart fibrosis.

Anemia	Heart and Kidney Fibrosis
Correction of anemia at 30 mg/kg (IV, TIW)	Anti-fibrotic activity achieved at 10 mg/kg (IV, TIW)