



Incidence and antiviral treatment of cytomegalovirus infection in infants with biliary atresia

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Accepted: 28 January 2023 / Published online: 11 February 2023

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Abstract

Purpose Patients with biliary atresia (BA) and cytomegalovirus (CMV) infection may have poorer outcomes after Kasai portoenterostomy (KPE) than uninfected patients, suggesting a rationale for antiviral treatment (AVT). We aimed to describe the incidence of CMV infection and of AVT in BA patients, and to detect any differences between infected and uninfected patients to conclude if AVT is of use.

Methods Data on BA patients who underwent KPE 2004–2020 were retrospectively collected, and the outcome was analyzed with regard to CMV status.

Results Fifteen out of forty-six (33%) BA patients had signs of ongoing CMV infection. They did not differ significantly from the CMV-negative patients regarding rate of prematurity, birth weight, or biochemical markers but were slightly older at KPE. All patients received steroids postoperatively and all patients with ongoing CMV infection received AVT with very good effect on viremia and without major side effects. The AVT consisted of oral valganciclovir (10–40 (– 58) mg/kg/d) or intravenous ganciclovir (5.3–11 mg/kg/d).

Conclusion Ongoing CMV infection is common in this group of patients. The viremia can effectively be treated with AVT without any major side effects. Larger, randomized studies are needed to clarify the possible effect on clinical outcome.

Keywords Cytomegalovirus · Biliary atresia · Ganciclovir · Valganciclovir · Kasai portoenterostomy · Survival with native liver

Introduction

Biliary atresia (BA) is a severe cholangiopathy in infants with an etiological heterogeneity. The first line of treatment for BA is Kasai portoenterostomy (KPE), which temporarily saves most infants but as many as 40% will need liver transplantation (LTx) in the long run. Timing of KPE is

important for outcome, with improved native liver survival in those operated before 60 days of age [5–7]. Even though the incidence of BA varies around the world from 1:5000 in Taiwan, to 1:10 000 in Japan, 1:14 000 in Sweden, and 1:20 000 in the United States [8–11], it is the most common reason for LTx in children [12, 13].

The etiology and pathogenesis of BA are not fully known. Several studies suggest that various viral infections could be of importance for the pathogenic mechanisms, for example cytomegalovirus (CMV), reovirus and rotavirus [12, 14–18]. A study from the UK showed that 10% of BA patients had CMV-IgM detected in serum and that this subgroup had a different histological appearance and a worse outcome [14], the latter was also seen in a Chinese study [19] and in a recently published meta-analysis including 784 patients [20]. A study from the group in the UK suggested that CMV-IgM positive BA patients could benefit from treatment with intravenous ganciclovir or oral valganciclovir [18]. A previous study from our center showed an incidence of 38% for ongoing CMV infection among Swedish infants with BA

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compared to 6% of age-matched controls, but no significant difference in the long-term outcome between CMV-positive and CMV-negative patients after portoenterostomy [15, 21]. In a recently published retrospective study, we compared data on incidence, impact and treatment of CMV infection in BA patients from ours and three other European centers. The novel findings of the present study are the in-depth data on our own expanded cohort, including details on the different effects of antiviral treatment [22].

Aim

It is of importance to know if CMV infection is associated with poorer outcome and thereby increased need for liver LTx and if that could be avoided with antiviral treatment (AVT). This retrospective study aimed to evaluate if there is still a high incidence of ongoing CMV infection in the Swedish BA population and to describe the treatment and outcome of these patients. We also wanted to know if the CMV-positive patients or their mothers are inherently different from the uninfected patients or their mothers which could be useful in future diagnostics.

Methods

Patient selection

This is a retrospective observational study including all 46 patients (26 males, 20 females) with BA who were diagnosed and treated at Karolinska University Hospital, Stockholm, Sweden in 2004–2020, this included the 37 patients born 2005–2018 who were described in a less detailed manner in the previous multicentre-based paper [22]. The last data were collected in November 2021, i.e., 1 year after KPE was performed in the youngest patient. Exclusion criteria were no KPE or unknown CMV status. Out of 52 patients, 6 were excluded, 4 females and 2 males. Five patients were excluded because they did not have KPE performed, and one patient was never tested for CMV. Four of the excluded patients had a primary LTx performed because of late diagnosis (one CMV positive and three CMV negative) and one patient had no surgery at all because of severe chromosomal abnormality with congenital anomalies including major heart malformations (CMV negative).

Outcome parameters

The primary outcome was 1-year survival with native liver. Other outcome parameters were clearance of jaundice and side effects from AVT. Clearance of jaundice was defined as total serum bilirubin < 20 µmol/L within 6 months after

KPE. Side effects from AVT were defined as elevated creatinine, lowered hemoglobin concentration, lowered platelet or white blood cells count and elevated liver enzymes after KPE and AVT compared to before the treatment.

Compared parameters

The patients were divided into two groups according to CMV status and the groups were compared regarding birth weight, prematurity, splenomegaly, age at KPE and laboratory findings before KPE. Splenomegaly was defined by the written report from the ultrasonographer. The mothers of the patients were compared regarding age, parity, and country of birth, according to chart data.

Diagnosis, surgery, and medical treatment

The BA diagnosis was established by hepatobiliary scintigraphy with good uptake to the liver but no excretion to the gut within 24 h, needle biopsy with histological pattern suggesting extrahepatic biliary disorder and finally confirmed at laparotomy where intraoperative cholangiogram was performed, if possible.

KPE was performed by either or both of two individual pediatric surgeons, one of them (JFS) participated in 38 out of 46 operations.

All patients were given corticosteroids, fat-soluble vitamins, and ursodeoxycholic acid.

Cytomegalovirus infection

CMV status was defined during admission to the hospital for investigation of cholestasis or had already been established at the referring hospital. The patients were considered CMV positive if CMV-IgM was detected in serum and/or CMV-DNA was detected in urine or blood. The level of CMV replication in those considered to be CMV positive was analyzed by quantitative PCR detection for CMV-DNA in blood according to the current hospital routine. In patients born before 2016, CMV-DNA by PCR was analyzed in whole blood, thereafter it was analyzed in plasma. The CMV-DNA levels in these two compartments have previously been shown to be comparable [23].

Statistical analysis

Continuous data were expressed as medians and total range. The data could not be assumed to be normally distributed due to small sample size and was, therefore, compared using nonparametric Mann–Whitney *U* test. Categorical data were compared with cross tabulation and Chi-square test.

Ethics

The regional ethics review board in Stockholm has approved retrospective studies of medical records. Registration number 2017/1394-31.

Results

Cytomegalovirus infection

Fifteen (33%) out of forty-six patients were CMV positive in blood or urine at some point before surgery, 1 of them was negative at 2 days of age but positive 13 days after surgery and was treated with AVT and was, therefore, regarded as CMV positive for the purpose of this study. Two of the CMV-positive patients did not receive AVT, presumably because of very low CMV-DNA level in blood. Those patients are included in the CMV-positive group except when the results for AVT are reported.

None of the patients could be proven to have congenital CMV infection because all positive samples were taken after 3 weeks of age.

Out of the 15 patients defined as infected, CMV was detected by PCR in serum or urine in all 15. Twelve of these patients were also tested for CMV antibodies but only four (33%) were positive for CMV-IgM.

Survival with native liver and clearance of jaundice

The 1-year survival with native liver was 55% ($n=17$) for CMV-negative patients and 47% ($n=7$) for CMV-positive patients.

Clearance of jaundice within 6 months after KPE was 42% ($n=14$) in the CMV-negative group and 27% ($n=4$) in the CMV-positive group. This is shown in Table 1.

Maternal features

Out of 46 patients 26 had mothers who were born in Sweden, 3 in other parts of Europe, 9 in West Asia, Iran or Afghanistan, 7 in North or East Africa, and 1 in South America. A map of maternal origin is shown in Fig. 1.

The mothers were all between 23 and 44 years of age when giving birth except for one who was 16 years. Parity was between 1 and 7 births (median 2).

Out of the 26 patients with a Swedish mother, 30% were CMV positive and out of the 20 patients whose mother was born outside of Sweden, 35% were CMV positive.

The median age for mothers in the CMV-negative group was 31 years and in the CMV-positive group 34 years ($p=0.08$). There was no significant difference in the parity of the mothers in the two groups.

Prematurity and birth weight

Thirty-nine patients were born full term, seven patients were born in gestational week 33–36, i.e., late preterm. The prematurity rate was 16% for CMV-negative patients and 13% for CMV-positive patients. During 2004–2020, the average percentage for premature births was 6% in the whole Swedish population, according to Swedish Medical Birth Register [24].

Of the 39 patients with available data on both gestational age and birth weight, only 1 was small for gestational age and 2 were large for gestational age.

Splenomegaly

Splenomegaly was detected in 33% ($n=10$) of the CMV-negative group and in 60% ($n=9$) in the CMV-positive group ($p=0.09$).

Laboratory findings in CMV-positive and CMV-negative patients

There was no significant difference between CMV-positive and CMV-negative patients regarding laboratory tests at the time of KPE: total bilirubin, conjugated bilirubin, AST, ALT, prothrombin time measured as international normalized ratio (INR), creatinine, hemoglobin, leukocyte count, thrombocyte count. These laboratory results are shown in Table 1.

Age at the time of surgery

The overall median age at the time of KPE was 71 days. It was 74 days (range 46–132) for CMV-positive and 68 days (range 32–130) for CMV-negative patients ($p=0.10$). The median age at KPE was 70 days for patients with a Swedish mother and 74 days for patients with a non-Swedish mother ($p=0.42$).

Antiviral treatment

Thirteen CMV-positive patients were given AVT at the discretion of the physician. There were some differences in treatment strategy regarding timing, duration, and dosage. Details about AVT are described in Table 2. The treatment was initiated before KPE in four patients and within 2–22 days after KPE in nine patients. The duration of AVT was 21–74 days (median 42 days); in one patient, it was prolonged because of LTx.

Six patients received only oral valganciclovir, four patients received only intravenous (IV) ganciclovir, and in three patients where treatment was initiated before KPE, they received first oral, then IV and then oral treatment

Table 1 Comparison between patients with biliary atresia that were positive or negative for cytomegalovirus (CMV) at the time of diagnosis

	CMV negative (31 patients)	CMV positive (15 patients)	<i>p</i> value
Comparison			
Preterm	5 (16%)	2 (13%)	0.80
Gestational age < 37 weeks			
Birth weight, kg	3.280	3.270	0.52
Mother born outside of Sweden	12 (42%)	7 (47%)	0.76
Maternal age, years	31 (range 23–41)	34 (range 16–44)	0.08
Splenomegaly, > 6 cm	10 (33%)	9 (60%)	0.09
Age at Kasai portoenterostomy, days	68 (range 32–130)	74 (range 46–132)	0.10
Laboratory findings prior to KPE (Normal range)			
Bilirubin $\mu\text{mol/L}$ (< 22 $\mu\text{mol/L}$)	163 (95–270)	156 (121–263)	0.85
Conjugated bilirubin $\mu\text{mol/L}$ (< 3 $\mu\text{mol/L}$)	131 (65–198)	137 (105–224)	0.32
ALT $\mu\text{kat/L}$ (< 0.85 $\mu\text{kat/L}$)	1.88 (0.18–5.36)	1.78 (0.59–6.20)	0.62
AST $\mu\text{kat/L}$ (< 1.4 $\mu\text{kat/L}$)	2.84 (0.71–7.71)	3.54 (1.72–8.30)	0.19
Prothrombin time (International normalized ratio) (< 1.2)	1.0 (0.8–1.6)	1.1 (0.9–1.3)	0.20
Hemoglobin concentration g/L (100–160 g/L)	99 (82–164)	107 (88–124)	0.07
White blood cell count $10^9/\text{L}$ (6–18 $\times 10^9/\text{L}$)	11.2 (6.9–21.3)	11.4 (4.7–17.8)	0.67
Platelet count $10^9/\text{L}$ (160–600 $\times 10^9/\text{L}$)	433 (292–869)	457 (145–795)	0.80
APRI score ^a	0.79	0.99	0.19
Outcome			
One-year survival with native liver	17 (55%)	7 (47%)	0.60
Clearance of jaundice within 6 months after KPE (bilirubin < 20 $\mu\text{mol/L}$)	16 (52%)	4 (27%)	0.11

Median laboratory data were analyzed the day before Kasai portoenterostomy. Total range in parentheses
The patients were considered CMV positive if CMV-IgM was detected in serum and/or CMV-DNA was detected in urine or blood/serum

^aAPRI score: AST to Platelet Ratio Index, (AST (IU/L)/40)/platelet count ($\times 10^9/\text{L}$) $\times 100$

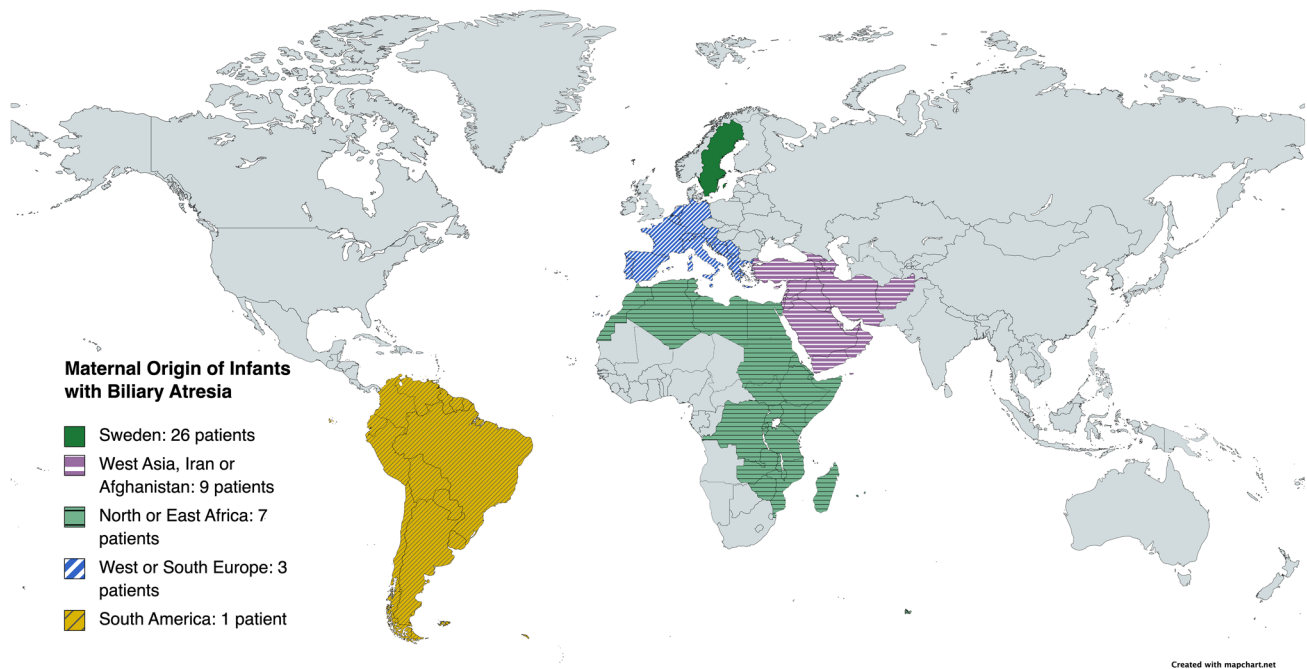
again. The intravenous dosage varied between 5 and 11 mg/kg/d. Oral dosage varied between 10 and 40 mg/kg/day, one patient received as much as 58 mg/kg/day. Most patients had their dosage altered after one or a few weeks, either decreased or increased at the discretion of the physician but antiviral effect was seen before altered dosage in all patients. The highest reported trough levels varied between 0 and 4.7 $\mu\text{mol/L}$.

All treated patients had lowered CMV levels at the first testing after initiating AVT, as shown in Table 2. The timing of the test varied between 5 and 24 days after initiating AVT. CMV levels after completed treatment was 0 IU/mL or 0–500 IU/mL for all 12 patients where it was measured.

There were some improvements in liver specific laboratory findings for the 13 patients who received AVT when

comparing before and after the surgery and AVT. There was no anemia, leukopenia, or elevated creatinine. Laboratory findings before and after AVT are shown in Table 3.

Nine out of ten CMV-positive patients who subsequently, at some point before November 2021, underwent LTx had CMV reactivation within 1 year after transplantation. Six of these were successfully treated with AVT during 1–2.5 months. Three patients were treated two or three times for reactivation during the first year after transplantation. One of the two patients who was CMV positive but did not receive AVT at the time of KPE was liver transplanted about 1 year after KPE and had reactivated CMV infection 6 weeks after LTx. The reactivation started shortly after treatment for transplant rejection and was successfully treated with oral valganciclovir for 4 weeks.



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Fig. 1 World map showing maternal of origin of infants with biliary atresia included in the study. Produced with <https://www.mapchart.net/>

Corticosteroids

All 46 patients in the present study were treated with prednisolone after KPE, starting 7 days after surgery. There was no difference in dosage or duration of the prednisolone treatment between CMV-positive and CMV-negative patients. The target-dose and the median-dose prednisolone both were 2 mg/kg for 14 days followed by 1 mg/kg for 7 days. The dose and the duration of corticosteroid treatment varied slightly between patients at the discretion of the physician.

Discussion

This study confirms that the incidence of ongoing CMV infection in Swedish patients with BA remains around 30%. This is true regardless of whether the mother is born in Sweden or not. The cause of the different incidence compared to the study from the UK [14] is not known; however, in the latter study, only CMV-IgM positivity was used to define infected patients. For comparison, studies from China, Brazil, South Africa, USA, India, and Norway show an incidence of 24–78% for CMV in patients with BA [17, 25–30].

It is not established to what degree CMV influences the development of BA and the outcome after KPE and whether the infection should be treated with antiviral drugs. However, in a retrospective report from the UK, AVT significantly improved outcome for CMV-positive patients when compared to untreated [18]. In accordance with that, we

found in our study that CMV infection effectively could be treated with AVT regarding the viremia level and that this coincided with biochemical improvement. However, no untreated CMV-positive control was available. In the study from the UK, most of the CMV-positive patients were not treated with steroids which may explain why those patients had better outcomes both regarding clearance of jaundice within 6 months (75%) and 1-year survival with native liver (75%). Quite importantly, the patients in the UK had KPE performed around 10 days earlier than the patients in our study which may clearly contribute to the better overall outcome.

CMV testing in all patients with neonatal cholestasis is of possible importance. However, its detection clearly does not rule out a BA diagnosis. The only finding in our CMV-positive BA patients that differed from the CMV-negative patients during the investigation of cholestasis was a trend toward a higher incidence of splenomegaly. In other aspects, the two groups were similar, i.e., no difference in gestational week, birth weight or laboratory findings; hence, it is important to test all BA patients to find the CMV-positive ones. However, screening for CMV in all newborns would not be of benefit for the BA patients because these patients seem to seldom have congenital CMV infection [31].

There were no obvious differences between the mothers of CMV-positive and CMV-negative patients. Neither country of origin, number of siblings nor the mothers' age did differ significantly. Therefore, for example, overcrowding or multiparity could not be confirmed as risk factors for CMV

Table 2 Antiviral treatment with IV ganciclovir or oral valganciclovir

Patient nr	1	2	3	4	5 ^a	6 ^a	7 ^a	8	9	10	11	12	13	Median
CMV-IgM	Negative	Positive	Negative	Positive	Positive	nd	Negative	Negative	Negative	Positive	Negative	nd	nd	
CMV-DNA urine	Positive	Positive	Positive	Positive	nd	Positive	Positive	Positive	Positive	Positive	Negative	Positive	Positive	
CMV-DNA blood/serum	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Negative	Positive	Positive	
Start AVT after KPE (days)	15	8	7	2	-6	-10	-1	18	22	21	13	8	-28	
CMV-DNA level in blood/serum before AVT (IU/mL)	1200	18,000	6500	12,000	2000	800	5400	6824	3824	1400	11,900	250	5099	
CMV level 5-24 days after AVT initiation (IU/mL)	110	2300	700	3300	250	0	800	0	250	0	250	250	250	
CMV level after AVT (IU/mL)	0	250	0	250	0	0	250	nd	0	0	0	0	250	
Ganciclovir first dosage (mg/kg/day)	11	11	11	5	10	10	10	nd	0	0	0	0	10	
Ganciclovir first dosage (mg/m ²)	204	192	187	92	187	175	181						187	
Ganciclovir first dosage duration (days)	14	14	21	13	15	6	8						14	
Ganciclovir second dosage (mg/kg/day)	5.5	5	5	9	Switch back to valganciclovir	Switch back to valganciclovir	Switch back to valganciclovir						5	
Ganciclovir second dosage (mg/m ² /day)	102	96	93	184									99	
Ganciclovir second dosage duration (days)	14	14	19	45 ^b									17	
Highest trough level ganciclovir treatment (ganciclovir μmol/L)	nd	nd	1.6	1.4	0.4	1.7	3.4						1.6	
Valganciclovir first dosage (mg/m ² /day)					20	22	10	31	22	20	30	19	32	
Valganciclovir first dosage duration (days)					375	416	181	666	386	370	547	400	660	
Valganciclovir second dosage (mg/kg/day)					20	16	20	14	31	40			20	
Valganciclovir second dosage (mg/m ² /day)					384	288	362	305	563	740			373	
Valganciclovir second dosage duration (days)					28	30	13 ^c	14	17	40			23	
Highest trough level valganciclovir treatment (ganciclovir μmol/L)					1.2	4.7	0.6	1.2	0	2.3	nd	0	2.5	

Detailed information about detection of cytomegalovirus (CMV) infection and antiviral treatment (AVT) regarding timing, duration, and dosage in 13 CMV-positive patients with biliary atresia

^a First treated orally, then IV, then orally again: 1. "Valganciclovir first dosage" 2. "Ganciclovir first dosage" 3. "Valganciclovir second dosage"

^b Then liver transplantation and prolonged treatment

^c Then increased dose step by step to maximum 58 mg/kg/d, in total treatment 74 days. nd = not done, IV = intravenous

Table 3 Laboratory findings in 13 patients with biliary atresia who received antiviral treatment for ongoing cytomegalovirus infection

Laboratory findings (Normal range)	Before KPE	After KPE and AVT	<i>p</i> value
Bilirubin $\mu\text{mol/L}$ (< 22 $\mu\text{mol/L}$)	156 (121–263)	105 (10–586)	0.02
Conjugated bilirubin $\mu\text{mol/L}$ (< 3 $\mu\text{mol/L}$)	137 (105–224)	95 (9–493)	0.03
ALT $\mu\text{kat/L}$ (< 0.85 $\mu\text{kat/L}$)	1.78 (0.59–6.2)	1.98 (0.37–4.74)	0.67
AST $\mu\text{kat/L}$ (< 1.4 $\mu\text{kat/L}$)	3.82 (1.72–8.3)	2.3 (1.07–4.74)	0.08
Prothrombin time (International normalized ratio) (< 1.2)	1.1 (0.9–1.3)	1.2 (0.9–2.1)	0.53
Hemoglobin concentration g/L (100–160 g/L)	110 (88–124)	111 (93–133)	0.89
White blood cell count $10^9/\text{L}$ (6–18 $10^9/\text{L}$)	13.1 (7.2–17.8)	10.9 (9.1–17.8)	0.5
Platelet count $10^9/\text{L}$ (160–600 $10^9/\text{L}$)	457 (145–795)	263 (110–726)	0.06
Creatinine $\mu\text{mol/L}$ (< 41 $\mu\text{mol/L}$)	17 (8–21)	13 (10–30)	0.27

Median laboratory findings. Total range in parenthesis

The numbers are from the time of KPE and from the last day of AVT or within 7 days after the last day of AVT

AVT antiviral treatment, KPE Kasai portoenterostomy

infection in this cohort. The incidence of prematurity in our whole BA cohort is higher than in the rest of the Swedish population. This is consistent with studies from Taiwan and the Netherlands where the incidence of BA was higher in preterm infants than in term infants [32, 33]. However, the prematurity rate did not differ when comparing CMV-positive and CMV-negative patients.

The limitation of this study is the small sample size and because, it is a retrospective study, there is heterogeneity in, for example, type of AVT. On the other hand, while several centers have reported the use of AVT in patients with biliary atresia and ongoing CMV infection [34], data on dosage, safety, and effect, as ours, are very scarcely found. Overall, the AVT used in this setting seemed safe. Data are lacking regarding the optimal trough levels to avoid side effects. In our center, we have used an empirically suggested level from experiences in children after solid organ transplantation. We found that if the trough levels were kept below 4 $\mu\text{mol/L}$, there were no negative effects from AVT such as bone marrow depression or impaired kidney function. Even though 9 out of the 13 highest ganciclovir trough levels in this cohort were below 2 $\mu\text{mol/L}$, the AVT was effective in reducing viremia. After LTx, the virus will commonly be reactivated at some point. We could not find that AVT after KPE was associated with difficult-to-treat CMV reactivation post LTx.

This study did not aim for and had no possibility to explain why there might be a difference in outcome for

BA patients with CMV infection than for those without. If indeed CMV-positive patients had been older at KPE, this could have indicated that the onset of the CMV-associated BA starts later in life, suggesting this subgroup to be a different entity. Alternatively, later diagnosis could be due to late referral as pointed out previously [27].

Conclusion

Ongoing CMV infection is common in BA patients and the viremia can effectively be treated without any major side effects. We would, therefore, suggest that a positive effect of AVT on outcome might still be postulated but that further studies in randomized multicenter settings are needed to clarify the possible effect of the treatment on clinical outcome.

Author contributions All authors contributed to the study conception and design. Data collection and analysis were performed by UL. The first draft of the manuscript was written by UL and all authors contributed to previous versions of the manuscript. All authors read and approved the final manuscript.

Data availability The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest The authors declare no competing interests.

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