LETTER TO THE EDITOR

Type VI Osteogenesis imperfecta: effect of plasma transfusion on bone metabolism

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To the Editor,

Osteogenesis imperfecta (OI) is a phenotypically and genetically heterogeneous group of inherited bone dysplasias characterized mainly by bone fragility and deformity (1). Of the various OI types, autosomal recessive-type VI OI (OMIM 613982) (2) has peculiar clinical and histological features. Neonates appear normal at birth, but they start fractures within 6 to 12 months of age, followed by severe, progressive deforming bone dysplasia, vertebral compressions and scoliosis, losing the ability to walk autonomously. Type VI OI is caused by homozygous or compounds heterozygous null mutations in the SERPINF1 gene (OMIM 172860), coding for pigment-epithelium derived factor (PEDF), a 418-amino acid secreted glycoprotein expressed in several tissues including osteoblasts (3, 4), well-known for its neurotrophic and antiangiogenic properties.

Patients with type VI OI have undetectable levels of serum PEDF (5) and show a weaker response to "standard" treatment with bisphosphonates (6). For this reason, it would be helpful to search for more effective treatment modalities, but replacement therapy using recombinant PEDF and/or mesenchymal stem cell therapy is currently not possible.

The observation that all null SERPINF1 mutant patients appear healthy at birth and do not have fractures until after 6 months of age may suggest a protective effect of circulating maternal PEDF during fetal development due to hypothetical placental passage which would persist in the first months of life. Moreover, unaffected heterozygotes parents, clinically asymptomatic, have PEDF circulating levels of about 1 μg/mL (4), which is lower than normal concentrations of about 5-10 μg/mL but enough for normal bone metabolism/development and a healthy status (7).

Keywords: osteogenesis imperfecta; PEDF; bone metabolism; bisphosphonates; plasma transfusion

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DISCLOSURE: ALL AUTHORS REPORT NO CONFLICTS OF INTEREST RELEVANT TO THIS ARTICLE.

The aim of this study on patients with type VI OI was to evaluate the efficacy and safety of PEDF administration using pharmaceutical grade plasma to provide a minimum amount of PEDF similar to the levels found in heterozygotes.

MATERIALS AND METHODS

The study was carried out at Pediatric Clinic C, University of Verona Medical School, a third level Paediatric Center for the Study of Rare Skeletal Diseases, partner of the European Reference Network for Rare Bone Disorders (ERN-BOND). The study protocol was approved by the local Ethics Committee (PEDFOI: Prog. n. 633CESC).

Inclusion criteria were children between 1- and 18-years-of-age with genetically and biochemically confirmed type VI OI. Exclusion criteria were previous transfusion adverse events. Informed written consent to participate in the study was obtained from each patient's family or guardians.

Ten patients aged 1-18 years were eligible to participate in the study. Clinical history was recorded with particular attention to the number of fractures, height or length in cm, weight in kg and body mass index (BMI = kg/m2). Height and weight SD values were calculated according to Italian growth charts. All subjects had already undergone several treatment periods using bisphosphonates (neridronate), with results lower than expected. All 10 patients were given vitamin D and calcium supplements for almost one year before participating in the study.

After being selected for inclusion, one patient (OI 63 - bedridden) declined to participate in the study protocol due to the clinical impossibility to be moved (to avoid fractures) because the family lived approximately 700 km from the hospital. Two other patients (OI 122 and OI 123 – 2 brothers) declined because of family financial difficulties (despite the possibility of financial support from the *Associazione Italiana Osteogenesis Imperfecta* - AsItOI). Three patients (OI 93, OI 94 and OI 162 – 3 sisters) did not continue

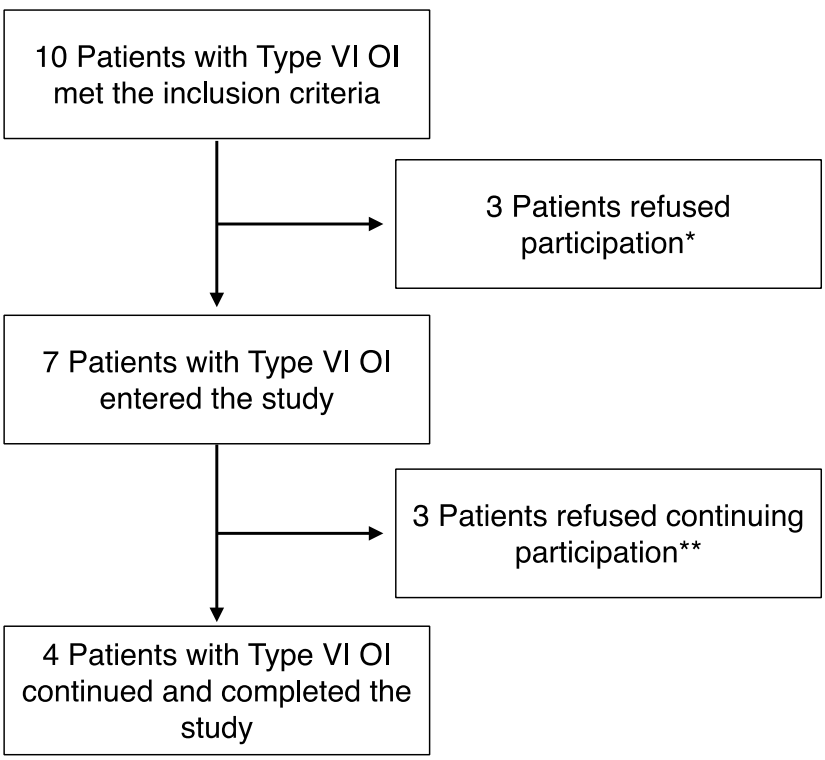

Fig.1. *Trial profile.*
**Patients refused participation: OI 63 for the clinical impossibility to be transported; OI 122 and OI 123 for the impossibility of parents to participate in the study due to work problems and economic difficulties (even if there was the possibility of financial support).*
*** Patients did not continue treatment after the first plasma transfusion due to problems with non-acceptance of transfusions and their frequency: OI 93, OI 94 and OI 162.*

their treatment after the first plasma transfusion because of family ethical problems in accepting transfusions and their frequency. Of the initial 10 patients, only four completed the study. Fig. 1 shows the study profile.

Once included in the study, pharmaceutical-grade plasma (Plasmasafe) (12-15 mL/Kg) was administered e.v. over 3 hours. Plasma used for the treatment came from the same production batch, and the PEDF content was measured before each transfusion (9.95 ± 2.2 μg/mL). The quantity per kg was empirically calculated to reach the theoretical concentration of about 1 μg/mL of PEDF in plasma patients. Plasma transfusions were repeated every month for 6 months with the same procedure giving the same plasma dose. The timetable of the study protocol is shown in Fig. 2.

Any plasma transfusion adverse events, such as hemodynamic overload, allergic-type transfusion reactions or non-haemolytic febrile reactions, were carefully evaluated. Vital signs before, during, and at the end of each transfusion session and in the first three hours immediately following were recorded. In addition, before the first plasma infusion and six months after the last plasma infusion, we determined antibody title, ran a nucleic acid test for hepatitis B virus (HBV), hepatitis C virus (HCV), tested for human immunodeficiency virus (HIV) and antibody title for syphilis in order to exclude potential transmission of infectious disease.

Biochemical and instrumental determinations

At baseline (T0), before each plasma transfusion (T4, before second plasma infusion, T5 - 3rd, T6 - 4th, T7 - 5th, T8 - 6th and T9 - 7th), and 6 months after the last plasma transfusion (T10), PEDF, bone metabolic markers [Ca, P, 25-OH VitaminD, PTH, bone alkaline phosphatase (bone ALP), osteocalcin (Oc), procollagen type 1 N-terminal propeptide (P1NP), dickkopf-1 (DKK1), sclerostin, C-terminal telopeptides of type I collagen (β CTX)], iron and ferritin were determined in serum or plasma; Ca and creatinine were measured in urine. PEDF determination was also repeated after 1 (T1), 2 (T2) and 7 days (T3) of first plasma administration to see the effective increase in the patients' bloodstream establish half-lives and record-level changes over time. At those same times, we also assayed DKK1, sclerostin and P1NP to evaluate the short-term response to PEDF, if present.

All samples were frozen immediately after collection and stored at -30°C until analysis. At baseline and after 12 months, bone mineral density was measured, and fracture rate was checked. In addition, serum Ca and P, iron and ferritin values and urinary Ca and creatinine values were determined using standard techniques.

Serum 25OH Vitamin D, intact 1–84 PTH, bone ALP and Oc were determined using a LIAISON analyzer and commercial methods (DiaSorin Inc, Stillwater, MN, USA): 25 OH Vitamin D total assay (intra- and interassay CV 5.1% and 5.8%, respectively; analytical sensitivity 10 nmol/L), 1-84 PTH assay (3.6% and 4.7%; 0.5 pg/mL), BAP OSTASE assay (4.6% and 6.1%, 1.5 μg/L), osteocalcin assay (5.0 and 6.0%; 0.5 ng/mL).

Serum intact N-propeptide of type I collagen (P1NP)

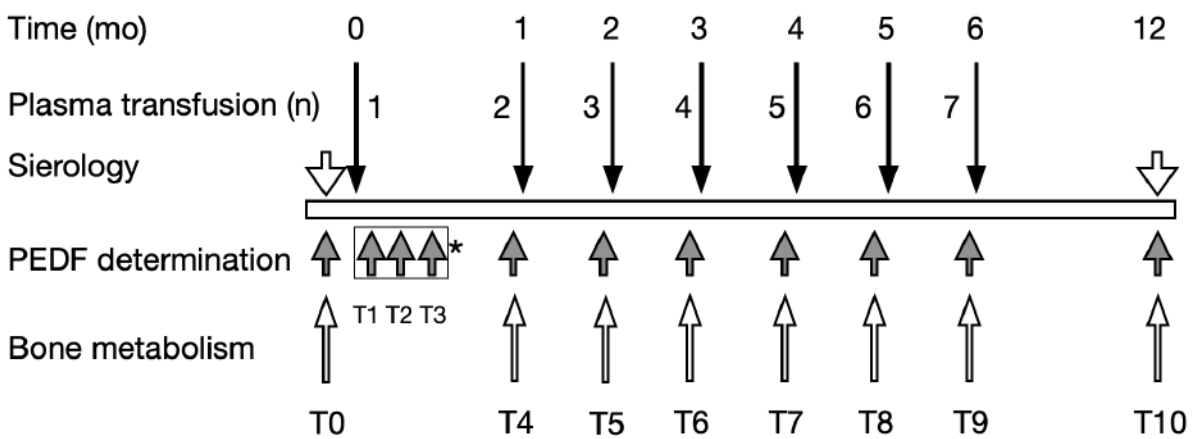

Fig. 2. *Study protocol timetable and flow chart. PEDF determination: 1, 2 and 7 days after first plasma transfusion.*

was measured using the IDS-ISYS Multi-Discipline automated analyzer (Immunodiagnostic System, Boldon, UK) based on chemiluminescence immunoassay (CLIA): intra- and interassay CVs were 4% and 5%, respectively, and analytical sensitivity was 2 ng/mL.

Serum DKK1 and sclerostin were measured by ELISA (Biomedica Medizinprodukte, Vienna, Austria); for DKK1 intra- and interassay CV were 7% and 8.2% respectively, analytical sensitivity was 0.38 pmol/L; for sclerostin, intra- and interassay CV were 5% and 6.9%, respectively, analytical sensitivity was 2.6 pmol/L.

Serum β-CTx was determined using electrochemiluminescence immunoassay (ECLIA): β-CrossLaps/serum (Roche Diagnostics GmbH, Mannheim, Germany). The intrassay and interassay coefficients of variation were 2.1% and 3.2 %, respectively; the analytical sensitivity of the assay was 0.07 ng/mL.

Circulating PEDF levels were measured with the *Human* PEDF ELISA Kit (BioVendor-Laboratornì medicìna a.s, Czech Republic) following the manufacturer's instructions. The intra- and interassay CVs were 4.0% and 6.6%, respectively; analytical sensitivity was 0.045 µg/mL.

Dual-energy x-ray absorptiometry (DXA)

Lumbar spine bone mineral density (BMD) (g/cm^2) was evaluated using Dual Energy X-ray Absorptiometry (DXA) (Hologic Discovery A, Hologic Inc., Waltham, MA, USA). The quality scan was assessed according to a strict quality control procedure. Instruments were calibrated daily with local spine phantom and periodically with a cross-calibration phantom. The values were expressed in g/cm^2 and Z-score (number of standard deviations compared to normal subjects of the same age and gender).

Statistical analysis

The data are expressed as mean ± standard deviation (SD). Due to the low number of type VI OI study patients, data are expressed as differences in SDs. T-tests were conducted to establish differences in plasma and biochemical markers. Statistical significance was set at $p<0.05$. The data were analyzed using the SAS program (SAS Institute Inc., Cary, NC, USA).

RESULTS

Anthropometric and clinical findings at baseline in all the type VI OI patients studied are presented in Table I. Parental consanguinity and homozygosity were found in 7 of 10 patients. Only in one homozygosity patient (OI63), there was no information on parental consanguinity. There was compound heterozygosity and non-consanguinity in 2 patients.

Anthropometric and clinical findings showed that the disease varies in severity, growth impairment,

Table I. *Genetic, Anthropometric and Clinical findings in patients affected by type VI OI at the beginning of the study (n = 10)*

Patient Id	OI 389	OI 60	OI 298	OI 343	OI 93	OI 94	OI 162	OI 122	OI 123	OI 63
Origin (Country)	Italy	Italy	Pakistan	Pakistan	Switzerland	Switzerland	Switzerland	Morocco	Morocco	Italy
Consanguinity between parents	no	no	yes	yes	yes	yes	yes	yes	yes	no
Mode of inheritance:	Compound hetero-zygosity	Compound hetero-zygosity	Homo-zygosity	Homo-zygosity	Homo-zygosity	Homo-zygosity	Homo-zygosity	Homo-zygosity	Homo-zygosity	Homo-zygosity
Gender	M	M	F	F	F	F	F	F	M	M
age (yrs)	14.8	13.2	12.4	5.4	16.3	11.6	8.5	14.4	12.4	17.5
Weight kg (SDS)	42.0 (-2.0)	35.0 (-1.9)	34.0 (-4.7)	15.6 (-1.8)	61.0 (-0.5)	25.0 (-2.7)	18.8 (-2.6)	32.1 (-3.4)	30.0 (-2.2)	39.2 (-5.2)
Length cm (SDS)	152.0 (-2.1)	132.0 (-3.4)	116.0 (-5.4)	105.0 (-1.5)	143.0 (-4.1)	118.0 (-4.5)	119.5 (-1.8)	136.0 (-3.7)	132.0 (-2.9)	140.0 (-5.8)
BMI kg/m^2 (SDS)	18.2 (-1.1)	20.1 (-0.1)	25.3 (1.3)	14.2 (-1.1)	29.8 (1.9)	17.9 (-0.5)	13.2 (-2.4)	17.3 (-1.5)	17.2 (-0.9)	19.9 (-0.9)
Age of first fracture (yrs)	6.1	1.2	1.1	0.9	0.8	0.5	1.0	1.2	0.8	0.5
Total n. of fractures	15	>30	24	6	>30	16	26	23	18	>30
Lumbar spine BMD (SDS)	-2.2	-4.1	-1.1	-3.5	-0.5	-1.9	-3.2	ND°	-3.0	-3.5
Walking capacity	Yes crutches	No wheelchair	No wheelchair	Yes crutches	No wheelchair	No wheelchair	Yes crutches	Yes crutches	Yes crutches	No bedridden

Patients OI 298 and OI 343 were two sisters; Patients OI 93, OI 94 and V4 were three sisters; Patients OI 122 and OI 123 were brothers. Gender: M = male; F = Female; SDS: Standard deviation score; Weight and length SDS values were calculated with respect to Italian growth charts (see text). Lumbar Spine BMD: Lumbar Spine Bone Mineral Density °ND: not detectable for vertebral arthrodesis

number of fractures and BMD. Fractures started a few months after birth, with a clear correlation between earlier age of presentation and clinical severity.

Only patient OI 389 (compound heterozygosity) showed a milder phenotype with fractures starting at 6 years. However, walking capacity was reduced in all patients and five were confined to a wheelchair (in 1 of them bedridden).

BMD varied according to vertebrae meshing and degree of scoliosis. Kyphoscoliosis was present in all patients, particularly in patient OI 122, where the lumbar spine BMD could not be evaluated due to vertebral arthrodesis. All patients had white sclerae, with no characteristic facies of typical OI.

Table II shows biochemical findings at baseline in our type VI OI patients. Bone metabolic markers showed high bone ALP, P1NP and β CTx with normal levels of osteocalcin, sclerostin and DKK1.

All patients had taken vitamin D and calcium supplements before the study and had normal levels of 25 OH vitamin D (>75 nmol/L). They continued calcium and vitamin D supplementation during the study (almost 1000 UI per day) and showed normal levels of 25 OH vitamin D, Ca, P and Ca/creatinine ratio in urine during the entire study period. In addition, all patients had an age-appropriate calcium intake in agreement with recommended daily allowances.

Interestingly, all patients showed low ferritin levels before and during the study, despite iron supplementation. In every case, faecal occult blood was negative, Giardia lamblia infestation and celiac disease were excluded. In a few cases, we found microcytic anaemia (OI 298, OI 343, OI 122, OI 123 and OI 63).

Plasma infusion

PEDF determinations before (T0), and at 1 (T1), 2 (T2) and 7 days (T3) after the first plasma infusion (in 5 out of 7 patients that received the first infusion), showed an increase from <0.045 μg/mL before the infusion to 1.36 ± 0.27 μg/mL at day 1, returning to <0.045 from day 2 onwards. In addition, we found a significant decrease in DKK1 ($p=0.05$) and a non-significant increase in P1NP levels the day after the first transfusion (T1), with a rapid return to previous levels in the following days. PEDF, P1NP, DKK1 and sclerostin levels at these times are shown in Fig. 3.

Table III shows the biochemical findings in the 4 type VI OI patients that completed the study. Bone metabolic markers persistently showed high bone ALP, P1NP and β CTx with normal levels of osteocalcin, sclerostin and DKK1. Biochemical markers of bone turnover, BMD and fracture rate did not significantly change during the study.

Adverse events

Only one patient (OI 298) had an urticarial reaction after the first transfusion, which resolved with an antihistamine. For subsequent transfusions, this patient required prior antihistamine medication. In all patients, there was a moderate improvement in asthenia.

DISCUSSION

Our hypothesis that a small increase in circulating

Table II. *Biochemical findings in patients with type VI OI at baseline (n = 10)*

Patient Id	OI 389	OI 60	OI 298	OI 343	OI 93	OI 94	OI 162	OI 122	OI 123	OI 63	M ± SD
PTH pg/mL	11.2	5.8	13.9	5.2	14.2	6.4	8.6	9.3	10.7	7.6	9.3 ± 3.2
Bone ALP μg/L	87.3	102.8	84.1	144.5	17.2	38.0	52.9	81.3	76.3	97.3	78.1 ± 35.6
Oc nmol/L	8.3	5.9	7.7	9.1	7.1	7.6	8.5	7.8	8.8	6.9	7.8 ± 0.9
P1NP ng/mL	238	482	217	631	137	221	260				312 ± 176*
DKK1 pmol/L	23.5	19.7	22.0	26.2	16.3	34.8	23.8				23.7 ± 5.8*
Sclerostin pmol/L	28.0	24.9	40.3	14.5	25.4	25.6	16.1				25.0 ± 9.3*
β CTx ng/mL	0.62	0.66	0.65	1.12	0.38	0.95	0.79	0.88	0.98	0.45	0.75 ± 0.24
Iron μmol/L	16.0	9.2	7.1	6.4	17.9	8.9	12.9	8.7	11.5	9.4	10.7 ± 3.8
Ferritin pmol/L	65.2	44.9	33.7	11.2	112.3	67.4	78.6	47.2	38.2	22.5	52.1 ± 23.6

**7 patients*

PEDF levels might correct the bone phenotype in OI type VI proved incorrect, at least in the ways we supposed. PEDF levels did increase as desired but returned immediately to undetectable values and consequently, bone metabolism markers and BMD did not change during the treatment period.

We could speculate that more frequent infusions over time with greater quantities of plasma or daily administration of PEDF could achieve better results. However, the only effect found was a significant decrease in DKK1 and a non-significant increase in P1NP levels the day after the first transfusion. This DKK1 behaviour could clarify the relationship between PEDF and the Wnt/β-catenin signalling pathway (8). However, besides the lack of persistence over time of circulating levels of PEDF, the action time in the early differentiation phase of osteoblast and skeletal development may be important. We can hypothesize that small quantities may be sufficient to get an action in the early stages of life (i.e., in the fetal/neonatal period), but not in later stages (9). Finally, bioavailability could be another essential factor and the action rather than endocrine could be paracrine or autocrine. The PEDF action mode is still unclear. In vitro, the addition to the culture medium does not always result in the desired effects, and in animal models, exogenous PEDF given to Serpinf1 $^{-/-}$ mice gave rise to different outcomes (10, 11).

The main limitation of our study is the small number of patients that completed it; this was because type VI OI is an extremely rare disease and the number of patients, which was sufficient at the time

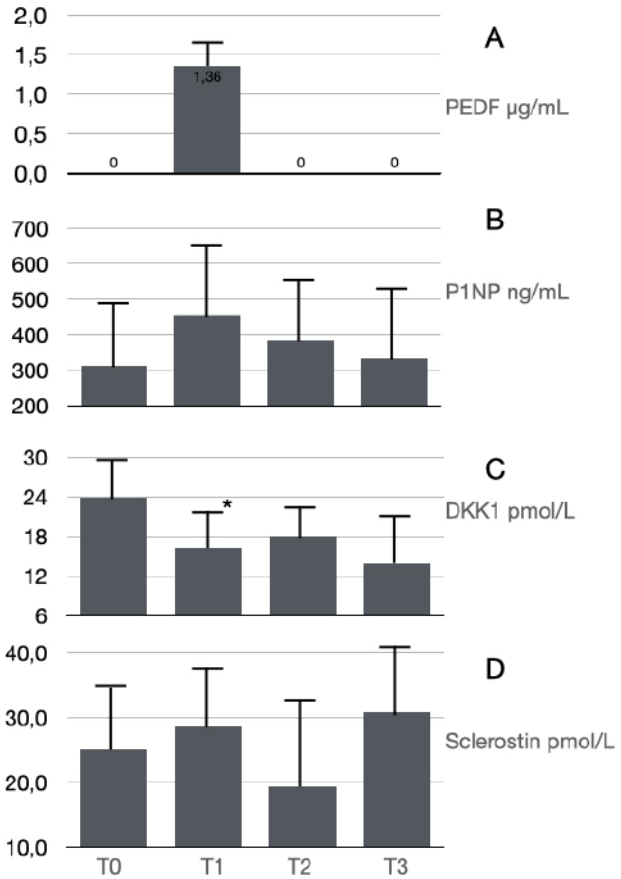

Fig. 3. *Biochemical determinations before, 1, 2 and 7 days after the first plasma infusion in 5 patients. **A)** PEDF µg/mL; **B)** P1NP ng/mL; **C)** DKK1 pmol/L; **D)** Sclerostin pmol/L. T0: before the 1st plasma infusion; T1: 1 day after the 1st plasma infusion; T2: 2 days after the 1st plasma infusion; T3: 7 days after the 1st plasma infusion.*
**Significantly decreased (p = 0.05) respect to T0.*

Table III. *Biochemical findings in the 4 Patients with type VI OI who completed the study (M ± SD)*

	T0	T4	T5	T6	T7	T8	T9	T10
PTH pg/mL	9.0 ± 4.2	11.1 ± 6.6	12.3 ± 4.8	11.7 ± 4.7	11.5 ± 6.0	13.4 ± 6.1	13.6 ± 6.7	13.8 ± 4.5
Bone ALP µg/L	104.5 ± 27.6	95.7 ± 13.8	106.7 ± 33.4	103.0 ± 32.4	104.7 ± 34.1	100.7 ± 36.0	125.0 ± 46.8	107.7 ± 51.8
Oc nmol/L	7.75 ± 1.36	9.83 ± 4.93	10.20 ± 3.65	10.55 ± 3.24	8.73 ± 3.27	8.90 ± 3.00	8.23 ± 3.58	10.50 ± 2.84
P1NP ng/mL	392 ± 199	374 ± 115	444 ± 177	378 ± 107	447 ± 164	357 ± 100	385 ± 126	406 ± 266
DKK1 pmol/L	22.9 ± 2.7	24.7 ± 1.9	19.3 ± 4.1	25.3 ± 10.5	22.6 ± 6.5	24.3 ± 9.7	25.8 ± 3.2	22.1 ± 4.2
Sclerostin pmol/L	27.6 ± 12.9	24.8 ± 12.9	23.9 ± 5.0	39.4 ± 19.4	22.7 ± 10.0	25.1 ± 10.7	21.5 ± 10.3	23.0 ± 16.6
β CTx ng/mL	0.76 ± 0.24	0.72 ± 0.15	0.87 ± 0.33	0.85 ± 0.28	0.84 ± 0.39	0.82 ± 0.34	0.72 ± 0.20	0.67 ± 0.19
Iron µmol/L	9.5 ± 4.5	11.2 ± 8.5	8.0 ± 2.9	9.5 ± 4.8	6.5 ± 3.9	5.7 ± 1.5	5.0 ± 1.8	9.5 ± 5.7
Ferritin pmol/L	38.8 ± 22.5	43.2 ± 35.2	38.8 ± 32.9	37.6 ± 20.7	41.0 ± 35.8	39.9 ± 28.1	29.2 ± 21.8	42.1 ± 35.7

T0: before the 1st plasma infusion; T4, before 2nd plasma infusion, T5 - 3rd, T6 - 4th, T7 - 5th, T8 - 6th, T9 - 7th; T10: 6 months after the last plasma transfusion.

of inclusion, subsequently declined due to various problems. In this regard, our small sample size limits the conclusions drawn from our results.

In conclusion, plasma infusion at the doses and intervals used in our study does not help modify bone metabolic markers and BMD in type VI OI patients. Replication of our study protocol in a multicenter with a larger number of subjects could be an option; however, further studies with other replacement therapy approaches or totipotent mesenchymal cell therapies are needed.

Conflict of interests:

The authors have no conflicts of interest to declare.

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