A Landscape Analysis of Valganciclovir Treatment for Congenital Cytomegalovirus Infection in the United States (US), 2008-2021

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BACKGROUND

- Congenital cytomegalovirus infection (cCMV) is associated with serious audiologic and neurodevelopmental impairment.
- There are no FDA-approved agents to prevent or treat cCMV infection.
- Six months of valganciclovir (which could include IV ganciclovir) [(v)GCV] initiated within the 1st month of life is recommended for newborns with moderate to severe disease [1,2]. This recommendation is based on data showing improved audiological and neurodevelopmental outcomes in children who received 6 months versus 6 weeks of treatment [3].
- The full extent of uptake of these recommendations is unknown. It is also unknown whether patients with less severe disease are being treated with (v)GCV. This knowledge gap impacts clinical development of antivirals for treatment of cCMV.
- The safety profile of (v)GCV has been well-established in other populations, but data from congenitally infected infants remain more limited [4].
- Insurance claims data can be a valuable resource to aggregate nationwide data for a rare pediatric condition [5].

OBJECTIVES

The ultimate goal of this work is to address knowledge gaps that impact the development of antivirals to treat cCMV. The specific aims of this study include:

- To assess features of (v)GCV treatment for infants with cCMV in the United States, with a focus on the following:
  - Changes in (v)GCV prescribing over time
  - Correlation of (v)GCV treatment and baseline disease severity
- To characterize the frequency and severity of hematologic toxicity associated with vGCV exposure.
- To assess audiological outcomes among children with cCMV, and to consider the impact of (v)GCV treatment on those outcomes.

METHODS

Main Analysis

- The FDA Sentinel System's Distributed Database [6] was used to identify three cohorts of infants with diagnosis codes reflecting cCMV infection from 2008-2021, as shown in Figures 1 and 2:
  - Group 1: all infants with cCMV diagnosed in the 1st 45 days of life
  - Group 2: Group 1 infants who were treated with (v)GCV within 45 days of cCMV diagnosis
  - Group 3: Group 1 infants who were treated with (v)GCV within 180d of cCMV diagnosis
- The codes used in this study largely followed what was done in a previous study of this kind [5].
- The study included infants diagnosed up to 45 days of life to allow sufficient time for cCMV-related codes to be identifiable in the infant's record. Because heath care encounters for neonates are often included in the maternal record, restricting the cCMV diagnosis to 21 days may lead to under-capture of cases.
- Characteristics assessed at baseline include demographic information and cCMV-associated clinical features documented within 15 days of cCMV diagnosis (note, 30 days was permitted for CNS radiology studies).
- Group 1 infants were categorized into one of four categories based on the presence/absence of baseline clinical features: asymptomatic; isolated hearing loss; clinical symptoms, no hearing loss; clinical symptoms with hearing loss
- Hearing loss was reassessed at 60 days, 180 days, and 365 days.
- Hematologic safety outcomes were assessed at 60 days and 180 days.
- Descriptive statistics were used to report the findings. No formal hypothesis testing was conducted.

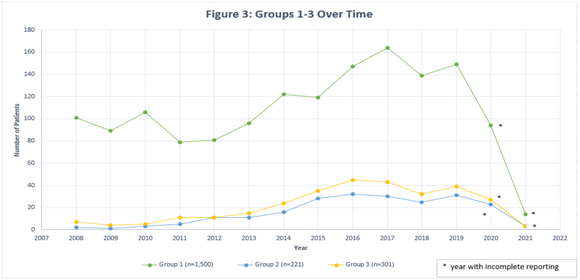
Secondary Analysis

- Duration of treatment was also assessed among all patients up to 5 years of age who received (v)GCV **AND** had a congenital CMV diagnosis code at any time code prior to, and through 45 days after, the first (v)GCV exposure.

RESULTS

Main Analysis

- A total of 1,500 infants with cCMV infection were identified (Group 1). At baseline, 405 (27%) were asymptomatic, 38 (3%) had isolated hearing loss, 963 (64%) had clinical symptoms without hearing loss, and 94 (6%) had clinical symptoms and hearing loss.
- Treatment with (v)GCV was initiated within 45 days of diagnosis for 221 (15%) infants (Group 2) and within 180 days for 301 (20%) infants (Group 3).
- Trends in diagnosis of cCMV and treatment with (v)GCV over time are shown by Group in Figure 3. Note: data from 2020 and 2021 are incomplete and the trend should be interpreted accordingly.



- The primary results of the study are summarized in Table 1.
  - Jaundice, thrombocytopenia, and brain abnormalities were the most common clinical manifestations at the time of diagnosis. These results are consistent with what has been reported in the literature.
  - Neutropenia occurred more frequently among children treated with (v)GCV but few needed treatment with G-CSF.
  - (v)GCV did not appear to increase the risk of severe anemia or thrombocytopenia requiring transfusions.
  - The proportion of patients with hearing loss increased in all groups, irrespective of (v)GCV exposure.

Secondary Analysis

- A total of 302 patients with a diagnosis of cCMV started (v)GCV before 5 years of age, as summarized in Table 2.
- The overall duration of treatment was variable and there was no clear association between baseline disease severity and length of treatment.

Table 2: Secondary Analysis Results, 2008-2021

	Duration of Treatment					
Baseline Disease Severity N (%)	**≤30 days N=0 n (%)**	**31-90 days N=104 n (%)**	**91-180 days N=84 n (%)**	**181-365 days N=107 n (%)**	**>365 days N=7 n (%)**	**Total N=302 n (%)**
Asymptomatic	0 (0%)	22 (21%)	15 (18%)	14 (13%)	0 (0%)	51 (17%)
Isolated hearing loss	0 (0%)	10 (10%)	7 (8%)	8 (7%)	2 (29%)	27 (9%)
Clinical symptoms, no hearing Loss	0 (0%)	56 (54%)	49 (58%)	60 (56%)	5 (71%)	170 (56%)
Clinical symptoms + hearing loss	0 (0%)	16 (15%)	13 (15%)	25 (23%)	0 (0%)	54 (18%)

Table 1: Main Analysis Results, 2008-2021

	Group 1: All infants N = 1,500	Group 2: (v)GCV within 45 days N=221	Group 3: (v)GCV within 180 days N=301
Demographic Characteristics			
Mean Age in days (Standard Deviation)	7.6 (11.5)	9.0 (12.3)	8.0 (11.8)
Sex			
Male	809 (53.9)	116 (52.5)	159 (52.8)
Female	691 (46.1)	105 (47.5)	142 (47.2)
Clinical Symptoms at Baseline			
Jaundice	731 (48.7)	105 (47.5)	144 (47.8)
Petechiae	84 (5.6)	33 (14.9)	37 (12.3)
Hepatomegaly	73 (4.9)	18 (18.1)	24 (8.0)
Splenomegaly	53 (3.5)	18 (18.1)	25 (8.3)
Microcephaly	123 (8.2)	36 (16.3)	50 (16.6)
Thrombocytopenia	542 (36.1)	97 (43.9)	141 (46.8)
Chorioretinitis	44 (2.9)	13 (5.9)	16 (5.3)
Brain abnormality	279 (18.6)	75 (34.0)	96 (31.9)
Hematological Safety Outcomes (60 days)			
Neutropenia	210 (14.0)	41 (18.6)	64 (21.3)
G-CSF†	6 (0.4)	3 (1.4)	4 (1.3)
pRBC transfusion‡	118 (7.9)	7 (3.2)	17 (5.6)
Platelet transfusion	85 (5.7)	14 (6.3)	23 (7.6)
Hematological Safety Outcomes (180 days)			
Neutropenia	244 (16.3)	57 (25.8)	85 (28.2)
G-CSF†	12 (0.8)	7 (3.2)	8 (2.7)
pRBC transfusion‡	122 (8.1)	7 (3.2)	19 (6.3)
Platelet transfusion	90 (6.0)	14 (6.3)	24 (8.0)
Hearing Loss			
Baseline	132 (8.8)	49 (22.2)	58 (19.3)
60 Days	204 (13.6)	87 (39.4)	103 (34.2)
180 Days	318 (21.2)	124 (56.1)	155 (51.5)
365 Days	387 (25.8)	138 (62.4)	175 (58.1)

† G-CSF: granulocyte colony stimulating factor
‡ pRBC: Packed red blood cells

Figure 1: Group 1 Design Diagram

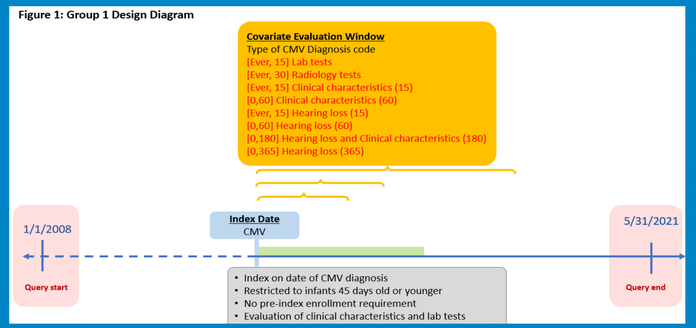
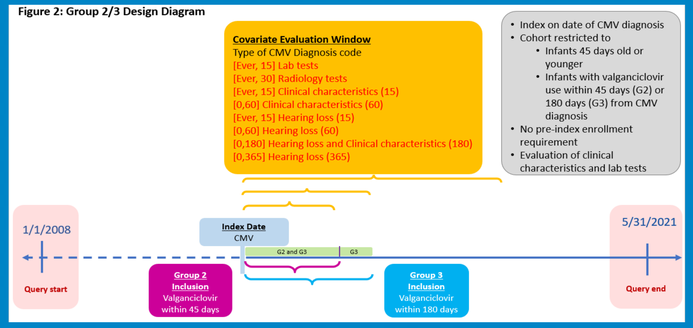


Figure 2: Group 2/3 Design Diagram



LIMITATIONS

- The positive predictive value of the cCMV billing codes are unknown as the codes were not validated. This likely overestimates the number of cCMV cases captured in our study.
  - The cohort may include children with suspected but unconfirmed cCMV.
  - Children with postnatally acquired CMV could potentially be misclassified as cCMV cases.
- The magnitude of hearing loss and degree of clinical symptoms are unknown.
- The results are descriptive in nature.
- Observational data, including claims data in Sentinel, are subject to inherent limitations such as differences in coding practices.
- Since these data come primarily from commercially insured children, the findings may not be generalizable to the US population at large.

CONCLUSIONS

- The study identified a large cohort of infants with cCMV, of whom 20% were treated with (v)GCV.
- Although clinical severity cannot be determined from claims data, the results suggest that (v)GCV treatment in the US may extend beyond the current recommendations.
  - Treatment with (v)GCV may not be limited to patients with moderate to severe disease at baseline. 17% of the treated population were asymptomatic around the time of cCMV diagnosis.
  - 80 patients (27%) began (v)GCV treatment outside of the neonatal period.
  - 114 patients (38%) received (v)GCV for longer than 6 months.
- Severe hematological events occurred infrequently.
- The proportion of patients with hearing loss increased over time, regardless of treatment.
- Additional work assessing patient-level data are needed to further our understanding of the current treatment landscape for cCMV. This work is ongoing by this study team.

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