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Original Article

Therapeutic effect of intravenous acyclovir in children with infectious mononucleosis and immune function

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Abstract: Objective: To explore the application value of intravenous acyclovir in children with infectious mononucleosis (IM) and its effects on immune function. Methods: The data of 136 children with IM treated in Anhui Provincial Children's Hospital from March 2019 to March 2022 were retrospectively analyzed. According to the inclusion and exclusion criteria, 98 children were selected. Among them, 45 children treated with routine ribavirin were assigned to the control group, and the other 53 children treated with intravenous acyclovir were enrolled into the observation group. The two groups were compared in terms of efficacy, incidence of adverse reactions, recovery time of clinical symptoms, and immune function indexes, IgG, IgA, IgM, white blood cell (WBC) count and lymphocyte proportion, before and 10 days after the treatment. Independent risk factors affecting efficacy were analyzed by multivariate logistic regression analysis. Results: The observation group showed a significantly higher overall response rate than the control group (P=0.025). The control group experienced significantly longer recovery time of body temperature returning to normal, cure time of isthmitis, time for lymph node reduction, and alleviation time of hepatomegaly than the observation group (P<0.05). Additionally, the control group presented with a significantly higher incidence of adverse reactions than the observation group (P=0.028). After treatment, the observation group showed significantly lower levels of IgG, IgA, IgM, WBC count and lymphocyte proportion than the control group (all P<0.010). Longer average course of disease (OR: 1.449, 95% CI: 1.095-1.918), higher admission temperature (OR: 6.996, 95% CI: 1.350-36.257), higher admission IgA level (OR: 4.735, 95% CI: 1.357-16.520) and higher admission IgG level (OR: 1.470, 95% CI: 1.012-2.134) were independent risk factors for ineffective efficacy, while acyclovir (OR: 0.058, 95% CI: 0.005-0.729) was an independent protective factor. Conclusion: In the treatment of IM, intravenous acyclovir can substantially improve the overall clinical response rate for patients, with less adverse reactions, and can greatly alleviate various clinical symptoms and signs including fever, isthmitis, cervical lymph node enlargement, and hepatosplenomegaly, with obvious regulating effects on the immune function, so it is worth popularizing and applying in clinical practice.

Keywords: Acyclovir, infectious mononucleosis in children, immune function, immunoglobulin

Introduction

Epstein barrvirus (EBV) is a B-lymphocyte virus of herpesviridae. With the human body as the main host, EBV is a common pathogen causing infectious diseases in children, which can invade various systems of the human body [1]. According to research statistics, the proportion of adults infected with EBV is as high as 90% worldwide [2]. Infectious mononucleosis (IM) is an infectious disease with typical symptoms including irregular fever, sore throat and lymph node enlargement, and its primary source is EBV [3]. EBV infection in infants and young children is usually asymptomatic, or it lacks obvious clinical symptoms. Once children or adolescents have EBV infection, they may suffer from IM, but IM in most of them is likely to be ignored because of its inconspicuous/mild symptoms [4]. IM can heal itself after infection, with favourable prognosis, but some patients will suffer serious symptoms and serious complications such as hepatosplenomegaly and organ injury. Without timely therapy, the disease can easily develop into a malignant disease related with chronic active EBV infection and results in multi-system damage [5].

Clinically, great attention has been attached to the treatment of patients with obvious IM symp-

toms. At the current stage, IM is mainly treated by supportive treatment, such as anti-inflammatory and analgesic drugs and necessary nutritional support. However, such a treatment scheme relies on the immune function of patients, and the recovery period is relatively long [6]. The clinical symptoms of IM are related with EBV-infected tissues and organs, and also linked to the corresponding immune response due to virus infection [7]. Some research advocates symptomatic and supportive treatment for IM, a self-limiting disease [8], but antiviral therapy for it has always been controversial. Whereas, a growing number of trails have verified that antiviral drugs are effective in the therapy of IM. As a traditional antiviral drug, ribavirin has been applied in clinical practice for a long time, but a high dosage of ribavirin will increase adverse drug reactions. Because of the long course of disease and high recurrence rate in children with IM, the effect of ribavirin alone is unsatisfactory [9]. Acyclovir is an antiviral drug usually adopted for infections triggered by the herpes simplex virus, which can effectively inhibit the synthesis of viral DNA [10]. The oral utilization rate of acyclovir can reach 20%, which can be adopted to treat mild viral infection. In cases of severe infection, intravenous infusion is preferred [11]. However, because of the unclear specific mechanism, the effect of intravenous acyclovir treatment on immune function of children with IM has not been fully elucidated. There are disputes about the effectiveness of various antiviral drugs in the treatment of IM [12], and few previous studies have compared the therapeutic effects of ribavirin and acyclovir on IM and their effects on immune function.

This study retrospectively analyzed the effects of intravenous acyclovir on children with IM and its influence on their immune function.

Methods and materials

Inclusion and exclusion criteria

Inclusion criteria: patients who had not received glucocorticoid therapy recently; patients with normal perceptual function, patients who were diagnosed with IM for the first time according to blood analysis and other laboratory tests. The Diagnostic criteria were as follows: The number of atypical lymphocytes ≥10% of total lymphocytes and/or total lymphocytes ≥5.0 × 10^9 lymphocytes in peripheral blood/L; and the presence of specific antibodies: (1) anti-viral capsid antigen (VCA)-IgM and anti-VCA-IgG antibodies were positive, while anti-EBV nuclear antigen (EBNA)-IgG antibodies were negative; (2) anti-VCA-IgM antibodies were negative, but anti-VCA-IgG antibodies were positive and the affinity was low [13]. Patients <18 years old, and those with detailed medical records.

Exclusion criteria: patients with hepatic or renal insufficiency, patients comorbid with other infectious diseases, patients with abnormal immune function or coagulation function, patients who had received hormones or immunosuppressants in the previous six months, patients with an impaired circulatory system, blood system or nervous system; patients who were allergic to the drugs adopted in this study; patients with dysfunction of vital organs.

Patient data

The data of 136 children with IM treated in Anhui Provincial Children's Hospital from March 2019 to March 2022 were retrospectively retrieved from electronic medical record database. According to the inclusion and exclusion criteria, 98 children were selected. Among them, 45 children treated with routine ribavirin treatment were assigned to the control group, and the other 53 children treated with intravenous acyclovir were enrolled into the observation group. This study was approved by the Medical Ethics Committee of Anhui Provincial Children's Hospital (ethnical approval number: 20190213). The flow chart of this study is shown in **Figure 1**.

Therapeutic regimen

After admission, children in both groups were given symptomatic treatment such as antipyretic, anti-inflammatory, enzyme lowering, antibiotics and myocardial nutrition treatments, and were routinely given hepatoprotective drugs before medication. On this basis, the control group was treated with 7.5 mg/kg ribavirin mixed in 100 mL 0.9% sodium chloride injection through intravenous drip, twice a day, for 10 days. The observation group was treated with 10 mg/kg acyclovir mixed in 100 mL 0.9% sodium chloride injection through intravenous drip, twice a day, for 10 days.

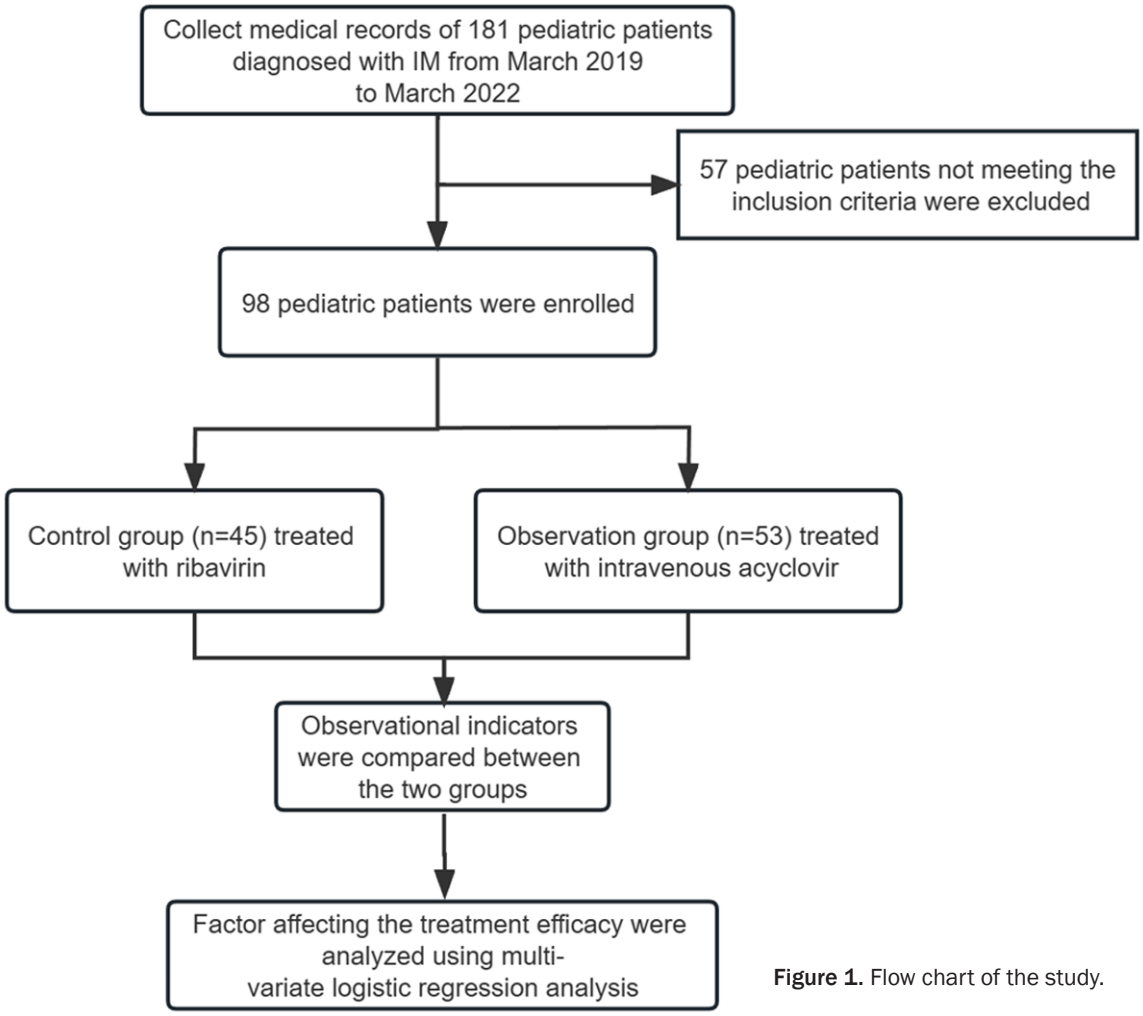

Figure 1. Flow chart of the study.

Collection of outcome measures

The general data and detection indexes of children were collected from the electronic medical record system and LIS inspection system. The general data included gender, onset age, average course of disease, admission body temperature, clinical manifestations (fever, isthmitis, and cervical lymph node enlargement), place of residence and enrolment in school. The detection indexes included efficacy, incidence of adverse reactions, recovery time of body temperature to normal, cure time of isthmitis, time for lymph node reduction and alleviation time of hepatomegaly in children. The immune function indexes of the patients before and after treatment were recorded, including immunoglobulin (Ig) G, IgA, IgM, white blood cell (WBC) count and lymphocyte proportion. The efficacy of treatment and treatment-related adverse reactions were collected 10 days after treatment. The IgG, IgA, IgM, WBC count and lymphocyte proportion were collected on the first day of admission and after 10 days of treatment.

Evaluation criteria of efficacy

Markedly effective: The patient had no recurrence of the disease during treatment, with body temperature returned to normal after treatment, and clinical symptoms completely disappeared; Effective: The patient had no recurrence of the disease during treatment, with body temperature that returned to normal after treatment, and clinical symptoms were greatly alleviated; Ineffective: None of the above criteria were met [14]. Overall response rate (%) = (number of cases with markedly effective treatment + number of cases with effective treatment)/total cases × 100%.

Table 1. Comparison of baseline data between the two groups

	Control group (n=45)	Observation group (n=53)	χ^2/t	*P* value
Gender			0.416	0.519
Male	26 (57.78)	34 (64.15)		
Female	19 (42.22)	19 (35.85)		
Age of onset (years)	4.1±1.2	4.3±1.3	0.786	0.434
Average course of disease (days)	6.4±3.8	5.9±3.2	0.707	0.481
Admission body temperature (°C)	38.4±0.7	38.5±0.5	0.822	0.413
Clinical manifestations				
Fever	41 (91.11)	45 (84.91)	0.872	0.350
Isthmitis	33 (73.33)	36 (67.92)	0.559	0.342
Cervical lymph node enlargement	37 (82.22)	41 (77.36)	0.354	0.552
Place of residence			0.342	0.559
Rural area	12 (26.67)	17 (32.08)		
Urban area	33 (73.33)	36 (67.92)		
Admission to school or not			0.536	0.464
Yes	13 (28.89)	19 (35.85)		
No	32 (71.11)	34 (64.15)		

Table 2. Comparison of efficacy between the two groups

	Control group (n=45)	Observation group (n=53)	χ^2	*P* value
Markedly effective	20 (44.44)	26 (49.06)	5.362	0.069
Effective	13 (28.89)	22 (41.51)		
Ineffective	12 (26.67)	5 (9.43)		
Overall response	33 (73.33)	48 (90.57)	5.041	0.025

Outcome measures

Primary outcome measures: The efficacy in the two groups was compared after treatment.

Secondary outcome measures: The incidence of adverse reactions including nausea, vomiting and rash was compared between the two groups. The recovery time of body temperature to normal, cure time of isthmitis, time for lymph node reduction and alleviation time of hepatomegaly in the two groups were recorded and compared. The two groups were also compared in terms of IgG, IgA, IgM, WBC and lymphocyte proportion before and 10 days after treatment.

Statistical analyses

All the collected data were statistically processed by SPSS26.0 software package and visualized by GraphPad Prism 7. The counting data were expressed by percentage (%) and analyzed using the chi-square test. The measurement data were expressed by Mean ± Standard deviation, and the inter-group and intra-group comparison were conducted using the independent-sample t test and paired t test, respectively. P<0.05 suggested a notable difference.

Results

Baseline data

According to statistics on baseline data of the two groups, the two groups showed no significant differences in gender, onset age, average course of disease, admission body temperature, clinical manifestations (fever, isthmitis, and cervical lymph node enlargement), place of residence and enrolment in school (all P>0.05, **Table 1**).

Comparison of efficacy

According to statistics on efficacy on the two groups, the observation group showed a significantly higher overall response rate than the control group (90.57% *vs.* 73.33%, P=0.025, **Table 2**).

Comparison of the incidence of adverse reactions

Both groups suffered adverse reactions including nausea, vomiting and rash. The control

Table 3. Comparison of adverse reactions between the two groups

	Control group (n=45)	Observation group (n=53)	χ^2	*P* value
Nausea	5 (11.11)	3 (5.66)	0.965	0.326
Vomiting	3 (6.67)	2 (3.77)	0.421	0.517
Rash	5 (11.11)	1 (1.89)	3.603	0.058
Total adverse reactions	13 (28.89)	6 (11.32)	4.806	0.028

Table 4. Comparison of clinical symptom recovery time between the two groups

	Recovery time of temperature returning to normal (days)	Cure time of isthmitis (days)	Time for lymph node reduction (days)	Alleviation time of hepatomegaly (days)
Control group (n=45)	6.88±1.23	8.34±2.06	7.65±1.84	7.80±1.86
Observation group (n=53)	6.22±1.04	7.17±1.63	6.84±1.34	6.74±1.37
t	2.879	3.138	2.515	3.242
P	0.005	0.002	0.014	0.002

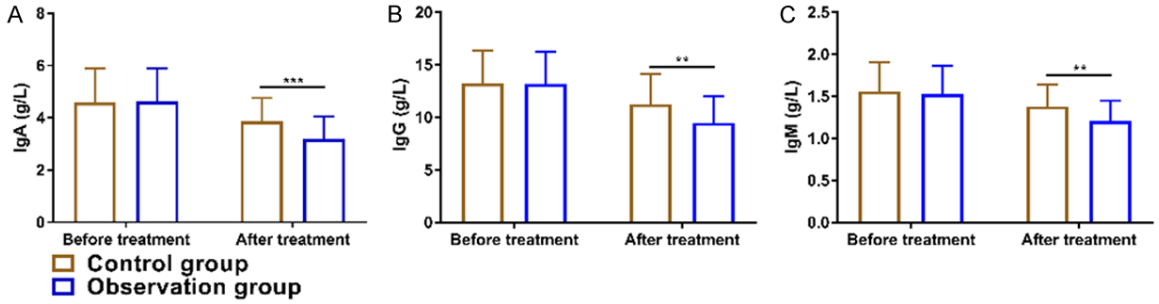

Figure 2. Changes of immune function before and after treatment. A. The observation group showed a notably lower IgA level than the control group (P<0.001). B. The observation group showed a notably lower IgG level than the control group (P=0.002). C. The observation group showed a notably lower IgM level than the control group (P=0.001). Notes: **P<0.010, ***P<0.001. IgG: immunoglobulin G, IgA: immunoglobulin A, IgM: immunoglobulin M.

group showed a significantly higher incidence of adverse reactions than the observation group (28.89% *vs.* 11.32%, P=0.028, **Table 3**).

Alleviation time of clinical symptoms

The alleviation time of clinical symptoms was compared between the two groups. According to the results, the observation group experienced notably shorter recovery time of body temperature returning to normal, cure time of isthmitis, time for lymph node reduction, and alleviation time of hepatomegaly than the observation group (all P<0.05, **Table 4**).

Changes of immune function before and after treatment

Before treatment, the two groups were not significantly different in the levels of IgA, IgG and IgM (P>0.05), while after treatment, the levels of them in both groups decreased notably, with notably lower levels in the observation group (all P<0.010, **Figure 2**).

Changes of WBC count in children before and after treatment

Before treatment, the two groups were not significantly different in WBC count and lymphocyte proportion (all P>0.05). After treatment, the WBC count and lymphocyte proportion of both groups decreased, and the observation group showed notably lower WBC count and lymphocyte proportion than the control group (all P<0.001, **Figure 3**).

Univariate analysis of factors impacting efficacy

All patients were divided into overall response group and ineffective group according to the

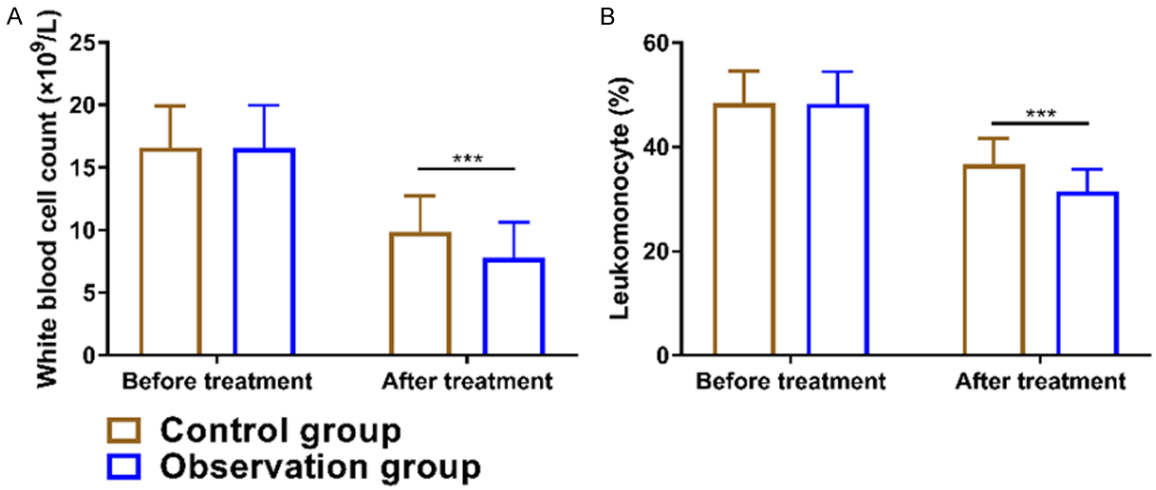

Figure 3. Changes of white blood cell count in children before and after treatment. A. The observation group showed a notably lower white blood cell count than the control group (P<0.001). B. The observation group showed a notably lower lymphocyte proportion than the control group (P<0.001). Notes: ***P<0.001.

Table 5. Univariate analysis of factors affecting the treatment efficacy

	Overall response Group (n=81)	Ineffective Group (n=17)	χ^2/t	P
Gender			0.760	0.383
Male	48 (59.26)	12 (70.59)		
Female	33 (40.74)	5 (29.41)		
Age of onset (years)	4.2±1.3	4.3±1.2	0.771	0.292
Average course of disease (days)	5.8±3.4	8.2±2.9	2.708	0.008
Admission body temperature (°C)	38.4±0.6	38.8±0.6	2.499	0.014
Clinical manifestations				
Fever	72 (88.89)	14 (82.35)	0.559	0.455
Isthmitis	53 (65.43)	16 (94.12)	5.549	0.019
Cervical lymph node enlargement	65 (80.25)	13 (76.47)	0.123	0.725
Place of residence			0.363	0.547
Rural area	25 (30.86)	4 (23.53)		
Urban area	56 (69.14)	13 (76.47)		
Admission to school or not			2.106	1.451
Yes	29 (35.80)	3 (17.65)		
No	52 (64.20)	14 (82.35)		
Admission IgA	4.47±1.32	5.28±0.74	2.444	0.016
Admission IgG	12.88±3.11	14.75±2.19	2.355	0.021
Admission IgM	1.51±0.32	1.73±0.30	2.603	0.011
Admission white blood cell count	16.20±3.39	18.47±2.09	2.651	0.009
Admission lymphocyte proportion	47.54±6.22	52.04±4.08	2.851	0.005
Treatment mode			5.041	0.025
Ribavirin	33 (40.74)	12 (70.59)		
Acyclovir	48 (59.26)	5 (29.41)		

Notes: IgG: immunoglobulin G, IgA: immunoglobulin A, IgM: immunoglobulin M.

efficacy. The two groups were found be to notably different in average course of disease, body temperature at admission, pharyngitis, admission IgA, admission IgG, admission IgM, admission WBC count, admission lymphocyte proportion and treatment mode (all P<0.05, **Table 5**).

Table 6. Multivariate analysis of factors affecting the treatment efficacy

Factors	B	S.E.	Wals	Sig.	Exp (B)	95% C.I. for EXP (B)	
						Lower limit	Upper limit
Treatment mode	-2.841	1.288	4.862	0.027	0.058	0.005	0.729
Average course of disease	0.371	0.143	6.719	0.010	1.449	1.095	1.918
Admission body temperature	1.945	0.839	5.371	0.020	6.996	1.350	36.257
Admission IgA	1.555	0.638	5.950	0.015	4.735	1.357	16.520
Admission IgG	0.385	0.190	4.099	0.043	1.470	1.012	2.134

Notes: IgG: immunoglobulin G, IgA: immunoglobulin A, IgM: immunoglobulin M.

Multivariate analysis of efficacy

The indexes with significant differences in univariate analysis were subjected to multivariate logistic regression analysis. As a result, higher average course of disease, higher admission body temperature, higher admission IgA and higher admission IgG were found to be independent risk factors for ineffective efficacy, while acyclovir was found to be an independent protective factor (**Table 6**).

Discussion

After EBV infection, EBV binds to the EBV receptor on B lymphocytes in a short time, activates T lymphocytes, destroys infected B lymphocytes, and invades pharyngeal lymphoma [15, 16]. Children are a susceptible group of EBV infection, and it is a multi-system disease that can damage the lymphoid tissue of the body [17, 18].

IM is mainly treated by symptomatic treatment and etiological treatment, and the main purpose of etiological treatment is to kill EBV. In this study, IM patients were treated with acyclovir or ribavirin. According to the results, compared with ribavirin, acyclovir contributes to a higher overall response rate and a lower incidence of total adverse reactions, which can more quickly reduce the recovery time of body temperature, cure time of isthmitis, time for lymph node reduction, and alleviation time of hepatomegaly.

Additionally, the control group showed a significantly higher incidence of adverse reactions than the observation group. The possible reason is as follows: Ribavirin is a powerful antiviral drug with a wide antibacterial spectrum, which can inhibit the monophosphate-5-phosphate dehydrogenase, prevent the monophosphate from transforming into guanylate, and inhibit the synthesis and replication of viral DNA and RNA to achieve the antiviral effect. Ribavirin can be adopted for the treatment of influenza virus, respiratory syncytial virus and other viral infections. However, it may trigger peripheral blood leukopenia and strong drug resistance, so its application is likely to be limited [19]. Acyclovir, a member of nucleoside anti-DNA virus drugs, is a specific drug for the therapy of varicella-zoster virus and herpes simplex virus infection. With ability to selectively inhibit the virus, it can substantially reduce the toxicity to normal cells and lower the side effects on children [20]. Studies by Keorochana et al. [21] and Usami et al. [22] have revealed that acyclovir can treat EBV infection and shorten the duration of symptoms in IM patients more quickly, which is consistent with the results of present study.

EBV antigen is one of the direct causes of IM. It can stimulate the secretion of body-specific antibodies and bind to EBV antigen-antibody complex. Additionally, EBV antigen can stimulate the abnormal proliferation of immune cells by complement, damaging the autoimmune system [23]. Kurtasova et al. [24] conducted a study on 65 children with IM and found altered immune status, elevated WBCs, lymphocytes and serum content of IgA, IgM and IgG. Shi et al. [25] have mentioned that WBC count and lymphocyte proportion increased significantly in patients with EBV infection, and IgA, IgG, IgM titers, WBC count and lymphocyte proportion in patients complicated with IM which were significantly higher than those in patients with respiratory tract infection and atypical infection. This is due to the excessive expansion of virus-specific CD8 T cells and more intense humoral immunity in patients with IM. This study has revealed that compared with ribavi-

rin, acyclovir treatment can significantly lower the levels of IgA, IgM, IgG, WBC count and lymphocyte proportion in the IM patients.

Gao et al. [26] have mentioned that EBV-induced inflammation can trigger the deposition of IgM, IgG, IgA and IgE, while reducing the inflammation degree can reduce leukocyte aggregation and the deposition of IgM, IgG, IgA and IgE. After being rapidly phosphorylated into activated acyclovir triphosphate in infected cells, acyclovir inhibits viral DNA polymerase to prevent virus replication and it also binds to the growing DNA chain under the action of DNA polymerase, interrupting the extension of DNA chain to inhibit virus replication, so as to substantially eliminate the virus and reduce the total threshold of virus, and finally lower the degree of inflammatory reaction and immune disorder of patients [27]. Finally, through multivariate logistic regression analysis, longer average course of disease, higher admission body temperature, higher admission IgA and higher admission IgG were found to be independent risk factors for ineffective efficacy, while acyclovir was found to be an independent protective factor. Therefore, in the clinical treatment, more attention should be paid to the children with the above factors and corresponding measures should be taken to improve the efficacy in time.

The study still has some limitations. EBV infection has been confirmed to play a crucial part in various diseases according to research on EBV infection-related disease, but the EBV infection-associated disease included in this study is relatively single, so it is of limited help to the study of pathogenesis of EBV infection. Secondly, EBV infection may give rise to multiple organ damage in children, but this study has not explored these effects in depth. We hope to further explore organ damage in children after IM in subsequent research.

To sum up, in the therapy of IM, intravenous acyclovir can substantially improve the overall clinical response rate, with less adverse reactions, and can greatly alleviate various clinical symptoms and signs such as fever, isthmitis, cervical lymph node enlargement, and hepatosplenomegaly, with obvious regulating effects on the immune function, so it is worth popularizing and applying in clinical practice.

Disclosure of conflict of interest

None.

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References

[1] Gao W, Wu J, Han Y and Fu X. Study on diagnostic value of results of EB virus nucleic acid quantification in whole blood lymphocyte and serum in children with EB virus infection. Cytokine 2022; 155: 155902.

[2] Dunmire SK, Verghese PS and Balfour HH Jr. Primary Epstein-Barr virus infection. J Clin Virol 2018; 102: 84-92.

[3] Shi T, Li J, Miao Y, Huang L and Tian J. Adenosine deaminase as a marker for the severity of infectious mononucleosis secondary to EBV in children. BMC Infect Dis 2022; 22: 164.

[4] Taylor GS, Long HM, Brooks JM, Rickinson AB and Hislop AD. The immunology of Epstein-Barr virus-induced disease. Annu Rev Immunol 2015; 33: 787-821.

[5] Dunmire SK, Hogquist KA and Balfour HH. Infectious mononucleosis. Curr Top Microbiol Immunol 2015; 390: 211-240.

[6] Naughton P, Healy M, Enright F and Lucey B. Infectious mononucleosis: diagnosis and clinical interpretation. Br J Biomed Sci 2021; 78: 107-116.

[7] Yanagi Y, Hara Y, Mabuchi S, Watanabe T, Sato Y, Kimura H and Murata T. PD-L1 upregulation by lytic induction of Epstein-Barr virus. Virology 2022; 568: 31-40.

[8] Ebell MH. Epstein-Barr virus infectious mononucleosis. Am Fam Physician 2004; 70: 1279-1287.

[9] Zekri AR, Abdullah D, Osman A, El-Rouby MN, Zayed N, Esmat G, Elakel W and Hafez HA. Epstein-Barr virus and interleukin-28B polymorphism in the prediction of response to interferon therapy in hepatitis C patients. Arab J Gastroenterol 2015; 16: 84-89.

[10] Pagano JS, Whitehurst CB and Andrei G. Antiviral drugs for EBV. Cancers (Basel) 2018; 10: 197.

[11] Klysik K, Pietraszek A, Karewicz A and Nowakowska M. Acyclovir in the treatment of herpes viruses - a review. Curr Med Chem 2020; 27: 4118-4137.

[12] Hu H, Deng H, Bi J, Xu Y, Li S, Xie Y, Sun X, Wang D, Li X, Ouyang W, Hu B, Zhang Y, Tang H, Fang C, Zhang H, Guo L, Wang C, Wang T, Yang F, Jiang T, Xie Z and Liu G. Clinical characteristics and effectiveness of antiviral agents in hospitalized children with infectious mononucleosis in China: a multicenter retrospective study. Pediatr Investig 2021; 5: 188-194.

[13] Mangaonkar AA, Tande AJ and Bekele DI. Differential diagnosis and workup of monocytosis: a systematic approach to a common hematologic finding. Curr Hematol Malig Rep 2021; 16: 267-275.
[14] Zhang S, Zhu Y, Jin Y, Sun H, Wang W and Zhan L. Difference between acyclovir and ganciclovir in the treatment of children with Epstein-Barr virus-associated infectious mononucleosis. Evid Based Complement Alternat Med 2021; 2021: 8996934.
[15] Ok CY, Li L and Young KH. EBV-driven B-cell lymphoproliferative disorders: from biology, classification and differential diagnosis to clinical management. Exp Mol Med 2015; 47: e132.
[16] Zhang F, Li W, Cui Q, Chen Y and Liu Y. Case report: immune microenvironment and mutation features in a patient with Epstein-Barr virus positive large B-cell lymphoma secondary to angioimmunoblastic T-cell lymphoma. Front Genet 2022; 13: 940513.
[17] Jons D, Zetterberg H, Malmestrom C, Bergstrom T, Axelsson M, Blennow K, Thulin M, Sundstrom P and Andersen O. Intrathecal immunoreactivity in people with or without previous infectious mononucleosis. Acta Neurol Scand 2020; 142: 161-168.
[18] Hussain M, Gatherer D and Wilson JB. Modelling the structure of full-length Epstein-Barr virus nuclear antigen 1. Virus Genes 2014; 49: 358-372.
[19] Clark V and Nelson DR. The role of ribavirin in direct acting antiviral drug regimens for chronic hepatitis C. Liver Int 2012; 32 Suppl 1: 103-107.
[20] Vouloumanou EK, Rafailidis PI and Falagas ME. Current diagnosis and management of infectious mononucleosis. Curr Opin Hematol 2012; 19: 14-20.
[21] Keorochana N. A case report of Epstein-Barr virus-associated retinal vasculitis: successful treatment using only acyclovir therapy. Int Med Case Rep J 2016; 9: 213-218.
[22] Usami O, Saitoh H, Ashino Y and Hattori T. Acyclovir reduces the duration of fever in patients with infectious mononucleosis-like illness. Tohoku J Exp Med 2013; 229: 137-142.
[23] Acharya R, Zeng X and Upadhyay K. Concomitant nephrotic syndrome and tubulointerstitial nephritis in a child with Epstein-Barr virus mononucleosis. BMJ Case Rep 2021; 14: e240108.
[24] Kurtasova LM, Tolstikova AE and Savchenko AA. Immunologic indexes, enzyme status of lymphocytes and functional activity of blood neutrophils in children with infectious mononucleosis caused by Epstein-Barr virus. Vestn Ross Akad Med Nauk 2013; 42-46.
[25] Shi T, Ding Q, Liu X, Ai G, Zhou H and Huang L. Concordance of adenosine deaminase with immunoglobulins and lymphocyte subsets in EBV-related diseases. Ital J Pediatr 2023; 49: 49.
[26] Gao X, Lampraki EM, Al-Khalidi S, Qureshi MA, Desai R and Wilson JB. N-acetylcysteine (NAC) ameliorates Epstein-Barr virus latent membrane protein 1 induced chronic inflammation. PLoS One 2017; 12: e0189167.
[27] Vashishtha AK and Kuchta RD. Effects of acyclovir, foscarnet, and ribonucleotides on herpes simplex virus-1 DNA polymerase: mechanistic insights and a novel mechanism for preventing stable incorporation of ribonucleotides into DNA. Biochemistry 2016; 55: 1168-1177.