Prevalence of viral co-infection among covid-19 cases in association with disease severity and oral hygiene

Zeina Sami Adham [(1)], Batool Hassan Al-Ghurabi [(2)]

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ABSTRACT

Background: In December 2019, an episode of COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARSCoV2) was reported in Wuhan, China and has spread around the world, increasing the number of contagions. Cytomegalovirus (CMV) and Epstein-Barr virus (EBV) are common herpesviruses that can cause persistent latent infections and affect the developing immune system. The study was conducted to explore the prevalence and reactivation of CMV and EBV antibodies in COVID-19 patients group in comparison to healthy group and to investigate the association between the presence of these viruses with each of severity of disease and oral hygiene.

Materials and Methods: Eighty Five subjects were participated in this case control study (50 patients with COVID-19 and 35 healthy controls), their age ranged from 18 to 77 years. Oral health status was established by oral hygiene index. Serum obtained from patients and controls was analyzed using ELISA to assess levels of anti- CMV and anti- EBV antibodies.

Results: The study revealed that the mean of anti-EBV IgG in patients was more significantly elevated ($p<0.01$) than that in controls. Otherwise, there was no significant difference ($p>0.05$) in levels of anti- EBV IgM, anti-CMV IgG and IgM between two groups ($P>0.05$). In addition, there were no significant differences between patients and controls ($p>0.05$) in the number and percentage of anti-EBV and anti-CMV antibodies. Interestingly, there was a significant increase in the level of anti-CMV IgM in severe cases as compared to mild cases ($P<0.01$). Furthermore, these results revealed that there were no significant differences ($P>0.05$) in levels of anti-viral antibodies in patients with good oral hygiene compared to patients with poor oral hygiene.

Conclusions: Higher frequency of anti-EBV IgG among patients indicates that latent infection is more common in COVID-19 patients. While an increased percentage of anti-CMV IgM indicated reactivation of latent infection and is related to disease severity suggesting that COVID-19 can cause cellular immune impairment.

Key words: COVID-19, Herpes virus, Cytomegalovirus, Epstein-Barr virus. **(Received: 11/7/2021, Accepted: 12/8/2021)**

INTRODUCTION

Coronaviruses are zoonotic viruses as they are transmitted between animals and humans. Coronavirus is a single RNA virus that has the ability to mutate and recombine rapidly. It is the causative agent of respiratory and intestinal infections in humans and animals [(1)]. A new coronavirus called (SARS-CoV-2) severe acute respiratory syndrome coronavirus 2 appears in Wuhan / China, causing an outbreak of abnormal viral pneumonia. This new coronavirus illness, commonly known as coronavirus disease 2019 (COVID-19), is exceedingly transmitted, and has spread fast all over the world [(2, 3)].

The significant prevalence of co-infections among SARS-CoV-2 patients is supported by mounting evidence, and their potential to worsen the clinical outcome of COVID-19. Dysfunction of immune function is considered as one of the reasons for high mortality in COVID-19, and reactivation of herpes viruses in patients is thought to be related to immune dysfunction [(4)].

CMV is a herpes virus that can remain dormant for the rest of one's life. The viral replication cycle will be resumed if the patient's immune system is compromised [(5, 6)]. CMV is a common pathogen of global clinical relevance, with worldwide seroprevalence ranging from 56% to 94% [(7)], can infect various human cells [(8)]. EBV is a ubiquitous herpes virus with which ~95% of healthy adults are infected [(9)]. EBV is transmitted through saliva and infects pharyngeal epithelial cells. When released from the epithelial cells, EBV infects B cells in the underlying tissue, where it might grow or go into a dormant condition, depending on the B cell environment and the state of the host immune response [(10)]. EBV viremia can also be considered as one of the measures of functional exhaustion of cellular immunity. Infection with the SARS-CoV-2 virus can result in antiviral cells becoming functionally exhausted, as well as a cytopathic effect [(11)]. In severe patients, reactivation of viruses such as herpes simplex, CMV, and EBV occurs, and functional exhaustion of cytotoxic lymphocytes is suggested as the cause. COVID-19 can cause cellular immune dysfunction so it can induce reactivation of the latent viruses [(12)]. Recently, the pathological report of COVID-19 dead patient suggested that there was over-activation of T cells, which to some extent led to severe immune

(1) Master Student, Ministry of health/ National center for drug control and research, Baghdad, Iraq.
(2) Professor, Department of Basic Science, College of Dentistry, University of Baghdad, Iraq.
Corresponding author's e-mail: zeina.adham@yahoo.com

injury in COVID-19 patients [13]. Furthermore, COVID-19 and EBV-induced infectious mononucleosis have symptoms such as fever, tiredness, myalgia, anorexia, and sore throat, implying a possible link. [14, 15]. Improving oral hygiene during a COVID-19 infection reduces the microbial load in the mouth and the risk of microbial super-infection [16]. It may be useful in reducing viral load in asymptomatic COVID-19 patients while also providing health professionals with a protective oropharyngeal hygiene strategy [17]. The point of this research was to explore the prevalence and reactivation of herpes viruses (CMV and EBV) in COVID-19 patients group in comparison to healthy group and to investigate the association between the presence of CMV and EBV with oral hygiene and severity of illness.

MATERIALS AND METHODS

Subject

Study groups: A total of 50 patients with COVID-19 (29 males and 21 females) were enrolled in this study, their age ranged (18-77) years. They were admitted to Baghdad Teaching Hospital/ Medical City from November 2020 to January 2021. All patients were diagnosed with SARS-Cov-2 infection, according to the World Health Organization criteria [18]. Real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assay was used to identify SARS-CoV-2 infection. The clinical classification of patients was categorized by disease severity into mild, moderate and severe, according to sign and symptoms by clinical management guidelines outlined in the diagnosis and treatment protocol for COVID-19. Control group consisted of 35 individuals (16 males and 19 females), their ages and sexes were matched to patients…, their ages ranged between (18-73) years.

Ethical Clearance

From Ethical Committee, College of Dentistry/ University of Baghdad

Inclusion criteria: The patients enrolled in this study and considered eligible must have met the following criteria; signs and symptoms of COVID-19 infection (fever, generalized malaise, cough and shortness of breath) and RT-PCR for COVID-19.

Exclusion criteria: Pediatric and pregnant patients, patients with chronic viral infection and systemic diseases, allergic rhinitis and chronic sinusitis, and patients who could not give informed consent were excluded from this study.

Oral examination: Oral examination was performed by the specialist dentist. The average individual or group debris and calculus scores are combined to obtain oral hygiene index, according to [19].

Oral Hygiene Index = Debris Index + Calculus Index

Sample collection: Three milliliter of venous blood was drawn from all subjects. Blood was transferred to sterile plain tube, and serum was separated by centrifugation at 3000 rpm for 10 min, then divided into small aliquots and kept at -20ºC until used for analysis.

Measuring of Anti-CMV and Anti-EBV antibodies

The level of anti-CMV and anti-EBV antibodies was determined by ELISA and performed as recommended in leaflet with kit (Demeditec/ Germany).

Statistical analysis: As shown by histograms and Smemirnove-Kolmogorove test, the data was non-parametric and described by median and the non-parametric tests of significance were advocated for use. P value less than the 0.05 was considered statistically significant.

RESULTS

The demographic and clinical features of the 85 subjects enrolled in this study are summarized in table (1). The present study showed that there were no significant differences in serum level of anti-CMV IgG and IgM antibodies between patients group and healthy controls group (P>0.05), table (2). The median serum level of CMV IgG in patient group was (2.19 U/ml) and for control group was (2.41 U/ml). The mean serum level of CMV IgM in patients group was (0.82±0.09 U/ml), and (0.71±0.05 U/ml) for healthy control.

Table 1: Demographic and clinical features in study and control groups.

Demographic and clinical features	Study groups		P-value
	Patients group N=50	Control group N=35	
Age (years)			
Mean ± SD	44.26±16.57	40.08±12.64	P>0.05
Gender			
Male	29 (58%)	19(54%)	P>0.05
Female	21 (42%)	16(46%)	
Disease severity			
mild	24 (48%)	-	
moderate	16 (32%)	-	
severe	10 (20%)	-	
Oral hygiene			
Good	30 (60%)	29 (83%)	
Poor	20 (40%)	6 (17%)	

Table 2: Case control difference in serum levels of anti-CMV IgG (U/ml) and anti-IgM(U/ml).

Anti-CMV Antibodies	Study groups		P-value
	Patients group N=50	Control group N=35	
Serum CMV IgG			
Min	1.60	0.96	
Max	3.48	3.49	0.610^{NS}
Median	2.19	2.41	
Mean Rank	41.84	44.66	
Serum CMV IgM			
Min	0.08	0.3079	
Max	2.89	1.7892	0.161^{NS}
Mean	0.82	0.71	
SE	0.09	0.05	

The mean serum level of anti-EBV IgG in patients group (1.53±0.08 U/ml) was significantly elevated ($p<0.01$) as compared with healthy controls (0.66±0.08 U/ml). On the other hand, there was no statistically significant difference ($p>0.05$) in median serum level of anti-EBV IgM between patients group (0.24 U/ml) and controls group (0.23 U/ml), table (3).

Table-3: Case control difference in serum levels of anti-EBV IgG (U/ml) and anti-EBV IgM (U/ml).

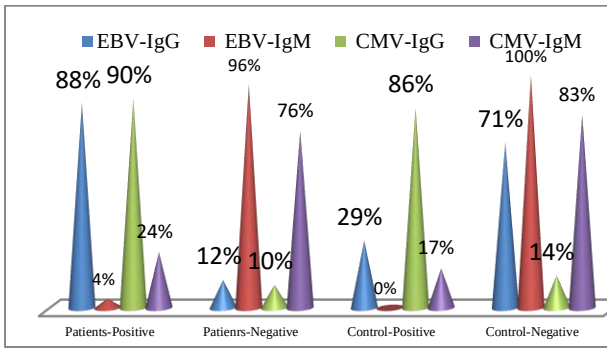
Anti-EBV Antibodies	Study groups		P-value
	Patients group N=50	Control group N=35	
Anti-EBV IgG			
Min	0.53	0.23	
Max	2.76	2.15	$<0.0001^{**}$
Mean	1.53	0.66	
SE	0.08	0.08	
Anti-EBV IgM			
Min	0.09	0.08	
Max	1.36	0.71	0.423^{NS}
Median	0.24	0.23	
Mean Rank	44.80	40.43	

In addition, there were no significant differences ($p>0.05$) in the prevalence of anti-CMV IgG and IgM between patients and controls. 45 (90%) patients were anti-CMV IgG positive and 5 (10%) were negative. For controls group it was found that 30 (86%) were positive, while 5 (14%) were negative. Besides, the presence of anti-CMV IgM in patient group found that 12 (24%) were positive and 38 (76%) were negative, for control group 6 (17%) were positive and 29 (83%) were

negative. The number and percentage of patients group who had positive result for anti-EBV IgG were 44 (88%), while 6 (12%) of patients were negative, and for control group 10 (29%) were positive and 25 (71%) were negative. Hence, there were no significant differences between patients and controls (p>0.05). Further, prevalence of anti-EBV IgM in patients group revealed that only 2 (4%) patients out of 50 were positive and the rest 48 (96%) were negative, while all controls were negative, table (4), figure (1).

Table-4: Prevalence of Anti-EBV and Anti-CMV Antibodies in Patients and Controls.

Anti-CMV and -EBV Antibodies	Patients group n=50		Control group n=35		P-value
	Frequency	Percentage	Frequency	Percentage	
Anti-CMV-IgG					
Positive	45	90%	30	86%	0.492 NS
Negative	5	10%	5	14%	
Anti-CMV-IgM					
Positive	12	24%	6	17%	0.591NS
Negativ	38	76%	29	83%	
Anti-EBV-IgG					
Positive	44	88%	10	29%	<0.000**
Negative	6	12%	25	71%	
Anti-EBV-IgM					
Positive	2	4%	0	-	0.509NS
Negative	48	96%	35	100%	



Figur-1: Prevalence of Anti-EBV and Anti-CMV Antibodies in Patients and Controls.

The results of serum anti-CMV and anti-EBV antibodies (IgG and IgM) levels in COVID-19 patients groups (severe, moderate and mild) were illustrated in table (5). There are non-significant differences (P>0.05) in levels of anti-CMV and anti-EBV antibodies (IgG and IgM) among three groups of patients. The level of anti-CMV IgG was in severe cases (2.48 U/ml), in moderate (2.40 U/ml) and in mild cases (2.11 U/ml). For serum anti-CMV IgM, the level in patients with severe, moderate and mild cases was (1.09±0.53 U/ml, 0.79±0.25 U/ml and 0.66±0.30 U/ml), respectively, and there was a significant increase in anti-CMV IgM level in severe cases as compared to mild cases, (P<0.01). Regarding anti-EBV IgG, the mean level of anti-EBV IgG in severe, moderate and mild group was (1.44±0.50 U/ml; 1.54±0.64 U/ml and 1.55±0.55 U/ml) respectively. On the other hand, the median level of anti-EBV IgM was (0.82 U/ml; 0.32 U/ml and 2.47 U/ml) respectively.

Table 5: Comparison the Levels of Serum Anti-CMV and Anti-EBV Antibodies (IgG and IgM) in Patients Group According to Severity Disease.

Serum Antibodies (U/ml)	Patients group			
	Severe N=10	Moderate N=16	Mild N=24	P-value
Anti- CMV IgG				
Median	2.48 aNS	2.40bNS	2.11cNS	0.236NS
Mean Rank	11.1	15.0	22.5	
Anti- CMV IgM				
Mean	1.09 aNS	0.79 bNS	0.66 c*	
SE	0.53	0.25	0.30	0.078NS
Anti- EBV IgG				
Mean	1.44aNS	1.54bNS	1.55cNS	0.874NS
SE	0.50	0.64	0.55	
Anti- EBV IgM				
Median	0.28 aNS	0.32 bNS	2.47 cNS	0.050NS
Mean Rank	13.70	13.83	28.5	

a: comparison between severe and moderate groups; b: comparison between moderate and mild groups; c: comparison between severe and mild groups ; NS: not significant; *: significant

Furthermore, the present results revealed that there were no significant differences (P>0.05) in serum levels of anti-CMV and anti-EBV antibodies in patients with good oral hygiene compared to patients with poor oral hygiene. The mean levels of serum anti-CMV IgM and anti-EBV IgG in patients with good oral hygiene were (0.89±0.68U/ml and 1.61±0.61U/ml), and for patients with poor oral hygiene were (0.72±0.45U/ml and 1.39±0.48U/ml). The median level of serum anti-CMV IgG and anti-EBV IgM in patients with good oral hygiene was (2.50U/ml and 0.24U/ml) as compared to that in patients with poor oral hygiene (2.10U/ml and 0.24U/ml), as shown in tables (6).

Table 6: Comparison the Levels of Serum Anti-CMV and Anti-EBV Antibodies (IgG and IgM) in patients group according to oral hygiene.

Serum Antibodies (U/ml)	Good Oral Hygiene N=30		Poor Oral Hygiene N=20
Anti- CMV IgG			
Min	1.68		1.60
Max	3.48		3.09
Median	2.50		2.10
Mean Rank	29.93		18.85
P-value		*0.060 NS*	
Anti- CMV IgM			
Min	0.08		0.25
Max	2.89		1.97
Mean	0.89		0.72
SD	0.68		0.45
P-value		*0.172 NS*	
Anti- EBV IgG			
Min	0.53		0.68
Max	2.76		2.24
Mean	1.61		1.39
SD	0.61		0.48
P-value		*0.090 NS*	
Anti- EBV IgM			
Min	0.09		0.1378
Max	0.65		1.365
Median	0.24		0.24
Mean Rank	24.45		27.08
P-value		*0.541 NS*	

DISCUSSION

SARS-CoV-2 infection research is currently the top priority for science communities all around the world, which is unsurprising. To our knowledge, this is the first study in Iraq to look into the impact of SARS-CoV-2 infection on CMV and EBV reactivation and prevalence in connection to oral health. Twenty COVID-19 patients had bad oral hygiene, according to the current study, and the severity of COVID-19 symptoms was considerably elevated in patients with poor oral hygiene. Furthermore, those who practiced good dental hygiene experienced a considerable reduction in the severity of their symptoms. This result was in correlation with the previous findings [20, 21], which indicated that the number of patients with poor oral health was considerably higher than the number of patients with good oral health, implying that mouth health may have a role in COVID-19 degeneration, whether owing to viral infection or secondary bacterial infection.

Co-infection of the SARS-CoV-2 with other microorganisms is a major feature in COVID-19 pathogenesis that can make correct diagnosis, treatment and prognosis difficult, as well as increase fatality rates [22]. There were no statistically significant variations in serum levels of anti-CMV antibodies between COVID-19 patients and healthy controls in this investigation. However, this study found that CMV reactivation occurred in 24 percent of the individuals.

Because CMV is latent in around 90% of persons, CMV viremia might be considered one of the indicators of cellular immunity's functional depletion. Infection with the SARS-CoV-2 virus can result in antiviral cells becoming functionally exhausted, as well as a cytopathic effect [12]. COVID-19 also exhibits acquired immunosuppression, such as lymphopenia, and a cytokine storm, with elevated levels of cytokines such as TNF-. TNF- could be a direct relationship between CMV reactivation and TNF-. In addition, SARS-CoV-2 stimulates macrophages by inducing a vicious cycle of M1 type macrophage polarization, which promotes the reactivation of latent CMV and fuels additional inflammation [23].

This finding is in agreement with previous research that found CMV reactivation was frequent more common in COVID-19 ARDS patients, with higher rates [24]. Moss and colleagues [25] speculated that any link between CMV infection and SARS infection's clinical outcome could be represented by the degree of SARS-CoV-2 viral replication or the quality of the subsequent immune reaction. Other studies [26, 27] indicated that CMV specific antibodies were the best predictors of infection risk, and COVID-19 patients had higher antibody responses to particular CMV and HSV-1 peptides than those who were not hospitalized.

Another finding in this study was a substantial rise in anti-CMV IgM levels in severe patients compared to mild and moderate illness patients, which was in consistent with another study [28] that found CMV reactivation was linked to the severity of COVID-19. If CMV is reactivated in COVID-19 patients and co-infects with SARS-CoV-2, the two viruses could have negative consequences. They' would be predicted to suppress or even kill T cells and natural killer cells stimulate macrophages and neutrophils in a chain reaction that leads to inflammation's point of no return, and then influence endothelial cells and thrombocytes to produce coagulation and thrombus formation—exactly as seen in COVID-19 patients [29].

With regard to anti-EBV antibodies, this study showed significant elevation in the levels of anti-EBV IgG in COVID-19 patients as compared to healthy individual, while there were no significant differences in levels of anti-EBV IgM between patients and controls. This result is in agreement with previous studies [28, 15] that indicated the presence of EBV co-infection with SARS-CoV-2 in COVID-19 patients. Likewise, [30] ….. reported that EBV infection is prevalent in humans and after primary infection the virus can persist in the body in a latent form. The higher rate of EBV co-infection (anti-EBV IgG) in the SARS-CoV-2 samples, as compared to other respiratory viruses, could be reflective of the high EBV instances in the general population or a result of lytic reactivation of the virus as observed under conditions of immunosuppression [30]. SARS-CoV-2-positive individuals, on the other hand, exhibited decreased rates of co-infections for all viral targets, including EBV, according to another study [31]. Furthermore, no significant variations in anti-EBV antibody levels were seen across three groups of patients in this investigation. This study, however, contradicts Chen and colleagues' findings, who found that median EBV levels in patients with severe COVID-19 disease were considerably greater than in patients with mild COVID-19 disease [28]. Furthermore, Mo et al. [25] discovered that EBV reactivation is linked to the severity of COVID-19. Anti-EBV and anti-CMV antibody levels were not significantly different between COVID-19 patients with good oral hygiene and patients with poor oral hygiene. This could be due to the small number of patients studied in this study, as well as the fact that there were fewer patients following subdivision, resulting in the lack of such an association. Individuals with poor oral hygiene are more likely to develop periodontitis, as there is a strong link between poor oral hygiene and the accumulation of dental plaque, which is a risk factor for periodontitis [32]. However, no available studies found to compare this result with it. The limitation in this work is that the sample size in this study was relatively small, as well as CMV and EBV DNA did not test. These findings showed that higher frequency of anti-EBV IgG among patients indicates that latent infection is more common in COVID-19 patients. An increased percentage of anti-CMV IgM indicated reactivation of latent infection and is related to disease severity suggesting that COVID-19 can cause cellular immune impairment.

CONCLUSION

These findings showed that higher frequency of anti-EBV IgG among patients indicates that latent infection is more common in COVID-19 patients. Further an increased percentage of anti-CMV IgM indicated reactivation of latent infection and is related to disease severity suggesting that COVID-19 can cause cellular immune impairment.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare that are relevant to the content of this article

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المستخلص

الخلفية : في كانون الأول ٢٠١٩، تم الابلاغ عن مرض كوفيد-١٩ و الذي يسببه فيروس كورونا -٢ المتلازمة التنفسية الحادة الوخيمة في ووهان ، الصين وانتشر في جميع أنحاء العالم ، مما زاد من عدد العدوى. يعد الفيروس المضخم للخلايا وفيروس إبشتاين- بار من فيروسات الهربس الشائعة التي يمكن أن تسبب عدوى كامنة مستمرة وتؤثر على الجهاز المناعي. أجريت هذه الدراسة للكشف عن انتشار وإعادة تنشيط الأجسام المضادة للفيروس المضخم للخلايا وفيروس إبشتاين- بار في المرضى المصابين ب كوفيد-١٩ مقارنة بالاصحاء وللتحقق من الارتباط بين وجود هذه الفيروسات مع كل من شدة المرض ونظافة الفم.

المواد والطرق العمل : شارك في هذه الدراسة خمسة وثمانين شخصًا (خمسون مريضًا مصابًا بـ كوفيد-١٩ و خمسة وثلاثون من الاصحاء) ، تتراوح أعمارهم بين ١٨-٧٧سنة. تم تحديد حالة صحة الفم من خلال مؤشر صحة الفم. و تم أجراء الفحص المناعي المرتبط بالانزيم على عينات المصل الذي تم الحصول عليه المرضى والاصحاء لتقييم مستويات الأجسام المضادة للفيروس المضخم للخلايا و والأجسام المضادة لفيروس إبشتاين- بار.

النتائج: كشفت الدراسة الحالية أن متوسط (الجلوبيولين المناعي- G) المضاد لفيروس إبشتاين- بار في المرضى كان مرتفعًا بشكل ملحوظ ($p<0.01$) مقارنةً بالاصحاء. بخلاف ذلك ، لم يكن هناك فرق ذات دلالة إحصائيًا ($p>0.05$) في مستويات الجلوبيولين المناعي-M المضاد لفيروس إبشتاين- بار ، والجلوبيولين المناعي – G و الجلوبيولين المناعي-M المضاد للفيروس المضخم للخلايا بين المجموعتين . بالإضافة إلى ذلك ، لم تكن هناك فروق ذات دلالة إحصائية ($P>0.05$) بين المرضى والاصحاء في عدد ونسبة الاجسام المضادة لفيروس إبشتاين- بار والأجسام المضادة للفيروس المضخم للخلايا (الجلوبيولين المناعي- G والجلوبيولين المناعي- M). ومن المثير للاهتمام ، أنه كانت هناك زيادة كبيرة في مستوى الجلوبيولين المناعي-M المضخم للخلايا في الحالات الشديدة مقارنة بالحالات الخفيفة ($P<0.01$) . علاوة على ذلك ، أظهرت هذه النتائج عدم وجود فروق ذات دلالة إحصائية($P>0.05$) في مستويات الأجسام المضادة للفيروسات في المرضى الذين يتمتعون بنظافة فموية جيدة مقارنة بالمرضى الذين يعانون من سوء نظافة الفم.

الاستنتاجات: أظهرت هذه النتائج أن التكرار العالي للاجسام المضادة لفيروس إبشتاين بار (الجلوبيولين المناعي- G) إلى أن العدوى الكامنة أكثر شيوعًا في المرضى. في حين أن النسبة المئوية المتزايدة من الأجسام المضادة للفيروس المضخم للخلايا (الجلوبيولين المناعي- M) يدل إلى إعادة تنشيط العدوى الكامنة وترتبط بشدة المرض مما يشير إلى أن مرض فيروس كورونا ٢٠١٩ يمكن أن يسبب اختلال وظيفي في المناعة الخلوية و يؤكد الارتباط السلبي بين الأجسام المضادة للفيروسات والبتيد المضاد للميكروبات في المرضى ضعف الاستجابة المناعية.