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Antiviral Treatment Duration and Relapse Risk in Gastrointestinal Cytomegalovirus Disease: A Retrospective Cohort Study

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Abstract

This study examined whether the length of antiviral therapy is associated with relapse in patients with gastrointestinal (GI) cytomegalovirus (CMV) disease, with particular attention to identifying factors that predispose patients to recurrence. Patients diagnosed with GI CMV disease at a tertiary care center between January 2008 and April 2019 were retrospectively reviewed. Relapse was defined as a confirmed recurrence of GI CMV disease occurring at least four weeks after completion of the initial course of antiviral therapy.

A total of 238 patients were included, comprising 145 (51.9%) cases of upper GI involvement and 93 (48.1%) cases of lower GI involvement. Among these patients, 27 (11.3%) experienced disease relapse. The median duration of antiviral treatment did not differ significantly between patients with relapse and those without relapse (21.0 vs 17.0 days, P = .13). Multivariate analysis identified hematologic malignancy (odds ratio, 3.73; P = .026) and ulcerative colitis (odds ratio, 4.61; P = .003) as independent predictors of relapse. Based on these findings, patients were categorized into high-risk (presence of at least one risk factor; relapse rate, 25.9%) and low-risk groups (no identified risk factors; relapse rate, 6.7%). Using this classification, 180 patients (75.6%) were assigned to the low-risk group and 58 patients (24.4%) to the high-risk group. Antiviral treatment duration was not associated with a significant difference in relapse rates within either risk category. Overall, relapse occurred in approximately one-tenth of patients following antiviral therapy, with hematologic malignancy and ulcerative colitis emerging as significant risk factors. These findings suggest that extending the duration of antiviral treatment may not effectively reduce the risk of relapse in GI CMV disease.

Keywords: Gastrointestinal cytomegalovirus disease, Antiviral therapy, Relapse

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Introduction

Cytomegalovirus (CMV) is recognized as a major opportunistic pathogen in immunocompromised populations, including recipients of solid organ transplants (SOT) and bone marrow transplants [1, 2]. Tissue-invasive CMV disease is defined by dominant clinical manifestations with involvement of a specific organ or tissue [3]. Among the various forms of tissue-invasive CMV infection, gastrointestinal (GI) CMV disease represents the most commonly encountered presentation [4]. Despite appropriate antiviral therapy, a subset of patients develops recurrent disease. Previous investigations have reported relapse rates ranging from approximately 23% to 33% in patients treated for primary CMV disease following SOT [5, 6].

Owing to concerns regarding disease recurrence, clinicians often extend the duration of antiviral therapy.

However, recent clinical guidelines emphasize that treatment duration should be tailored according to the patient's clinical improvement and evidence of virologic clearance rather than a fixed treatment length [7, 8]. Nevertheless, data addressing the optimal duration of antiviral therapy in relation to specific anatomic manifestations of CMV disease remain limited. In a prior study evaluating endoscopic response in patients with upper GI CMV disease, prolonged antiviral therapy of 28 days or longer was not identified as an independent predictor of relapse [9]. Consequently, unlike the management of CMV retinitis, several authors have suggested that most patients achieve satisfactory clinical outcomes with antiviral treatment lasting between two and four weeks [10]. In contrast, other experts continue to advocate for an induction phase of antiviral therapy lasting two to three weeks, followed by an extended period of maintenance treatment [11]. Given these discrepancies, we investigated the relationship between antiviral treatment duration and relapse of GI CMV disease, with a specific focus on identifying factors associated with disease recurrence.

Materials and Methods

Study population

We conducted a retrospective cohort analysis involving adult patients aged 18 years or older who were diagnosed with upper or lower gastrointestinal (GI) cytomegalovirus (CMV) disease and hospitalized at Asan Medical Center, a tertiary referral and teaching hospital in Seoul, Republic of Korea, between January 2008 and April 2019. Initially, 249 patients were identified. Individuals who did not receive antiviral therapy for GI CMV disease (n = 9) and those younger than 18 years (n = 2) were excluded, resulting in the final study population. Extracted clinical data included demographic information, presenting clinical manifestations, comorbid conditions, anatomical distribution of GI involvement, endoscopic characteristics, therapeutic outcomes, and occurrence of disease recurrence. All enrolled patients were treated with antiviral medications, most commonly ganciclovir or valganciclovir. Antiviral therapy was maintained until clinical symptoms subsided and CMV antigenemia resolved or until polymerase chain reaction (PCR) testing of blood or tissue samples showed negative results. Procedures for CMV antigenemia assays and PCR testing followed previously established protocols [12, 13]. The study was approved by the institutional review board of Asan Medical Center (approval number 2020-0104). Given the retrospective design, the requirement for informed consent was waived.

Definitions

The diagnosis of GI CMV disease was categorized into proven, probable, and possible cases, based on modified criteria derived from the Infectious Diseases Society of America guidelines [3]. Proven GI CMV disease required the presence of gastrointestinal symptoms, endoscopically visible mucosal abnormalities, and confirmation of CMV infection in tissue specimens through histopathology or immunohistochemistry. Probable GI CMV disease was defined by compatible GI symptoms and tissue-based evidence of CMV infection in the absence of gross mucosal lesions on endoscopy. Possible GI CMV disease was defined as detection of CMV DNA by PCR analysis of biopsy specimens. Relapse of GI CMV disease was defined as the reappearance of GI CMV disease at least four weeks after completion of the initial antiviral treatment in patients with a previously documented episode [3]. Patients were considered immunocompromised if they had underlying conditions such as human immunodeficiency virus infection, malignancy, liver cirrhosis, or chronic kidney disease, or if they were receiving immunosuppressive agents or systemic corticosteroid therapy [14].

Statistical analyses

Continuous variables were summarized using either means with standard deviations or medians with interquartile ranges, depending on data distribution. Group comparisons for continuous variables were performed using the Student t test or the Mann–Whitney U test, as appropriate. Categorical variables were summarized as frequencies and percentages and compared using the chi-square test or Fisher exact test. To identify factors associated with relapse of GI CMV disease, univariate logistic regression analyses were first conducted. Variables demonstrating a P value below .2 in univariate analyses were subsequently included in a multivariable logistic regression model using a backward elimination (Wald) approach to determine independent predictors. Associations are presented as odds ratios (ORs) with 95% confidence intervals (CIs). Statistical significance was defined as a P value less than .05. All analyses were carried out using SPSS software for Windows, version 21.0 (IBM Corp., Armonk, NY).

Results and Discussion

Patient characteristics and clinical outcomes

Between January 2008 and April 2019, 249 hospitalized patients with a diagnosis of gastrointestinal (GI) cytomegalovirus (CMV) disease were initially identified for retrospective evaluation. Of these, 11 patients were excluded from the analysis: 9 patients did not receive antiviral therapy for GI CMV disease and 2 patients were younger than 18 years of age. Consequently, the final

study cohort comprised 238 adult patients who met the inclusion criteria and were included in the analysis **(Figure 1)**.

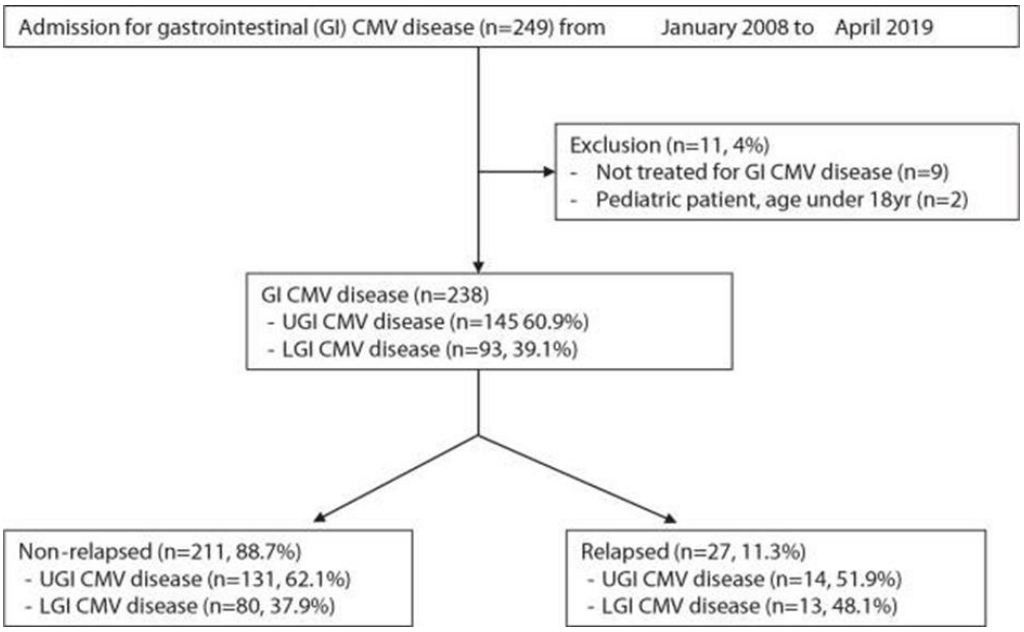

Figure 1. Flowchart of study inclusion.

The baseline characteristics and clinical outcomes of the study population are summarized in **Table 1**. Of the 238 included patients, 145 (51.9%) had involvement of the upper gastrointestinal tract, while 93 (48.1%) presented with lower GI CMV disease. The median duration of antiviral therapy was 18.0 days (interquartile range [IQR], 14.0–25.5). Disease recurrence occurred in 27 patients (11.3%). The median follow-up period was longer in patients who experienced relapse compared with those who did not (452 days [IQR, 319.8–632] vs 257 days [IQR, 102–1129], respectively). The median interval from completion of initial treatment to relapse was 127.0 days (IQR, 32.0–261).

Regarding presenting manifestations, hematochezia and melena were observed more frequently in the relapsed group than in the nonrelapsed group (51.9% vs 27.0%, P = .008). With respect to comorbid conditions, ulcerative colitis was significantly more prevalent among patients with relapse compared with those without relapse (37.0% vs 10.9%, P = .001), whereas no other underlying diseases showed a statistically significant difference between groups. Immune status was not associated with relapse occurrence. Furthermore, the length of antiviral therapy did not differ significantly between patients who developed relapse and those who did not (median duration, 21.0 days vs 17.0 days; P = .13) **(Table 1)**.

Table 1. Clinical characteristics and outcomes in patients with nonrelapsed and relapsed GI CMV disease.

Variable	Total (n=238)	Nonrelapsed (n=211)	Relapsed (n=27)	P-value
Median age (IQR), years	59 (48–67)	59 (48–64)	59 (51–65)	0.943
Proportion of males (%)	149 (62.6)	131 (62.1)	18 (12.1)	0.643
Initial symptoms and signs at presentation (%)				
Fever or chills	22 (9.2)	20 (9.5)	2 (7.4)	1.000
Nausea or vomiting	30 (12.6)	26 (12.3)	4 (14.8)	0.757
Blood in stool or black tarry stool	71 (29.8)	57 (27.0)	14 (51.9)	0.008
Diarrhea	54 (22.7)	49 (23.2)	5 (18.5)	0.583
Underlying conditions or procedures (%)				
Diabetes mellitus	55 (23.1)	49 (23.2)	6 (22.2)	0.908
Ulcerative colitis	33 (13.9)	23 (10.9)	10 (37.0)	0.001

Crohn's disease	4 (1.7)	3 (1.4)	1 (3.7)	0.384
Other conditions*	37 (15.5)	35 (16.6)	2 (7.4)	0.215
Hosts with normal immune function	65 (27.3)	56 (86.2)	9 (13.8)	0.456
Hosts with weakened immune systems† (%)	173 (72.7)	155 (73.5)	18 (66.7)	0.456
Solid tumors	30 (12.6)	27 (12.8)	3 (11.1)	1.000
Blood-related cancers	25 (10.5)	20 (9.5)	5 (18.5)	0.176
Organ or tissue transplants	108 (45.4)	99 (46.9)	9 (33.3)	0.182
Solid organ transplants	100 (42.0)	92 (43.6)	8 (29.6)	0.166
Stem cell transplants	10 (4.2)	9 (4.3)	1 (3.7)	0.891
Chronic renal disease	22 (9.2)	20 (9.5)	2 (7.4)	1.000
Liver scarring	9 (3.8)	9 (4.3)	0	0.603
HIV infection	7 (2.9)	7 (3.3)	0	1.000
Medications prior to GI CMV diagnosis (%)				
Steroid usage‡	147 (61.8)	129 (61.1)	18 (66.7)	0.578
Immunosuppressive drug usage§	151 (63.4)	134 (63.5)	17 (63.0)	1.000
Management of acute transplant rejection (%)	9/108 (8.3)	9/99** (9.1)	0/9 (0)	1.000
Preventive measures against CMV		(%)	37/108 (34.3)	32/99 (32.3)
CMV involvement in upper gastrointestinal tract (%)	145 (60.9)	131 (62.1)	14 (51.9)	0.305
CMV involvement in lower gastrointestinal tract (%)	93 (39.1)	80 (37.9)	13 (48.1)	0.305
Classification of GI CMV disease (%)				
Confirmed¶	195 (81.9)	173 (82.0)	22 (81.5)	1.000
Likely#	19 (8.0)	17 (8.1)	2 (7.4)	1.000
Potential**	24 (10.1)	21 (10.0)	3 (11.1)	0.742

Risk factors associated with the relapse of GI CMV disease

The factors associated with recurrence of gastrointestinal CMV disease are summarized in **Table 2**. On univariate analysis, initial presentation with hematochezia or melena was significantly associated with relapse. In addition, several underlying conditions, including hematologic malignancy, solid organ transplantation, and ulcerative colitis, were identified as potential risk factors.

After adjustment for confounding variables in the multivariate model, hematologic malignancy (odds ratio [OR], 3.73; 95% confidence interval [CI], 1.17–11.86; P = .026) and ulcerative colitis (OR, 4.61; 95% CI, 1.70–12.49; P = .003) remained independently associated with an increased risk of relapse of GI CMV disease.

Table 2. Univariate and multivariate analyses of the risk factors of relapse of gastrointestinal cytomegalovirus disease.

Factors	Crude OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Presenting symptom or indicator				
Blood in stool or black tarry stool	2.91 (1.29–6.57)	0.010		
Hosts with intact immunity	0.72 (0.31–1.70)	0.456		
Comorbid conditions				
Blood cancers	2.17 (0.74–6.36)	0.158	3.73 (1.17–11.86)	0.026
Solid organ transplants	0.54 (0.23–1.30)	0.171		
Ulcerative colitis	4.81 (1.97–11.75)	0.001	4.61 (1.70–12.49)	0.003

Length of antiviral therapy	1.00 (0.98–1.02)	0.911

Association between antiviral treatment duration and relapse risk

Patients were further stratified according to relapse risk using the independent predictors identified in the multivariate analysis. Those with either hematologic malignancy or ulcerative colitis were classified as having a high probability of recurrence, with an observed relapse rate of 25.9%. Patients lacking both risk factors were categorized as low risk, with a relapse rate of 6.7%. Based on this stratification, 58 patients (24.4%) were assigned to the high-risk group and 180 patients (75.6%) to the low-risk group.

When relapse rates were evaluated in relation to the total length of antiviral therapy, no statistically meaningful differences were detected within either risk category.

Reported relapse rates following completion of antiviral therapy for an initial episode of CMV disease vary widely across patient populations. In recipients of solid organ or bone marrow transplantation, recurrence rates ranging from 23% to 33% have been described [5, 6, 15]. More specifically, Sia *et al.* [5] observed relapse in 12.5% of cases, while Humar *et al.* [6] reported a recurrence rate of 21%. Among individuals living with human immunodeficiency virus, recurrence of CMV antigenemia or gastrointestinal involvement has been documented in up to 39% of patients [16]. These discrepancies likely reflect differences in host immune function, comorbid conditions, and the organs affected by tissue-invasive CMV disease.

Treatment strategies for CMV disease often vary by the site of infection. Prolonged antiviral regimens are commonly employed in CMV retinitis, whereas shorter courses are frequently used in gastrointestinal disease. Importantly, accumulating evidence suggests that extending antiviral therapy does not substantially reduce the likelihood of relapse [17–19]. In a study of transplant recipients, Eid *et al.* [17] found no significant association between relapse of GI CMV disease and either prolonged induction therapy or subsequent maintenance treatment. Similarly, Asberg *et al.* [20] demonstrated comparable relapse rates in patients with CMV disease, including GI involvement, regardless of maintenance valganciclovir use. Collectively, these findings call into question the routine use of extended or maintenance antiviral therapy for the prevention of relapse in GI CMV disease.

The findings of the present large retrospective cohort reinforce this growing body of evidence. Our results indicate that longer durations of antiviral therapy do not confer a protective effect against recurrence of GI CMV disease. From a biological perspective, the rapid turnover of gastrointestinal epithelial cells and the relatively high penetration of ganciclovir into GI mucosal tissue, compared with ocular tissue, may explain why extended antiviral exposure offers limited additional benefit in this setting.

Previous studies have identified several factors associated with CMV disease relapse, including the extent of tissue involvement, persistent CMV DNAemia at the end of induction therapy (day 21), lung transplantation, CMV donor-seropositive/recipient-seronegative status, and recent treatment for acute rejection [5, 6, 17, 18, 21, 22]. In immunocompetent individuals, critical illness appears to be a major predisposing factor for tissue-invasive CMV disease [23]. Among patients with malignancies, independent risk factors for GI CMV disease include male sex, low body mass index, lymphopenia, hematologic malignancy, corticosteroid therapy, and red blood cell transfusion within the preceding month [24].

In our cohort, which included approximately 25% immunocompetent patients, relapse was significantly more frequent in the high-risk group (25.9%) compared with the low-risk group (6.7%). High-risk patients were defined as those exhibiting at least one of the two independent predictors identified in multivariate analysis: hematologic malignancy or ulcerative colitis. Clinicians often extend antiviral therapy in patients deemed high-risk for relapse. However, stratified analysis according to relapse risk demonstrated that longer antiviral treatment did not significantly reduce the rate of GI CMV disease recurrence.

This study has several limitations. First, as a retrospective investigation conducted at a single tertiary referral center, selection bias cannot be excluded. Prospective, multi-center cohort studies would be valuable for establishing more robust recommendations regarding the optimal duration of antiviral therapy for GI CMV disease. Second, the study population was heterogeneous with respect to underlying conditions and immune status, both of which may influence relapse risk and potentially reduce statistical power. Despite this variability, the inclusion of a substantial number of immunocompetent patients likely contributed to the relatively low overall relapse rate and provides important insights into GI CMV disease in this population. Third, CMV-specific T-cell responses were not assessed, though recent evidence suggests that cellular immunity may predict CMV disease recurrence [25]. Finally, given the high seroprevalence of CMV (>95%) among Korean adults, most cases in this study likely represented reactivation rather than primary infection [26]. Future studies in populations with varying CMV prevalence and the incorporation of immunologic markers may help tailor antiviral therapy and predict relapse more accurately.

Conclusion

In conclusion, approximately 10% of patients with GI CMV disease experienced relapse following antiviral therapy, with hematologic malignancy and ulcerative colitis being prominent risk factors. Our findings indicate that prolonging antiviral treatment may not effectively prevent recurrence of GI CMV disease.

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Ethics statement: None

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