Systemic Corticosteroid Therapy for Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in Vietnam: Clinical Evaluation and Analysis of Serum Cytokines

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Abstract

BACKGROUND: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe cutaneous adverse drug reactions. There are some immunological and genetic factors which are believed to be involved in the pathogenesis of SJS/TEN. The treatment of SJS/TEN is still controversial in which several studies showed variable results.

AIM: The aim of this study is to evaluate clinically the efficacy of systemic corticosteroid and to analyze some related cytokines in the treatment of SJS/TEN.

METHODS: This open, pilot, and uncontrolled study were conducted at the National Hospital of Dermatology and Venereology, in Hanoi, Vietnam, from October 2017 to September 2019. Methylprednisolone was indicated from the first day of hospitalization with the dose of 0.5–2.5 mg/kg/day (calculated according to prednisolone dose) once daily. It was continued until the patients got re-epithelialization. The efficacy of methylprednisolone was evaluated by observing clinically and analyzing related cytokines before and after the treatment.

RESULTS: The mean time of re-epithelialization was 15.9 days, of hospitalization was 15.9 days (range 5–30 days). There was no in-hospital mortality in this study. The most common complication was transient glycemia (40.6%), there were early suspected. Recent study demonstrated that granulysin is a key mediator for disseminated keratinocyte death in SJS/TEN [16], [17]. Keratinocytes become extensive death because of apoptosis and/or necroptosis [18], [19]. This seems to be initiated by drug-specific cytotoxic T cell, amplified by natural killer cells. Some cytotoxic proteins, cytokines, and chemokines produced by these cells have involvement in the pathogenesis of SJS/TEN [19]. Among them, tumor necrosis factor-alpha (TNF-α) [20], Fas ligand (FasL) [21], and perforin/granzyme B [22] were early suspected. Recent study demonstrated that granulysin is a key mediator for disseminated keratinocyte death in SJS/TEN [23].

The treatment of SJS/TEN is still controversial in which several studies showed variable results, including systemic corticosteroid [24], cyclosporine [25], [26], intravenous immunoglobulin (IVIG) [27], etanercept [28], thalidomide [29], and plasmapheresis [5]. Cytotoxic T cells and Fas-FasL,
which play an essential role in the pathogenesis of SJS/TEN, are disabled by cyclosporine [26] and IVIG [27], [29], respectively. Hence, cyclosporine and IVIG are theoretically effective drugs in the management of SJS/TEN [5]. Corticosteroid has been used in the treatment of SJS/TEN for a long time. Proponents emphasize the important of high-dose corticosteroid indicated early in the disease development to block inflammation. On the other hand, systemic corticosteroid increases the risk of infection and sepsis [24]. In Vietnam, systemic corticosteroid has traditionally been used as the first choice to treat SJS/TEN due to its experience of use, being available and cheap cost. This study was conducted to evaluate clinically the efficacy of systemic corticosteroid and to analyze some related cytokines in the treatment of SJS/TEN.

Methods

Study design and ethical clearance

This open, pilot, and uncontrolled study had been approved by the Ethical Review Committee on Research Involving Human Subjects, Hanoi Medical University (Number 04NCS17, dated February 8, 2018). Written consent was obtained from all participants. It was conducted at the National Hospital of Dermatology and Venereology, in Hanoi, Vietnam, from October 2017 to September 2019.

Patients

In total, 32 patients with SJS/TEN were enrolled. The SJS/TEN patients had their vital signs, systemic symptoms, and the percentage of body surface area affected (skin detachment) examined. SJS and TEN were classified in accordance with Bastuji-Garin [1]. They were included if they met the following criteria: aged more than 17 years, admission <10 days after onset (that was defined as the day mucocutaneous or ocular lesions were first eroded or ulcerated) of SJS/TEN. Exclusion criteria were prior treatment with other immunosuppressive drugs (IVIG, cyclosporine, cyclophosphamide), history of osteoporosis or stomachache, uncontrolled diabetes mellitus, psychiatric disorders, human immunodeficiency virus positivity, and cases of multi-organ failure and sepsis.

Therapy

Systemic corticosteroid (methylprednisolone) was intravenously indicated from the 1st day of hospitalization with the dose of 0.5–2.5 mg/kg/day (calculated according to prednisolone dose), once daily. It was continued until the patients got re-epithelialization. No other immunosuppressant was administered. Barrier nursing, topical treatment, ambient temperature of 30°C, fluid and electrolyte balance, and high calorie-containing diet were considered in each patient. Antibiotics were considered if strongly suspected or evident of bacterial infection or sepsis.

Clinical evaluation

The patients were evaluated clinically daily for the entire period of hospitalization. Efficacy of methylprednisolone was assessed by the average number of days of hospitalization, rate of re-epithelialization, the rate of in-hospital mortality and the tolerance to methylprednisolone. The onset in patients with SJS/TEN was defined as the day mucocutaneous or ocular lesions were first eroded or ulcerated. Re-epithelialization was defined as complete healing of the skin without any erosion.

Analysis cytokines

For 32 SJS/TEN patients, we took blood samples at two time points: (1) at the day of hospitalization, (2) at the day of re-epithelialization. All blood samples were left to coagulate at room temperature 10–20 min, then centrifuged in 20 min at a speed of 2000–3000 r.p.m, finally serum was taken and stored at –80°C until proceeding the cytokine measurement. We measured serum interferon-gamma (IFN-γ), TNF-α, interleukin (IL)-2, IL-4, IL-5, IL-13, IL-10 levels by using the fluorescence covalent microbead immunosorbent assay (ProcartaPlex Immunoassay Panels kit, Thermo Fisher Scientific, USA).

Statistical analysis

Data entry and analysis were conducted by using SPSS software version 16.0 (IBM, Armonk, NY, USA). The Wilcoxon tests were used to compare quantitative variables before and after the treatment. Differences were considered to be statistically significant at p < 0.05.

Results

Characteristics of the patients

There were 32 patients with SJS/TEN (15 SJS patients, 17 TEN patients) participating in our study. Characteristics of patients with SJS/TEN are shown in Table 1. The mean age of patients was 48.8 ± 13.9, range 21–72 years (62.5% males; 37.5% females). The most common causative drugs of SJS/TEN were traditional medicine (18.8%), allopurinol (18.8%), and carbamazepine (12.5%). There were 11 patients...
(34.4%) with unknown culprit drugs. Fourteen patients (43.8%) were treated with systemic corticosteroid before being hospitalized. The time between the onset and the day of hospitalization was 5.9 ± 2.8 days.

**Systemic corticosteroid treatment**

The mean dose of corticosteroid was 1.6 mg/kg/day (range 0.7–2.5 mg/kg/day). No patient was indicated with pulse methylprednisolone therapy. The mean time of re-epithelialization was 15.9 days (range 9–31 days), of hospitalization was 15.9 days (range 5–30 days), as shown in Table 1. There was no in-hospital mortality in this study. The common complications during the treatment with systemic corticosteroid were transient glycemia (40.6%), decreasing blood potassium level (21.9%), bronchitis-pneumonia (12.5%), and candidiasis on the mouth (9.4%), there was no patient with sepsis (Table 2).

**Table 1: Characteristics of patients with SJS/TEN**

| Characteristics                      | SJS (n = 15) | TEN (n = 17) | SJS/TEN (n = 32) |
|--------------------------------------|-------------|-------------|------------------|
| Age, years (Range)                  | 43.9 ± 14.4 | 53.2 ± 12.3 | 48.8 ± 13.9      |
| Sex, n (%)                          | (21–72)     | (30–69)     | (21–72)          |
| Male                                 | 11 (73.3)   | 9 (62.9)    | 20 (62.5)        |
| Female                               | 4 (26.7)    | 8 (47.1)    | 12 (37.5)        |
| Causative drugs, n (%)              |             |             |                  |
| Carbamazepine                        | 3 (20)      |             | 4 (12.5)         |
| Allopurinol                          | 4 (26.7)    |             | 6 (18.8)         |
| Traditional medicine                 | 1 (6.7)     |             | 4 (12.5)         |
| Antibiotics                          | 1 (6.7)     |             | 2 (6.2)          |
| NSAIDs (diclofenac, phenylbutazon)   | 1 (6.7)     |             | 2 (6.2)          |
| Thalidomide                          | 0 (0)       | 1 (5.9)     | 1 (3.1)          |
| Unkonw                               | 5 (33.3)    | 8 (41.2)    | 11 (34.4)        |
| Taking systemic corticosteroid before hospitalization, n (%) |           |             |                  |
| Yes                                  | 5 (33.3)    |             | 14 (43.8)        |
| No                                   | 7 (46.7)    |             | 2 (6.2)          |
| Delay of administration              | 3.7 ± 1.3   |             | 3.7 ± 1.7        |
| The mean dose of systemic corticosteroid (calculated according to prednisolone dose), mg/kg/day | 1.4 ± 0.5 |             | 1.6 ± 0.5        |
| (Range)                              | (0.7–2.4)   |             | (0.8–2.5)        |
| The time of hospitalization, Days    | 13.1 ± 3.8  |             | 15.9 ± 6.7       |
| (Range)                              | (9–23)      |             | (9–31)           |
| The time of re-epithelialization, Days | 18.4 ± 4.1 |             | 15.9 ± 4.8       |
| (Range)                              | (11–31)     |             | (9–31)           |

**Table 2: Complications of SJS/TEN patients treated with systemic corticosteroid (n = 32)**

| Complications                          | n  | %      |
|----------------------------------------|----|--------|
| Transient glyemia                      | 13 | 40.6   |
| Decreasing blood potassium level       | 7  | 21.9   |
| Bronchitis-pneumonia                   | 4  | 12.5   |
| Candidiasis on the mouth               | 3  | 9.4    |
| Sepsis                                 | 0  | 0      |

**The changes of cytokines**

At the day of re-epithelialization, serum concentrations of TNF-α, IFN-γ, IL-2, IL-5, IL-13, and IL-10 were significantly lower than those at the day of hospitalization (p < 0.05 or p < 0.001). Serum levels of IL-4 did not have significant differences between 2 time points (p > 0.05). The most significant changes were with serum TNF-α and IFN-γ levels. These findings are shown in Figure 1.

**Discussion**

In this study, we evaluated the use of systemic corticosteroid as a primary treatment in 32 SJS/TEN patients who were managed in a single dermatology center. There were the following important results. First, we found that the use of systemic corticosteroid had possibly contributed to the survival of all patients. Second, the treatment was most often well tolerated despite having some side effects such as transient glycemia, decreasing blood potassium level, bronchitis-pneumonia, and candidiasis on the mouth, but not sepsis. Third, systemic corticosteroid decreased significantly serum levels of some proinflammatory and anti-inflammatory cytokines, especially with TNF-α and IFN-γ.

The precise action of corticosteroid in inflammatory diseases remains not well understood. They have pleomorphic immune-modulating effects through inhibition of numerous cytokines [30], [31]. The use of corticosteroids in SJS/TEN is controversial with various results. Retrospective analysis of the EuroSCAR data indicated a lower mortality in German patients (but not French patients) treated with corticosteroids compared with controls receiving supportive care alone [24]. Others studies showed that the observed mortality rate is lower than the predicted mortality rate that was estimated based on SCORTEN [32]. Corticosteroid therapy in SJS/TEN is carefully considered because of the possibility of...
delayed healing and the risk of infection [5]. However, short courses of high-dose corticosteroids in early SJS/TEN give a good rational, as immune mechanisms are directly responsible for the cascade of events leading to apoptosis [32]. In the study by Kardaun and Jonkmann, 12 patients received 100 mg or 1.5 mg/kg of intravenous dexamethasone (a potent glucocorticoid, about 7 times as potent as the same dose of prednisolone) for 3 days and were reported to have a decreased mortality compared with SCORTEN [32]. Hirahara et al. presented a series of eight patients with SJS/TEN who received 1000 mg of intravenous methylprednisolone on 3 consecutive days, followed by either a tapering course of oral prednisolone or a further 2 days of half-dose intravenous methylprednisolone. No patient died despite a SCORTEN-predicted mortality of 1.6 [31].

Our findings can support to the benefit of corticosteroid therapy in the survival of SJS/TEN patients.

The mean delay to the administration of using corticosteroid therapy in this study was 3.7 days (from the onset), the mean dose was 1.6 mg/kg/day prednisolone equivalent that lasted until re-epithelialization. It means that corticosteroid was given quite late and for too long during the process. This can explain the high rate of side-effects in this study, although they were transient (glycemia, decreasing blood potassium level). The general negative opinion of corticosteroid suggests that during the healing phase, corticosteroid may indeed impair wound healing and promote sepsis [32]. But we did not observe any SJS/TEN patient with sepsis. SCORTEN could not be measured because blood bicarbonate test was not available in the study settings. Hence, we did not calculate the predicted mortality number. Actually, there was no in-hospital mortality. This finding can be comparable with the result of other treatments in SJS/TEN, for example, ciclosporine, etanercept, or pulse methylprednisolone therapy.

In SJS/TEN, IFN-γ has been reported to play a key role by initiating the cytotoxic activities [33], which is a shared mechanism connecting the involvement of TNF-α and FasL [20]. The apoptotic effects of IFN-γ can also be explained by its transcriptional regulation of a variety of genes that are vital for apoptosis, such as TNFα receptor, Fas/FasL, caspase-1, -4, and -8 [21], [34], [35], [36]. Finally, IFN-γ contributes to the antigen mediated immunopathology by upregulation of MHC molecules [37], [38], [39]. Activated T cells secrete large amounts of TNF-α and IFN-γ, which have the ability to induce inducible nitric oxide synthase expression and nitric oxide production by keratinocytes, resulting in FasF upregulation and Fas-mediated keratinocyte apoptosis [20]. Etanercept therapy would act by blocking this inflammatory pathway via TNF-α inhibition [28].

Cytokine receptors may be involved strongly in the recruitment of inflammatory cells in the lesion skin [33]. There was a sharp polarization towards a T help (Th) 1 pattern in erythema multiforme, while the SJS/TEN lesions showed a mixed Th1/Th2 pattern [33]. In this study, both Th1-derived cytokines (TNF-α, IFN-γ, IL-2) and Th2-derived cytokines (IL-5, IL-13) decreased their serum levels at the day of re-epithelialization compared with those at the day of hospitalization. Hirahara et al. showed that at day 4 after methylprednisolone administration, mean levels of IFN-γ, TNF-α, IL-6, and IL-10 were decreased compared with pre-administration levels (day 0), but only changes in IFN-γ and IL-6 reached statistical significance. At day 19, a significant reduction in the mean levels of IFN-γ, TNF-α, and IL-6 was observed compared with levels before administration of methylprednisolone [31]. In this study, the change of IFN-γ, TNF-α, and IL-10 serum levels were consistent with those in Hirahara’s study. The decrease in proinflammatory cytokine levels suggests that corticosteroid therapy may contribute to the survival of all SJS/TEN patients.

The present study is not large, lacks a control group and the predicted mortality number based on SCORTEN. However, it has some advantages because its results were evaluated with regard to not only the clinical progress but also the measurement of cytokine levels before and after treatment. All patients were seen by the same dermatologists at a single dermatology center.

**Conclusion**

The systemic corticosteroid is a good choice in the treatment of SJS/TEN. It can reduce serum levels of some important cytokines that help SJS/TEN patients with avoiding mortality. However, side effects and the time of using systemic corticosteroid should be concerned.

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