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Efficacy and safety of switching therapy from chenodeoxycholic acid to cholic acid in Japanese patients with bile acid synthesis disorders

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ABSTRACT

Objectives: This study aimed to assess the safety and efficacy of cholic acid (CA) treatment over 74 weeks in Japanese patients with inherited enzymatic bile acid synthesis disorders (BASD).
Methods: This phase 3, open-label, single-arm study enrolled four Japanese patients diagnosed with BASD, including two with 3β-hydroxy-Δ^5-C_{27}-steroid dehydrogenase/isomerase (HSD3B7) deficiency and two with Δ^4–3-oxosteroid 5β-reductase (SRD5B1) deficiency. The patients had received chenodeoxycholic acid (CDCA) treatment but were switched to CA treatment. Treatment efficacy was evaluated by measuring serum and urinary bile acid levels and liver-related biomarkers, and adverse events were evaluated to monitor safety.
Results: The daily CA doses ranged from 3.8 to 13.7 mg/kg/day. Laboratory values of liver-related biomarkers were maintained within normal ranges or improved. Bile acid analysis revealed CDCA replacement with CA in serum within the initial few weeks of CA treatment. Urinary concentrations of toxic bile acid metabolites associated with liver damage were higher than serum. Adverse effects from CA treatment were mild to moderate, and no treatment discontinuations were due to adverse events.
Conclusions: CA treatment over 74 weeks resulted in favorable efficacy and safety outcomes in Japanese patients with BASD, consistent with previous studies. These results support the utility of CA as a therapeutic option for Japanese patients with BASD.

1. Introduction

Bile acids are a category of steroids that are biosynthesized from cholesterol in the liver. Bile acid synthesis disorders (BASD) are inherited in an autosomal recessive manner, resulting in enzyme deficiencies affecting the bile acid biosynthetic pathway [1,2]. These defects in the pathway cause the accumulation of unusual bile acid metabolites. Unusual bile acids are highly cytotoxic, causing damage to hepatocytes and, thereby, cholestatic liver injury beginning in infancy [1,2]. In Japan, ten patients, including five with 3β-hydroxy-Δ^5-C_{27}-

Abbreviations: BASD, bile acid synthesis disorders; HSD3B7, 3β-hydroxy-Δ^5-C_{27}-steroid dehydrogenase/isomerase; SRD5B1, Δ^4–3-oxosteroid 5β-reductase; CYP7B1, oxysterol 7α-hydroxylase; CA, cholic acid; CDCA, chenodeoxycholic acid; GCA, glycocholic acid; UDCA, ursodeoxycholic acid; LC/MS, liquid chromatograph mass spectrometry; ALT, alanine aminotransferase; AST, aspartate aminotransferase; D-Bil, direct bilirubin; PT, prothrombin time; 25OH-D, 25-hydroxyvitamin D; Cr, creatinine; DCA, deoxycholic acid; LCA, lithocholic acid; TEAEs, treatment-emergent adverse events; SAEs, serious treatment-emergent adverse events.

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steroid dehydrogenase/isomerase (HSD3B7) deficiency (OMIM 607765), three with Δ^4–3-oxosteroid 5β-reductase (SRD5B1) deficiency (OMIM 235555), one with oxysterol 7α-hydroxylase (CYP7B1) deficiency (OMIM 603711), and one with bile acid-CoA: amino acid N-acyltransferase deficiency (OMIM 619232) have been identified [3–6].

Treatment for patients with BASD includes oral cholic acid (CA) [7–11], chenodeoxycholic acid (CDCA) [12,13], glycocholic acid (GCA) [14], ursodeoxycholic acid (UDCA) [7,12], fat-solvent-vitamin replacement, and liver transplantation [12,15–18]. Oral administration of primary bile acids such as CA and CDCA reduces the production of toxic intermediates by downregulating bile acid synthesis, reducing abnormal bile acid metabolites [7]. Oral CDCA treatment is particularly effective in patients with HSD3B7 and SRD5B deficiencies [13,18–20]. CA has a long history of use as a treatment for congenital dysbiosis of bile acid metabolism in Europe and the United States. Its efficacy and safety have been empirically confirmed [7–11]. Cell Therapies Research & Services, a French pharmaceutical company, started the development of CA as a pharmaceutical product, especially for patients with HSD3B7 and SRD5B deficiency, and applied to the European Medicines Agency for manufacturing and marketing authorization in 2013. The application was approved as a pharmaceutical product (product name: Orphacol® Capsules 50 mg) in the same year. In 2015, the U.S. Food and Drug Administration approved Cholbam® (CA) (Travere Therapeutics, Inc., San Diego, CA, USA) capsules for the treatment of pediatric and adult patients with BASD and peroxisome biogenesis disorder 1a due to single-enzyme deficiency. Currently, in Europe and the USA, primary bile acid treatment with oral CA is the first-line treatment for patients with HSD3B7 and SRD5B deficiency.

In Japan, however, CDCA, a drug for cholelithiasis, is used off-label as a treatment for BASD because CA is not commercially available [13]. This study aims to establish the safety and efficacy of CA treatment over 74 weeks in Japanese patients with BASD.

2. Methods

2.1. Patients

We performed a phase 3, open-label, single-arm study of CA (the investigational drug was labeled as RM1319, RegMed Company, Ltd., Tokyo, Japan) in Japanese BASD patients. Four patients were enrolled from July 2020 to June 2023, two with HSD3B7 deficiency and two with SRD5B1 deficiency (Table 1). The patients were numbered consecutively from P1 to P4 based on their enrollment order. The diagnosis of BASD was definitively confirmed through urine bile acid analysis using the liquid chromatograph mass spectrometry (LC/MS) method and gene analysis. The study did not define any specific exclusion criteria. All the patients had received CDCA therapy (Last dose: 3.4–7.6 mg/kg/day) and were switched to CA therapy.

2.2. Treatment protocol

CA was given once or twice per day along with meals. The usual initial dose was 5–15 mg/kg/day, which was determined by the investigator or sub-investigator based on the levels of intermediate metabolites of bile acids in serum or urine, laboratory values, and the patient's systemic condition. The dose of CA should typically not be less than 50 mg/day and should not exceed 500 mg/day.

2.3. Efficacy assessment

Efficiency assessment, which included measurement of serum and urinary levels of bile acids and serum liver-related biomarkers (alanine aminotransferase [ALT], aspartate aminotransferase [AST], direct bilirubin [D-Bil], prothrombin time [PT], and 25-hydroxyvitamin D [25OH-D]), was performed at variable intervals from baseline to 74 weeks. Serum and urinary bile acid analyses were performed using LC/MS as described previously [21]. In all cases, urinary creatinine (Cr) was measured by the Jaffe method using a spectrophotometer [22]. Urinary bile acid concentrations were expressed in millimoles per mole of creatinine (mmol/mol Cr) [23], and serum bile acid concentrations in micromoles per liter (μmol/L). The following substances were measured: (1) CA, which is RM1319 itself; (2) deoxycholic acid (DCA), a secondary metabolite of RM1319; (3) CDCA, the previous therapeutic drug, and (4) lithocholic acid (LCA), a secondary metabolite of CDCA. Levels of 3β-hydroxy-Δ^5-bile acids were used to evaluate the status of HSD3B7 deficiency, while Δ^4–3-oxo-bile acid levels were used to measure SRD5B1 deficiency. All patients underwent ultrasonography before and during the CA treatment.

2.4. Safety assessment

The safety assessment involved monitoring for any adverse events during treatment, referred to as treatment-emergent adverse events (TEAEs), and any serious adverse events (SAEs).

2.5. Ethical considerations

This study was approved by the Institutional Review Board of Juntendo University (Registration Number: 2010–010, approval number: RM1319–301). Thereafter, all participating hospitals (Kyoto Prefectural

Table 1
Clinical features of the patients enrolled in this study.

Patients No.	P1	P2	P3	P4
Diagnosis	SRD5B1 deficiency	HSD3B7 deficiency	HSD3B7 deficiency	SRD5B1 deficiency
Sex (M/F)	M	F	M	F
Age at enrolment	11 years	46 years	6 mo	10 years
Height (cm)	152.5	149.9	65.4	142.3
Weight (kg)	37.0	66.0	6.1	34.0
Time since diagnosis (months)	138.2	295.6	4.8	121.8
Duration of CDCA treatment	10 years	24 years	2 mo	10 years
Age at diagnosis	6 mo	22 years	2 mo	9 mo
Mutations	Compound heterozygous c.580-14a > g c.797G > A (p.Arg266Gln)	Homozygous c.805_811del (p.E269fs*49)	Compound heterozygous c.805_811del (p.E269fs) c.839G > T (p.Gly280Val)	Compound heterozygous c.688G > A (p.Gly223Glu) c781C > T (p.Arg261Cys)
Initial laboratory data				
GGT (U/L)	44	27	42	61
ALT (U/L)	441	45	735	229
D-Bil (mg/dL)	3.4	4.5	5.5	3.6
STBA (μmol/L)	ND	4.1	42	5.2
Education/employment	General education	General education/employed	Pre-school	General education

GGT: γ-glutamyltransferase, ALT: alanine aminotransferase, D-Bil: direct bilirubin, STBA: serum total bile acids, ND: Not done.

University, Kurume University, and Saitama Medical University) and their respective research ethics committees granted study approval. Informed consent was obtained from one patient and the parents of the remaining three subjects prior to enrollment in the study. The study complied with the 1964 Helsinki Declaration and its later amendments (as revised in Edinburgh in 2000) or with comparable ethical standards.

3. Results

3.1. Dose of oral CA administration

In this study, different daily doses of CA were administered to the four participants. Patient P1 received 4.2–10.8 mg/kg/day, patient P2 received 6.0–7.6 mg/kg/day, patient P3 received 3.8–13.7 mg/kg/day, and patient P4 received 8.8–11.4 mg/kg/day. One infant (P3) had the medication mixed with milk once a day, which was later changed to baby food or medication aids after Visit 4 (6 weeks). The other three participants took the medication as capsules twice daily throughout the study period. Completion rates of CA dosing during the study period were consistently high, ranging from 93.8 % to 100 %, indicating adherence to medication schedules.

3.2. Findings of ultrasonography and clinical laboratory data

No nodules were observed on liver ultrasonography in any of the patients before nor during the RM1319 treatment. At the start of RM1319 administration, patient P3 exhibited elevated AST, ALT, and D-Bil levels, indicating cholestasis, although no coagulopathy was observed. All three parameters decreased significantly after RM1319 administration, reaching the reference range around 20 weeks later and remaining within it thereafter. For the other three patients (P1, P2, and P4), all the parameters were within the normal range at the start of RM1319 administration and maintained throughout the treatment period of 74 weeks (Fig. 1). Serum 25-OHD levels were low in patient P3, who had cholestasis at the start of RM1319. The 25-OHD value increased with the cholestasis improvement, suggesting a vitamin D deficiency due to biliary congestion rather than as an effect of RM1319 administration (Fig. 1).

3.3. Bile acid analysis

3.3.1. Concentrations of CDCA and CA before and after RM1319 treatment

BASD patients are typically unable to biosynthesize CA and CDCA adequately. Most of the CA and CDCA detected in the patient's blood samples are considered to be derived from external administration of the therapeutic drug. Based on this, the sum of CA and DCA (secondary metabolite of CA) levels and that of CDCA and LCA (secondary metabolite of CDCA) levels were defined as the concentration of RM1319 and pretreated CDCA, respectively. After switching CDCA treatment to RM1319 treatment, serum concentrations of CDCA and RM1319 reversed in all patients within two weeks of treatment, and RM1319 typically replaced CDCA within three to six weeks of treatment (Fig. 2). In patient P3 with HSD3B1 deficiency, concentrations of RM1319 increased significantly from weeks 2 to 4 of treatment but then decreased dramatically by week 10 (Fig. 2).

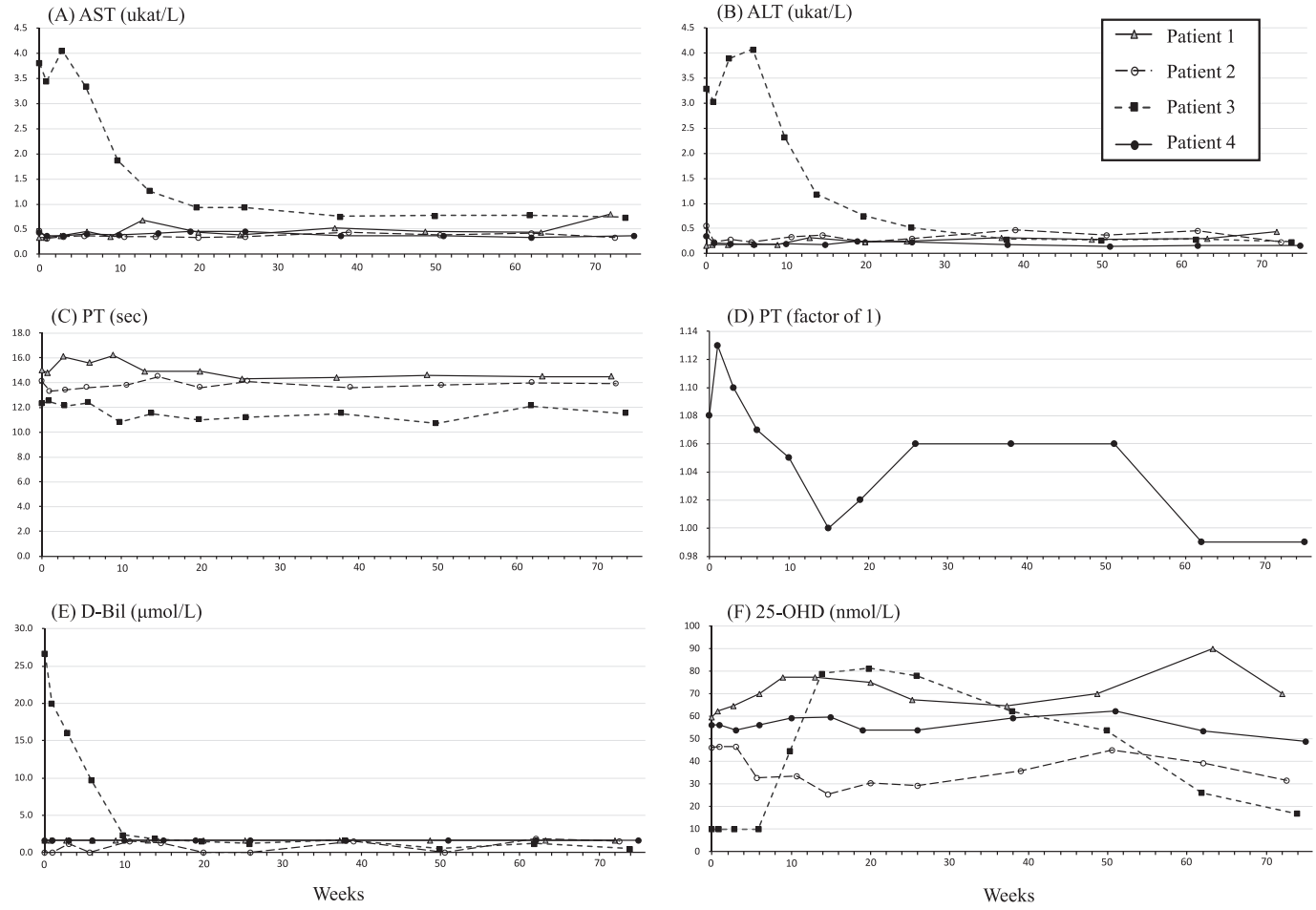

Fig. 1. Change from baseline over time in (A) alanine aminotransferase [AST], (B) aspartate aminotransferase [ALT], (C, D) prothrombin time [PT], (E) direct bilirubin [D-Bil], and (F) 25-hydroxyvitamin D [25OH-D] levels.

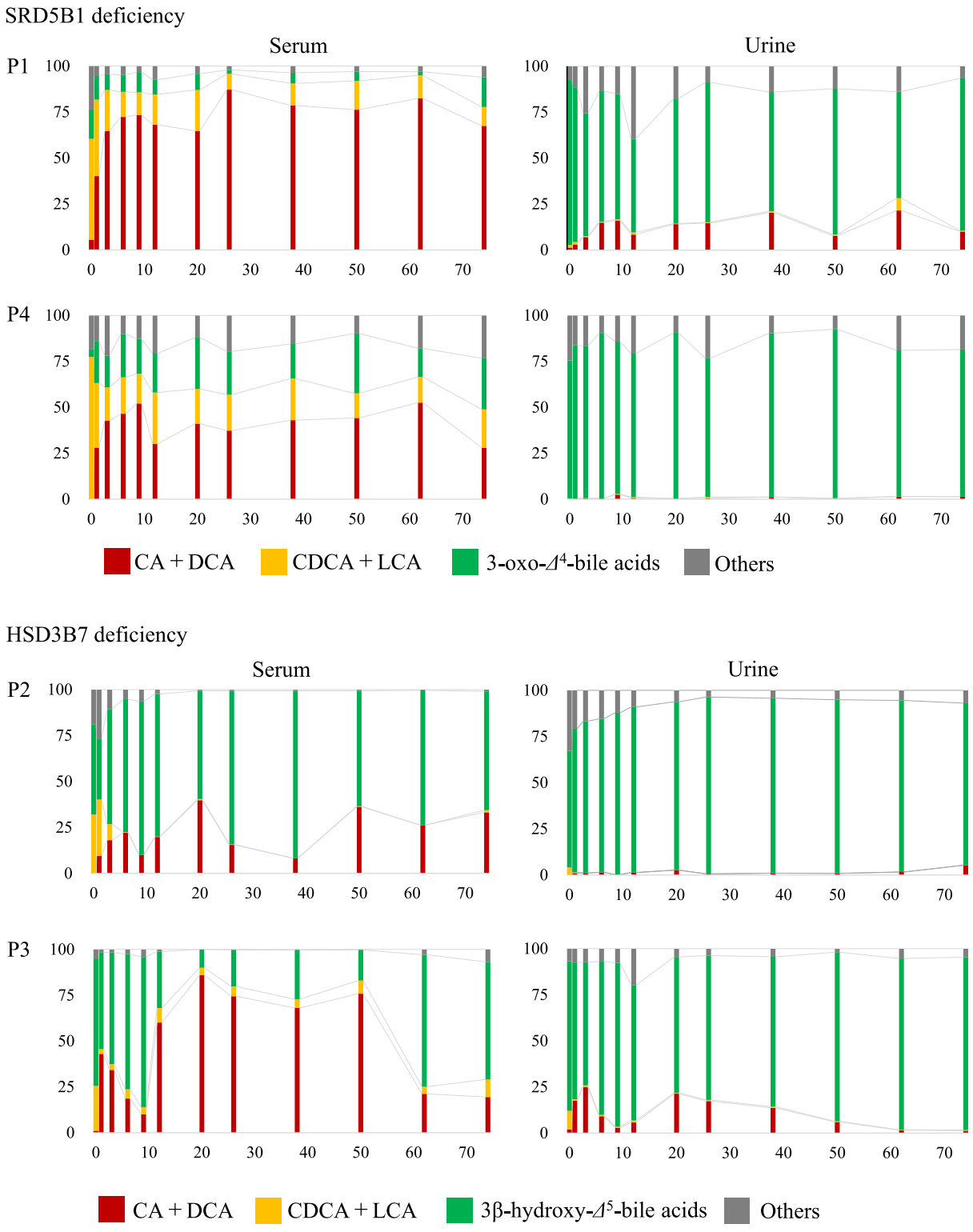

Fig. 2. The ratio of usual (CDCA, CA) to unusual bile acids in total bile acids. The vertical axis shows the percentage, and the horizontal axis shows the week. CA: cholic acid, DCA: deoxycholic acid, CDCA: chenodeoxycholic acid, LCA: lithocholic acid.

3.3.2. Concentration of unusual bile acids before and after CA treatment

At the time of the switch from CDCA to RM1319, patient P1 with SRD5B1 deficiency had a urinary Δ^4–3-oxo-bile acid concentration of 3.33 mmol/mol Cr, which remained at similar levels throughout the 74-week treatment period. In patient P4 with SRD5B1 deficiency, the concentration of urinary Δ^4–3-oxo-bile acids was 2.65 mmol/mol Cr at the start of treatment, increasing obviously to 22.34 mmol/mol Cr at 20 weeks, and then gradually decreased to 5.14 mmol/mol Cr at 74 weeks. Serum Δ^4–3-oxo-bile acid levels showed a similar trend as their urinary levels in each patient. However, the proportion of Δ^4–3-oxo-bile acids relative to total bile acids in urine was higher (median 79.37 %, range: 51.04–91.84 %) than its proportion in serum (median 15.81 %, range: 1.90–32.51 %) (Table 2, Fig. 2).

Patient P2 with HSD3B1 deficiency showed an increase in urinary

Table 2
Bile acid analysis in patients with SRD5B1 deficiency.

Patient No.	Visit	Week	Urine (mmol/mol Cr)							Serum (μmol/L)						
			TBA	CA + DCA	%	CDCA+LCA	%	3-oxo-Δ^4- bile acids	%	TBA	CA + DCA	%	CDCA+LCA	%	3-oxo-Δ^4- bile acids	%
P1	V1	0	3.71	0.05	1.35	0.05	1.35	3.33	89.76	3.13	0.17	5.43	1.72	54.95	0.50	15.97
	V2	1	5.76	0.17	2.95	0.08	1.39	4.83	83.85	8.56	3.44	40.19	3.56	41.59	1.10	12.85
	V3	3	1.84	0.13	7.07	0.01	0.54	1.23	66.85	9.37	6.06	64.67	2.09	22.31	0.80	8.54
	V4	6	3.69	0.55	14.91	0.02	0.54	2.62	71.00	8.79	6.36	72.35	1.20	13.65	0.80	9.10
	V5	9	3.12	0.50	16.03	0.02	0.64	2.13	68.27	7.26	5.33	73.42	0.89	12.26	0.80	11.02
	V6	12	3.35	0.28	8.36	0.04	1.19	1.71	51.04	8.87	6.04	68.09	1.46	16.46	0.70	7.89
	V7	20	3.06	0.43	14.05	0.01	0.33	2.08	67.97	9.05	5.86	64.75	2.01	22.21	0.80	8.84
	V8	26	2.05	0.30	14.63	0.01	0.49	1.56	76.10	9.41	8.20	87.14	0.81	8.61	0.20	2.13
	V11	38	2.56	0.52	20.31	0.02	0.78	1.66	64.84	5.17	4.06	78.53	0.62	11.99	0.30	5.80
	V14	50	4.87	0.38	7.80	0.03	0.62	3.86	79.26	15.98	12.18	76.22	2.51	15.71	0.80	5.01
	V17	62	2.09	0.45	21.53	0.14	6.70	1.21	57.89	5.80	4.78	82.41	0.73	12.59	0.11	1.90
	V20	74	4.36	0.44	10.09	0.02	0.46	3.61	82.80	6.92	4.67	67.49	0.71	10.26	1.12	16.18
P4	V1	0	3.52	0.00	0.00	0.33	0.33	2.65	75.28	4.48	0.00	0.00	3.47	77.46	0.18	4.02
	V2	1	18.05	0.07	0.39	0.05	0.05	15.04	83.32	9.35	2.63	28.13	3.28	35.08	2.14	22.89
	V3	3	11.00	0.07	0.64	0.01	0.01	9.11	82.82	4.48	1.91	42.63	0.82	18.30	0.77	17.19
	V4	6	14.33	0.07	0.49	0.05	0.05	12.88	89.88	7.10	3.30	46.48	1.41	19.86	1.67	23.52
	V5	9	9.11	0.23	2.52	0.37	0.37	7.55	82.88	6.99	3.64	52.07	1.13	16.17	1.33	19.03
	V6	12	10.20	0.07	0.69	0.42	0.42	7.97	78.14	4.82	1.45	30.08	1.35	28.01	1.02	21.16
	V7	20	24.79	0.10	0.40	0.02	0.02	22.34	90.12	8.08	3.32	41.09	1.53	18.94	2.26	27.97
	V8	26	23.95	0.14	0.58	0.65	0.65	18.06	75.41	8.97	3.35	37.35	1.75	19.51	2.12	23.63
	V11	38	13.52	0.17	1.26	0.00	0.00	12.05	89.13	9.36	4.03	43.06	2.12	22.65	1.76	18.80
	V14	50	11.52	0.04	0.35	0.25	0.25	10.58	91.84	4.86	2.15	44.24	0.65	13.37	1.58	32.51
	V17	62	9.26	0.14	1.51	0.01	0.01	7.36	79.48	5.82	3.06	52.577	0.81	13.92	0.91	15.64
	V20	74	6.42	0.09	1.40	0.02	0.02	5.14	80.06	14.51	4.07	28.05	3.03	20.88	4.03	27.77

Cr: creatinine, TBA: total bile acids, CA: cholic acid, CDCA: chenodeoxycholic acid, LCA: lithocholic acid, P: patient, V: visit.

Table 3
Bile acid analysis in patients with HSD3B1 deficiency.

Patient No.	Visit	Week	Urine (mmol/mol Cr)							Serum (μmol/L)						
			TBA	CA + DCA	%	CDCA+LCA	%	3β-hydroxy-Δ^5-bile acids	%	TBA	CA + DCA	%	CDCA+LCA	%	3β-hydroxy-Δ^5-bile acids	%
P2	V1	0	2.91	0.00	0.00	0.12	4.12	1.84	63.23	4.77	0.02	0.42	1.51	31.66	2.34	49.06
	V2	1	9.34	0.09	0.96	0.04	0.43	7.27	77.84	12.91	1.24	9.60	3.95	30.60	4.28	33.15
	V3	3	16.76	0.18	1.07	0.01	0.06	13.77	82.16	17.45	3.16	18.11	1.52	8.71	10.92	62.58
	V4	6	17.02	0.25	1.47	0.00	0.00	14.15	83.14	17.41	3.87	22.23	0.04	0.23	12.59	72.31
	V5	9	39.28	0.10	0.25	0.00	0.00	34.44	87.68	33.43	3.35	10.02	0.00	0.00	27.92	83.52
	V6	12	17.22	0.23	1.34	0.00	0.00	15.44	89.66	19.82	3.93	19.83	0.03	0.15	15.39	77.65
	V7	20	9.85	0.26	2.64	0.00	0.00	8.98	91.17	11.69	4.66	39.86	0.07	0.60	6.88	58.85
	V8	26	15.21	0.09	0.59	0.00	0.00	14.57	95.79	10.87	1.69	15.55	0.03	0.28	9.08	83.53
	V11	38	17.00	0.17	1.00	0.00	0.00	16.11	94.76	17.07	1.41	8.26	0.00	0.00	15.55	91.10
	V14	50	13.66	0.13	0.95	0.00	0.00	12.83	93.92	11.95	4.33	36.23	0.03	0.25	7.51	62.85
	V17	62	8.78	0.14	1.59	0.00	0.00	8.16	92.94	10.04	2.64	26.29	0.00	0.00	7.36	73.31
	V20	74	3.76	0.20	5.32	0.00	0.00	3.30	87.77	11.15	3.70	33.18	0.14	1.26	7.20	64.57
P3	V1	0	171.83	3.46	2.01	17.29	10.06	139.44	81.15	53.20	0.57	1.07	13.00	24.44	36.99	69.53
	V2	1	207.20	36.34	17.54	1.76	0.85	153.54	74.10	70.33	30.25	43.01	1.79	2.55	37.24	52.95
	V3	3	240.16	59.86	24.93	2.36	0.98	160.33	66.76	96.12	32.99	34.32	2.98	3.10	58.47	60.83
	V4	6	520.28	47.60	9.15	4.07	0.78	432.54	83.14	108.11	20.19	18.68	5.48	5.07	79.81	73.82
	V5	9	164.44	4.82	2.93	0.91	0.55	146.26	88.94	39.22	3.92	9.99	1.55	3.95	32.15	81.97
	V6	12	11.87	0.69	5.81	0.13	1.10	8.71	73.38	11.55	6.94	60.09	0.92	7.97	3.56	30.82
	V7	20	7.93	1.70	21.44	0.03	0.38	5.84	73.64	13.65	11.73	85.93	0.56	4.10	1.36	9.96
	V8	26	9.87	1.72	17.43	0.06	0.61	7.72	78.22	8.45	6.29	74.44	0.45	5.33	1.69	20.00
	V11	38	6.83	0.94	13.76	0.04	0.59	5.55	81.26	9.59	6.52	67.99	0.46	4.80	2.57	26.80
	V14	50	14.91	0.90	6.04	0.06	0.40	13.66	91.62	23.01	17.45	75.84	1.65	7.17	3.85	16.73
	V17	62	31.44	0.50	1.59	0.07	0.22	29.21	92.91	17.73	3.76	21.21	0.68	3.84	12.77	72.02
	V20	74	19.04	0.25	1.31	0.06	0.32	17.86	93.80	19.80	3.85	19.44	1.90	9.60	12.71	64.19

Cr: creatinine, TBA: total bile acids, CA: cholic acid, CDCA: chenodeoxycholic acid, LCA: lithocholic acid, P: patient, V: visit.

Table 4
Treatment-emergent adverse events and serious adverse events.

Events	Total no. of events	Number of patients (%)
	20	4 (100)
Infectious and parasitic diseases	6	3 (75)
Nasopharyngitis	3	2 (50)
Tinea pedis	1	1 (25)
Herpetic dermatitis	1	1 (25)
Oral herpes	1	1 (25)
Immune system disorders	2	1 (25)
Seasonal allergies	2	1 (25)
Metabolic and nutritional disorders	1	1 (25)
Hypocalcemia	1	1 (25)
Nervous system disorders	2	2 (50)
Headache	2	2 (50)
Ocular disorders	1	1 (25)
Dry eye	1	1 (25)
Respiratory, thoracic and mediastinal disorders	2	2 (50)
Allergic rhinitis	1	1 (25)
Oropharyngeal pain	1	1 (25)
Skin and subcutaneous tissue disorders	2	2 (50)
Eczema	1	1 (25)
Solar dermatitis	1	1 (25)
Musculoskeletal and connective tissue disorders	3	2 (50)
Joint pain	1	1 (25)
Muscle pain	1	1 (25)
Limb pain	1	1 (25)
General/systemic disorders and administration site conditions	1	1 (25)
Fever	1	1 (25)

If an event occurred multiple times within the same case, it was counted as one patient.
The number of cases was determined by the total number of events.

concentration of 3β-hydroxy-Δ^5 bile acids from 1.84 to 34.44 mmol/mol Cr at 10 weeks of treatment. However, it decreased thereafter to 3.30 mmol/mol Cr at 74 weeks (Table 3). The concentration of 3β-hydroxy-Δ^5 bile acids in patient P3 with HSD3B1 deficiency was 139.44 mmol/mol Cr at the start of treatment, increasing significantly to 432.54 mmol/mol Cr after 6 weeks, and then gradually decreased to 17.86 mmol/mol Cr at 74 weeks. The levels of 3β-hydroxy-Δ^5 bile acids in serum showed similar variations as their concentrations in urine. Compared to serum, urine contained a higher proportion of 3β-hydroxy-Δ^5 bile acids (median: 85.41 %, [range: 63.23–95.79 %] vs. 63.52 % [9.96–91.10 %], respectively) (Table 3, Fig. 2).

3.4. Treatment-related adverse events and serious adverse events

TEAEs occurred in all patients (20 events in total), and the most common TEAEs in the overall population were nasopharyngitis and seasonal allergies (both occurring in 50 % of patients) (Table 4). These TEAEs were mainly mild or moderate in severity. The investigator considered the majority of TEAEs to be unrelated to the study treatment. Hypocalcemia as a TEAE occurred in one patient (P1), which was considered as possibly being related to treatment. The hypocalcemia in this patient was mild, occurred on day 6 after the start of CA administration, and resolved after 38 days without any dose reduction of the drug or treatment for hypocalcemia. There were no TEAEs or SAEs for which the study drug had to be discontinued or withdrawn, or a procedure involving the addition of significant concomitant therapy had to be performed. At the time of treatment commencement, P1, P3, and P4 were 11, 0, and 10 years old, respectively. They experienced an appropriate increase in height and weight throughout the 74-week period.

4. Discussion

In Japan, CDCA was used instead of CA for the treatment of BASD, since the latter was not available for clinical use in Japan until 2023. Based on the results of this study involving four BASD patients, Orphacol® Capsules 50 mg was included in insurance coverage in Japan in June 2023 and is now used commercially. Until this time, patients were treated with the lowest possible dose of CDCA (4.0 to 7.8 mg/kg/day) because CDCA is more hepatotoxic than CA [13,24]. Primary bile acids (CA and CDCA) down-regulate their own biosynthesis pathways, which decrease toxic and unusual bile acid production through suppressing activation of the farnesoid X receptor and the CYP7A1 gene encoding cholesterol 7α-hydroxylase, the rate-limiting enzyme for bile acid synthesis [7,25].

CA therapy has been shown to be effective and safe in patients with HSD3B7 and SRD5B1 deficiencies without causing liver damage [7–11]. Heubi et al. reported the efficacy of CA in 54 BASD patients (35 with HSD3B7 deficiency, 10 with SRD5B1 deficiency, and 9 with others or unknown) enrolled over 18 years from 1992 to 2009. During a follow-up period of 145 weeks (range: 0–545 weeks), no study drug-related SAEs or drug-related deaths were reported, and improvements were observed in urine bile acid metabolite scores, liver chemistries, height, and weight percentiles [8]. Subsequent follow-up studies by the same researchers have confirmed the effectiveness and safety of CA treatment [9]. Additionally, Gonzales et al. reported that CA treatment was effective in 15 BASD patients, including 13 with HSD3B7 deficiency and 2 with SRD5B1 deficiency [11]. The median age at last follow-up was 24.3 years (range: 15.3–37.2), median follow-up with treatment was 21.4 years (range: 14.6–24.1), and notably, five female patients experienced ten uneventful pregnancies during treatment [11]. CA treatment is a safer option during pregnancy since CDCA is contraindicated for use during pregnancy.

We previously reported the long-term outcome and efficacy of CDCA treatment in five Japanese patients with HSD3B1 deficiency ($n = 3$) and SRD5B1 deficiency ($n = 2$) [13]. Of these five patients, one with HSD3B1 deficiency (P2) and two with SRD5B1 deficiency (P1 and P4) participated in this phase 3 study. P1, 2, and 4 received CDCA treatment for at least 10 years, but patient P3, with cholestatic liver disease that had not yet resolved, received CDCA for only 8 weeks. We evaluated clinical and laboratory findings and bile acid profiles during 74 weeks in these four Japanese patients, including one newly diagnosed patient with HSD3B1 deficiency (P3). Interestingly, the proportion of 3-oxo-Δ^4-bile acids in patients with SRD5B1 deficiency and 3β-hydroxy-Δ^5 bile acids in patients with HSD3B1 deficiency remained consistently high levels during CA treatment. Still, one patient (P3) had improved liver function, and the other three (P1, P2, and P4) maintained stable liver function without deterioration. Reducing the absolute amount of unusual bile acids would be critical to avoid liver damage. Further, all patients had freedom from treatment complications. Thus, these Japanese BASD patients had good short- and mid-term CA treatment outcomes. Since this phase 3 study is the first to introduce oral treatment for BASD in Japan, future long-term follow-up is needed to understand its real-world efficacy.

Ultra-trace amounts of CA and CDCA have been detected in both SRD5B1 deficiency and HSD3B1 deficiency patients, even before any therapeutic intervention [13]. In a previous mouse model, the existence of several alternative pathways for bile acid biosynthesis has been demonstrated [26]. Primary bile acids, such as CA and CDCA, are detected even in SRD5B1 and HSD3B1 knockout mice [27,28]. This study detected trace amounts of CDCA and LCA during CA therapy, which might be caused by the presence of unknown alternative pathways or sensitivity issues with LC/MS methods.

In this study, the percentages of unusual bile acids in urine, such as Δ^4–3-oxo-bile acids and 3β-hydroxy-Δ^5 bile acids, were consistently higher than those in serum. According to Kimura et al., CDCA treatment can cause a similar effect [13]. This suggests that unusual bile acids that are associated with liver damage are excreted through the kidneys

during treatment with CA as well as with CDCA. Although combination therapy with CA and a low dose of CDCA might be an option, the dosages need to be considered in light of the physiological ratio of the two bile acids.

Over the past 30 years, only 10 definitive patients of BASD have been diagnosed in Japan [6]. BASD is characterized by normal to low serum total bile acids and γ-glutamyltransferase levels, despite elevated direct bilirubin levels in patients with cholestasis [1]. Due to its rarity, diagnosing BASD is challenging due to its clinical similarity to infantile cholestatic diseases, such as biliary atresia. We recently reported the development of affordable and time-saving sample screening methods using dried blood spot-based newborn screening [29]. With the accumulating evidence for CA treatment in BASD, early diagnosis and appropriate treatment are expected to improve patient prognosis significantly.

5. Conclusion

This study evaluated the efficacy and safety of CA treatment in four Japanese BASD patients over 74 weeks and showed favorable efficacy and safety. The results are similar to those of previous studies, mainly in Europe and the United States. We believe that this drug is a therapeutic agent for Japanese patients with BASD.

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Institutional review board statement

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of Juntendo University (Registration Number: 2010–010, approval number: RM1319–301).

Informed consent statement

Informed consent was obtained from all subjects involved in the study.

CRediT authorship contribution statement

Mitsuyoshi Suzuki: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Hajime Takei:** Writing – review & editing, Writing – original draft, Visualization, Investigation, Data curation. **Hiromi Suzuki:** Investigation, Methodology. **Jun Mori:** Resources, Investigation. **Satoru Sugimoto:** Resources, Investigation. **Tatsuki Mizuochi:** Resources, Investigation. **Akira Ohtake:** Resources, Investigation. **Hisamitsu Hayashi:** Writing – review & editing, Supervision. **Akihiko Kimura:** Writing – review & editing, Supervision, Conceptualization. **Hiroshi Nittono:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Project administration, Conceptualization.

Declaration of competing interest

The authors have no conflicts of interest to disclose.

Data availability

The data that has been used is confidential.

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