CASE REPORT

Combining an antiviral with rituximab in EBV-related haemophagocytic lymphohistiocytosis led to rapid viral clearance; and a comprehensive review

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SUMMARY

Epstein-Barr virus (EBV)-related haemophagocytic lymphohistiocytosis (EBVr-HLH) has a better prognosis when the virus is rapidly cleared, but the best antiviral approach is controversial. We present a patient to whom the therapeutic standard rituximab was co-administered with valacyclovir and an HLH-specific treatment with favourable viral and clinical responses. We conducted an extensive literature review and contacted several world reference centres and experts to inquire about their approaches and experience. We conclude that antivirals are infrequently used for EBVr-HLH, despite their laboratory-proven and likely clinical beneficial effect on some EBV-related diseases. However, the role of antivirals remains obscure. Concerns about their lack of efficacy are based on observational data and reports of the cellular tropism of EBV. Therefore, the adjunct use of antivirals may be considered when myelotoxicity is not the primary concern, and related outcomes should be systematically recorded to produce higher quality evidence.

BACKGROUND

Epstein-Barr virus (EBV) is a member of the ubiquitous γ herpes viruses that primarily cause infectious mononucleosis or subclinical infection. EBV immortalises infected B cells. Expansion of EBV-infected B cells is typically controlled by mechanisms involving the natural killer (NK) cells, EBV-specific cytotoxic T lymphocytes and γ interferon. However, via interactions with activated macrophages, conditions such as EBV-related haemophagocytic lymphohistiocytosis (EBVr-HLH), lymphoproliferative disease (LPD) and chronic active EBV may emerge when aberrations of this control mechanism occur.¹

HLH is a syndrome that occurs at the rate of 1:3000 paediatric hospital admissions.² It is to a variable degree a genetically determined condition. Immune dysregulation in patients with HLH leads to a failure to control activated macrophages after these cells have fulfilled their task.³ Therefore, immune insufficiency coexists with a consequent cytokine storm of tumour necrosis factor α , interleukins 2, 6, 10 and 18, interferons and other factors. This systemic inflammation may lead to multiorgan failure and blood cell phagocytosis in lymphoid tissues.^{4 5} According to the revision of the HLH-94 protocol of the Study Group of the Histiocyte Society, HLH diagnosis and treatment with etoposide and dexamethasone requires

fulfilment of either the genetic criteria or five (occasionally four) of the following criteria: (1) temperature $\geq 38.5^{\circ}\text{C}$; (2) ≥ 2 of: haemoglobin (Hgb) $< 9\text{ g/dL}$, platelets $< 100\,000/\mu\text{L}$, neutrophils $< 1000/\mu\text{L}$; (3) splenomegaly; (4) fasting triglycerides $> 265\text{ mg/dL}$ or fibrinogen $< 150\text{ mg/dL}$; (5) haemophagocytosis in lymphoid tissue (not pathognomonic or required³); (6) blood ferritin $> 500\text{ ng/mL}$; (7) NK cell activity tests showing low or absent NK cell activity; and (8) elevated soluble interleukin-2 receptor (sCD25).² Haemopoietic stem cell transplantation (HSCT) is indicated in cases of poor response to therapy, central nervous system (CNS) involvement (along with intrathecal methotrexate and hydrocortisone), positive genetic test, or malignancy. Survival is $\sim 50\%$ with treatment. Without treatment, patients die within months. The main barrier to treatment is delay in diagnosis, which is, indeed, challenging, as HLH is a protean condition.⁶ *Management guidelines stress the importance of trigger elimination.* EBV is the most notorious infectious agent, but data on EBV-targeted therapy are very limited. Rituximab is an anti-CD20 monoclonal antibody that destroys B cells, the major ‘factories’ and reservoirs of the virus. Rituximab is the primary agent for EBV-targeted therapy. Alemtuzumab, a monoclonal anti-CD52 antibody, serves as a treatment for HLH by destroying both B and T cells, and some experts believe that, in EBVr-HLH it is a more effective alternative to rituximab because the virus in HLH passes to T and NK cells, especially in populations of Asian and Hispanic origin. However, both medications target the cellular, but not the lytic, phase of the virus. The lytic phase requires the use of antiviral agents, but few studies have been published on the efficacy of these agents, and no randomised controlled trials (RCTs) have investigated their additive effect on standard treatment. Given the dearth of research in this area and the high rates of EBV found in young populations, this report describes the rapid viral response of a 16-year-old male patient with extremely severe HLH after treatment with a combination of rituximab and valacyclovir, which has motivated our investigation about the role of antivirals in EBVr-HLH, especially because of the young age affected by this highly fatal syndrome.

CASE PRESENTATION AND INVESTIGATIONS

A 16-year-old man with an unremarkable medical history and a serologically confirmed infectious

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mononucleosis syndrome over the previous 6 weeks experienced persistent fever, thrombocytopenia, lymphadenopathy, hepatosplenomegaly and sinusitis, per whole body CT. After a rapid deterioration over several hours, he was admitted to the ICU in a coma. He was in shock resistant to extremely high doses of norepinephrine and epinephrine. Initial studies demonstrated shock liver (alanine aminotransferase (ALT)/aspartate aminotransferase (AST): thousands), anuric acute renal failure, diffuse intravascular coagulation (DIC; international normalised ratio 6.6, partial thromboplastin time (PTT)>160 s, fibrinogen 70 mg/dL, D-dimers>maximal limit), bone marrow failure (Hgb<7 g/dL, low reticulocytes, platelets ~10 000/ μ L, white cell count high, subsequently <2000/ μ L), ferritin 33 300 (follow-up: 62 290) μ g/L, triglycerides 590 mg/dL, total bilirubin 4 mg/dL, lactate dehydrogenase (LDH) 17 700 U/L. His echocardiogram showed an ejection fraction of 30%. Admission viral load (VL; serum EBV DNA) was 100 000 copies/mL. Other studies for microbes that could coexist (including other herpesviruses) were negative. An axillary lymph node biopsy was negative for lymphoma.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis included several systemic diseases, most important of which were, septic shock with multiorgan dysfunction syndrome, autoimmune lymphoproliferative syndrome, liver failure, drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), and thrombotic thrombocytopenic purpura (TTP)/hemolytic-uremic syndrome (HUS). In general, HLH tends to have a more evident multisystem involvement and/or higher ferritin, LDH and/or triglyceride levels than these conditions. Another consideration was HLH with a trigger and/or background other than EBV, such as another infection, malignancy, immune abnormality or autoimmune or rheumatic disease, in which the term *macrophage activation syndrome* applies. While several of these factors are theoretically possible, EBV is the most usual infectious trigger. Notably, a genetic predisposition is frequently present in HLH cases; therefore, genetic tests must be promptly performed to determine a possible need for allogeneic HSCT. The primary concern of our patient was X linked LPD (or, less likely, XMEN).^{2 7} The admission findings fulfilled the criteria for an extremely severe HLH diagnosis (please see the Discussion section) that was associated with septic shock and multiorgan failure. A ferritin level >1000 μ g/L is generally caused by a malignancy or haemochromatosis and is less likely caused by liver disease, infections or renal failure than inflammatory diseases.⁸ Yet the specificity of ferritin >10 000 μ g/L for HLH was >96%, in another series.⁹ The combination of high ferritin and pancytopenia, DIC and multiorgan involvement, including the liver and CNS, particularly in the context of EBV, strongly suggested HLH.

TREATMENT

The shock was treated as septic, and the rate of norepinephrine that was required to maintain a mean arterial pressure >60 mm Hg was exceeded by several times the maximal dosage rate studied in trials^{10 11} and the maximum reported in the literature, except for one case.¹² Inotropes and vasopressors were weaned by the following day. The patient was started on etoposide and dexamethasone on day 5 of admission, according to the HLH-94 protocol, plus rituximab, which may be the best-studied and most appropriate therapy affecting the offending virus. We added oral valacyclovir (continuous venovenous hemofiltration (CVVHDF) dosed as 750 mg daily in two divided doses) to target EBV more aggressively in this extremely

severe HLH. Multiple blood product transfusions, erythropoietin and filgrastim were also used during the period of myelosuppression.

FOLLOW-UP

The nadir of the platelets reached was 5000/ μ L; and the absolute neutrophil count was zero. Over the following 4–6 weeks, system dysfunctions (blood, cardiac, renal, nervous, metabolic and HLH indices) improved. The VL from 100 000 copies/mL in serum decreased to 500 in 11 days; and was 0 on days 14, 17 and 21 after antiviral treatment institution. While eradicating the trigger of HLH is a fundamental part of treatment, as discussed below, we may not know the attributable benefit of each element of treatment—including the antivirals (unless each element is investigated by a separate RCT). Sadly, the patient died 5 months after admission from complications that were unrelated to the focus of the discussion that follows, despite the initial favourable response.

DISCUSSION

We present a case of EBVr-HLH to discuss the elimination of the triggering agent by the addition of an antiviral to the standard of care, rituximab (375 mg/m²/week for up to 4 weeks), and to supplement the literature regarding the possible benefits of this practice. He presented with a VL of 100 000 copies/mL and exhibited undetectable VL on day 14, which is a very positive response. Repeated assessments of the VL thereafter demonstrated sustained complete viral clearance, hence the likelihood that the observed zero VL represented a spontaneous or a random variation is low. The average decrease of VL in similar cases was investigated by the Rituximab Study Group, as presented below, along with our review of related practices.

Implementation of the HLH-94 protocol has led to a 6-year survival rate of 54%.⁶ EBVr-HLH may be more prevalent in Asia, and it exhibits a dismal prognosis.¹³ An observational period, a course of steroids, cyclosporine and/or intravenous immunoglobulin (IVIG) is occasionally successful in mild cases.¹⁴ An active EBV infection, malignancy, fibrinogen <150 mg/dL, platelet count (PLT)<40 000/ μ L and/or LDH $\geq$ 1000 U/L, in a series review,¹⁵ coexistence of bilirubin >1.8 mg/dL and ferritinaemia >20 300 ng/mL on diagnosis in another;¹⁶ a high VL in a third one;¹⁷ and coagulopathy, oedema, hepatic or renal failure, CNS involvement, LDH>5000, ALT, AST>800, ferritin >10 000, Hgb<7, platelet <50 000/ μ L and neutrophils <500/ μ L in a fourth study,¹⁸ indicate a grave prognosis, requiring etoposide-based therapy.¹³ Our patient exhibited most of these indices of severity. Even worse, he also presented with severe cardiomyopathy, as the ejection fraction was only 30% while on extremely high flow of norepinephrine, despite an adequate hydration state and adrenal function. Cardiomyopathy is not rare in HLH, and echocardiogram is routinely performed on diagnosis.⁷ However, the cardiac function improved within 1 week. This suggests septic rather than HLH-related cardiomyopathy.¹⁹ Yet no clear lines can fully separate the two entities. Chemical mediators, such as endotoxins, cytokines and nitric oxide, causing decreased response of myofibril to Ca²⁺ and downregulation of β -adrenergic receptors, appear to be the main mediators of sepsis-induced cardiomyopathy.^{20–24}

Current knowledge suggests that the viral activity in EBVr-HLH is much more intense than that in infectious mononucleosis; and that, it correlates to the clinical manifestations of the syndrome. Furthermore, viral activity critically affects the outcome of EBVr-HLH.²⁵ A large retrospective study

Table 1 Comparison of our patient to a study of reference in the literature²⁶ (36 patients, prior to vs 2–4 weeks after the first course of rituximab-based chemoimmunotherapy, in which 36% of patients were not on antivirals; presented values are median). Ferritin is one surrogate for HLH activity (Lin *et al* 2011)²⁷

	Treatment duration	VL (copies/mL)	Ferritin (µg/L)
Chellapandian <i>et al</i> ²⁶	2–4 week	114 200 to 225*	4260 to 1150
Our patient	2 week	100 000 to zero	46 500 to 2100

*In 22 patients (61%), VL dropped to <1000 copies/mL (n=14) or below the limits of detection (n=8).

HLH, haemophagocytic lymphohistiocytosis; VL, viral load.

demonstrated that rituximab caused a 500-fold VL reduction (median VL prerituximab: 114 200 copies/mL; median VL post: 225 copies/mL; average number of infusions: 3), and this reduction improved the efficacy of the HLH-specific treatment.²⁶ Table 1 compares our patient's response to dual EBV targeting therapy with the median response of the patients in the aforementioned study, conducted by Chellapandian *et al*,²⁶ which included patients who were treated with (64%) or without (36%) antivirals. We stress the limited existing research and note that the major objective of the present report is to highlight the need for further investigation of the effect. The efficacy of the strategy to deplete the B cells, which produce and store EBV, may not be successful in all races. The virus in EBVr-HLH primarily proliferates in T and NK cells in Japanese individuals, in which therapeutic infusions of EBV-specific cytotoxic T lymphocytes were ineffective.^{16 28} Accordingly, in one case, a persistently high VL was observed despite rituximab treatment.²⁹ Furthermore, T-cell infection is a typical feature of EBVr-HLH regardless of ethnic background. Therefore, evaluation of cell type-specific infection has been suggested when targeted therapy is employed.³⁰ Hence, one study reported that after induction with immunochemotherapy, HLH went into remission after induction with alemtuzumab—a monoclonal anti-CD52 that destroys both T and B lymphocytes.³¹

What is the evidence in the literature of antiviral use in EBVr-HLH? Some case reports describe this combination, but no studies evaluated the pure benefit of antiviral use as an adjunct to standard therapy. For instance, a combination of acyclovir (750 mg/day), methylprednisolone (1 g/day for 3 days), IVIG (20 g/day for 3 days) and gabexate (an antitumour necrosis factor agent, 2 g/day) administered in an effort to avoid the toxicity of chemotherapy, induced remission in one case of a pregnant woman.³² Similarly, the combination of IVIG, α interferon and steroids was successful in two patients.^{33 34} In another case, the addition of ganciclovir to high EBV-titre IVIG and cyclosporine resulted in clinical and VL remission after no clinical or VL response to etoposide. These authors noted that antivirals appear to enhance the standard therapy.³⁵ We attempted to further broaden the pool of existing information on EBV—targeting strategies, and searched for answers to the following questions: (1) For which conditions, other than HLH, has valacyclovir been successfully used? (2) For which conditions other than those found in (1) were other antivirals and/or rituximab successfully used? In both (1) and (2) above, we used the characterisation *successful* to denote a potentially positive contribution to treatment according to the report. (3) What is the current practice of several world experts for targeting EBV in EBVr-HLH?

We thus searched the PubMed database using the terms 'Epstein-Barr virus+Valacyclovir'; then other antiherpetics (Adefovir, Valomaciclovir, Acyclovir, Famciclovir, Foscarnet, Cidofovir, Brivudin, Valganciclovir, Penciclovir, Ganciclovir, Vidarabine) and Rituximab sequentially replaced the term 'Valacyclovir'.

In answering (1), valacyclovir was used successfully mostly in combination with other therapies, and on grounds of immune dysregulation—including post-transplant patients, HIV, etc—in EBV-related cases of encephalitis/various forms of CNS infection,^{36 37} severe/complicated (eg, with hepatic involvement)/chronic infectious mononucleosis,³⁸ hepatitis,³⁹ chronic fatigue syndrome,⁴⁰ hairy leukoplakia,⁴¹ hydroa vacciniforme,⁴² various types of LPDs (eg, Burkitt lymphoma),⁴³ oral papulosis,⁴⁴ periodontitis⁴⁵ and lymphocytic myocarditis.⁴⁶ For these conditions, which may coexist, other antiherpetics have also been used.

In terms of question (2), several antivirals, including rituximab, have been used for a number of conditions; for example, cases of uveitis (valganciclovir),⁴⁷ interstitial pneumonitis with pancytopenia (acyclovir),⁴⁸ cutaneous amyloidosis (acyclovir),⁴⁹ vasculitis (eg, of CNS and or eye—acyclovir),^{50 51} keratoconjunctivitis (acyclovir),⁵² interstitial nephritis (acyclovir),⁵³ erythema multiforme (acyclovir),⁵⁴ acute retinal necrosis (acyclovir),⁵⁵ transverse myelitis (ganciclovir),⁵⁶ oesophagitis (acyclovir),⁵⁷ epithelial cell tumours and haematological malignancies (ganciclovir),^{58 59} other malignancies (cidofovir)⁶⁰ and other blood dyscrasias (ganciclovir).⁶¹ A 2010 review reported favourable outcomes of antiviral treatment in most immunocompetent patients with severe manifestations (mainly neurological: meningoencephalitis, cerebellitis, Guillain-Barre, facial nerve palsy, myelodysplasia) in which antivirals had been used (mainly acyclovir, along with steroids).⁶² Finally, in addition to EBVr-HLH and LPD/lymphomas, rituximab has been successfully used for (EBV-related) lymphomatoid granulomatosis-like diseases,⁶³ autoimmune haemolytic anaemia,⁶⁴ pancytopenia/multisystemic infectious mononucleosis syndrome,^{65 66} leiomyosarcoma,⁶⁷ CNS infections⁶⁸ and in primary EBV infection on grounds of X linked LPD aiming to prevent a fulminant course.⁶⁹

(3) A limited subset of world experts who were (co-) authors of cardinal article references, who work in world reference centres treating and investigating this syndrome, based on their participation at the Annual HLH Conference 2015 at the HLH Center of Excellence (Cincinnati Children's Hospital, USA) were conducted by email and asked about their practice and opinion of using antiviral(s) with rituximab for EBVr-HLH. We received responses from the Cincinnati Children's Hospital Medical Centre/HLH Centre of Excellence; the Children's Healthcare of Atlanta, Emory University; the Children's National Health System (Washington DC, USA); the University of Minnesota Medical School; the Children's Research Center at Mayo Clinic; the Hospital for Sick Children, Toronto University; the Texas Children's Hospital; the Children's Hospital/University of Colorado School of Medicine; and UCLA (please see Acknowledgements statement). All responses stated that *evidence for the role of antivirals is insufficient*; the virus resides in the cells and nuclei where these agents have no activity. However, rituximab exhibits activity in these sites. *Approximately half reported administering antivirals infrequently as a second-line treatment. Their major concern was treatment-induced myelosuppression.* The most frequently used was ganciclovir (along with HLH-94+rituximab, and occasionally IVIG). Other points:

- ▶ 'For certain patient groups, especially East Asian and Hispanics, the EBV is not only in B-cell compartments, it is also in T and NK cell compartments. These patients may not respond completely to B-cell-directed therapy (rituximab), some clinicians have tried alemtuzumab to decrease the disease burden in T-cell compartment. Many of these patients have chronic active EBV that can evolve to HLH or lymphoma. Many patients can have concomitant reactivation of cytomegalovirus (CMV), so they might be on ganciclovir or foscarnet to prevent or to treat CMV'.
- ▶ 'I had two patients (both men) whose EBV load responded well to rituximab alone (plus dexamethasone/etoposide). The HLH initially improved. However, after a few weeks the EBV load rose again and the HLH recurred despite flow cytometry for lymphocyte subsets showing zero CD20+ lymphocytes. We assumed the EBV moved to the T cells'.
- ▶ 'Valuable time is often lost entertaining the diagnosis and whether we should first treat the infection (by using antivirals)'.

In conclusion, we provide a case in which an antiviral combined with rituximab may have contributed to the treatment of EBVr-HLH in the absence of solid guidelines. The positive viral response in this syndrome with very high mortality, in which targeting the cause improves the outcome and for which the rarity makes an RCT difficult, has motivated the present investigation, which concludes that this combination needs to be considered, reported and/or studied to provide more evidence of its efficacy. As long as the role of antivirals remains to be determined,⁷⁰ it is reasonable to assume that, since they act on the lytic phase of the virus, they probably accelerate the clearance rate. However, the degree of these effects and the impact of side effects must be determined to establish the safety and efficacy of these agents. Therefore, a hard end point, such as survival benefit, rather than the effect on viral elimination should be set to answer this question. The main side effect of concern for most experts contacted is further bone marrow suppression. Yet most HLH fatalities correlate more strongly with the duration of the syndrome (due to multiorgan failure from the prolonged cytokine storm) rather than with its acute complications (the latter are correlated with bone marrow suppression, eg, sepsis, bleeding,⁷¹ which is a concern of the safety of antiviral use). The addition of an antiviral may be used with an aim to shorten disease duration (and severity), an effect requiring investigation; but it also may aggravate the aforementioned, yet less fatal in the ICU-controlled setting, acute complications.

Learning points

- ▶ The addition of an antiviral to rituximab and haemophagocytic lymphohistiocytosis (HLH)-specific therapy could be considered during the treatment of Epstein-Barr virus-related HLH (EBVr-HLH) in which bone marrow suppression is not the immediate threat, particularly if viral load is high or persistent.
- ▶ Ferritin level, D-dimers, fibrinogen and triglycerides may serve as a low-cost quick screening tool for HLH in young patients.
- ▶ Ideally a randomised controlled trial is required to define the role of antivirals in EBVr-HLH. Until then, management of EBVr-HLH needs to be recorded in detail and reported to a general registry.

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