Review

A systematic review on the role of adjunctive corticosteroids in herpes simplex virus encephalitis: is timing critical for safety and efficacy?

Ciro Ramos-Estebanez[1], Karlo J Lizarraga[2], Amedeo Merenda[2]*

[1]Neurocritical Care Division, Department of Neurology, Case Western University, Cleveland, OH, USA
[2]Neurocritical Care Division, Department of Neurology, University of Miami Miller School of Medicine, Miami, FL, USA

*Corresponding author e-mail: Ciro.RamosEstebanez@UHhospitals.org

Background: Most herpes simplex virus encephalitis (HSVE) patients become disabled despite antiviral therapy. Adjunctive corticosteroid therapy may improve outcomes.
Methods: This was a systematic review of the literature addressing the use of corticosteroids in HSVE.
Results: Data suggesting that steroids decrease the immunological response and enhance viral replication originated from non-neural microenvironments. Early steroid administration might be harmful because initial damage in HSVE is mediated by viral replication. Steroid treatment improves outcomes in animal models by inhibiting the subsequent inflammatory response. Clinical observations support a similar benefit in symptomatic HSVE patients. Cerebrospinal fluid inflammatory markers might guide appropriate timing in future clinical practice.
Conclusions: Experimental and clinical observations suggest a benefit from adjunctive steroid therapy in HSVE. Nevertheless, current evidence is not yet sufficient to endorse this approach as a standard of practice.

Introduction

Herpes simplex virus (HSV) encephalitis (HSVE) is the most common cause of sporadic encephalitis in humans [1–3]. More than 90% of HSVE cases are attributable to HSV type-1 (HSV-1). Approximately 5% of them are caused by HSV type-2 [4]. HSVE is a severe disease, often leading to high morbidity (40%) and mortality (up to 15% in treated cases and 70% in untreated cases) [5–7]. The typical clinical presentation includes a rapid onset of fever and impaired consciousness, often accompanied by focal neurologic signs and seizures. The current treatment of choice is the viral replication inhibitor acyclovir. Although highly effective in reducing mortality, it only results in complete recovery in one-half of patients [5–7]. Steroid therapy is not a mainstay adjunctive therapy in HSVE given the concern of immunosuppression [8–10]. However, there are data supporting a beneficial anti-inflammatory effect. We reviewed the evidence about this therapy in animal and human studies.

Methods

A search of the English literature in BIOSIS, CINAHL Plus, ISABEL/DynaMed and PubMed with the terms 'steroids', 'corticosteroids', 'glucocorticoids' and 'herpes simplex virus encephalitis' originated 77 papers. Original articles, published between 1970 and March 2013, were included. Retrospective work was considered. Reviews, letters to the editor, oral communications and non-specific studies were omitted.

Results

Animal experimental data suggest that adjunctive corticosteroid therapy provided days after inoculation has a beneficial effect by means of decreasing the inflammatory cascade while not increasing the viral load or DNA viral copies. Conversely, steroid therapy prior to or concomitant with the infection seems harmful (Table 1). Two human studies, a small case series and non-randomized retrospective trial (Table 1), suggest a favourable outcome for patients who receive corticosteroids as an adjuvant therapy in HSVE. Further details are provided in Additional files 1 and 2.

Discussion

Most information on steroid effects in HSVE is derived from animal models (that is, mouse, rat and rabbit). As

Table 1. Summary of published literature about the use of corticosteroids in animal and human herpes simplex virus encephalitis

Reference	Steroid treatment onset	Treatment modality[a]	Reported benefits	Adverse effects
Animal experiments				
Baringer, *et al.* [33] (rabbit)	1 DBI	Isolated	–	Delay in viral clearance
Thompson, *et al.* [30] (rat)	1 DPI	Adjunctive	Reduced area of HSV antigen staining	–
Meyding-Lamadé, *et al.* [31] (mice)	1 DPI	Adjunctive	Decreased brain HSV DNA copies, decreased iNOS transcripts	–
Meyding-Lamadé, *et al.* [32] (mice)	14 DPI	Adjunctive	Decreased brain viral load, reduced severity of MRI abnormalities	–
Sellner, *et al.* [39] (mice)	1 DPI	Adjunctive	Decreased inflammatory chemokine expression (that is, CCL5, CXCL9, CXCL10 and CXCL11)	–
Sergerie, *et al.* [43] (mice)	0 DPI	Isolated	–	Severe clinical presentation, decreased survival
Sergerie, *et al.* [43] (mice)	3 DPI	Isolated	Decreased viral TK, decreased inflammatory cytokines (that is, TLRs, IFN, TNF), decreased neuronal degeneration, reduced severity of symptoms, increased survival rate	–
Human case reports				
Upton, *et al.* [45]	Not reported	Isolated	Improved outcome	–
Habel, *et al.* [44]	3 DAS	Isolated	Clinical improvement	–
Habel, *et al.* [44]	3 DAA	Isolated	Clinical and EEG improvement	–
Musallam, *et al.* [48]	9 DAA	Adjunctive	Clinical improvement	–
Mesker, *et al.* [49]	5 DAA	Adjunctive	Clinical improvement	–
Lizarraga, *et al.* [21]	5 DAA	Adjunctive	Clinical improvement	–
Human case series				
Nakano, *et al.* [47] (5 patients)	5 DAS, > 21 DAS	Adjunctive	Clinical improvement	–
Kamei, *et al.* [46] (45 patients)	0 DAA	Adjunctive	Predictor of good outcome	–

[a]Treatment modalities defined as administration of isolated steroid therapy without antivirals or adjunctive steroid and antiviral therapies. DAA, days after admission; DAS, days after symptom onset; DBI, days before inoculation; DPI, days post-inoculation; EEG, electroencephalogram; HSV, herpes simplex virus; IFN, interferon; iNOS, inducible nitric oxide synthase; MRI, magnetic resonance imaging; TK, thymidine kinase; TLR, Toll-like receptor; TNF, tumour necrosis factor.

opposed to what happens in humans, HSV is usually not spontaneously reactivating and there is no coinfection with other viruses in experimental models. Nevertheless, HSV and its animal host can be genetically engineered to study particular immunological responses at certain times after viral inoculation, as shown in Additional file 1. The initial viral replication is followed by a prominent inflammatory response, which perpetuation has proven to be detrimental for the animal host. The attenuation of this delayed response with corticosteroids and other immunomodulators has produced exciting results in these models. Despite of the abovementioned differences, several observations argue in favour of similar benefits for humans.

Is steroid therapy a risk factor for HSVE?

The nasal mucosa is the main portal of direct entry of HSV into the central nervous system (CNS). Olfactory neurons connect with limbic structures of the temporal lobes, where primary HSVE mostly localizes. HSV can also reach the CNS through the infection of sensory fibres innervating oral (that is, herpes labialis), nasal or ocular (that is, herpes keratitis) surfaces. Local natural killer (NK) and $CD8^+$ T-lymphocytes generally control these initial infections [11]. However, HSV is able to progress to the corresponding olfactory bulb or trigeminal ganglia via retrograde transport, where it establishes lifelong latency. $CD8^+$ T-cells infiltrate the ganglion and play a crucial role in maintaining HSV dormancy, preventing its reactivation and further retrograde progression to cause HSVE [12].

This is critical for corticosteroids, which are known to impair both NK and $CD8^+$ T-cell functions [13–15]. Consequently, corticosteroids may increase susceptibility to HSVE through this mechanism in two different ways. Firstly, they impair the local control of the primary infection, and thereby allow the spread of an increased viral load to the CNS. Secondly, corticosteroids may

also promote reactivation of latent HSV. In the case of HSVE, the proportion of cases caused by either primary infection or reactivation is unclear [16].

Systemic immunosuppression, including that induced by chronic steroid use, is associated with disseminated HSV muco-cutaneous lesions. However, it does not appear to influence HSVE incidence [17,18]. Remarkably, local immunosuppression induced by irradiation of olfactory, limbic, temporal lobe and/or trigeminal circuits may well predispose to HSVE [19–21]. Moreover, discontinuing steroids in these patients might lead to a more severe clinical picture [19–21]. These observations support both a more prevalent role of primary versus reactivation-dependent HSVE, and a local moreso than systemic immune mechanism in the pathogenesis of HSVE.

Viral structures stimulate local innate immune responses in CNS-resident cells. Toll-like receptors (TLRs) initiate this critical response, acting mostly through nuclear factor (NF)-κB-mediated pathways. TLR2 and TLR9 mediate the production of interferon (IFN) and tumour necrosis factor (TNF) by $CD8^+$ T-cells in the trigeminal ganglia [22]. As previously mentioned, this is essential to preserve viral latency. Furthermore, TLR3- and TLR9-dependent IFN production is crucial for early control of HSV replication in the CNS [23,24]. Deficiency of UNC-93B1, an important molecule in TLR3, TLR9 and IFN pathways, has been associated with increased HSVE mortality in mice and with familial adult-onset HSVE in humans [25]. Due to its known ability to inactivate NF-κB [26], corticosteroids might be detrimental at these early stages of HSVE.

Later, inflammatory cytokines (TNF and interleukin [IL]-6) and chemokines (monocyte chemoattractant protein [MCP]-1 and IL-8) are produced via TLR2 [23]. Thus, the perpetuation of TLR2-dependent responses can have detrimental consequences. In fact, the absence of TLR2 improved survival in HSVE in mice [23]. Moreover, evidence from canine steroid-responsive meningitis-arteritis supports beneficial anti-inflammatory effects of steroids in TLRs pathways [27].

Is there a role for steroid therapy during HSVE?

Glucocorticoids exert their immunosuppressant effects predominantly by inhibiting the expression of cytokines and adhesion molecules. Steroids inactivate NF-κB [26], a key molecule in the early TLR-initiation of viral replication control via IFN [23,24], and the delayed TLR-induction of inflammatory reaction via TNF, IL-1 and IL-6 [23].

Evidence against an indication for steroids

Physicians are generally reluctant to use steroids during HSVE. Indeed, some studies suggest that steroids might enhance HSV pathogenicity by decreasing the immunological response and enhancing viral replication [28,29]. Further evidence has suggested that psychological stress-related endogenous steroids impair the local $CD8^+$ T-cell response to mucosal HSV-1 infection, thus allowing for increased pathogenicity in a rodent model [14,15]. However, the former experiments were carried on non-neural cell cultures and tissues. Therefore, the specific micro-environmental neuro-immunological responses that take place during HSVE were not addressed. Besides, animal models showed that steroid therapy does not correlate with HSV dissemination or viral load [30–34]. Interestingly, immunocompetent HSVE-infected rabbits treated with steroids were as able to clear the virus from the brain as their controls [33]. Finally, even if the viral load were enhanced by steroid therapy, quantitative viral markers do not correlate with radiological changes [35,36] or clinical outcomes [34,37] (Table 1 and Additional files 1 and 2); therefore, we feel there is no compelling evidence against the use of steroids in HSVE.

Data supporting steroids

We believe that the delayed use of corticosteroids may be beneficial in HSVE by decreasing the activation of several inflammatory pathways occurring after the initial viral replication [29,38,39]. Actually, adjunctive corticosteroid administration has been advantageous in the treatment of other infectious diseases with an exaggerated inflammatory response, such as bacterial meningitis [40], tuberculous meningitis [41] and herpetic keratitis [42]. In HSVE, animal models [30–34,39,43] (Table 1 and Additional file 1) and human reports support the use of corticosteroids, either isolated [44,45] or combined with acyclovir [46–49] (Table 1 and Additional file 2). The ongoing GACHE trial will hopefully shed definitive light about the role of corticosteroids as adjunctive therapy to acyclovir [50].

Is the time of onset of steroid therapy important in HSVE?

Animal models have shown that CNS HSV replication quickly rises during the first 4 days post-inoculation, declining during the following 8 days [30,33]. We know that the initial neurological injury is triggered by neuronal cell death directly mediated by viral replication. The TLR3- and TLR9-dependent IFN response aims to control this initial damage [18,19]. At 4 to 8 days post HSV inoculation, there is a significant increase in CNS pro-inflammatory molecules. Experimental models evidence that increases in CNS pro-inflammatory molecules involve the expression of inducible nitric oxide synthase (NOS) [31], matrix metalloproteinases [38] and specific cytokines (TNF, IL-1 and IL-6) and chemokines (CCL5, CXCL9, CXCL10, CXCL11, MCP-1 and IL-8) [34,35,39,43,51]. These animal

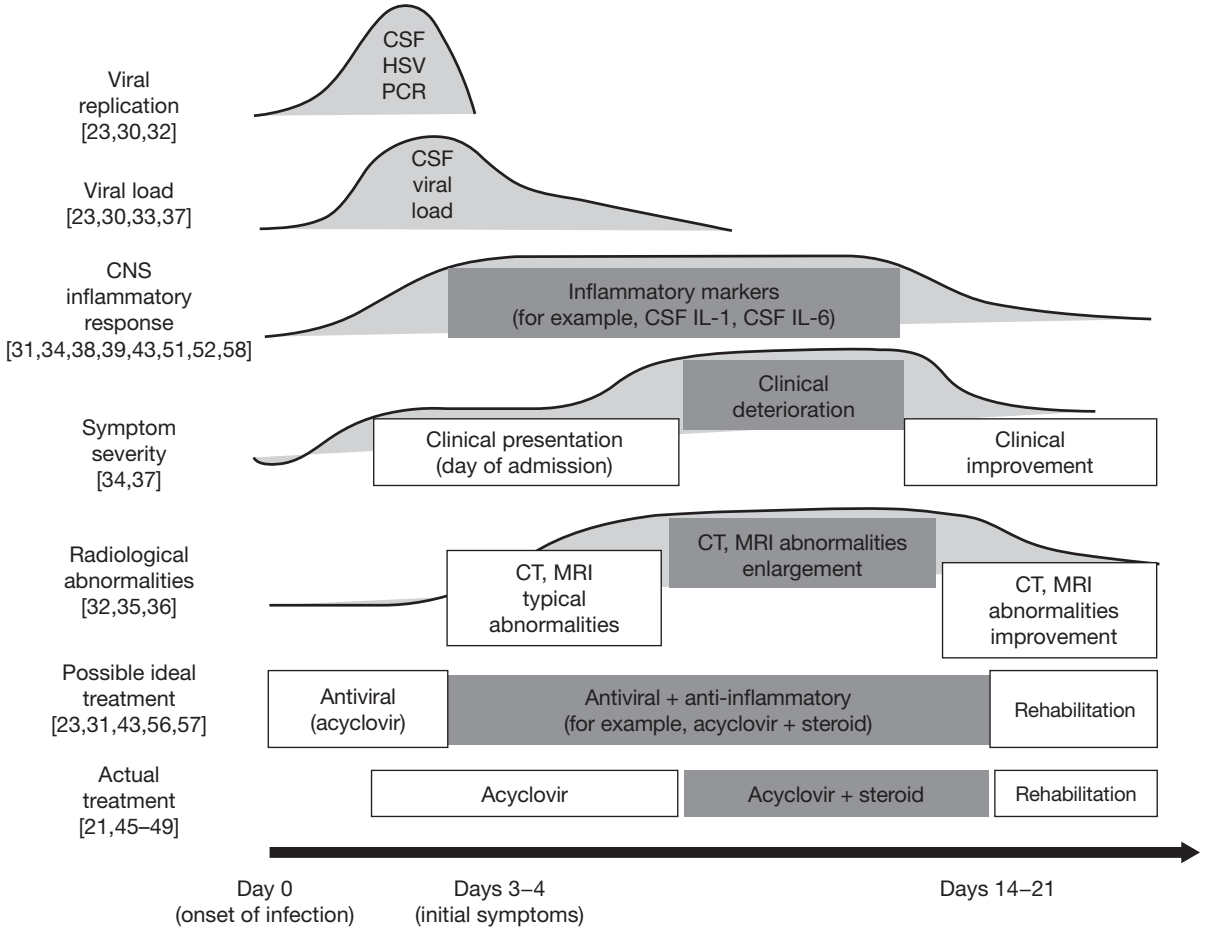
studies suggest that the effect of steroids in HSVE vary depending on the time of administration (Table 1, Figure 1 and Additional file 1).

Neuronal viral invasion might be enhanced by the HSV-induction of brain NOS inhibition [31,52]. This phenomenon occurs in the early stages of HSV infection [52]. Therefore, premature administration of steroids during the course of the disease might be detrimental. Animals treated with inhibitors of NOS prior to HSV infection had higher mortality and viral titres [53]. By contrast, when this treatment was started 1 to 3 days post-HSV-inoculation, symptoms decreased and survival increased [31,54].

Steroid treatment in mice HSVE was associated with improved survival rates if started on the third day after HSV inoculation, as compared to therapy onset on the day of inoculation [43]. Remarkably, this delayed steroid therapy was also associated with reduced expression of both inflammatory and viral genes [43]. Symptomatic HSVE is possibly heralding an inflammatory burden in animal models [30,31,33]. These would suggest that any symptomatic patient could potentially benefit from steroid adjunctive therapy (Table 1, Figure 1 and Additional file 1).

Interestingly, it seems that animal studies support delayed treatment with steroids on HSVE. This

Figure 1. Herpes simplex virus encephalitis clinical, pathophysiological and radiological correlates



CNS, central nervous system; CSF, cerebrospinal fluid; CT, computerised tomography; HSV, herpes simplex virus; IL, interleukin; MRI, magnetic resonance imaging.

observation contrasts with the early use of steroids recommended in other CNS infections (for example, bacterial meningitis), highlighting the relevance that different temporal inflammatory patterns play in their pathophysiology and treatment. Notably, corticosteroids promote anti-inflammatory properties in monocytes [55]. Thus, recovery from inflammation-related damage in HSVE might also be promoted by steroids.

The role of other immunomodulators in the treatment of HSVE is promising, yet unclear. The time of administration again appears to be critical. Early use of IFN in addition to acyclovir could improve virus elimination [56]. Moreover, TLR agonists and/or antagonists used at specific times post-infection have been successful in mice [57]. Overall, we feel corticosteroids would remain as an inexpensive and widely available option to ameliorate the harmful inflammatory response in HSVE.

Are there any prognostic markers in HSVE?

Clinicians may decide to start steroid therapy in HSVE based on clinical symptoms, viral load and radiological data. However, these factors do not clearly correlate with HSVE severity or outcome [34,35]. Conversely, initial cerebrospinal fluid (CSF) IFN-γ and maximum IL-6 levels were significantly higher in patients who had a poor outcome. Besides, CSF IL-6 concentrations decreased more rapidly in patients who received corticosteroids [58]. These CNS inflammatory markers could be used to initiate steroids at the right time in HSVE (Figure 1).

Conclusions

In summary, although most HSVE therapeutic regimens do not include the use of steroids, experimental and clinical observations suggest that their adjunctive use could substantially improve outcomes. We recommend the use of adjunctive steroids in HSVE. However, current evidence is not yet sufficiently robust to support inclusion of this approach as a guideline [8–10]. A large randomized clinical trial comparing acyclovir alone and acyclovir plus dexamethasone both initiated on patient admission is currently addressing this question [50] (Additional file 2).

Disclosure statement

The authors declare no competing interests.

Additional files

Additional file 1: A table displaying a comprehensive summary of published literature about corticosteroids in animal HSVE can be found at http://www.intmedpress.com/uploads/documents/2858_Ramos-Estebanez_Additionalfile1.pdf

Additional file 2: A table displaying a comprehensive summary of published literature about corticosteroids in human HSVE can be found at http://www.intmedpress.com/uploads/documents/2858_Ramos-Estebanez_Additionalfile2.pdf

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