mitochondrial cocktail in mitochondrial disorders has been reported with some success in certain cases. Whether or not mitochondrial cocktail is useful for this FDXR-associated disorder has not been reported. Our trail of treatment seemed not successful for the proband. Further studies may be needed.

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More renal genetics specialists are needed: Experience from a tertiary medical center

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Introduction: Chronic kidney disease (CKD) is one of leading global public health problems with 37 million Americans affected and among those, 10% have a monogenic origin. That means nearly three million Americans suffer a genetic kidney disease. However, the training in Renal Genetics for both geneticists and genetic counselors are not sufficient to meet the demand from patients and referring providers. Here we present our experience from the Renal Genetics Clinic in the Cleveland Clinic, a tertiary medical center.
Methods: A cohort of cases in the Renal Genetics Clinic in the Cleveland Clinic, Cleveland, Ohio, over two-year period was analyzed.
Results: Between January 2019 and January 2021, 186 new patients were referred to Renal Genetics Clinic in the Cleveland Clinic. The care team include three geneticists, three nephrologists, and three genetic counselors. There was tenfold increase in the referrals compared to that in the previous two-year period before the start of Renal Genetic Clinic. The referrals came from different specialties including Nephrology (69%), Primary Care (6%), Genetics (5%), Endocrinology (5%), Hematology (4%), Rheumatology (4%), OBGYN (2%), Hepatology (2%) Urology (1%), Cardiology (1%), and Neurology (1%). Presentation of patients are variable with glomerular disease (40%), cystic kidney disease (24%), electrolyte disorders (24%), congenital anomalies of kidneys and urinary tract (8%), kidney stones and nephrocalcinosis (3%), and tubulointerstitial disease (1%). 80% patients had insurance covered for the genetic work up which included chromosomal microarray, single gene test, multi-gene panel, or exome sequencing. 49% patients had pathogenic or likely pathogenic findings, 27% were heterozygous carriers for autosomal recessive disorders, 20% had negative testing, and 4%had high risk alleles for APOL1 gene. With the genetic results, 40% patients received an adjustment in the management including initiation or discontinuation of medications.
Conclusion: The need from patients and referring providers for Renal Genetics Clinic has been increasing, which suggests more attention and efforts are needed to train specialists in Renal Genetics. Renal Genetics Clinic is very important for the management of patients with genetic kidney diseases and a majority of patients received insurance coverage for renal genetics testings in our practice.

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Continued improvement in adults with acid sphingomyelinase deficiency after 2 years of olipudase alfa in the ASCEND placebo-controlled trial

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Introduction: Acid sphingomyelinase deficiency (ASMD), also historically known as Niemann-Pick disease A (OMIM #257200) and B (OMIM#607616), is a rare and debilitating lysosomal storage disease caused by pathogenic variants in *SMPD1* gene. Deficient activity of the lysosomal enzyme acid sphingomyelinase (ASM) leads to sphingomyelin accumulation in various organs. Visceral manifestations of ASMD include interstitial lung disease and pulmonary dysfunction, splenomegaly, hepatomegaly, dyslipidemia, thrombocytopenia, and anemia and are present across ASMD phenotypes (ASMD type A, B and A/B). In more severe cases of ASMD (ASMD type A), there are also central nervous system manifestations. No disease-specific treatment is currently approved for patients with ASMD. Olipudase alfa, an intravenous-recombinant-human ASM, is in late-stage development (Sanofi Genzyme) for the non-central-nervous-system manifestations of ASMD in children and adults. Two open-label trials, a phase 1b trial in 5 adults (NCT01722526) and a phase 1/2 trial in 20 children with chronic ASMD (ASCEND-Peds, NCT02292654) demonstrated improvement of pulmonary function, reduction of liver and spleen volume, reversal of dyslipidemia, decreased disease biomarkers, and in children, improved growth. A phase 2/3 placebo-controlled trial, the ASCEND study (NCT02004691) in 36

adults with ASMD who had splenomegaly and pulmonary dysfunction, has completed its primary analysis. Olipudase-alfa-treated patients compared to placebo-treated patients (1:1 randomization) had statistically significant increases in percent-predicted diffusing capacity of carbon monoxide (DL_{CO}) and statistically significant decreases in spleen and liver volume after 1 year of placebo or olipudase alfa. Thirty-five of 36 patients continued in an open-label trial extension including 17 of the 18 patients who initially received placebo in the first year and all 18 patients who received olipudase alfa. Here we report Year 2 results of the ASCEND trial for the former placebo group after 1 year of olipudase alfa treatment and for the initial olipudase alfa group after 2 years of olipudase alfa treatment.

Methods: All patients underwent gradual dose-escalation to 3.0 mg/kg every 2 weeks for approximately 14 weeks when starting olipudase alfa. Efficacy outcomes include percent-predicted DL_{CO}, spleen volume, liver volume, lung high-resolution computerized tomography (HRCT) scores for ground glass appearance, histopathologic clearance of sphingomyelin in the liver, platelet count, plasma lyso-sphingomyelin, liver function, and lipid profile. Change from baseline results are presented as least-square mean (analysis of covariance [ANCOVA]) percent change ± standard error of the mean (SEM), except for ground glass appearance, which is the least-square mean ANCOVA absolute change from baseline, and percent liver tissue area occupied by sphingomyelin and plasma lyso-sphingomyelin, which are presented as mean changes ± standard deviation (SD). Absolute values at Baseline, Year 1, and Year 2 are presented as mean ± SD (Table).

Results: Overall, 33 of 35 patients completed Year 2 of ASCEND; one former placebo patient withdrew due to COVID-19 travel restrictions, and one continuing olipudase alfa patient withdrew consent. COVID-19 travel restrictions also resulted in at least one missed assessment in six patients. In Year 2, improvements for patients in the former placebo group paralleled the olipudase alfa group in the primary analysis while clinical improvement continued for patients who received 2 years of olipudase alfa (Table). For patients in the former placebo group, percent-predicted DL_{CO} increased by 28.0 ±6.2% (n=10); spleen volume decreased by 36.0 ±3.0% (n=11); liver volume decreased by 30.7 ±2.5% (n=11), and platelet count increased by 21.7 ±6.4% (n=15). In patients with 2 years of olipudase alfa treatment, percent-predicted DL_{CO} increased by 22.2 ±3.4% (n=17) at Year 1 and 28.5±6.2% at Year 2 (n=10); spleen volume decreased by 39.5 ±2.4% (n=17) at Year 1 and 47.0 ±2.7% (n=14) at Year 2; liver volume decreased by 27.8 ±2.5% (n=17) at Year 1 and 33.4 ±2.2% (n=14) at Year 2, and platelet count increased by 16.6 ±4.0% at Year 1 (n=18) and 24.9 ±6.9% (n=13) at Year 2. HRCT ground glass appearance score decreased 0.30 ±0.5 (n=14) at Year 2 for patients in the former placebo group and decreased by 0.45 ±0.13 (n=18) at Year 1 and 0.48 ±0.07 (n=16) at Year 2 for patients continuing to receive olipudase alfa. Liver sphingomyelin clearance at Year 2 was 93.3 ±5.0% (n=10) for patients in the former placebo group and 92.7 ±5.8% at Year 1 (n=13) and 98.4 ±2.0% at Year 2 (n=10) for patients continuing to receive olipudase alfa. Plasma lyso-sphingomyelin decreased by 79.4 ±11.3% (n=14) for patients in the former placebo group and by 78.0 ±11.1% (n=18) at Year 1 and 64.4 ±28.5% (n=15) at Year 2 for patients continuing to receive olipudase alfa; several patients had transient increases due to missed infusions. Alanine aminotransferase decreased by 45.2 ±34.4% (n=15) for patients in the former placebo group, and by 36.5 ±8.4% (n=18) in Year 1 and 32.0 ±10.2% (n=12) in Year 2 for patients continuing to receive olipudase alfa. For patients in the former placebo group, high-density lipoprotein cholesterol (HDL-C) increased by 59.7 ±9.7% (n=14) and low-density lipoprotein cholesterol (LDL-C) decreased by 27.5 ±6.8% (n=13) in Year 2. For patients continuing to receive olipudase alfa, HDL-C increased by 40.0 ±6.8% (n=18) in Year 1 and 64.4 ±10.5% (n=12) in Year 2 and LDL-C decreased by 25.8 ±4.8% (n=18) in Year 1 and 23.0 ±7.1% (n=12) in Year 2. Overall, 99% of treatment-emergent adverse events were mild or moderate, with one treatment-related serious adverse event (extrasystoles in patient with previously documented cardiomyopathy). No patient discontinued due to an adverse event.

Conclusion: During Year 2 of ASCEND, patients crossing over from placebo to olipudase alfa had the same magnitude and time course of clinical improvement seen in patients receiving olipudase alfa for 1 year, while continuing olipudase-alfa patients had sustained or further improvements. Olipudase alfa reduced sphingomyelin storage in the liver and lyso-sphingomyelin in plasma. Clinically, olipudase alfa improved pulmonary function, reduced splenomegaly and hepatomegaly, and improved liver function and dyslipidemia for up to 2 years. These results are consistent with the published 30- and 42-month data for adults reported in the long-term extension of the open-label Phase 1b study. Treatment with olipudase alfa reduces manifestations of chronic ASMD in adults and has sustained efficacy.

	Placebo-Olipudase alfa (N=18) (Mean ±SD)			Olipudase alfa-olipudase alfa (N=18) (Mean ±SD)		
Parameter	Trial Baseline	Year 1	Year 2	Trial Baseline	Year 1	Year 2
% predicted DL_{co}	48.5 ± 10.8 (n=18)	49.9 ±11.1 (n=17)	61.9 ±11.4 (n=10)	49.4 ± 11.0 (n=18)	59.4 ±12.5 (n=17)	66.9 ±15.4 (n=10)
Spleen volume (multiples of normal)	11.2 ± 3.8 (n=18)	11.2 ±4.2 (n=17)	7.7 ±2.9 (n=11)	11.7 ± 4.9 (n=18)	7.2 ±3.6 (n=18)	6.0 ±2.7 (n=14)
Liver volume (multiples of normal)	1.62 ± 0.5 (n=18)	1.6 ±0.5 (n=17)	1.1 ±0.3 (n=11)	1.44 ± 0.3 (n=18)	1.0 ±0.2 (n=17)	1.0 ±0.1 (n=14)
Platelet count (10^9/L)	115.6 ± 36.3 (n=18)	120.2 ± 43.1 (n=16)	140.0 ± 50.8 (n=15)	107.2 ± 26.9 (n=18)	123.1 ± 25.8 (n=18)	133.6 ± 29.6 (n=13)
Lung HRCT ground glass appearance score	0.53 ±0.6 (n=18)	0.70 ±0.7 (n=17)	0.22 ± 0.4 (n=14)	0.65 ±0.7 (n=18)	0.15 ±0.3 (n=18)	0.13 ±0.3 (n=16)
ALT (IU/L)	44.7 ±30.8 (n=18)	42.2 ±25.4 (n=16)	17.3 ±6.8 (n=15)	40.8 ±28.3 (n=18)	20.5 ±9.9 (n=18)	19.7 ±8.5 (n=12)
HDL cholesterol (mg/dL)	20.7 ±9.8 (n=18)	19.9 ±7.9 (n=16)	30.7 ±12.7 (n=14)	23.8 ±8.4 (n=18)	31.5 ±9.4 (n=18)	38.6 ±11.2 (n=12)
LDL cholesterol (mg/dL)	154.8 ±65.1 1.0 (n=17)	137.3 ±34.0 (n=15)	106.5 ±36.8 (n=14)	137.4 ±28.6 (n=18)	99.5 ±27.3 (n=18)	105.5 ±41.9 (n=12)

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