anemia, and had been splenectomized at the age of 48 with clinical improvement and an increase in hemoglobin level (Table 1). Before splenectomy she had required occasional transfusion therapy.

Her father and sister had the typical hematologic features of β-thalassemia minor whereas her mother had normal red cell indices with a borderline Hb $A_2$ level (Table 1) and no α-globin gene triplication.[3]

Direct sequencing[4] of the propositus' β-globin gene showed compound heterozygosity for the Mediterranean β IVSI-1 (G-A) mutation and for a recently described 5' UTR +33 C-G mutation (Figure 1). These mutations were confirmed respectively by *BsaB* I and *Nla* IV amplified DNA digests. The IVSI-1 (G-A) mutation is present in her father's and sister's β-globin gene and the 5' UTR +33 (C-G) mutation is present in her mother's β-globin gene.

The C to G mutation in the +33 position of the β-globin gene was first described in two unrelated Greek Cypriot families[5] associated with β haplotype II (– + + – + + +) according to Orkin.[6] In the present case the 5' UTR +33 (C-G) mutation is associated with β haplotype V ( + – – – – + –) suggesting an independent origin for the mutation in this family.

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***Key words***

*Thalassemia intermedia, silent thalassemia*

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## Peri-operative use of recombinant human erythropoietin in Jehovah's Witnesses

**The care of Jehovah's Witnesses who refuse blood transfusion on religious grounds is a continuing clinical challenge. Options for treating these patients are limited. We present the cases of four Jehovah's witnesses (2 males, 2 females, mean age 54.7 years) who successfully underwent total hip arthroplasties (one of them twice) with peri-operative rHuEpo support.**

Sir,

Four patients refused allogeneic and autologous blood transfusion based on religious convictions. The patients' hematologic data are shown in Table 1. We administered rHuEpo pre-operatively to a total dose of 10,000 IU (not corrected for body weight), three times weekly subcutaneously, thirty days prior to operation in order to achieve a Hb ≥14 g/dL. Administration was continued for another thirty days after surgery in order to avoid cardiopulmonary complications due to low Hb levels. Ferrous sulfate (300 mg) was also administered *per os* daily. Complete blood counts, erythropoietin levels and ferritin levels were monitored throughout the study period and the values at the initiation of rHuEpo administration, on the day of the operation and at the end of the therapy are presented in Table 1.

Five total hip arthroplasties (onr patient had two operations) were performed successfully, without any blood transfusion and no complication due to excessive blood loss or low Hb levels were noted. Hb levels after a 30-day rHuEpo administration were significantly increased (Table 2). A significant increase was also noted in erythropoietin (epo) levels (Table 2). No significant changes were noted in either ferritin levels or the number of white blood cells and platelets.

rHuEpo administration was well tolerated. No change was observed in the patients' blood pressure, renal and hepatic function were within normal ranges and there was no evidence of deep venous thrombosis in the postoperative period.

Patient #1 underwent two operations. After the second one she presented with severe melena due to an acute stress ulcer. Although her Hb value was less than 4.5 g/dL she repeatedly refused a blood transfusion and was transferred to the intensive care unit for supportive therapy, where she was only administered rHuEpo and iron supplements on a daily basis. After two months her Hb value had increased up to 10 g/dL and she was discharged in an excellent condition.

The refusal of Jehovah's Witnesses to accept transfusions has accelerated the administration of rHuEpo in the perioperative setting, especially in joint replacements[1,2] because of the elective nature of these operations. Although thrombotic events complicate rHuEpo treatment in renal failure, in a recent integrated analysis by de Andrade *et al.*,[3] rHuEpo administered in elective orthopedic surgery patients was not identified as a risk factor for thrombotic/vascular events. In addition, in a multicenter, double–blind, placebo-controlled study[4] the incidence of deep vein

**Table 1. Patients' hematologic data at the initiation of rHuEpo treatment, on the day of operation and thirty days after.**

| | *At the initiation of rHuEpo treatment* | | | | | *On the day of operation* | | | | | *30 days after surgery* | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Cases* | *1* | | *2* | *3* | *4* | *1* | | *2* | *3* | *4* | *1* | | *2* | *3* | *4* |
| *Gender/age (years)* | *F/58* | | *M/46* | *F/60* | *M/55* | *F/58* | | *M/46* | *F/60* | *M/55* | *F/58* | | *M/46* | *F/60* | *M/55* |
| | *A** | *B** | | | | *A** | *B** | | | | *A** | *B** | | | |
| Hemoglobin, g/dL | 11.0 | 11.2 | 13.2 | 10.2 | 13 | 14.8 | 14.7 | 17.1 | 14.5 | 16.5 | 13.8 | 10.6 | 14.4 | 13.8 | 14.2 |
| WBC x $10^9$ | 6.2 | 7.1 | 6.7 | 7.3 | 7.5 | 6.5 | 6.8 | 7.4 | 7.1 | 6.9 | 6.8 | 8.2 | 7.2 | 7.1 | 7.2 |
| Platelets x $10^9$ | 180 | 145 | 200 | 251 | 220 | 200 | 171 | 156 | 180 | 195 | 170 | 220 | 200 | 180 | 190 |
| Erythropoietin, mU/mL | 20 | 15 | 20 | 18 | 22 | 200 | 150 | 180 | 160 | 190 | 200 | 250 | 220 | 230 | 210 |
| Ferritin, ng/dL | 25 | 18 | 35 | 24 | 38 | 30 | 20 | 38 | 20 | 32 | 20 | 10 | 18 | 22 | 24 |

*A* = first operation; B* = second operation; F= female, M= male*

**Table 2. Mean hemoglobin and erythropoietin levels at the initiation of rHuEpo administration and at the day of surgery.**

| | *At the start of rHuEpo treatment* | *At the day of the surgery* |
|---|---|---|
| Mean hemoglobin, g/dL ± SD | 11.7±1.31 | 15.52±1.19 |
| Mean erythropoietin mU/mL ± SD | 19±2.64 | 176±20.7 |
| Wilcoxon's signed rank test | $p<0.05$ | $p<0.05$ |

thrombosis was not different from that observed in placebo recipients.

In summary, the peri-operative use of rHuEpo in our patients had beneficial results and all operations were performed as scheduled avoiding any blood transfusion and its associated risks. We believe that rHuEpo is an attractive, safe and effective alternative to allogeneic and autologous blood transfusion, not only for Jehovah's witnesses but for all patients scheduled for orthopedic surgery.

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***Key words***

*Erythropoietin, perioperative use, Jehovah's Witnesses, and elective orthopaedic surgery.*

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## Methylenetetrahydrofolate reductase gene polymorphism and coronary artery disease in Taiwan Chinese

**Hyperhomocysteinemia has been identified as an independent risk factor for occlusive vascular diseases. The C667T 5, 10-methylenetetrahydrofolate reductase (MTHFR) genotype is correlated with increased plasma homocysteine levels especially under the condition of low plasma folate level. This is the first report about the frequency of C667T MTHFR in coronary artery disease and normal controls in Taiwan Chinese.**

Sir,

Mild to moderate hyperhomocysteinemia has been documented as an independent risk factor for coronary, cerebral and peripheral arteriosclerotic disease.[1,2] In addition to deficiencies in vitamins $B_6$, $B_{12}$, folic acid and some pathologies, namely renal and hepatic insufficiency, reduced activity of the enzymes cystathionine-synthase (CBS) or 5, 10-methylenetrahydrofolate reductase (MTHFR) are the most common factors responsible for higher plasma homocysteine levels. The most common genetic defect that results in mild hyperhomocysteinemia is a C to T substitution at nucleotide 677 of the MTHFR gene, that converts an alanine to a valine residue.[3] This mutation results in thermolabile MTHFR; homozygotes for the mutation have about 30% and heterozygotes about 65% of the MTHFR activity found in individuals without the mutation.[4] Homozygotes for the mutation also have elevated circulating homo-