RESEARCH ARTICLE

Hematopoietic Stem Cell Transplantation in an International Cohort of Colony Stimulating Factor-1 Receptor (CSF1R)-Related Disorder

CME

Hemmo A.F. Yska, MD,[1,2] Marianne Golse, MD,[3,4] Shanice Beerepoot, MD,[2,5] Stefanie Hayer, MD,[6,7] Caroline Bergner, MD,[8] Anderson Rodrigues Brandao de Paiva, MD, PhD,[9,10] Cecilia Marelli, MD, PhD,[11] Natalia Julia Palacios, MD,[12] Yudy Llamas Osorio, MS,[13] Camille Huiban, MS,[1] Georg Franke, MD,[14] Friederike Wortmann, MD,[15] Udo Holtick, MD, PhD,[16] Xavier Ayrignac, MD, PhD,[17] Marjo S. van der Knaap, MD, PhD,[2,5] Ludger Schöls, MD,[6] Vincent Perlbarg, PhD,[18] Damien Galanaud, MD, PhD,[3,4] Moniek A. de Witte, MD, PhD,[19] Nicole I. Wolf, MD, PhD,[2,5] Stéphanie Nguyen, MD, PhD,[20] Fanny Mochel, MD, PhD,[1,21*]
and the International CSF1R-RD Working Group

ABSTRACT: Background: Colony stimulating factor-1 receptor (CSF1R)-related disorder (CSF1R-RD) is an autosomal dominant, rapidly progressive, demyelinating disease leading to death usually within a few years. Because of the central role of *CSF1R* in microglia functions, allogeneic hematopoietic stem cell transplantation (HSCT) has been suggested as a therapy for CSF1R-RD.

Objectives: To report multicenter clinical (Expanded Disability Scoring Scale [EDSS]), neurocognitive), neuroimaging (Sundal score), and biological (neurofilament light chain [NfL]) outcomes after HSCT in CSF1R-RD.

Methods: We report an international cohort of 17 adult patients (8 females/9 males, 43.3 ± 9.4 years) who were treated in seven transplant centers. Patients were evaluated for a median of 2.5 years post-HSCT, including one patient with follow-up of 8 years. We also report neurological outcomes of the first child transplanted to date with biallelic *CSF1R* variants.

Results: In the first 6 months post-HSCT, 2 patients died from early complications of myeloablative transplantation, and clinical and radiological severity scores worsened in most surviving adult patients. At 12 months post-HSCT, most patients completely stabilized or improved in certain clinical domains. Radiological scores fully stabilized or slightly improved in all but one of the patients. Plasma/serum NfL sharply decreased in most patients after transplantation. Notably, 7/8 adult patients who received a reduced-intensity conditioning regimen displayed similar neurological outcomes as patients who underwent myeloablative transplantation.

[1]INSERM U 1127, CNRS UMR 7225, Sorbonne Universités, UPMC Univ Paris 06 UMR S 1127, Institut du Cerveau, ICM, Paris, France; [2]Amsterdam UMC, Location AMC, Department of Child Neurology, Amsterdam Leukodystrophy Center, Emma Children's Hospital, Amsterdam, The Netherlands; [3]Laboratoire d'Imagerie BiomédicaleSorbonne Université, INSERM, CNRS, Paris, France; [4]Department of Neuroradiology, AP-HP, Pitié-Salpêtrière University Hospital, Paris, France; [5]Cellular & Molecular Mechanisms, Amsterdam Neuroscience, Amsterdam, The Netherlands; [6]Department of Neurology and Hertie-Institute for Clinical Brain Research, German Center of Neurodegenerative Diseases (DZNE), Tübingen, Germany; [7]Institute of Medical and Human Genetics, Charité - Universitätsmedizin Berlin, Berlin, Germany; [8]Clinic of Neurology, University Hospital Leipzig, Leipzig, Germany; [9]Hospital das Clínicas da Universidade de São Paulo, Neurogenetics Unit, São Paulo, Brazil; [10]Mendelics Análise Genômica, São Paulo, Brazil; [11]Reference Center for Neurogenetic DiseasesMontpellier University, EPHE, INSERM, CHU Montpellier, Montpellier, France; [12]Unidad de Enfermedades Metabólicas, Servicio de Neurología, Hospital Sant Joan de Déu, Esplugues, Spain; [13]Neurology Department, Dublin Neurological Institute, Mater University Hospital, Dublin, Ireland; [14]Medical Department, Hematology, University of Leipzig Faculty of Medicine, Leipzig, Germany; [15]Klinik für Hämatologie und Onkologie, Universitätsklinik Schleswig-Holstein, Lübeck, Germany; [16]Department I of Internal Medicine, Medical Faculty and University Hospital of Cologne, University of Cologne, Cologne, Germany; [17]Montpellier University, INM, INSERM, Reference Center for Adult Leukodystrophies, CHU Montpellier, Montpellier, France; [18]BrainTale SAS, Strasbourg, France; [19]Department of Hematology, University Medical Center Utrecht, Utrecht, The Netherlands [20]Department of Hematology, AP-HP, Pitié-Salpêtrière University Hospital, 75013 Paris, France; [21]Department of Medical Genetics, Reference Centers for Adult Neurometabolic Diseases and Adult Leukodystrophies, AP-HP, Pitié-Salpêtrière University Hospital, Paris, France

*__Correspondence to:__ Prof. Fanny Mochel, Department of Medical Genetics, Reference Centers for Adult Leukodystrophies, Paris Brain Institute, La Pitié-Salpêtrière University Hospital, Paris, France; E-mail: fanny.mochel@icm-institute.org

Hemmo A.F. Yska and Marianne Golse contributed equally to this work.

Shanice Beerepoot and Stefanie Hayer contributed equally to this work.

Moniek A. de Witte, Nicole I. Wolf, and Stéphanie Nguyen contributed equally to this work.

Relevant conflict of interest: V.P. is a co-founder and employee of BrainTale SAS.
Funding agency: No funding was received in respect of this work.

Received: 18 April 2025; **Revised:** 13 June 2025; **Accepted:** 17 June 2025

Published online 12 July 2025 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.30282

Conclusions: After an initial clinical and radiological deterioration in the first 6 months post-transplantation, HSCT can halt disease progression in patients with CSF1R-RD, regardless of their presenting clinical symptoms. The possibility of reduced conditioning regimens in CSF1R-RD opens the way to treat older patients.

Key Words: CSF1R-RD; adult-onset leukoencephalopathy with axonal spheroids and pigmented glia; hematopoietic stem cell transplantation; demyelination; neuroinflammation; neurofilament light chain

Adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP), or colony stimulating factor-1 receptor-related disorder (CSF1R-RD) according to recent nomenclature, is a severe neurodegenerative disease.[1] It is caused by pathogenic variants in CSF1R, which encodes a protein involved in the division, differentiation, motility, and survival of macrophages and microglia.[2,3] Without treatment, the mean survival of patients with CSF1R-RD is 6.8 years.[4] The clinical picture comprises a combination of cognitive, psychiatric, pyramidal, extrapyramidal, and sensory symptoms.[4,5] Penetrance is, however, incomplete and there may be a greater number than anticipated of pathogenic variants in asymptomatic individuals.[6,7] Magnetic resonance imaging (MRI) abnormalities have been well described in CSF1R-RD and include diffuse, and sometimes asymmetric, white matter lesions predominantly in the frontal and frontoparietal regions, often accompanied by diffusion restriction, callosal atrophy, and calcifications in the periventricular and subcortical white matter.[8-10] Because CSF1R plays a central role in the functions of macrophages and microglia,[11] hematopoietic stem cell transplantation (HSCT) has been considered as a possible therapy for CSF1R-RD. Case series have indicated that HSCT can halt progression of the disease but are limited by small patient numbers of single-centers and short-term follow-up.[12-15]

Validated outcome measures to assess the efficacy of HSCT are currently lacking. The variability in disease progression, with some patients experiencing cognitive impairments while others face mainly motor decline, complicates the evaluation of HSCT in CSF1R-RD. MRI scores such as the Sundal score may provide objective outcomes but their correlation to clinical outcomes and their change over time have not been investigated in detail.[8-10] The same holds true for the biomarker neurofilament light chain (NfL) in blood.[16] The aim of the current work was to evaluate the effect of HSCT on CSF1R-RD using standardized clinical, radiological, and biological outcome measures collected from an international cohort of 17 adult patients and 1 child with CSF1R-RD, transplanted in seven centers and with follow-up periods of up to 8 years.

Methods

The study was approved by the ethics board of INSERM (IRB00003888), which determined that patient consent was not required.

Study Description

All patients that underwent HSCT in the participating centers were included. Seventeen adult patients with a pathogenic or likely pathogenic monoallelic variant in the *CSF1R* gene were included in this study. Patients were transplanted between 2016 and 2023 in seven centers in four countries (Table 1). Data were collected retrospectively over a period of at most 8 years after transplantation. One patient with biallelic *CSF1R* variants and presenting with a pediatric onset of neurological symptoms was also included and analyzed separately.

Transplantation centers provided information on donors and recipients, including conditioning regimen, source of hematopoietic stem cells (peripheral blood, bone marrow, or cord blood), anti-thymocyte globulin treatment, and graft-versus-host disease (GvHD) prophylaxis. Follow-up included documentation of the presence and severity of GvHD, infections, and other complications.

Clinical outcomes before and after HSCT included standard neurological examination and scoring of the Expanded Disability Scoring Scale (EDSS). Cognitive and psychiatric abnormalities were described qualitatively. Additionally, standardized neurocognitive evaluations were performed in the Paris cohort ($n = 5$).

MRI scans were evaluated by a neuroradiological team at the Paris Brain Institute (M.G., D.G., and F.M.) using the total Sundal score (maximum 57) and its atrophy and white matter subscores.[8] Scoring was based on fluid-attenuated inversion recovery (FLAIR) images. Special attention was paid to diffusion restriction. As an exploratory analysis, the diffusion tensor imaging (DTI) markers fractional anisotropy (FA) and medial diffusivity (MD) were evaluated in the Paris cohort ($n = 4$) by means of the calibrated and standardized BrainQuant pipeline.[17,18] FA and MD are related to white matter tissue integrity, where lower FA and higher MD are generally

TABLE 1 *Baseline characteristics of adult patients with colony stimulating factor-1 receptor-related disorder (CSF1R-RD) (n = 17).*

Characteristic	n (%) or mean (SD)
Female/male	8 (47%)/9 (53%)
Transplantation center	
Paris, France	5 (30%)
Amsterdam, The Netherlands	5 (30%)
Leipzig, Germany	2 (12%)
Sao Paolo, Brazil	2 (12%)
Montpellier, France	1 (6%)
Lübeck (Tübingen), Germany	1 (6%)
Köln (Tübingen), Germany	1 (6%)
Clinical family history for CSF1R-RD	9 (53%)
Age at symptom onset (years)	41.1 (9.2)
Symptoms	
Psychiatric	15 (88%)
Cognitive	14 (82%)
Extrapyramidal	10 (59%)
Spasticity	9 (53%)
Muscle weakness	8 (47%)
Decreased vibration sense	8 (47%)
Dysarthria	7 (41%)
Cerebellar signs	6 (35%)
Urinary incontinence	6 (35%)
Dysphagia	2 (12%)
Fecal incontinence	0 (0%)
Age at transplantation (years)	43.3 (9.4)
Delay diagnosis to transplantation (months)	24.7 (16.9)
Graft	
Peripheral blood	8 (47%)
Bone marrow	8 (47%)
Cord blood	1 (6%)
Conditioning regimen	
Myeloablative	9 (53%)
Reduced intensity	6 (35%)
Reduced toxicity	2 (12%)

Abbreviations: CSF1R-RD, colony stimulating factor-1 receptor-related disorder; SD, standard deviation.

considered to reflect pathological changes. The acquisition and processing protocol are described in the Supplementary Figures section.

When available, participating institutions provided plasma/serum levels of NfL, a biomarker previously validated in CSF1R-RD.[16] As NfL is age-dependent, a reference range between 0 and 20 pg/mL was used to encompass all the ages of patients included in this cohort.[19]

Statistical Analyses

Data are presented as percentage, mean, and standard deviation (SD) for normally distributed data or median and interquartile range (IQR) for non-normally distributed data. The association between EDSS and Sundal scores was quantified using Spearman's correlation coefficient only for timepoints where both values were available.

Results

Characteristics of Adult Patients with CSF1R-RD

We included 8 females and 9 males with CSF1R-RD, whose characteristics are summarized in Table 1 and detailed in Table S1. Patient-13 has been partly described.[13] *CSF1R* variants are listed in Table S2.

Most patients were index cases. Mean age at symptom onset was 41.1 ± 9.2 years and mean age at HSCT was 43.3 ± 9.4 years. The most common symptoms at the time of transplantation were psychiatric and cognitive abnormalities (88% and 82%, respectively). Patients often suffered from behavioral changes, anxiety, and depression. Cognitive symptoms included bradyphrenia, memory problems, dysexecutive syndrome/apraxia, and attention deficits. Asymmetric motor symptoms such as reduced limb strength and spasticity were relatively common (47% and 53%, respectively). Extrapyramidal signs (59%) comprised tremors, rigidity, hyperkinesia, bradykinesia, freezing, and postural instability. Mean EDSS at the time of transplantation was 4.5 ± 1.8, reflecting a moderate level of disability where most patients (76%) could still walk independently.

HSCT in Adult Patients with CSF1R-RD

Adult patients with CSF1R-RD underwent HSCT between 2016 and 2023. The average time between symptom onset and transplantation was 24 ± 17 months. Table S3 provides details about HSCT procedures. Eight patients received hematopoietic stem cells derived from peripheral blood, including 4 with ex vivo T-cell depleted grafts, 8 patients received bone marrow, and 1 patient received cord blood. Apart from the cord blood, 12 patients received cells from HLA-identical donors, 3 patients from related haplo-identical donors, and 1 patient from a mismatched unrelated donor. Apart from the cord blood, 8 patients underwent a

myeloablative conditioning regimen and 8 patients a reduced intensity or reduced toxicity conditioning (ie, reduced busulfan dose intensity). Four patients (23.5%) developed grade I-II acute GvHD with gastrointestinal and/or cutaneous manifestations. For 3 patients, GvHD symptoms resolved within 6–9 months. The fourth patient developed organizing pneumonia at 6 months, which was attributed to GvHD, and was still oxygen-dependent at 1-year follow-up, but symptoms had disappeared at 2.5 years post-transplantation. Chimerism data were available for 15/17 patients, and full chimerism was obtained in all patients except Patient-3 who underwent graft failure and Patient-6 (93% chimerism at 1 year) who received haplo-identical cells from his father.

Two patients (11.8%) died rapidly from complications related to transplantation. Both underwent myeloablative conditioning. Patient-1 was in their 30s and presented with rapidly progressive motor and sensory complaints (EDSS 6.5). HSCT was performed using cord blood cells 2 years after symptom onset but, within 2 months, the patient experienced a massive, generalized *Aspergillus* infection with respiratory failure. Patient-3 was in their 40s and experienced depression, cognitive, motor sensory, and extrapyramidal symptoms (EDSS 4.0). HSCT was performed 1year after symptom onset with peripheral blood cells (10/10 matched unrelated donor). Pancytopenia after graft failure was quickly observed in combination with multiple infections. The patient declined a new transplantation and died 3 months later.

Neurological Evolution of Adult Patients with CSF1R-RD after HSCT

Except for the 2 patients who died, median follow-up after HSCT for the adult patient cohort was 2.5 years (2–8 years). For those patients where data were available, within the first 6 months after transplantation 11/14 patients (79%) experienced new symptoms or worsening of existing ones, as illustrated by a median increase of their EDSS by 1 point (Fig. 1A). Data for both the 6- and 12-month timepoints were available for 12 patients. At 12 months post-HSCT, 3/12 patients (25%) stabilized clinically, 2/12 patients (17%) experienced both worsening and improvement of symptoms, and 7/12 patients (58%) experienced clinical improvement compared with 6 months post-HSCT (Fig. 1A). At the latest timepoint available (2–8 years), and compared with baseline, 7/15 patients (47%) had deteriorated (for 3 patients only cognitively, and for 4 patients only motorically), 3/15 patients (20%) had a combination of both improvement and worsening of cognitive or motor function, 4/15 patients (27%) had improved in either or both domains, and 1/15 patients (7%) had remained stable (Fig. 1A, Table S4). Among the patients (Patient-8, -11, -14, -15, -16) who experienced clinical improvements post-HSCT in motor and/or cognitive domains (Fig. 1A and Table 2), 1 patient (Patient-8) returned to his baseline motor functioning due to apathy, interruption of physiotherapy, and reduced mobilization.

Standardized neurocognitive testing (Table 2) revealed improved performances in 4/5 patients (Patient-14, -15, -16 and -17) and stabilization in Patient-13. The cognitive abilities of Patient-14, whose presenting symptoms were constructional apraxia and dysexecutive symptoms, deteriorated at 1-year post-transplant but then strikingly improved up to 4 years. This had a major impact on the patient's quality of life, from being dependent for all daily life activities before transplant to living independently after 3 years post-transplant.

Neuroradiological Evolution of Adult Patients with CSF1R-RD after HSCT

We observed a wide range of Sundal scores ranging from 12.5(/57) to 41(/57) at baseline. Twelve of 13 patients (92.3%) with longitudinal imaging data showed an increase in their total score on their first post-HSCT scan (ie, 6 or 12 months after transplantation) (Fig. 1B). The median increase for the white matter score was 3.0 (0.1–5.5), for the atrophy score 1.0 (0.0–2.8), and for the total score 3.75 (1.1–8.3) after a median of 8 months (6.0–11.8) (Figs 1B and S1). Sundal scores then fully stabilized at 12 months post-HSCT in 10/13 patients (77%), slightly worsened in 1 patient (Patient-14), and slightly improved in 2 patients (Patient-7 and -10) (Fig. 1B). Sundal scores were positively correlated to EDSS values ($R = 0.31$, $P = 0.018$) (Fig. 2). Five patients were scanned using a 3D FLAIR sequence at all available timepoints (Patient-13 to -17). Lesion load decreased over time in three of them (Fig. 2A, C). Diffusion weighted imaging (DWI) in these 5 patients showed that areas of restricted diffusion tended to disappear after HSCT (Fig. 2B, D), sometimes several years post-transplant (Patient-13). Figure S3 illustrates longitudinal changes in MD in 2 patients by means of images generated by the BrainQuant pipeline. The least affected French patient, Patient-15, showed improved FA (data not shown) and decreasing MD after transplantation, which coincided with clinical improvements. The three other French patients with more advanced disease at baseline (Patient-14, -16, -17) had stable, markedly elevated FA and MD that did not change over time despite clinical improvements, as shown for MD in Patient-14 (Fig. S3).

Changes in NfL Levels of Adult Patients with CSF1R-RD after HSCT

Plasma/serum NfL levels ($n = 12$) ranged from 11.9 to 261.7 pg/mL at baseline (Fig. 1C, Table S5). NfL levels decreased rapidly after HSCT in most patients. Three individuals initially demonstrated increased NfL

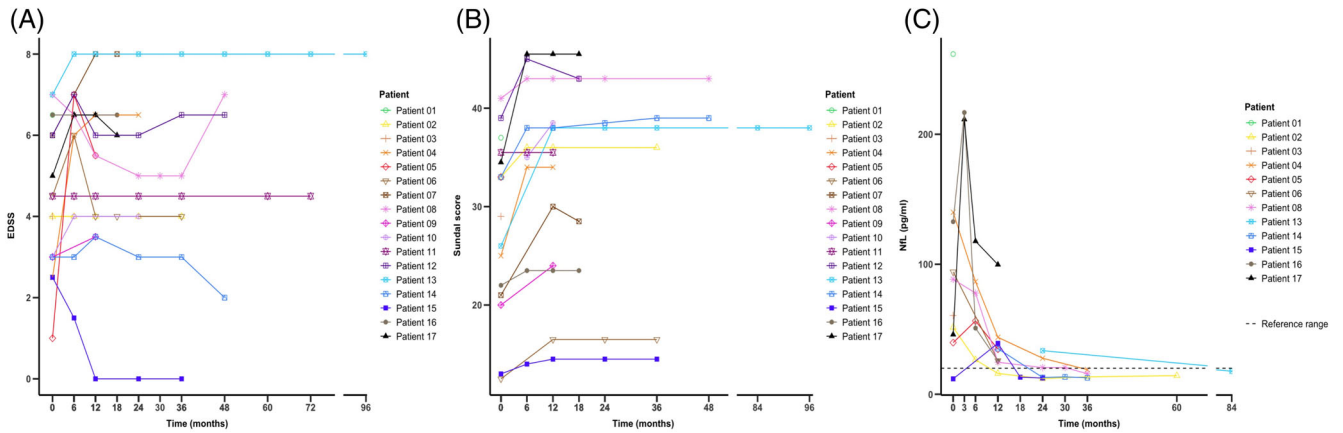

FIG. 1. Clinical, neuroradiological, and biological evolution of 17 patients with CSF1R-RD with hematopoietic stem cell transplantation (HSCT). T = 0 represents time of transplantation. (A) Clinical evolution with Expanded Disability Scoring Scale (EDDS). Besides the 2 patients who died a few months after transplant, the EDSS increased for 9/15 patients during the first 6 months post-HSCT but then stabilized (10/15) or improved (5/15) – nonetheless, Patient-8 returned to his baseline score at 4 years post-HSCT. (B) Neuroradiological evolution with the Sundal score. The total Sundal score increased in 12/13 patients during the first 6 months post-HSCT but then stabilized in 10/13 patients. (C) Plasma/serum neurofilament light chain (NfL) (pg/mL) is presented on the y-axis. NfL increased slightly in 4/12 patients shortly after transplantation but decreased afterwards in all patients.

levels followed by a decrease within the first year (Fig. 1C). NfL levels further decreased or remained stable beyond 1-year post-HSCT and returned to normal values in 5 patients (Fig. 1C, Table S5).

Transplantation of a Pediatric Patient with Homozygous *CSF1R* Pathogenic Variants

One pediatric patient with a biallelic *CSF1R* pathogenic variant (c.2498C>T, p.Thr833Met) was transplanted in 2020 under the age of 10 years. Total intelligence quotient (IQ) was 79 (Wechsler Intelligence Scale for Children [WISC-V]) with mostly alterations in working memory, processing speed, motor coordination, and information processing. On examination, the child displayed muscle weakness in the legs and cerebellar signs, but no bone abnormalities as seen in the BANDDOS phenotype.[20,21] Brain MRI showed a typical ALSP pattern with confluent white matter abnormalities predominantly in the parieto-occipital regions. The patient underwent a myeloablative bone marrow transplantation 7 months after symptom onset from a 10/10 related-matched donor. HSCT resulted in CMV-reactivation and hemorrhagic cystitis. Six months after transplantation, the total IQ was 60 with a deterioration in processing speed, verbal comprehension, visuospatial abilities, and fluid reasoning. The child also developed neurogenic bladder and muscle weakness had worsened. Four years after transplantation, the patient is cognitively stable and has completed the first year of secondary school with curricular support but requires help for almost all day-to-day activities because of important motor involvement. Brain MRI has shown extension of white matter lesions to frontal regions with marked atrophy, as seen in adult patients with CSF1R-RD.

Discussion

Unlike the natural history of CSF1R-RD, a rapidly progressive neurodegenerative disease leading to death within a few years,[4,5] this international cohort shows that HSCT can halt disease progression usually after 6 months post-transplantation, as reflected by the arrest of brain demyelination, major decrease of NfL plasma/serum levels, and often stabilization or even improvement of clinical symptoms. Within the first 6 months post-HSCT, 2 patients had died, and clinical and radiological scores had worsened in most surviving patients, likely related to the toxicity of HSCT and the delay in stem cells engrafting. However, from 12 months post-HSCT, most surviving patients stabilized or improved clinically while radiological scores fully stabilized, or slightly improved, in all patients but one. Previous studies have suggested that HSCT can be a therapy for CSF1R-RD.[12-15,22] This cohort provides clinical, radiological, and biological data up to 8 years of follow-up supportive of HSCT being a major therapeutic option for patients with CSF1R-RD, especially if performed at an early disease stage. This report should also have consequences for HSCT national insurance policies in CSF1R-RD.

In this study, patients with CSF1R-RD suffered most often from psychiatric, cognitive, extrapyramidal, and pyramidal symptoms. These symptoms have been described as core manifestations and diagnostic criteria for CSF1R-RD.[23] The prevalence of psychiatric and cognitive symptoms in this study was higher (82%)

TABLE 2 *Neurocognitive outcomes in five adult patients with colony stimulating factor-1 receptor-related disorder (CSF1R-RD) before and after hematopoietic stem cell transplantation.*

	Patient-13			Patient-14			Patient-15			Patient-16			Patient-17		
Neurocognitive outcome	**M0**	**M12**	**M96**	**M0**	**M12**	**M48**	**M0**	**M12**	**M24**	**M0**	**M12**	**M24**	**M0**	**M12**	**M24**
WAIS-IV (Wechsler Adult Intelligence Scale)															
Verbal Comprehension Index - PRO	–	–	–	92	71	112	77	81	81	94	10674	104	88	75	88
Perceptual Reasoning Index - PRO	–	–	–	**62**	**58**	76	**68**	76	86	74	**74**	80	76	64	**82**
Working Memory Index - Subtest Digit Span	10	11	7	10	**4**	10	5	5	6	7	9	11	5	**4**	**4**
Processing Speed Index - Subtest Symbol Search	–	–	–	**1**	–	**1**	6	7	8	5	**5**	6	**3**	**3**	**7**
Digit span															
Auditory (/19)	10	11	7	10	**4**	10	5	5	6	7	9	11	5	**4**	4
Visual (/19)	–	–	–	**1**	**1**	**1**	10	9	12	–	9	7	6	5	7
TMT (Trail Making Test)															
TMT A (s)	–	–	–	**315**	**341**	**117**	35	28	32	**104**	128	**70**	56	**120**	**51**
TMT B (s)	–	–	–	**>344**	–	–	103 + **1 P**	74	77	**180**	252	**113**	**207**	NA	NA
BRIEF – A (Behavior Rating Inventory of Executive Function – Adult) – Global Executive Composite							46	41	51	–	89	**77**	63	–	51
Metacognition Index	–	–	–	–	–	–	56	41	51	–	86	**81**	63	–	47
	–	–	–	–	–	–	40	42	52	–	83	**67**	62	–	54
Orientation (/10)	–	–	–	**7**	**7**	8	10	10	10	–	9	10	10	6	**9**
16-Item Free and Cued Recall															
Immediate Recall (/16)	16	16	16	14	15	15	16	16	16	16	14	16	**13**	11	**13**
Free Recall three trials (/48)	31	**23**	26	**8**	**8**	**17**	35	39	39	30	34	44	**18**	10	**15**
Total Recall three trials (/48)	48	48	47	**34**	45	48	47	48	47	47	48	48	44	40	40
Delayed Free Recall (/16)	12	**8**	**10**	**2**	**3**	**2**	14	14	12	11	12	14	**6**	3	**3**
Delayed Total Recall (/16)	16	15	16	**14**	15	16	16	16	16	16	16	16	**13**	13	**15**
ROCF (Rey–Osterrieth Complex Figure) – Immediate Recall (/36)	–	–	–	–	–	–	25	23	26	**4**	NA	NA	**11**	–	16
Deno40 (/40)	–	–	–	39	40	40	**37**	**38**	39	39	**39**	39	39	37	**39**
Verbal Fluency															
Category Fluency (Animals)	**15**	**15**	**17**	**19**	**9**	25	23	27	25	–	31	40	**6**	**9**	**18**
Letter Fluency (P)	**5**	**15**	**13**	**9**	**7**	26	11	11	**8**	–	**21**	18	**4**	1	**4**
ROCF (Rey–Osterrieth Complex Figure) – Copy (/36)	–	–	–	**6**	–	**28**	35	**32**	34	**28**	14	**29**	**25**	**10**	**28**
VOSP (Visual Object and Space Perception Battery)															
Incomplete Letters	–	–	–	19	19	20	–	–	–	17	20	20	–	19	-
Number Location	–	–	–	**1**	**2**	**6**	7	8	7	7	9	10	10	8	7

(Continues)

TABLE 2 *Continued*

Neurocognitive outcome	Patient-13			Patient-14			Patient-15			Patient-16			Patient-17		
	M0	M12	M96	M0	M12	M48	M0	M12	M24	M0	M12	M24	M0	M12	M24
STAI (The State–Trait Anxiety Inventory)															
State Anxiety	–	–	–	–	–	–	51	24	34	54	73	**48**	51	–	45
Trait Anxiety	–	–	–	–	–	–	**56**	35	37	**62**	76	**68**	50	–	47
BDI (Beck Depression Inventory)	–	–	–	–	–	–	**11**	3	**6**	**11**	**26**	**20**	**11**	–	14

Note: Abnormal values are indicated in bold type.
Abbreviations: M, month; NA, not available; P, perseveration; PRO, prorate.

than previously described,[5] including in a recent study focused on a Chinese population (43%).[24] Unlike what was suggested,[25] we did not identify cognitive impairments as a negative predictor. Still, we did not transplant patients with pronounced cognitive deficit who were unable to consent to HSCT. Also, the child with a biallelic *CSF1R* variant experienced the most severe cognitive and motor deterioration during the first year post-transplant but has stabilized since.

It should be noted that some patients experienced motor and cognitive improvements even years after HSCT, for example, excellent cognitive outcome 4 years after HSCT for Patient-14 and full recovery to an asymptomatic status for Patient-15. Further to clinical stabilization, the effect of HSCT was clearly noticeable on radiological and biological markers. Most patients exhibited full stabilization of the Sundal score after an initial increase during the first 6 months post-HSCT. Patient-15 showed clear improvement of DTI parameters which coincided with clinical improvements. These new methods of calibrated and standardized DTI showed similar improvements in patients with X-linked adrenoleukodystrophy (X-ALD) who were successfully treated.[26] In contrast, FA and MD were not sensitive to change in more advanced CSF1R-RD patients, likely due to marked DTI alterations at baseline. Notably, the Sundal score of 1 patient has remained stable up until 8 years while diffusion restriction continued to improve beyond 3 years post-transplantation. As regards clinical outcomes, this suggests that the disease-modifying effects of HSCT can continue for years post-transplant in CSF1R-RD. The clinical and radiological initial worsening after transplantation has been reported in X-ALD,[27,28] but the possibility of subsequent improvement in CSF1R-RD after HSCT is intriguing and may be partially explained by CSF1R restricted expression to macrophages and microglia. These observations support important research areas aiming at targeting innate immune cells as neuroregenerative therapies.[29] Plasma NfL decreased rapidly after transplantation, which illustrates the sensitivity of NfL as a biomarker of treatment response and the long-term effects of transplant. NfL was shown to be elevated in presymptomatic individuals with *CSF1R* pathogenic variants,[16] but future studies should investigate whether NfL and/or brain DTI can detect disease onset so as to provide the best therapeutic window for HSCT.

Two patients died rapidly from early complications of myeloablative HSCT, including the only patient who received cord blood. Only 4 patients suffered from GvHD – noticeably, none who received peripheral blood stem cells – and manifestations were mild in most cases. Historically, myeloablative conditioning with cerebral penetration was considered preferable to facilitate microglia reconstitution and mitigate the effect of rejections in non-malignant disease.[30-33] However, in patients of older age – as is frequently the case with CSF1R-RD – a myeloablative conditioning of a full graft may lead to severe toxicity. Remarkably, 7/8 patients who received a reduced-intensity or reduced-toxicity conditioning regimen had similar neurological outcomes as patients who underwent a myeloablative HSCT. This indicates that reduced conditioning regimens may suffice to halt disease progression in CSF1R-RD so that more fragile patients, especially older patients, may be eligible for HSCT. Another consideration is that the mean time between symptom onset and transplantation was approximately 2 years. As shown in other leukodystrophies, early symptomatic patients may benefit the most from treatment.[34,35] This emphasizes the need to counsel family members of affected individuals. Systematic treatment of presymptomatic individuals is, however, not recommended because of the incomplete penetrance of the disease.[6]

HSCT is currently the only intervention for symptomatic patients with CSF1R-RD. This study has provided new insights into medium- and long-term effects of HSCT thanks to the relatively large number of treated individuals and the international background of our cohort. This is especially useful considering that the clinical trial testing TREM2 agonist in patients with CSF1R-RD (NCT05677659) has been stopped in the absence of beneficial effects on biomarker or clinical efficacy endpoints (https://investors.vigilneuro.com/news-releases/news-release-details/vigil-neuroscience-

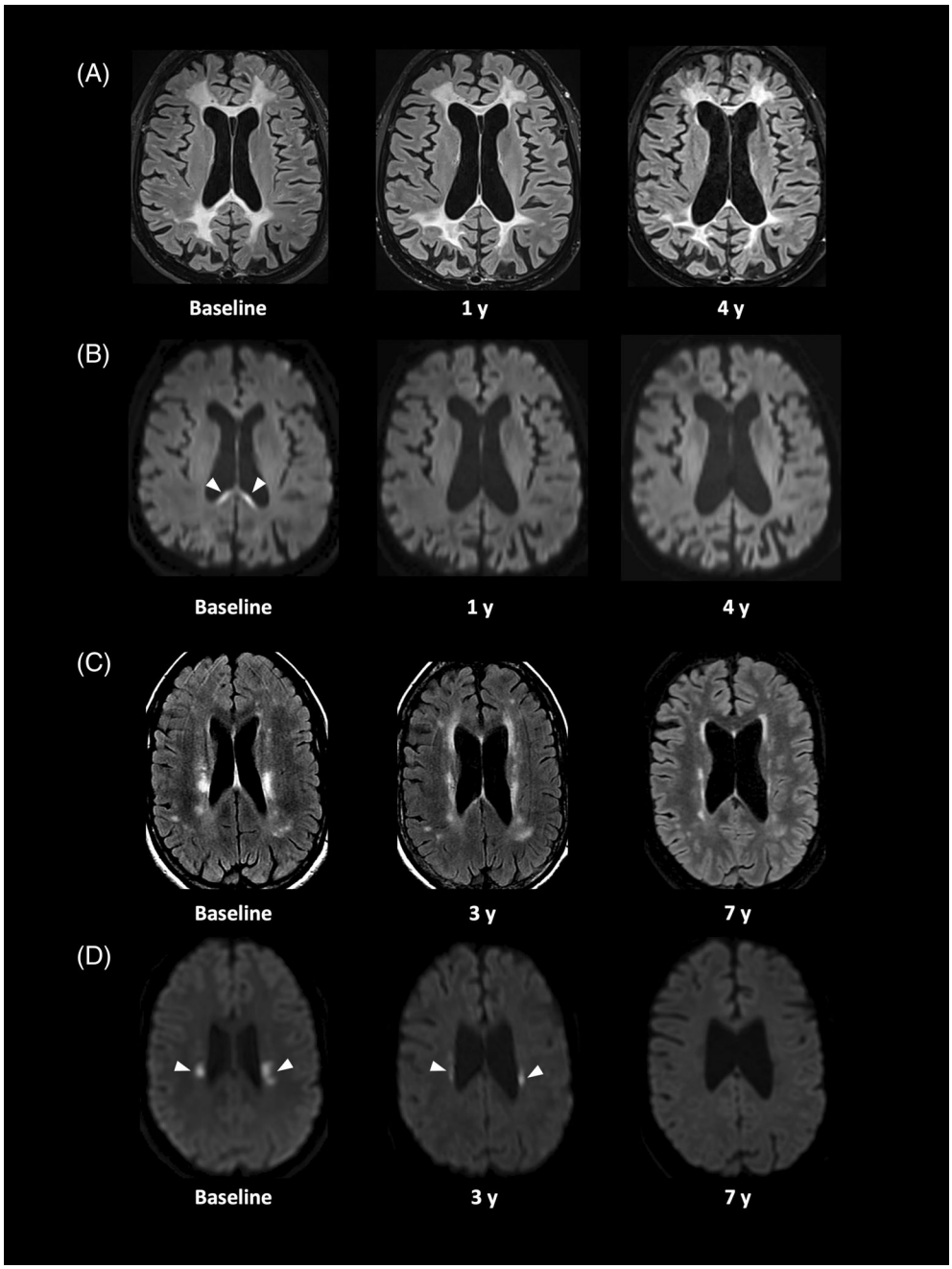

FIG. 2. Changes in white matter lesions in CSF1R-RD patients with transplantation. (A) Patient-14 presented with extensive fluid-attenuated inversion recovery (FLAIR) hyperintensities in the frontal and parietal white matter at baseline. Lesions decreased in size from 1 year onwards after transplantation, in parallel with atrophic evolution. (B) Diffusion weighted imaging (DWI) of the same patient, exhibiting restricted diffusion in callosal lesions at baseline, that disappeared early after transplantation. (C) Patient-13 presented with areas of FLAIR hyperintensity in the centra semiovalia at baseline. Lesions progressively decreased in thickness and extent over a period of 7 years, in parallel with atrophic evolution. (D) DWI of the same patient, exhibiting restricted diffusion in lesions of the centra semiovalia at baseline. Diffusion abnormalities progressively decreased over time and disappeared at 7 years post-HSCT.

provides-update-iluzanebart-phase-2-ignite). Study limitations comprise the retrospective nature of the data, as well as the unblinded assessment of the EDSS and MRI scans. Research would benefit from even larger international cohort studies and academic registries for long-term follow-up. This would allow better definition of standardized HSCT protocols and refine criteria about who would benefit the most from HSCT. While the data presented here do not allow the definition of clinical or radiological cut-off references for who should be transplanted, we observed that, after the initial deterioration in the first 6 months post-transplantation, HSCT can halt disease progression in patients with CSF1R-RD even with advanced motor

stages and/or moderate cognitive alterations. Patients with a broad phenotypic spectrum may therefore be eligible for transplantation. Because HSCT remains a burdensome and risky procedure, and patients may not be eligible (eg, absence of matched donors, comorbidities), alternative treatments are still needed.

Author Roles: (1) Research Project: A. Conception, B. Design, C. Execution, D, Supplied Data; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the First Draft, B. Editing the Final Version.
H.A.F.Y.: 2C, 3A, 3B.
M.G.: 2B, 3A, 3B.S.B.: 2B, 3B.
S.H.: 1D, 3B.
C.B.: 1D, 3B.
A.R.B.d.P.: 1D, 3B.
C.M.: 1D, 3B.
N.J.P.: 1D, 3B.
Y.L.O.: 1D, 3B.
C.H.: 2B, 3B.
G.F.: 1D, 3B.
F.W.: 1D, 3B.
U.H.: 1D, 3B.
X.A.: 2B, 3B.
M.S.v.d.K.: 1D, 3B.
L.S.: 1D, 3B.
V.P.: 3B
D.G.: 1D, 3B.
M.A.d.W.: 2B, 3B.
N.I.W.: 1B, 2B, 3A, 3B.
S.N.: 2B, 3B.
F.M.: 1A, 1B, 1C, 1D, 2C, 3B.

Financial Disclosures: S.B., C.H., N.I.W., and F.M. are co-investigators for the NCT05677659 trial in Adult Leukoencephalopathy with axonal Spheroids and Pigmented glia (Vigil). In addition, N.I.W. is advisor and/or co-investigator for trials in other leukodystrophies (Shire/Takeda, Orchard, Evidera, Ionis, PassageBio, Sana Biotech). F.M. is advisor and/or co-investigator for trials in X-linked adrenoleukodystrophy (Minoryx Therapeutics, Braintale). M.S.v.d.K. is co-investigator for the ION_373_CS in Alexander disease (Ionis). She is on patent P112686US00 "Therapeutic effects of Guanabenz treatment in vanishing white matter" and on patent P112686CA00 "The use of Guanabenz in the treatment of vanishing white matter". She is initiator and principal investigator of the Guanabenz trial (https://www.clinicaltrialsregister.eu/ctr-search/trial/2017-001438-25/NL).

Data Availability

Anonymized data not published within this article will be made available on request from any qualified investigator.

References

1. Dulski J, Muthusamy K, Lund TC, Wszolek ZK. CSF1R-related disorder: state of the art, challenges, and proposition of a new terminology. Parkinsonism Relat Disord 2024;121:105894. https://doi.org/10.1016/j.parkreldis.2023.105894
2. Pixley FJ, Stanley ER. CSF-1 regulation of the wandering macrophage: complexity in action. Trends Cell Biol 2004;14(11):628–638. https://doi.org/10.1016/j.tcb.2004.09.016
3. Chitu V, Gokhan Ş, Nandi S, Mehler MF, Stanley ER. Emerging roles for CSF-1 receptor and its ligands in the nervous system. Trends Neurosci 2016;39(6):378–393. https://doi.org/10.1016/j.tins.2016.03.005
4. Konno T, Yoshida K, Mizuno T, et al. Clinical and genetic characterization of adult-onset leukoencephalopathy with axonal spheroids and pigmented glia associated with CSF1R mutation. Eur J Neurol 2017;24(1):37–45. https://doi.org/10.1111/ene.13125
5. Papapetropoulos S, Gelfand JM, Konno T, et al. Clinical presentation and diagnosis of adult-onset leukoencephalopathy with axonal spheroids and pigmented glia: a literature analysis of case studies. Front Neurol 2024;15:1320663. https://doi.org/10.3389/fneur.2024.1320663
6. Wade C, Runeckles K, Chataway J, Houlden H, Lynch DS. CSF1R-related disorder: prevalence of CSF1R variants and their clinical significance in the UK population. Neurol Genet 2024;10(4):e200179. https://doi.org/10.1212/NXG.0000000000200179
7. Schmitz AS, Raju J, Köhler W, et al. Novel variants in CSF1R associated with adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP). J Neurol 2024;271(9):6025–6037. https://doi.org/10.1007/s00415-024-12557-0
8. Sundal C, Van Gerpen JA, Nicholson AM, et al. MRI characteristics and scoring in HDLS due to CSF1R gene mutations. Neurology 2012;79(6):566–574. https://doi.org/10.1212/WNL.0b013e318263575a
9. Codjia P, Ayrignac X, Mochel F, et al. Adult-onset leukoencephalopathy with axonal spheroids and pigmented glia: an MRI study of 16 French cases. AJNR Am J Neuroradiol 2018;39(9):1657–1661. https://doi.org/10.3174/ajnr.A5744
10. Kinoshita M, Oyanagi K, Matsushima A, et al. Adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP): estimation of pathological lesion stage from brain images. J Neurol Sci 2024;461:123027. https://doi.org/10.1016/j.jns.2024.123027
11. Konno T, Kasanuki K, Ikeuchi T, Dickson DW, Wszolek ZK. CSF1R-related leukoencephalopathy: a major player in primary microgliopathies. Neurology 2018;91(24):1092–1104. https://doi.org/10.1212/WNL.0000000000006642
12. Tipton PW, Kenney-Jung D, Rush BK, et al. Treatment of CSF1R-related leukoencephalopathy: breaking new ground. Mov Disord 2021;36(12):2901–2909. https://doi.org/10.1002/mds.28734
13. Mochel F, Delorme C, Czernecki V, et al. Haematopoietic stem cell transplantation in CSF1R-related adult-onset leukoencephalopathy with axonal spheroids and pigmented glia. J Neurol Neurosurg Psychiatry 2019;90(12):1375–1376. https://doi.org/10.1136/jnnp-2019-320701
14. Gelfand JM, Greenfield AL, Barkovich M, et al. Allogeneic HSCT for adult-onset leukoencephalopathy with spheroids and pigmented glia. Brain 2020;143(2):503–511. https://doi.org/10.1093/brain/awz390
15. Żur-Wyrozumska K, Mensah-Glanowska P, Piątkowska-Jakubas B. The first allogeneic hematopoietic stem cell transplantation in a Polish patient with adult-onset leukoencephalopathy with spheroids and pigmented glia. Mov Disord 2022;37(7):1570–1572. https://doi.org/10.1002/mds.29068
16. Hayer SN, Krey I, Barro C, et al. NfL is a biomarker for adult-onset leukoencephalopathy with axonal spheroids and pigmented glia. Neurology 2018;91(16):755–757. https://doi.org/10.1212/WNL.0000000000006357
17. Puybasset L, Perlbarg V, Unrug J, et al. Prognostic value of global deep white matter DTI metrics for 1-year outcome prediction in ICU traumatic brain injury patients: an MRI-COMA and CENTER-TBI combined study. Intensive Care Med 2022;48(2):201–212. https://doi.org/10.1007/s00134-021-06583-z
18. Velly L, Perlbarg V, Boulier T, et al. Use of brain diffusion tensor imaging for the prediction of long-term neurological outcomes in patients after cardiac arrest: a multicentre, international, prospective, observational, cohort study. Lancet Neurol 2018;17(4):317–326. https://doi.org/10.1016/S1474-4422(18)30027-9
19. Vermunt L, Otte M, Verberk IMW, et al. Age- and disease-specific reference values for neurofilament light presented in an online interactive support interface. Ann Clin Transl Neurol 2022;9(11):1832–1837. https://doi.org/10.1002/acn3.51676
20. Beerepoot S, Verbeke JIML, Plantinga M, et al. Leukoencephalopathy with calcifications, developmental brain abnormalities and skeletal dysplasia due to homozygosity for a hypomorphic CSF1R variant: a report of three siblings. Am J Med Genet A 2024;194(11):e63800. https://doi.org/10.1002/ajmg.a.63800
21. Guo L, Bertola DR, Takanohashi A, et al. Bi-allelic CSF1R mutations cause skeletal dysplasia of dysosteosclerosis-Pyle disease spectrum and degenerative encephalopathy with brain malformation. Am J Hum Genet 2019;104(5):925–935. https://doi.org/10.1016/j.ajhg.2019.03.004

22. Eichler FS, Li J, Guo Y, et al. CSF1R mosaicism in a family with hereditary diffuse leukoencephalopathy with spheroids. Brain 2016; 139(Pt 6):1666–1672. https://doi.org/10.1093/brain/aww066

23. Konno T, Yoshida K, Mizuta I, et al. Diagnostic criteria for adult-onset leukoencephalopathy with axonal spheroids and pigmented glia due to CSF1R mutation. Eur J Neurol 2018;25(1):142–147. https://doi.org/10.1111/ene.13464

24. Wu J, Cheng X, Ji D, et al. The phenotypic and genotypic spectrum of CSF1R-related disorder in China. Mov Disord 2024;39(5):798–813. https://doi.org/10.1002/mds.29764

25. Dulski J, Heckman MG, White LJ, Żur-Wyrozumska K, Lund TC, Wszolek ZK. Hematopoietic stem cell transplantation in CSF1R-related leukoencephalopathy: retrospective study on predictors of outcomes. Pharmaceutics 2022;14(12):2778. https://doi.org/10.3390/pharmaceutics14122778

26. Golse M, Weinhofer I, Blanco B, et al. Leriglitazone halts disease progression in adult patients with early cerebral adrenoleukodystrophy. Brain 2024;147(10):3344–3351. https://doi.org/10.1093/brain/awae169

27. Kühl JS, Suarez F, Gillett GT, et al. Long-term outcomes of allogeneic haematopoietic stem cell transplantation for adult cerebral X-linked adrenoleukodystrophy. Brain 2017;140(4):953–966. https://doi.org/10.1093/brain/awx016

28. Waldhüter N, Köhler W, Hemmati PG, et al. Allogeneic hematopoietic stem cell transplantation with myeloablative conditioning for adult cerebral X-linked adrenoleukodystrophy. J Inherit Metab Dis 2019;42(2):313–324. https://doi.org/10.1002/jimd.12044

29. Minhas PS, Latif-Hernandez A, McReynolds MR, et al. Restoring metabolism of myeloid cells reverses cognitive decline in ageing. Nature 2021;590(7844):122–128. https://doi.org/10.1038/s41586-020-03160-0

30. Colella P, Sayana R, Suarez-Nieto MV, et al. CNS-wide repopulation by hematopoietic-derived microglia-like cells corrects progranulin deficiency in mice. Nat Commun 2024;15(1):5654. https://doi.org/10.1038/s41467-024-49908-4

31. Capotondo A, Milazzo R, Politi LS, et al. Brain conditioning is instrumental for successful microglia reconstitution following hematopoietic stem cell transplantation. Proc Natl Acad Sci U S A 2012; 109(37):15018–15023. https://doi.org/10.1073/pnas.1205858109

32. Boelens JJ, Wynn RF, O'Meara A, et al. Outcomes of hematopoietic stem cell transplantation for Hurler's syndrome in Europe: a risk factor analysis for graft failure. Bone Marrow Transplant 2007; 40(3):225–233. https://doi.org/10.1038/sj.bmt.1705718

33. Aldenhoven M, Jones SA, Bonney D, et al. Hematopoietic cell transplantation for mucopolysaccharidosis patients is safe and effective: results after implementation of international guidelines. Biol Blood Marrow Transplant 2015;21(6):1106–1109. https://doi.org/10.1016/j.bbmt.2015.02.011

34. Cartier N, Aubourg P. Hematopoietic stem cell transplantation and hematopoietic stem cell gene therapy in X-linked adrenoleukodystrophy. Brain Pathol 2010;20(4):857–862. https://doi.org/10.1111/j.1750-3639.2010.00394.x

35. Boucher AA, Miller W, Shanley R, et al. Long-term outcomes after allogeneic hematopoietic stem cell transplantation for metachromatic leukodystrophy: the largest single-institution cohort report. Orphanet J Rare Dis 2015;10:94. https://doi.org/10.1186/s13023-015-0313-y

Appendix A

International CSF1R-RD Working group

Wolfgang Köhler, Angeles Garcia-Cazorla, Laetitia Souchet, Boris Chaumette, Bernardo Blanco, Magali Barbier, Bruno Stankoff, Anne-Laure Dubessy, Florence Robert-Varvat, Audrey Riou, Sacha Weber, Benjamin Bender, Nathalie Fegueux, Patrice Ceballos, Nicolas Menjot de Champfleur, Sylvain Lehmann, Clarisse Cara-Dallière, Pierre Labauge, Caroline Lindemans, Fernando Freua, Livia Mariano, Leandro Tavares Lucato, Gustavo Bruniera Peres Fernandes, Claudio M. de Gusmão, José Ulysses Amigo Filho, Fernando Kok, Laia Turon, Isabel Badell, Iván López Torija, Marta Gomez.

Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.