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Concise report

Haploidentical α/β T-cell and B-cell depleted stem cell transplantation in severe mevalonate kinase deficiency

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Abstract

Objective. Mevalonic aciduria represents the most severe form of mevalonate kinase deficiency (MKD). Patients with mevalonic aciduria have an incomplete response even to high doses of anti-cytokine drugs such as *anakinra* or *canakinumab* and stem cell transplantation (SCT) represents a possible therapy for this severe disease.
Methods. We report the first two children affected by severe MKD who received haploidentical α/β T-cell and B-cell depleted SCT. Both patients received a treosulfan-based conditioning regimen and one received a second haploidentical-SCT for secondary rejection of the first.
Results. Both patients obtained a stable full donor engraftment with a complete regression of clinical and biochemical inflammatory signs, without acute organ toxicity or acute and chronic GvHD. In both, the urinary excretion of mevalonic acid remained high post-transplant in the absence of any inflammatory signs.
Conclusion. Haploidentical α/β T-cell and B-cell depleted SCT represents a potential curative strategy in patients affected by MKD. The persistence of urinary excretion of mevalonic acid after SCT, probably related to the ubiquitous expression of MVK enzyme, suggests that these patients should be carefully monitored after SCT to exclude MKD clinical recurrence. Prophylaxis with anakinra in the acute phase after transplant could represent a safe and effective approach. Further biological studies are required to clarify the pathophysiology of inflammatory attacks in MKD in order to better define the therapeutic role of SCT.

Key words: mevalonate kinase deficiency, haploidentical SCT, children

CLINICAL SCIENCE

Rheumatology key messages

- Haploidentical α/β T-cell and B-cell depleted SCT represents a potential curative strategy in patients affected by MKD.
- Treosulfan represents an efficacious and well-tolerated conditioning regimen.
- The persistence of urinary excretion of mevalonic acid after SCT was not associated with a flare of the underlying disease.

Introduction

Mevalonate kinase deficiency (MKD) is an autosomal recessive inherited inborn error of metabolism characterized by a wide spectrum of clinical manifestations [1]. Mevalonic aciduria (MA) represents the more severe and rare clinical phenotype that occurs during the neonatal period with neuropsychomotor delay and growth failure, dysmorphic features, periodic fever with

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acute inflammation involving joints, skin and abdominal organs. On the extreme of the spectrum there are patients with a normal development presenting with recurrent fever episodes separated by intervals of complete well-being, previously known as Hyper IgD syndrome [1]. While in Hyper IgD patients the residual MVK enzymatic activity is calculated to be around 20–30%, children with MA present a severely reduced MVK activity (<1%) leading to accumulation of mevalonic acid and its excretion in the urine. In the latter the prognosis is poor, and more than 50% of affected children die during acute inflammatory crisis [2, 3]. Current management of MKD is based on modulation of the autoinflammatory mechanisms with biologic anti-cytokine drugs, such as anti-interleukin 1 (anakinra or canakinumab) or anti-tumor necrosis factor-alpha with a good effect in patients with Hyper IgD syndrome [1, 4]. However, patients with severe MKD and MA may present an incomplete response even to high doses of anti-cytokine drugs [5]. Rarely, allogeneic stem cell transplantation (SCT) has been proposed as a potential treatment for these patients [6, 7], according to the hypothesis that donor-derived mononuclear cells could represent a source of MVK enzyme. This report describes the clinical findings and outcome of two children affected by severe MKD who received haploidentical α/β T-cell and B-cell depleted SCT.

Methods

The procedures we followed were in accordance with our Italian scientific society association ethical standards and with the Declaration of Helsinki principles. The parents of younger children had previously signed a consent form allowing the use of their anonymous clinical data for research. The data of these patients are stored in an institutional database and are available on request from the corresponding author.

Results

The first patient (already described) [8] was a female born from consanguineous parents at 37 weeks gestation (weight: 2680 g) after caesarean section for decreased uterine artery blood flow. During the neonatal period, she developed fever associated with an increase of inflammatory parameters, respiratory failure, cutaneous rash, and growth failure. Based on clinical suspicion of MA, urinary mevalonic acid was quantified and was shown to be markedly increased (7024 μmol/mmol creatinine, n.v. <0.1 μmol/mmol). She received treatment with anakinra (3.3 mg/kg/day subcutaneous) with improvement in clinical findings. The diagnosis of MKD was confirmed by genetic sequencing that revealed the homozygous missense mutation (p.T237S) in the MVK gene. Both parents were heterozygous carriers. At the age of 15 months, the patient underwent haploidentical α/β T-cell and B-cell depleted SCT from peripheral blood of her mother and anakinra was discontinued a few days before the transplant. The myeloablative conditioning regimen (RC) performed and the graft cell dose are detailed in Table 1. Thrombocytes and neutrophils engraftment occurred 13 and 18 days after SCT, respectively. Neither early nor late complications were observed, in particular no acute or chronic graft vs host disease (GvHD) occurred and full donor chimerism (100% donor cells) was confirmed during the follow-up. After the SCT, despite the complete absence of autoinflammatory symptoms, significant urinary excretion of mevalonic acid persisted (>3000 μmol/mmol creatinine). Currently, 1 year after the transplant, the patient is in a persistent very good clinical condition with normal growth curve and neuropsychomotor development. The complete donor chimerism (100%) was confirmed in peripheral blood and no inflammatory symptoms related to MA occurred.

The second patient was a male, born preterm at 30 weeks gestation (weight: 1700 g) after caesarean section for non-immune foetal hydrops. Surgical closure of a patent ductus arteriosus was performed after birth. During the neonatal period, the child had recurrent episodes of fever, hepatosplenomegaly, pericardial and pleural effusion, joint pain, cutaneous rash. The neuropsychomotor development was rather delayed, the patient presented axial hypotonia and oculomotor apraxia. Genetic evaluation showed a compound heterozygosis in the MVK gene: p.R124K (inherited from the mother) and p.L297I mutation (inherited from the father). MVK activity in the patient was <2 ng/ml (n.v. 125–395 mg/ml), with increased urinary excretion of mevalonic acid (1004.8 μmol/mmol creatinine), while both parents showed a level of MVK activity mildly reduced. The patient received anakinra (2 mg/kg/day) with normalization of the inflammatory clinical manifestations. Two months later, for recurrence of severe thrombocytopenia associated with increase in transaminases, the patient received steroids and a higher dose of anakinra (10–15 mg/kg/daily) for 2 months, but since fever and inflammatory attacks persisted, anakinra was replaced by canakinumab (7.5 mg/kg subcutaneous every 3 weeks) with improvement in clinical symptoms. In order to avoid further neurologic impairment and control of inflammatory syndrome, the patient was proposed for an allogeneic SCT and, in the absence of a matched related or unrelated donor, the child, at the age of 22 months, underwent an haploidentical α/β T-cell and B-cell depleted SCT from his father after a treosulfan-based myeloablative CR (Table 1). Canakinumab was discontinued 7 days before. Seventeen days after SCT, the patient developed a systemic acute inflammatory disease with fever, increase in inflammatory parameters, acute respiratory and renal failure, suggestive of pre-engraftment syndrome because an increase of donor-derived cells in peripheral blood was observed (64% donor chimerism). The patient received steroids and anakinra (intravenous, 8–10 mg/kg divided into three doses, daily) and non-invasive mechanical ventilation.

Table 1 Patients and transplantation features

	Patient 1	Patient 2
Main clinical features at diagnosis		
Best clinical control reached with pre-SCT treatments	Fever attack every 2–3 weeks during anakinra therapy	Continuous mild fever and rash during canakinumab therapy
Mevalonic acid in urine (mmol/mol Cr)		
Before haplo-SCT	1029.6	533.7
After haplo-SCT	>3000 (after 12 months from SCT)	>3000 (after 6 months from SCT)
Conditioning regimen	Thiotepa 8 mg/kg day -7 Treosulfan 10 g/m^2 day -6, -5, -4, 8 Fludarabin 40 mg/m^2 day -6, -5, -4, -3 ATG-Grafalon® 4 mg/kg day -4, -3, -2 Rituximab 200 mg/^{2} day -1	
Haploidentical graft cell dose	• CD34$^+$: 15.08 × 10^6/kg • TCR CD3$^+\alpha\beta$: 0.69 × 105/kg • CD19$^+$: 3.1 ×10^5/kg	• CD34$^+$: 15.6 × 10^6/kg • TCR CD3$^+\alpha\beta$: 0.60 × 10^5/kg • CD19$^+$: 1.52 × 10^5/kg
Conditioning regimen before 2nd haplo-SCT	–	Fludarabine 40 mg/m^2 day -5, -4, -3, -2 Busulphan 3.2 mg/kg day -4, -3, -2 Alemtuzumab 0.2 mg/kg day -10, -9, -8, -7, -6
PBSC haploidentical infused in 2nd SCT	–	• CD34$^+$: 16.5 × 10^6/kg; • TCR CD3$^+$ $\alpha\beta$: 0.49 × 10^5/kg • CD19$^+$: 1.2 × 10^5/kg

SCT: stem cell transplantation; PBSC: peripheral blood stem cell; ATG: anti-thymocytes globulin.

His clinical condition improved, but a graft failure was documented 26 days after SCT. Steroids were discontinued while anakinra was maintained at the same dosage, in order to prevent MKD-related inflammatory events after rejection. One month later, a second SCT was performed from the same donor (his father) (Table 1).

During the engraftment phase, the patient again developed a systemic acute inflammatory syndrome with respiratory failure, successfully treated with steroids. The engraftment was completely reached at the 18th and 32nd day after the second haplo-SCT for neutrophils and platelets, respectively, with a stable full donor chimerism. Twenty-five days after the second haplo-SCT, the patient worsened again with acute respiratory failure. Cardiac ultrasound demonstrated a pre-capillary pulmonary hypertension related to stenosis of the pulmonary arteries and the patient underwent cardiac catheterism and therapy with vasodilator agents. This event has been correlated to a late consequence of the ductus arteriosus surgical treatment. Anakinra was tapered and it was discontinued 50 days after the second haplo-SCT. The period after discharge was uneventful and neither acute or chronic GvHD nor infections were observed. Currently, 8 months after the second haplo-SCT, the patient is in good health, with stable full-donor chimerism, no more fever or other inflammatory symptoms were observed and his neuropsychomotor development improved considerably. Mevalonic acid was continuously detected at high levels in his urine (>3000 μmol/mmol creatinine).

Discussion

To date, a total of six patients with severe MKD who received allogeneic SCT have been reported [7–13] (Table 2). A complete response of autoinflammatory disease after SCT was described in all but one, who experienced a relapse of fever attacks requiring treatment with anti-IL1 drugs (canakinumab), despite a stable full-donor engraftment [11]. To our knowledge, the patients described in this report are the first two MKD-children receiving haploidentical α/β T-cell and B-cell depleted SCT.

In the first patient, this platform of haplo-SCT with treosulfan-based CR allowed a prompt and stable full-donor engraftment to be obtained with complete regression of clinical and biochemical inflammatory signs, without acute organ toxicity or acute or chronic GvHD. The second patient experienced life-threatening acute systemic inflammatory syndrome after the same haplo-SCT protocols, managed with anakinra and steroids but a secondary graft failure occurred. A complete engraftment was finally reached after a second haplo-SCT, complicated by similar life-threatening acute systemic inflammatory syndrome during the pre-engraftment phase. The recurrence of engraftment or pre-engraftment syndrome in this patient could suggest that in children with a severe phenotype of MKD, the higher inflammatory response may induce the development of engraftment or pre-engraftment syndrome. In these two patients the urinary excretion of mevalonic acid did not decrease after haplo-SCT but became higher than in the pre-transplant period,

TABLE 2 Patients with MA who received allogeneic HSCT reported in the literature

Case, age, gender	Mutation	Clinical symptoms	Therapy before SCT	Type of SCT source of cells	Conditioning regimen	GvHD prophylaxis	GvHD and other SCT complication	Outcome	Last follow-up
3 yrs, male (Neven *et al*. 2007) [7]	G326R (976 G > A) missense mutation in homozygosis	Hepato-splenomegaly, hepatitis, anaemia, thrombocytopenia. Increase in inflammatory parameters, axial hypotonia, ataxia	Etanercept, Anakinra (until day +25 from SCT)	Related SCT, BM cells 26.2×10^6 $CD34^+$/kg	Busulphan Cyclophosphamide	CsA, MMF	Absent GvHD TAM	FD MK activity of 64% +12 mos Decrease of urinary MA	+15 mos Alive No symptoms Only ataxic remained
8 yrs, male (Arkwright *et al*. 2007) [10]	Polymorphism of *TNFRSF1A* gene	Recurrent episodes of fever	Salicylic acid, steroids, CsA, Anakinra, Etanercept	Related SCT, BM cells Unknown number of cells	Unknown	CsA, Tac	Acute/chronic GvHD viral infections (Adenovirus, BK virus, VZV),	FD Unknown urinary MA	+16 mos Alive No symptoms
15 days, female (Chaudhury *et al*. 2012) [12]	803 T > C (I268T) + 928 G > A (V310M) in homozygosis	Urinary infection, growth failure, recurrent fever, spastic diplegia, cholestatic hepatic failure with cirrhosis (liver transplantation at 4 yrs)	Tacrolimus MMF steroids Anakinra after liver transplant	Unrelated SCT at 6.5 yrs PBSC cells 6×10^6 $CD34^+$/kg	Busulphan Fludarabine	Tac, MMF	PRES Chronic GvHD, CMV reactivation	FD Unknown urinary MA	+2.5 yrs Alive No symptoms
10 days, male (Erdol *et al*. 2016) [13]	G336S (c.1006 G > A) mutation in homozygosis	Hepato-splenomegaly, ascites	FANS Steroids Canakinumab	Related SCT, BM cells Unknown number of cells	Unknown	Unknown	Sepsis	FD Reduction of urinary MA	+3.5 mos Died from sepsis
2 yrs, male (Giardino *et al*. 2015) [9]	c.32G > A (p.V8M) mutation in homozygosis	Recurrent fever, arthritis, hepato-splenomegaly, anaemia, hypotonia, cerebral atrophy, increase in inflammatory parameters	FANS Steroids Anakinra	Unrelated SCT CB cells 0.64×10^6 $CD34^+$/kg	Busulphan Cyclophosphamide	CsA, ATG	Acute GvHD Microangiopathy PRES Sepsis, pulmonary aspergillosis, CMV reactivation	FD Reduction of urinary MA	+6 yrs Alive No symptoms
14 months, female (Szymanski *et al*. 2019) [11]	Homozygosity for missense variant (Leu297Ile) in exon 10 of the *MVK* gene	Thrombocytopenia, anaemia abdominal ascites, respiratory difficulties, oliguria and acute kidney injury	Steroids Anakinra	Unrelated SCT CB cells Unknown number of cells	Alemtuzumab, Thiotepa Melphalan	CsA, MMF	Several infections Urinary MA became zero 3 months post-transplant	FD	+18 mos Clinical relapse Urinary MA level elevated, canakinumab 100% donor

SCT: stem cell transplantation; GvHD: graft vs host disease; CsA: ciclosporin A; Tac: tacrolimus; MK: mevalonate kinase; MA: mevalonic acid; PRES: posterior reversible encephalopathy syndrome; TAM: thrombotic microangiopathy; ATG: anti-thymocyte globilin; ECP: extracorporeal photopheresis; FD: full donor; FANS: non steroideal anti-inflammatory; BK: BK polioma virus; VZV: varicella zooster virus; BM: bone marrow; CB: cord blood.

remaining stable at very high levels (>3000 μmol/mmol creatinine) but in absence of any inflammatory signs (Supplementary Fig. S1, available at *Rheumatology* online). This could be explained by the evidence that MVK enzyme is ubiquitously expressed [3–14], playing a crucial role in the early stages of the isoprenoid biosynthesis pathway, and its deficiency persists in tissues after SCT with a continuous accumulation and urinary excretion of mevalonic acid, but with control of inflammatory response by the replacement of donor-derived monocyte in liver and other tissues. The efficacy and safety of anakinra, administered i.v. at high dosage in patient 2 during the first phase after the second haplo-SCT, could suggest its potential utility as prophylaxis of inflammatory complications after SCT in autoinflammatory diseases.

Regarding haplo-SCT in this disease, the negative selection of α/β T cells and B cells confirmed engraftment with a low risk of acute and chronic GvHD, satisfying immune reconstitution and with a low risk of infective complications [15].

In conclusion, haploidentical α/β T-cell and B-cell depleted SCT represents a potential curative strategy in patients affected by MKD. The persistence of urinary excretion of mevalonic acid after SCT suggests that these patients should be carefully monitored after SCT to exclude MKD clinical recurrence. The prophylaxis with anakinra in the acute phase after transplant could be a safe and effective approach. Further biological studies are required to clarify the pathophysiology of inflammatory attacks in MKD in order to better define the therapeutic role of SCT.

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Data availability statement

Available with reasonable request.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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