

IRON DEPLETION DYNAMICS AND SAFETY OF THERAPEUTIC ERYTHROCYTAPHERESIS VERSUS CONVENTIONAL PHLEBOTOMY IN PATIENTS WITH HAEMOCHROMATOSIS

P. Lodemann¹, G. Schorer¹, J. Ries², B.M. Frey¹

¹Blutspende Zurich, Rutistrasse 19, 8952 Schlieren, Switzerland; www.blutspendezuerich.ch

²Department of Transfusion Medicine, University Clinic Freiburg, Germany

BLUTSPENDE ZÜRICH
●●●●●

Background

Hereditary Haemochromatosis (HH, OMIM 235200) is one of the most common genetic disorders in the Caucasian population with a prevalence of 2-5 in 1000 but variable penetrance. Accumulation of iron leads to tissue damage with clinical symptoms mainly presenting in the 4th to 6th decade of life. Currently, therapeutic phlebotomy (TP) as the standard treatment to reduce iron load can prevent organ damage and, if treatment is done regularly and in asymptomatic individuals, life expectancy is normal. By TP, 450 to 500 mL of blood is removed weekly until the serum ferritin level is 10 to 20 µg/L, and maintained at <50 µg/L thereafter. Dependent on the geno- and phenotype, necessary TP frequency varies, and treatment schedule of weekly TP during 2-3 years maybe warranted. Therapeutic erythrocytapheresis (TE¹) removes up to 5fold more iron as compared to TP and became an alternative treatment option.

Methods

Included were patients with a new diagnosis of haemochromatosis. The treatment options (TP vs. TE) were applied after randomization and its efficacy was assessed prospectively. Parameters of iron metabolism from 5 patients depleted via TP (450ml whole blood) and 6 patients with TE (360ml Ec-concentrate, apheresis done on ALYX, Fenwal)^{4,5} where measured on each donation day until they reached the endpoint of ferritin (SF) <50µg/l. Parameters measured were: hemoglobin (Hb [g/dl]), Serum-Ferritin (SF [µg/l]), soluble Transferrinreceptor (sTfR [µg/l]), C-reactive Protein (CRP [mg/dl]) and GPT. Calculated from these were total Body Iron (TBI^{2,3}) and Ferritin-Index (= sTfR [mg/l] / log (SF [mg/l])). Tolerability and side effects were recorded using a standardized questionnaire and a rating system.

Results

Table 1: Enrolled Patients

	TE	TP
Patients (n)	6	5
Age (years)	50 (34-59)	45.4 (28-67)
male/female	6/0	4/1
Mutation	3 C282Y/C282Y 2 C282Y/H63D 1 H63D/wild	2 C282Y/C282Y 2 H63D/H63D 1 C282Y/S65C

Table 2: Patients Baseline Status study-entry

CRP was in normal range (data not shown)

	Hb [g/dl]	Ferritin [µg/l]	sTfR [mg/l]	B-iron [mg/kg]	Ferritin Index	GPT [U/l]
TE Pat. 1	15.3	758	1.03	18.8	0.94	49
TE Pat. 2	15.1	984	0.75	21.1	0.62	65
TE Pat. 3	14.3	1510	0.70	23.0	0.53	71
TE Pat. 4	15.2	1678	0.63	23.8	0.46	59
TE Pat. 5	17.2	1024	0.64	22.0	0.50	74
TE Pat. 6	16.4	613	2.46	18.4	0.88	115
TP Pat. 1	15.9	409	1.14	16.2	1.17	22
TP Pat. 2	16.5	222	1.20	13.7	1.38	64
TP Pat. 3	16.5	1280	1.56	19.0	1.40	108
TP Pat. 4	14.5	725	0.70	20.3	0.59	29
TP Pat. 5	16.6	364	2.05	17.2	0.80	28

Table 3: Average characteristics at study-entry and -endpoint Median (Range)

	TE (n=6)	TP (n=5)
Intervall between each donation (d)	14 (10-25)	14 (6-40)
Days till endpoint reached (Ferritin<50)	163 (55-258)	103 (50-257)
Number of phlebotomies at endpoint	11 (5-15)	8 (6-18)
Ferritin at entry [µg/l]	1004 (613-1678)	409 (222-1280)
Decrease of ferritin	103 (85-145)	38 (32-155)
Body iron at entry [mg/kg]	21.6 (18.4-23.8)	17.2 (13.7-20.3)

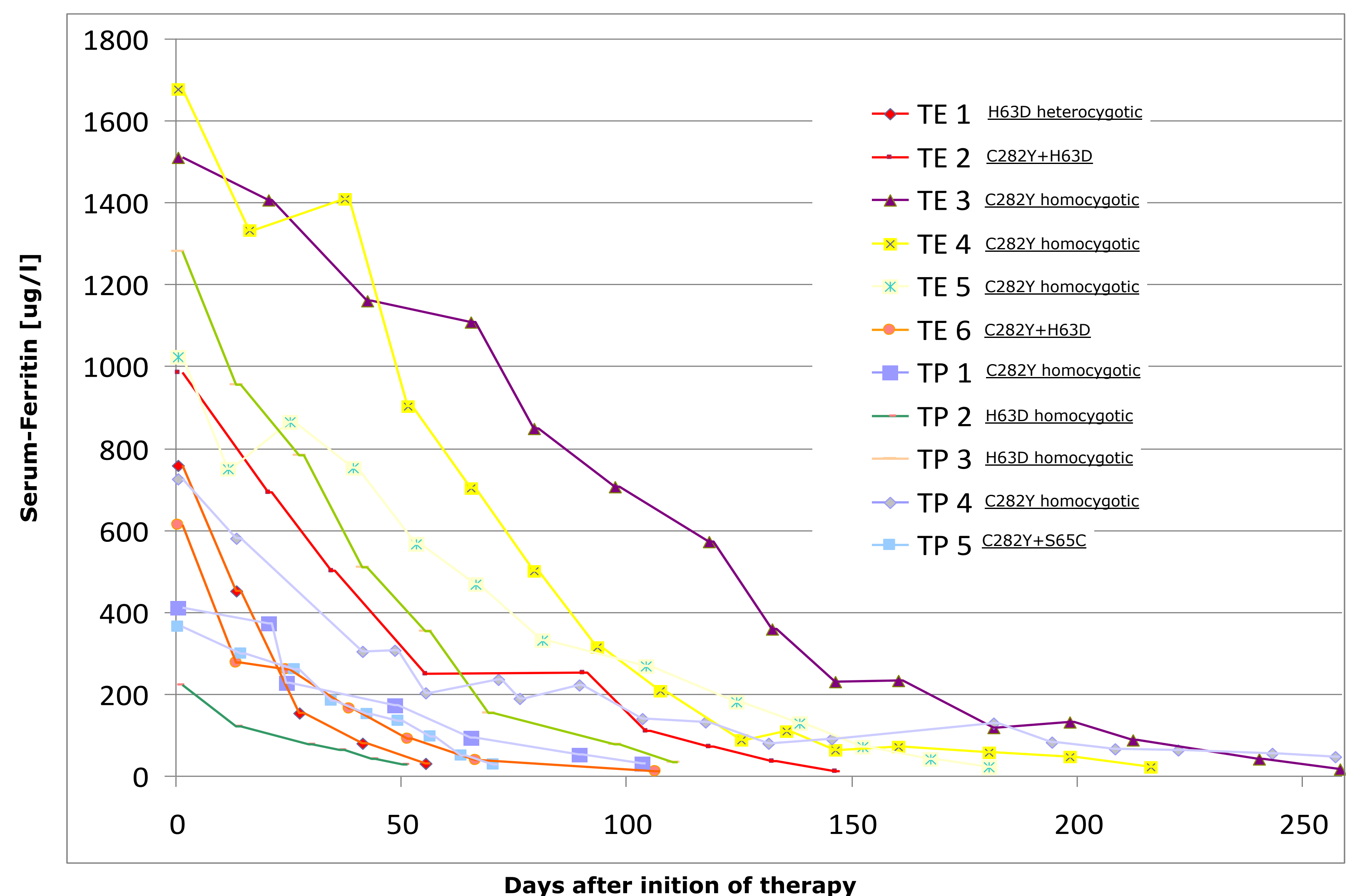
Table 4: Depletion of TBI Mean Values (standard deviation)

	TE (n=6)	TP (n=5)
Body iron at endpoint (Ferritin<50 µg/l)*	2.1 (0.64)	5.7 (2.43)
TBIentry-TBIendpoint*	19.1 (3.11)	11.5 (2.98)
Depletion of Body Iron per procedure*	2.0 (1.21)	1.33 (1.13)

*: p<0,05

Figure 1: Ferritin Concentration in the course of therapy

Each datapoint represents one depletion, TE=apheresis, TP=phlebotomy



Figures 2+3: Comparison of Total Body Iron (TBI) in TE vs. TP

Whole column=Initial TBI; Black Column=TBI at endpoint (SF<50 µg/l; black written values in the white box). The height of the red column (yellow written values) reflects body iron loss due to therapy minus the compensative enteral absorbed iron.

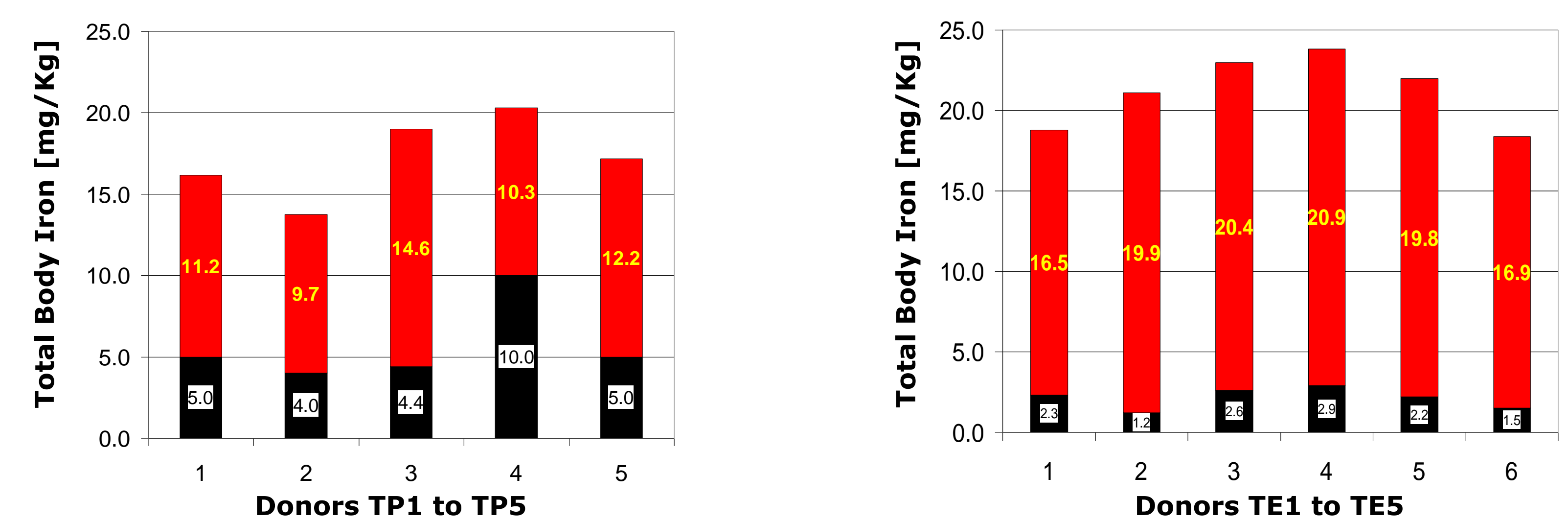
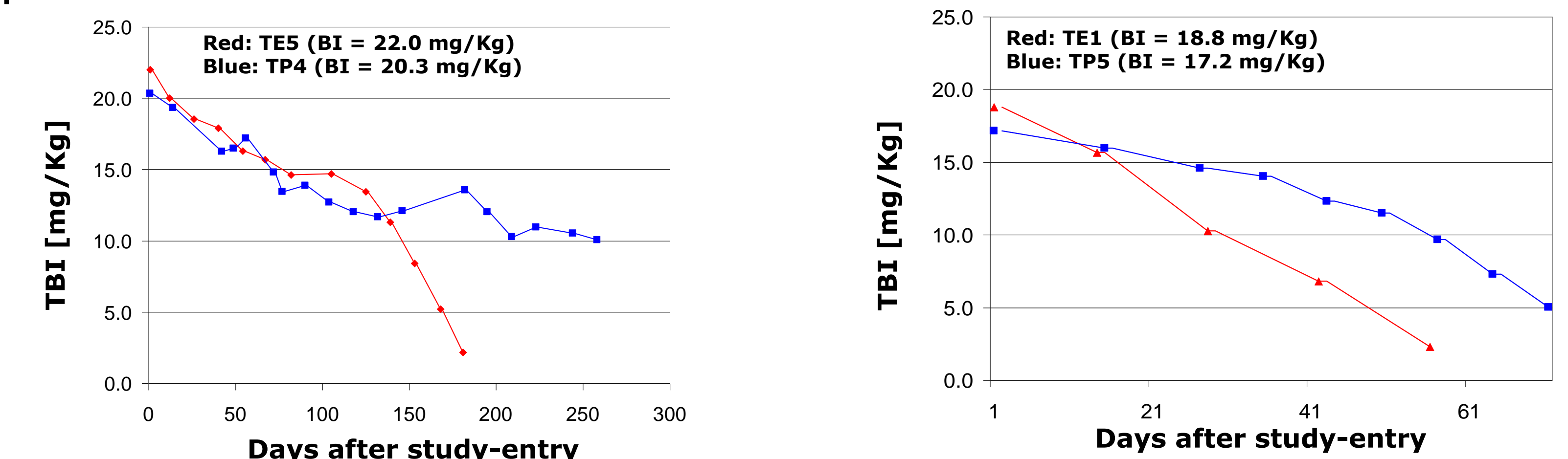


Figure 4+5: TBI in TE versus TP

Two examples of matched pair comparison of cases with similar phenotypic expression of disease (similar TBI at entry). Depending on intervention the improved iron depletion efficacy is illustrated by more pronounced and sustained reduction of TBI over time



Discussion

Regarding ferritin alone makes it difficult to compare depletion efficacy of TE versus TP (Table 3, Figure 1): theoretically, twice as much iron should be removed in TE versus TP^{4,5}. As in the TE-group, average ferritin at study-entry was higher, but average interval of donation was comparable, it is not suitable to compare parameters like the medium days till the endpoint is reached or the number of phlebotomies necessary to reach the endpoint. Instead, analyzing sTRF and TBI indicates that more TBI was depleted by TE versus TP at the endpoint, and TBI at endpoint is in average higher in TP versus TE (Table 4, Figures 2 and 3). With respect to the known variability in phenotypic expression of disease, a matched pair analysis regarding TBI in TE versus TP underlines that TE may be more efficient than TP (Figure 4+5). So far, only few publications deal with the efficacy of iron depletion comparing TE and TP. Rombout-Sestrienkova et. al. retrospectively analyzed historic records of 6 haemochromatosis patients (each, TE and TP)⁶, Vecchio et. al. compare clinical results of 98 patients with different causes of erythrocytosis where they clearly demonstrate the advantages of the longer donation interval of in TE versus TP patients.⁷

Conclusion

Preliminary data of this randomized, prospective study investigating the iron metabolism during the initial depletion cycles after diagnosis show that both TP and TE proved to be safe (data not shown) and efficient, with only minor differences in the occurrence of adverse events. Nevertheless, our data indicate that TE leads to more profound iron depletion than TP, which is possibly mediated by a stimulation of erythropoiesis. The clinical significance of this difference is to date unclear.

References

1. M. Valbonesi et. al.; Transfusion Science; Vol. 22 (3), June 2000, Pages 183-194
2. James D. Cook et al., Blood, May 2003, 3359-3364
3. Total Body Iron = TBI = -(log (sTfR[mg/l] / Ferritin [mg/l]) - 2.8229) / 0.1207
Reference Values: ♂ (20-65yr, US): 9.82 mg/kg and ♀ (20-65yr, US): 5.5 mg/kg according to Ref. 1.
4. TP: 450ml Whole Blood; estimated iron loss: 250-300mg
5. TE: 360ml concentrate (Hk 60+-10%); estimated iron loss: 500-600mg
6. Rombout-Sestrienkova, Koek GH. et. al. Transfus Apher Sci. 2007 Jun;36(3):261-76.
7. Vecchio et. al.; Blood Transfus. 2007 Jan;5(1):20-3.