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ORIGINAL ARTICLE

# Hematopoietic Stem Cell Transplantation in ARPC1B Deficiency

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## Abstract

Mutations in the ARPC1B isoform component of human actin-related protein 2/3 complex have been recently associated with an inborn error of immunity characterized by combined immunodeficiency, allergies, autoinflammation, and platelet abnormalities. Currently, indications on the management of this novel disease and information on its outcome are lacking. We report the first case series of 7 children with a homozygous mutation in ARPC1B gene who underwent allogeneic-HSCT (allo-HSCT). All patients presented an early clinical onset, characterized by recurrent infections, failure to thrive and gastrointestinal bleeding episodes complicated with neonatal hemorrhagic enteritis in 3 cases, and macrophage activating syndrome in 2. Allo-HSCT was performed at the median age of 1.83 years after a myeloablative conditioning regimen in all cases. Engraftment occurred in all patients with full donor chimerism in 6 out of 7. The clinical course after engraftment was uneventful in 3 out of 7 children; 2 patients developed a grade 1–2 acute graft-versus-host disease (GvHD), and 1 patient a grade 1 chronic-GvHD. JC virus-related progressive multifocal leukoencephalopathy was diagnosed in one patient 13 months after haploidentical-HSCT and successfully managed with donor-derived viral-specific T-cell infusion. Only one patient had a fatal outcome 3 months after HSCT because of sepsis, after veno-occlusive disease, and transplant-associated microangiopathy. At a median follow-up of 19 months (range 3–110), 6 out of 7 patients are alive and disease-free. The severity of the clinical phenotype at diagnosis and the high survival rate, with limited transplant-related morbidity, strongly support the indication to allo-HSCT for patients with this diagnosis.

**Keywords** ARPC1B deficiency · Allogenic-HSCT · Primary immunodeficiency · Autoinflammatory disease

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## Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) represents an established curative treatment for several primary immunodeficiencies (PIDs) with reported survival rates higher than 90% depending on diagnosis, age, and overall patient status at the time of transplantation [1–4]. These results, reached over the years due to the advances in donor selection, graft manipulation, conditioning regimens (CR), and treatment of complications, have led to HSCT indication in newly diagnosed patients with several forms of PIDs. Many novel genetic mutations associated with combined immunodeficiency have been described [5, 6] and some of these present a variable phenotype in which autoimmunity, auto-inflammatory pattern, and infection susceptibility are associated, requiring immunosuppressive and anti-inflammatory therapies [7]. Some of these inflammatory and immunological disorders are associated with defects of actin-binding molecules [8–11], confirming actin cytoskeleton central role in almost all stages of immune system function [12–14]. Human actin-related protein 2/3 complex (Arp 2/3), required for actin filament branching, consists of seven evolutionarily conserved subunits (Arp2, Arp3, and ARPC1–5). In mammals the ARPC1 and ARPC5 subunits are each encoded by two isoforms that are 67% identical. ARPC1B is prominently expressed in blood cells even if protein expression is detectable also in the lung, intestine, urinary tract, and skin among other tissues [15]. ARPC1B biallelic mutation results in a combined immunodeficiency, allergy, and "auto-inflammation" that has been recently described, resembling Wiskott-Aldrich syndrome (WAS) [16], characterized by early clinical onset, recurrent infections related to impaired T-cell function, and migration, allergic manifestations, bleeding tendency, and platelet abnormalities [ 17–23]. In this emerging disease, although the indication for allogeneic HSCT (allo-HSCT) should be considered for other PIDs [24, 25], there is still no evidence regarding the transplant outcomes in terms of survival and quality of life and of the possible persistence of extra-hematopoietic defects due to ARPC1B deficiency.

We report the outcome of the first series of 7 children who underwent allo-HSCT because of a homozygous mutation in ARPC1B gene.

## Materials and methods

Seven patients with a diagnosis of primary immune deficiency caused by *ARPC1B* mutation underwent allo-HSCT in 6 different centers (Italy, Germany, Spain, USA, Israel, Greece); six of them have been reported in previous studies [16, 19, 21] in which this novel syndrome has been described.

Data have been retrospectively collected for each patient using a questionnaire distributed to participating centers with patients' clinical features, genetic, pre-transplant treatments, conditioning regimen (CR), donor type, stem cell (SC) source, engraftment, early and late toxicities, acute and chronic graft versus host disease (a- and c-GvHD), post-HSCT infections, donor chimerism, and survival. Engraftment was defined as neutrophils count $> 0.5 \times 10^9$/L for at least 3 consecutive days and platelet count > 50,000/L without platelet transfusion in the previous 5–7 days.

## Results

Patients' demographic, clinical features, and treatments performed before HSCT are reported in Table 1. Table 2 summarizes HSCT features and outcomes.

All patients presented with a very early clinical onset during the first months of life (range 9 days–6 months) with life-threatening events occurring in 5, including neonatal hemorrhagic enteritis in 3 (P2, P3, P6), and macrophage activating syndrome (MAS) requiring pediatric intensive care unit admission in 2 patients (P1 and P4). In P1 MAS occurred at the age of 1 month triggered by CMV infection and was controlled by steroids and antiviral treatment (ganciclovir), while in P4 MAS developed at the 9th day of life and required multiple lines of therapies including methylprednisolone and anakinra followed by dexamethasone, tocilizumab, and etoposide.

Failure to thrive was a common feature in almost all patients, as well as gastrointestinal bleeding episodes, with thrombocytopenia reported in 3 patients (P2, P3, and P6). Cutaneous leukocytoclastic vasculitis have been observed in P1 and P2, with histologic confirmation.

The clinical course before allo-HSCT was characterized by recurrent bacterial and viral infections in all patients, as showed in Table 1, while no fungal infection has been reported. The patient who underwent allo-HSCT at the older age (P2, 15 years) developed a severe chronic lung disease secondary to recurrent staphylococcus pulmonary infections with multiple bronchiectasis and large pneumatocele, that required surgical lobectomy, performed at the age of 7. This patient required immunosuppressive treatment including sirolimus and mycophenolate for a cutaneous leukocytoclastic vasculitis. Such therapy allowed clinical control but lead to an increase of infection incidence.

The median age at transplant was 1.83 years (range, 0.15–15.16). For all patients the indication to allo-HSCT was the poor control of clinical autoimmune and auto-inflammatory symptoms and the recurrence of infections events. P3, P6, and P7 underwent transplant without prior trial of alternative treatments, since they had an older

**Table 1** Patients' features

| N | Gender/Origin | Mutation | Age at symptoms onset | Age at genetic diagnosis | Clinical features | | | Family history | Pre-transplant treatments and outcome |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | At onset | Other | Infectious diseases episodes | | |
| P1 | Male/Italian | Homozygous c.622G > T p.Val208Phe | 2 months | 5 years | - MAS (triggered by CMV): cytopenia, splenomegaly; maculopapular rash | - Enterorrhagia<br>- Growth failure<br>- Enlarged lymph nodes and spleen<br>- Cutaneous rash, vasculitis skin | - Recurrent otitis (MDR pseudomonas)<br>- chronic CMV viremia | Negative | - TMP-SMX prophylaxis<br>- Steroids and sirolimus (good response on lymphoadenopahty and splenomegaly) |
| P2 | Male/Italian | Homozygous c.64 + 1G > C (donor splice site) | 1 month | 15 years | - Neonatal hemorrhagic enteritis<br>- Poor growth | - Enterorrhagia/ immune enteritis<br>- Thrombocytopenia*<br>- Lung disease (multiple bronchiectasis, pneumatocele, lobectomy)<br>- Severe eczema<br>- Food allergy (cow milk protein intolerance)<br>- Inhalant allergy (asthma attacks)<br>- Vasculitis skin | - Recurrent pulmonary infections (*Staphylococcus* spp.)<br>- *Salmonella typhi*<br>- Extensive warts | Negative | - MMF + Sirolimus (good response of vasculitis, discontinued due to increased infection rate)<br>- Steroid<br>- TMP-SMX prophylaxis<br>- Inhalant steroid + B2agonist |
| P3 | Male/Somalian | Homozygous c.392 + 2 T > C (donor splice site) | 2 weeks | 14 months | - Neonatal hemorrhagic enteritis<br>- Diffuse skin rash/ eczema | - Multiple episodes of hematemesis<br>- Hemorrhagic gastritis<br>- Hematochezia requiring hospitalization and NJ feeds<br>- Hypothyroidism<br>- Atopic dermatitis<br>- Failure to thrive<br>- Autoimmune thrombocytopenia*<br>- Food allergy (milk/ dairy with milk) | - Adenovirus enteritis<br>- Campylobacter enteritis<br>- Central line infection; pneumonia and oral mucositis<br>- Recurrent MSSA pustulosis/folliculitis<br>- Pancreatitis | Older sibling dead for sepsis at 2 months of life during severe gastrointestinal bleeding | - Thyroidreplacement<br>- Naso-jejunal feeds<br>- Antibiotic therapy as indicated for acute infection<br>- Topical steroids for excematous rash |
| P4 | Female/Moroccan | Homozygous c.491_495 del ins CCTGCCC p.Phe164Serfs*31 | 9 days | 9 months | - MAS requiring PICU admission for respiratory distress and anasarca | - Episode of DVT related to central line<br>- Arterial hypertension<br>- Axial hypotonia | - Multiple septic events (candida spp., *Enterobacter cloacae*)<br>- CMV infection | Older sibling dead for MOF in adenoviral infection | - Methylprednisolone + anakinra<br>- Tocilizumab + cyclosporin<br>- Dexamethasone + etoposide |

**Table 1** (continued)

| N | Gender/Origin | Mutation | Age at symptoms onset | Age at genetic diagnosis | Clinical features | | | Family history | Pre-transplant treatments and outcome |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | At onset | Other | Infectious diseases episodes | | |
| P5 | Male/Moroccan | Homozygous c.311G > C p.Trp104Ser | 1 month | 2 years | - Eczema<br>- RSV bronchopneumonia | - Growth failure | - Enteritis (*Campylobacter*)<br>- Skin abscesses (*P. aeruginosa* + *K. Pneumoniae*)<br>- Otitis media (*P. aeruginosa*)<br>- Lymphadenitis with abscess<br>- Erysipelas<br>- Gross generalized molluscum contagiosum<br>- EBV infection | Negative | - Recurrent antibiotic treatment<br>- Steroids |
| P6 | Male/Persian Jew | Homozygous c.623_624delTC (p.V208fs) | 1 month | 2 month | - Neonatal hemorrhagic enteritis<br>- Severe eczema<br>- Failure to thrive | - GI bleeding colitis<br>- Thrombocytopenia*<br>- Bleeding tendency | - Multiple infections since 1 month of age: pneumonia, otitis, skin infections | Negative | - Multiple antibiotic treatments<br>- TMP-SMX prophylaxis<br>- IVIG |
| P7 | Male/Afghan | Homozygous c.783G > A (splice region variant) | 6 months | 10 months | - Severe lower respiratory tract infection | - Eczema, food allergy, and allergic asthma (anaphylactic shock with formula milk)<br>- Autoimmune hypothyroidism<br>- Failure to thrive | - Recurrent bronchiolitis<br>- Pneumonia<br>- Skin abscess (perianal abscess due to *Pseudomonas aeruginosa*) | Older sibling dead for CNS infection at 3 years of age | - Hypoallergic diet, topical agents for eczema<br>- Oral Montelukast and nebulized fluticasone (preventive<br>- Asthma therapy)<br>- TMP-SMX prophylaxis |

*Baseline platelets value < $150{,}000 \times 10^9$/L (P2: $70 \times 10^9$/L; P3: $50 \times 10^9$/L; P6: $85 \times 10.^9$/L)

*CMV*, cytomegalovirus; *CNS*, central nervous system; *DVT*, deep vein thrombosis; *MAS*, macrophage activating syndrome; *MDR*, multi-drug resistant; *MMF*, mycophenolate mofetil; *MOF*, multi-organ failure; *PICU*, pediatric intensive care unit; *RSV*, respiratory syncytial virus; *TMP-SMX*, trimethoprim/sulfamethoxazole

**Table 2** Transplant's features and outcome

| N | HSCT features | | | | | | Outcome | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Age at HSCT (years) | Donor type | SC source | Graft manipulation | Conditiong Regimen *(cumulative dose)* | Post-HSCT in vivo GvHD prophylaxis | Engraftment *(day after HSCT)* | | Chimerism *(% of donor-derived cells at the last follow-up)* | Acute GvHD *(grade—organs involved)* | Chronic GvHD *(grade—organs involved)* | Infections | | Other HSCT-related complications | Sur-vival | Follow up *(months after HSCT)* |
| | | | | | | | Neu-tro-phils | Plate-lets | | | | Type of germ/ infection | Clinical manifestation | | | |
| P1 | 5,25 | HAPLO Father | PB | αβ+/ CD19+ negative selection | ✓ TT 8 mg/m$^2$<br>✓ Treo 42 mg/ m$^2$<br>✓ Fluda 160 mg/m$^2$<br>✓ Rituximab 200 mg/m$^2$<br>✓ ATG 12 mg/ kg | None | 13 | 13 | DC *100%* | No | No | ✓ *Staphy-lococcus epidermidis oxacillin-* R *(blood cultures)*<br>✓ CMV *viremia*<br>✓ Metapneu-movirus *(pharyngeal swab)* | None | None | Alive | 54 |
| P2 | 15,16 | HAPLO mother | PB | αβ+/ CD19+ Negative selection | ✓ TT 8 mg/m$^2$<br>✓ Treo 42 mg/ m$^2$<br>✓ Fluda 160 mg/m$^2$<br>✓ Rituximab 200 mg/m$^2$<br>✓ ATG 12 mg/ kg | None | 13 | 14 | DC *100%* | 1 Skin | 2 Skin | ✓ *Staphylococ-cus aureus (blood cultures)*<br>✓ CMV *viremia*<br>✓ EBV *viremia*<br>✓ BK virus *viremia*<br>✓ JC virus *in CSF*<br>✓ HHV6 *viremia* | ✓ PML JC virus related<br>✓ HC BK virus related | Lymphadenitis | Alive | 48 |
| P3 | 1,83 | MUD (10/10) | PB | *None* | ✓ Fluda 150 mg/m$^2$,<br>✓ Bus 12 mg/ kg (target AUC: 5000 uMol * min) | ✓ PT-Cy<br>✓ FK506<br>✓ MMF | 16 | 17 | DC *99%* | No | No | NO | n.a | None | Alive | 15 |
| P4 | 0,75 | MUD (9/10) | BM | *None* | ✓ Fluda 140 mg/m$^2$<br>✓ Bus 24 mg/kg (target AUC: 75,000 ng/ mL*h)<br>✓ ATG 10 mg/ kg | ✓ CyA<br>✓ MTX | 18 | 35 | DC *100%* | 2 Skin | No | ✓ *Klebsiella pneumonia (blood cultures)*<br>✓ CMV *viremia*<br>✓ Metapneu-movirus *(pharyngeal swab)* | Sepsis KP related | Respiratory distress/ MAS | Alive | 19 |

**Table 2** (continued)

| N | HSCT features | | | | | | Outcome | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Age at HSCT (years) | Donor type | SC source | Graft manipulation | Conditiong Regimen *(cumulative dose)* | Post-HSCT in vivo GvHD prophylaxis | Engraftment *(day after HSCT)* | | Chimerism *(% of donor-derived cells at the last follow-up)* | Acute GvHD *(grade—organs involved)* | Chronic GvHD *(grade—organs involved)* | Infections | | Other HSCT-related complications | Survival | Follow up *(months after HSCT)* |
| | | | | | | | Neutrophils | Platelets | | | | Type of germ/infection | Clinical manifestation | | | |
| P5 | 5,75 | MRD | BM | *None* | ✓ TT 5 mg/m$^2$<br>✓ Treo 42 mg/m$^2$<br>✓ Fluda 160 mg/m$^2$<br>✓ Alemtuzumab 0.5 mg/kg | ✓ CyA<br>✓ MMF | 22 | 20 | SMC* | No | No | NO | n.a | None | Alive | 110 |
| P6 | 0,25 | MRD | BM | *None* | ✓ Bus (according to weight of patient) for 16 dose<br>✓ Fluda 160 mg/m$^2$<br>✓ ATG 10 mg/kg | ✓ CyA<br>✓ MMF | 18 | NA | DC *99%* | No | No | ✓ *Escherichia coli*<br>✓ Staphylococcus epidermidis<br>✓ *Enterocco faecalis*<br>✓ *Klebsiella pneumonia*-CRE<br>✓ CMV *viremia* | Sepsis *E. coli* related *(PICU admission)* | VOD<br>TA-TMA | Dead | 3 |
| P7 | 1 | MRD | BM | *None* | ✓ Bus 16 mg/kg<br>✓ Fluda 150 mg/m$^2$<br>✓ ATG (dose n.a.) | ✓ CyA<br>✓ MTX | 23 | 18 | TMC** | No | No | ✓ *Leuconostoc pseudomesenteroides*<br>✓ CMV *viremia* | Sepsis | None | Alive | 16 |

*% of donor-derived cells at the last follow up: CD3 + 93.6%, CD15 + 5.1%; CD3 − 28%

**% of donor-derived cells: 78% at 1 months, 98% from the second month until the last follow-up

*BM*, bone marrow; *Bus*, busulfan; *CMV*, cytomegalovirus; *CRE*, carbapenem-resistant Enterobacteriaceae; *CSF*, cerebrospinal fluid; *DC*, donor chimerism; Fluda, fluidarabine; *HAPLO*, haploidentical donor; *HC*, hemorrhagic cystitis; *MAS*, macrophage activating syndrome; *MRD*, matched related donor; *MUD*, matched unrelated donor; *PB*, peripheral blood; *PICU*, pediatric intensive care unit; *SMC*, stable mixed chimerism; *TA-TMA*, transplant-associated thrombotic microangiopathy; *TMC*, transient mixed chimerism; *Treo*, treosulfan; *TT*, thiotepa; *VOD*, veno-occlusive disease

**Table 3** Platelets' count, immune subsets, and Ig-level after HSCT *(at last follow up)*

| Patients | P1 | P2 | P3 | P4 | P5 | P6 | P7 |
|---|---|---|---|---|---|---|---|
| Platelet count ($\times 10^9$/L) | 245 | 160 | 250 | 129 | 170 | NA | 254 |
| Immune subsets ($\times 10^9$/L) | | | | | | | |
| ➢ CD3 + CD4 + | 1729 | 750 | 1282 | 1100 | 2549 | NA | 2230 |
| ➢ CD19 + | 537 | 200 | 247 | 370 | 517 | NA | 690 |
| ➢ CD3-16 + 56 + | 360 | 300 | 336 | 240 | 352 | NA | 1670 |
| Ig level | | | | | | | |
| ➢ Ig G (mg/dL) | 540 | 483 | 831 | 856 | 1140 | NA | 574 |
| ➢ Ig M (mg/dL) | 57 | 53 | 71.3 | 108 | 57 | NA | 60 |
| ➢ Ig A (mg/dL) | 111 | 259 | 303 | 154 | 189 | NA | 79 |
| ➢ Ig E (kU/L) | NA | NA | 6.57 | 3.8 | 2.04 | NA | - |
| Timing in months after transplant (= follow-up) | 54 | 48 | 15 | 19 | 110 | 3 | 16 |

brother with a similar phenotype who died due to severe complications represented by sepsis at 2 months of life during severe gastrointestinal bleeding (P3), adenoviral infection with a multi-organ failure while awaiting HSCT (P4), and an unidentified infection of the central nervous system at 3 years of age (P7), respectively.

The SC donor was a matched related (MRD) in 3 transplants (P5, P6, and P7), a matched unrelated (MUD) in 2 (P3 and P4), while P1 and P2 received a TCR-$\alpha\beta^+CD19^+$-depleted HSCT from an haploidentical parent. The CR was myeloablative in all transplants, busulfan based in 4, and treosulfan based in the remaining 3.

Engraftment occurred in all patients after a median of 18 days for neutrophils (range, 13–23 days) and 17 days for platelets (range, 13–35 days) after allo-HSCT. No episodes of graft rejection have been reported and 5 out of 7 patients showed a stable full donor chimerism; transient mixed chimerism has been reported in P7 and stable mixed chimerism in P5 (Table 2). This patient (P5) showed a complete donor chimerism in the first post-engraftment phase (99% at 1 month) that evolved into mixed chimerism from the 6th month after HSCT (65% on whole blood); at 1 year after HSCT, he showed a high donor-derived percentage in T-cells (CD3 + 94%) that remained stable in the following years (93% more than 9 years after HSCT), and a low percentage in CD15 + and CD3 − (64% and 42%, respectively) that further decreased in the following years (5% and 28%, respectively, at last follow-up).

The clinical course after engraftment was uneventful in 3 out of 7 patients (P1, P3, and P5), with neither significant post-transplant infections nor GvHD. GvHD was reported in 2 children (P2 and P4) after engraftment; P2 developed grade 1 cutaneous acute-GvHD that did not require systemic treatments and, 6 months later, a grade 2 cutaneous c-GvHD, successfully treated with systemic steroid. P4 developed a grade 2 cutaneous and gastrointestinal acute GvHD, with a complete response to steroid therapy.

One patient (P6) had a severe outcome after HSCT, represented by the development of veno-occlusive disease (VOD) and transplant-associated thrombotic microangiopathy (TA-TAM), treated with defibrotide and eculizumab, respectively, obtaining only their partial control; this patient died 3 months after HSCT because of a Carbapenem-resistant Enterobacteriaceae sepsis.

Of note, P2 developed 13 months after HSCT a severe JC virus-related encephalitis, with severe neurological impairment due to *progressive multifocal leukoencephalopathy*, that was successfully managed with donor-derived viral-specific T-cell infusions (CTL infusion). This patient suffered neurological sequelae with the persistence of ataxia and tremors at the last follow-up [26].

At a median follow-up of 19 months (range 3–110), 6 to 7 patients are alive and disease-free. This was proven by the absence of all clinical, immunological, and hematological signs of underlying disease after transplantation. In particular, all patients alive after transplantation reached a complete immune reconstitution with immunophenotype and immunoglobulins within the normal range (Table 3), in absence of any major infective events. Furthermore, the patients who presented thrombocytopenia as a disease sign showed a normal platelet level, as expected after HSCT. Of note, also the patient with stable mixed chimerism (P5) showed hematological count cells and immunological subsets within the normal range.

## Discussion

In this report, we describe the clinical features, transplant details, and outcomes of 7 patients who underwent allo-HSCT for a PID caused by *ARPC1B* germline mutations.

To the best of our knowledge, this is the first case series reported on this topic, which enables the community to derive useful information for the clinical management of this emerging and challenging diagnosis. The severe clinical phenotype at diagnosis and the high survival rate with limited transplant-related morbidity support the indication to allo-HSCT for patients with ARPC1B deficiency. Furthermore, despite the protein being expressed also in non-hematopoietic tissues, absence of clinically evident intrinsic defects in other organs and the efficacy of allo-HSCT in controlling disease manifestations suggest a non-redundant role of ARPC1B protein only in the hematopoietic system. It is possible that in other tissues, the different ARP isoforms are able to compensate for the defect. Indeed, it seems that lack of one isoform is correlated to overexpression of the others [27] as we also observed in our previous work where we detected an evident upregulation of ARPC1A protein in ARPC1B-deficient cells [17].

The main limitations of our report include the small number of patients and the retrospective nature of the study that excludes patients with ARPC1B deficiency undiagnosed or that did not reach transplantation. However, the present data support the fundamental message of the feasibility and efficacy of allo-HSCT in ARPC1B deficiency [17–23, 28].

We found that most patients underwent transplantation because of the severe phenotype characterized by life-threatening infective events or inflammatory and/or autoimmune presentations; in particular, in three of them, the indication was further strengthened by the presence of family history of death of a sibling due to complications of the same condition.

Allogeneic HSCT led to successful resolution of immune deficit with sustained donor chimerism and excellent survival in 6 patients. Interestingly, the patient with mixed chimerism (P5) is also alive and free of symptoms, suggesting that a mixed chimerism with the prevalence of T-cells from donor could be sufficient to control the expression of the disease. Of course, more patients with mixed chimerism should be observed to confirm this hypothezis.

Only one patient died (P6) after HSCT because of sepsis from Gram-negative bacteria; this patient received allo-HSCT from MRD at 2 months of age after the occurrence of severe infections performed following a CR including busulphan administered at weight-adapted dose but without AUC-based dose adjustment; the latter [29], together with the age < 1 year [30], represent recognized risk factors for VOD, occurred in this patient. Differently, all the other patients received myeloablative CR at a reduced toxicity profile treosulfan based or busulphan based with dose adjusted on AUC.

The other major complication observed in these patients after HSCT has been JC encephalitis in P2 occurred during steroid treatment for c-GvHD; of note, this patient underwent T-depleted haploidentical transplant at 15 years of age, after a long history of infections and in the presence of chronic lung disease; these conditions increase the risk of GvHD [31], also in T-depleted haploidentical HSCT, and likely contributed to delayed immune reconstitution and, therefore, to viral infection susceptibility.

Similarly to other PID patients, also for patients with ARPC1B deficiency, the goal of allo-HSCT is to correct the dysregulation of the immune system with the resolution of autoinflammatory and autoimmune manifestations and with the control of infective events. The performance of allo-HSCT with the use of myeloablative CR with low early and late toxicity, as treosulfan, could allow reaching these results. In case of the absence of MRD and considering the relevance of an early allo-HSCT in improving the outcome, the choice of a haploidentical familiar donor, promptly available, should be considered in ARPC1B as in other PIDs, in which different platforms of haplo-HSCT with graft manipulation for T-depletion [32–34] or without T-depletion but using post-transplant cyclophosphamide as GvHD prophylaxis [35] allow to achieve excellent results.

## Conclusions

In conclusion, in this series of patients, we found that most patients with ARPC1B mutations tolerated transplant conditioning, with a high rate of engraftment, resolution of immunodeficiency, autoinflammation, and autoimmunity. Active infections and clinically significant comorbidities at the time of transplant are the main potential risk factor contributing to adverse events in the acute post-transplant phase. More data are needed to confirm the indication and the timing for transplant and to refine conditioning regimens as well as management of patients with significant inflammatory and autoimmune manifestations before HSCT. National and international immunodeficiency and transplant registries should be queried to examine reported outcomes in larger patient cohorts, comparing those of transplanted and not transplanted patients.

**Author Contribution** SG, SV, MF, and MG contributed to the study conception and design. All other authors contributed to the clinical management and data collection, each for patients belonging to their own center. Material preparation, data collection, and analysis were performed by SG and FL. The first draft of the manuscript was written by SG. All authors contributed to manuscript revision and approved its final version.

The datasets generated during the current study are available from the corresponding author on reasonable request.

## Declarations

**Ethics Approval** This study, performed in line with the principles of the Declaration of Helsinki, is an observational retrospective study that collects pseudo-anonymized data. The Research Ethics Committee of each Centre involved has confirmed that no ethical approval is required.

**Consent to Participate** Informed consent to participate in retrospective study was obtained from the parents of all individual participants included in the study.

**Consent for Publication** Not applicable

**Conflict of Interest** The authors declare no competing interests.

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