The role of tumor necrosis factor-alpha (TNF-α) inhibitor in steven johnson syndrome/toxic epidermal necrolysis (SJS/TEN) management: a systematic review

Icasia Yuseli Kurnia*

ABSTRACT

Background: Steven Johnson Syndrome and Toxic Epidermal Necrolysis are dermatologic emergencies with high mortality rates characterized by extensive skin involvement. TNF-α has a role in inducing the production of granulysin that enhances keratinocyte cell death. Thus, the use of TNF-α inhibitors such as etanercept and infliximab is promising to halt the disease progression. This systematic review aims to evaluate the efficacy of TNF-α inhibitor in SJS/TEN management.

Method: A systematic review using an online database was conducted based on PRISMA guidelines. Inclusion criteria were studied about the role of TNF-α inhibitor in SJS/TEN management. The exclusion criteria were a letter to the editor, commentary report, review, meta-analysis, study not used humans as a study subject, not available in full text and not in English or Bahasa Indonesia.

Conclusion: TNF-α inhibitors such as etanercept and infliximab promise therapy to halt SJS/TEN progression.

Keywords: etanercept, infliximab, steven johnson syndrome, toxic epidermal necrolysis, TNF-alpha inhibitor.

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INTRODUCTION

Severe cutaneous adverse reactions (SCARs) are life-threatening disease; the most severe forms of SCARs consists of Steven Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN). Steven Johnson Syndrome and TEN are the same disease spectrum characterized by extensive necrosis and detachment of the epidermis and mucosal epithelium due to immune-mediated reactions. The other skin involvement of SJS/TEN is erythematous macules, a positive Nikolsky sign defined as flaccid bullae, which rapidly progress into mucocutaneous erosions and ulcerations. The difference between SJS and TEN in the area of epidermal detachment, SJS is marked by epidermal detachment below 10% body surface area (BSA) while TEN is more than 30% BSA. The epidermal detachment between 10-30% BSA is defined as overlapping SJS/TEN.

Both SJS and TEN are rare cases but have a high mortality rate. The SJS/TEN can occur at any age, but mostly in 20-40 years old. The overall incidence of SJS and TEN has been estimated at 1 to 6 cases per 1 million person-years and 0.4 to 1.2 cases per million person-years, respectively. The risk of SJS/TEN increases with age; therefore, the highest incidence in older adults is more than 65 years old. In comparison, the cases in pediatric are estimated at 20% of overall cases. The SJS/TEN cases are more frequent in women than men, with a ratio of 1.5:1. The mortality rate for moderate-severe cases is estimated at 5-15%, varying from approximately 10% for SJS to almost 50% for TEN. Increasing age, significant comorbidity, and greater extent of skin detachment correlate with poor prognosis. A prognosis score (SCORTEN) has been widely used as a prognostic factor for SJS/TEN.

The pathophysiology of SJS/TEN is still unclear, but previous studies have stated it is due to immune-complex mediated hypersensitivity or classified as hypersensitivity reactions type III or IV. The etiology of immune hypersensitivity reactions in SJS/TEN is possibly due to four main cases such as drugs, infections, malignant diseases and idiopathic.

Immunopathologic studies showed the presence of cytotoxic cells, including natural killer T-cells (NKT) and drug-specific CD8+ lymphocytes in early lesions that secrete several cytokines such as...
tumor necrosis factor-alpha (TNF-α) that facilitate extensive epidermal and mucosal necrosis. Tumor necrosis factor-alpha (TNF-α) is believed induced epithelial cell death, both directly and indirectly, through granulysin or Fas ligand expression. This mechanism causes a cell-mediated cytotoxic reaction against keratinocytes leading to massive apoptosis that manifests as extensive skin involvement.\textsuperscript{2,3} The other study also found an increase in TNF-α level serum and blister fluid in patients with TEN.\textsuperscript{4} Based on these findings, the utilization of biological therapies such as TNF-α inhibitors is believed can halt the progression of SJS/TEN by reducing the TNF-α concentrations. There are several types of TNF-α inhibitors, such as etanercept and infliximab. Several studies also suggested that TNF-α inhibitors are an effective treatment for SJS/TEN.\textsuperscript{5-18} In this systematic review, we will discuss the role of TNF-α inhibitors in SJS/TEN management.

**METHODS**

**Search strategy**

An online literature search was conducted on an online journal database published five years before (2018-2022) in Google Scholar, PubMed and Cochrane library. A Boolean operator was used to specify the findings with keyword ("steven johnson syndrome" OR "toxic epidermal necrolysis" OR "SJS" OR "TEN") AND ("tumor necrosis alpha inhibitor" OR "TNF-α inhibitor" OR "etanercept OR "infliximab") to specify the finding result further.

**Study eligibility**

We included a study with some eligibility criteria using a PRISMA diagram, as seen in Figure 1. We did literature screening from the online database based on the search strategy keywords in the first step. The irrelevant or duplicated study was eliminated. In the second step, the abstract and full-text version of the studies were evaluated and assessed according to the eligibility criteria. The inclusion criteria were: study about the role of TNF-α inhibitor in SJS/TEN management. In contrast, the exclusion criteria were a letter to the editor, commentary report, review, meta-analysis, study not using human as a study subject, not available in full text and not in English or Bahasa Indonesia.

**Data gathering and selection**

Two reviewers gathered data to select a study that fulfilled the eligibility criteria. Next, the chosen study was assessed independently by the reviewer based on the study quality assessment and its evidence, then included for further analysis. All studies were read carefully and in detail to extract the principle of the literature.

**Study quality assessment**

We used a critical appraisal checklist from the Joanna Briggs Institute for study quality assessment. The checklist used for each study is different based on the study design, and each item gives one point. The study is classified as good quality if the score is more or at least half of the maximum total points.

**RESULTS**

**Study Characteristics**

Five hundred ninety-five studies were retrieved from three online databases: Google Scholar, PubMed, and Cochrane library. After excluding duplicate studies and irrelevant titles, 32 studies were assessed for the eligibility criteria. Eighteen studies did not meet the inclusion and exclusion criteria; thus, fourteen literature
## Table 1. Characteristic of study regarding physical rehabilitation for long Covid-19 patients.

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of Study</th>
<th>Study subject</th>
<th>BSA (%)</th>
<th>CORTEN (mean)</th>
<th>Treatment</th>
<th>Outcome</th>
<th>Study result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bakir et al., 2021, Saudi Arabia</td>
<td>Case report</td>
<td>11 y.o female patient with TEN due to Pfizer COVID-19 vaccine.</td>
<td>&gt; 30%</td>
<td>2</td>
<td>Two doses of 50 mg/ml etanercept s.c.</td>
<td>New lesion development, side effects, healing time</td>
<td>New lesion stops developing two days after treatment, complete healing after 22 days, and no side effect.6</td>
</tr>
<tr>
<td>Chafranska et al., 2019, Denmark</td>
<td>Case report</td>
<td>Seven y.o male pediatric patient with TEN due to M. pneumoniae.</td>
<td>&gt; 30%</td>
<td>Not stated</td>
<td>Single dose of 5 mg/kgBW infliximab i.v.</td>
<td>Re-epithelization, healing time</td>
<td>Re-epithelization starts three days after treatment and completes healing after one month.6</td>
</tr>
<tr>
<td>Chahal et al., 2018, USA</td>
<td>Case report</td>
<td>19 y.o female with TEN due to meningococcal B vaccine.</td>
<td>80%</td>
<td>1</td>
<td>Single-dose of 50mg/ml etanercept s.c</td>
<td>Re-epithelization, healing time</td>
<td>Re-epithelization starts three days after injection; the patient is discharged after seven days.7</td>
</tr>
<tr>
<td>Coulombe et al., 2019, Canada</td>
<td>Case report</td>
<td>17 y.o male patient with TEN due to carbamazepine.</td>
<td>45%</td>
<td>1</td>
<td>Single-dose of 50mg/ml etanercept s.c combination with dexamethasone and cyclosporine.</td>
<td>Healing time</td>
<td>On the 4th day, the vesicles were healed, and the patient was discharged after 14 days.6</td>
</tr>
<tr>
<td>Dreyer et al., 2021, USA</td>
<td>Retrospective cohort study</td>
<td>22 SJS/TEN patients • Group I (etanercept alone): 9 patients • Group II (etanercept vs IVIG): 4 patients • Group III (IVIG or supportive care alone): 9 patients</td>
<td>I: 30% II: 30% III: 23%</td>
<td>I: 2.1 II: 2.3 III: 2.4</td>
<td>I: Single-dose of 50 mg/ml etanercept s.c II: Etanercept + IVIG II: IVIG or supportive care alone.</td>
<td>Re-epithelization, the mortality rate</td>
<td>Re-epithelization rate was faster in group I than in group II (7.5 vs. 8.9 days), and mortality in groups I and II was lower than in group III (0 vs. 33%). Etanercept is more effective if given quickly and less effective after IVIG or steroid.9</td>
</tr>
<tr>
<td>Faris et al., 2020, USA</td>
<td>Case report</td>
<td>• 71 y.o female patient with TEN due to lamotrigine • 74 y.o female patient with TEN due to TMP-SMX • 40 y.o female patient with SJS/TEN overlap due to TMP-SMX</td>
<td>I: &gt;90% II: &gt;90% III: &gt;25%</td>
<td>Not stated</td>
<td>Cyclosporine + single dose of 50 mg etanercept s.c</td>
<td>Re-epithelization, length of stay, side effect</td>
<td>All of the patients died; only one patient showed re-epithelization after therapy. The combination of etanercept with other immunosuppressive agents should be avoided, and inclusion and exclusion criteria for etanercept usage should be established.10</td>
</tr>
<tr>
<td>Gavigan et al., 2018, Canada</td>
<td>Case report</td>
<td>11 y.o female pediatric patient with SJS/TEN overlap due to ciprofloxacin and TMP-SMX.</td>
<td>25%</td>
<td>Not stated</td>
<td>Two doses of etanercept 25 mg every 24 hours.</td>
<td>Re-epithelization, adverse reactions</td>
<td>No adverse reaction was found, and etanercept halted the progression of skin involvement in our patient.11</td>
</tr>
<tr>
<td>Pham et al., 2018, USA</td>
<td>Retrospective cohort study</td>
<td>53 patients with SJS/TEN (23 male, 30 female): • Group I (Etanercept): 13 patients • Group II (Non-etanercept): 40 patients</td>
<td>I: 54.3% II: 46.3%</td>
<td>I: 3 II: 2.1</td>
<td>I: Single dose 50 mg etanercept s.c II: IVIG + wound care</td>
<td>Mortality rate, length of stay, infectious complication</td>
<td>There is no difference in mortality, infectious complication, intubation rate, or lower Los in the etanercept group.12</td>
</tr>
<tr>
<td>Shen et al., 2020, Taiwan</td>
<td>Case report</td>
<td>11 y.o female patient with TEN due to HHV-7.</td>
<td>60%</td>
<td>Not stated</td>
<td>Two doses of 25 mg etanercept s.c</td>
<td>Healing time, Los</td>
<td>Fever and rash progression stopped on day 6; the patient was discharged on day 23.13</td>
</tr>
<tr>
<td>So et al., 2018, USA</td>
<td>Case report</td>
<td>51 y.o female patient with SJS due to botulinum toxin.</td>
<td>10%</td>
<td>Not stated</td>
<td>Single-dose of 50 mg etanercept s.c</td>
<td>Healing time, Los, side effect</td>
<td>Desquamation on day 4, discharged on day 15, no side effect was found.</td>
</tr>
<tr>
<td>Torres-Navarro et al., 2020, Spain</td>
<td>Retrospective cohort study</td>
<td>18 SJS/TEN patients (male: 3, female: 15)</td>
<td>&lt;10-90% 0-3</td>
<td>Only four patients received a single dose of 50 mg etanercept</td>
<td>Mortality, Los</td>
<td>No mortality in patients treated with etanercept with LoS range from 11 to 24 days.18</td>
<td></td>
</tr>
</tbody>
</table>
met eligibility criteria and were included in the qualitative analysis, as seen in Figure 1. The included studies consist of ten case reports (71.4%), three retrospective cohort studies (21.4%) and only one randomized controlled trial (7.2%). Studies come from several countries such as Canada, China, Denmark, Saudi Arabia, Spain, Taiwan and USA.

All of the studies used humans as a study subject, with predominantly female patients (60.3%). The subject age varies from 11-74 years old, with three pediatric cases recorded from the analysis. The causative agents of SJS/TEN in the study included in this systematic review are predominantly caused by medication such as trimethoprim-sulfamethoxazole (TMP-SMX) and carbamazepine lamotrigine, ciprofloxacin, nimesulide, acametopin and botulinum toxin. The other etiology was vaccination (Pfizer COVID-19 vaccine and meningococcal B vaccine) and infectious agent (Mycobacterium pneumoniae and Human Herpesvirus-7). The lowest total body surface area (BSA) of skin involvement lesion in all studies was below 10%, and the highest was 90%. Out of 14 studies involved, only seven studies stated the SCORTEN, which ranges from 0 until 3. There are two kinds of TNF-α inhibitors used in the study, etanercept and infliximab. Two retrospective studies compared etanercept and IVIG treatment, while one RCT compared etanercept and corticosteroid.

Several outcomes were evaluated, such as re-epithelization, healing time, length of stay, mortality rate, side effects and complications of TNF-α inhibitors as a therapy for SJS/TEN. The detailed characterization of the study is described in Table 1.

Quality assessment result of the study
Quality assessment of the study using Joanna Briggs Institute checklist according to each study design. We used three checklists to assess the study quality: critical appraisal checklist for experimental study, case report, and cohort study. Each item from the checklist contributed to one point. A study is considered good quality if it got half or more maximum total points and regarded as low quality if it got less than the half-maximal entire point. The two reviewers evaluated the quality of the study independently to avoid bias. Of eleven studies involved, all were considered good quality, with a total point range from 6 to 8.

TNF-α Inhibitors Usage in SJS/TEN Management
From the qualitative analysis, we found two kinds of TNF-α inhibitors used to manage SJS/TEN; etanercept and infliximab. Eleven studies used etanercept alone for therapy; four used a combination of etanercept with other medications such as cyclosporine, corticosteroid and Intravenous Immunoglobulin (IVIG); only one study used infliximab. Etanercept was given with doses ranging from 25-50 mg subcutaneously, which can be a single dose or two doses. Three studies used 25 mg etanercept subcutaneously for pediatric patients in two doses. The other studies in the adult population used a single dose of 50 mg etanercept subcutaneously. A randomized controlled trial by Wang et al. used etanercept based on the patient’s body weight. Etanercept was given 25 mg for bodyweight below 65 kg and 50 mg otherwise. Case report by Coulombe et al. used a combination of 50 mg etanercept with cyclosporine and dexamethasone in a 17-year-old patient. Other case reports by Faris et al. used a single-dose 50 mg etanercept and cyclosporine combination. The only study that used infliximab was a case report by Chafranska et al. in a 7-years old male pediatric patient with TEN due to M. pneumoniae. The patient was given 5 mg/kg body weight of infliximab intravenously.

TNF-α Inhibitors Effectivity in SJS/TEN Management
Out of 14 studies included in this systematic review, we have summarized the effectivity of TNF-α inhibitors in SJS/TEN management as follows:

1. Faster healing time and re-epithelization

All of the included studies in our systematic review stated that etanercept and infliximab effectively fasten healing time and re-epithelization in SJS/TEN patients. Bakir et al. reported a female patient with TEN...
due to the COVID-19 vaccine given two doses of etanercept 50 mg s.c on the first- and second-day admission found no new lesion on the patient after two days from the first dose. The complete healing was recorded after 22 days after therapy. The other study by Chahal et al. and Coulombe et al. also stated the same; they found re-epithelization started three days after etanercept injection, and blisters were healed on the 4th day. Study by Shen et al. found that rash progression was stopped at day 6, while a study by So et al. found desquamation started four days after the etanercept injection. Desquamation process usually begins after the rash of measles fades, marked by the shedding of epithelium. A retrospective cohort study by Dreyer et al. involved 22 patients into three groups consisting of etanercept only, a combination of etanercept and IVIG and IVIG only, and found that the re-epithelization rate was faster in the group that received etanercept only compared with etanercept + IVIG (7.5 vs. 8.9 days). Those studies also recommend quick use of etanercept for better effectiveness, and it is less effective if given after other therapy such as steroids or IVIG. They also found treatment using etanercept followed by IVIG could be helpful for some patients with severe cases that are not adequate with etanercept only.

In another study, case report Faris et al. reported three SJS/TEN patients with >90% BSA, and all of the patients died. The three patients got a combination therapy of cyclosporine and a single dose of 50 mg etanercept. They suggested some criteria for etanercept usage: avoid the combination of etanercept and other immunosuppressive agents, should not be given to patients with presumed or active infection, and must be given within five days of symptom onset. A RCT study by Wang et al. compared the group treated with etanercept and corticosteroid and found that the group treated with etanercept had a faster skin healing time than the corticosteroid group (14 vs. 19 days). Their study also found etanercept significantly decreased the TNF-α and granulysin levels in blister fluids and plasma after the treatment (45.7%–62.5%, \( p > 0.05 \)). These findings suggested the capability of etanercept in inhibiting TNF-α and granulysin secretion in blister of SJS/TEN patients.  

2. Reduce the length of stay
Several studies showed that therapy with TNF-α inhibitors could reduce the length of stay or in-hospital duration of SJS/TEN patients. Because etanercept and infliximab could accelerate skin re-epithelization and halted the SJS/TEN progresses. Thus the in-hospital period also can be reduced. The length of stay of the SJS/TEN patient treated with etanercept was between 7-24 days, while the LOS of the patient treated with infliximab was not stated, but the patient treated with infliximab completed the healing process after one month. Study by Pham et al. found shorter LOS in patients treated with etanercept than in patients treated with IVIG (9.8 vs. 16.4, \( p=0.11 \)). A cohort study by Dreyer et al. found one patient that was treated with a single dose of etanercept then followed by IVIG, resulting in rapid recovery and discharge after only one week of hospitalization.

3. Reduce SCORTEN and mortality rate
The mortality rate of SJS/TEN was quite high; thus, a prognostic factor was developed to assess the severity and mortality rate of SJS/TEN patients. The score of toxic epidermal necrolysis (SCORTEN) was used to evaluate the mortality rate, consisting of several parameters with one point for each item. The parameter was age >40 years old, heart rate >120 times/minute, history of cancer or hematologic malignancy, BSA involved >10%, serum urea level >10 mM, serum bicarbonate level >20 mM, and serum glucose level >14 mM. An RCT study by Wang et al. found that etanercept decreased the SCORTEN-based predicted mortality rate, which the predicted and observed rates, 17.7% and 8.3%, respectively. They also found a lower mortality rate for the etanercept treatment group than for the corticosteroid treatment group (8.3% vs. 16.3%, \( p=0.266 \)). A retrospective cohort study by Torres-Navarro et al. involved 18 SJS/TEN patients and found no mortality in all patients treated with etanercept. While the study by Pham et al. found no significant difference in mortality rate between patients treated with etanercept and IVIG. A cohort study by Dreyer et al. found a lower mortality rate in patients treated with etanercept or a combination of etanercept and IVIG compared with patients treated with IVIG and supportive care only (0 vs. 33%).

4. Minimal complications and side effects
No study included in our systematic review found side effects or adverse reactions regarding the use of TNF-α inhibitors in SJS/TEN management. TNF-α inhibitors, especially etanercept showed minimal complications; as stated by Pham et al., they found lower infection complications in the etanercept group compared with the non-etanercept group (38.5% vs. 57.5%, \( p=0.58 \)). An RCT study by Wang et al. found that patients treated with etanercept had a lower incidence of gastrointestinal hemorrhage than patients treated with corticosteroid (2.6% vs. 18.2%; \( p=0.03 \)). Case reports by Gavigan et al. and Zander et al. also found no side effects or adverse reactions in pediatric patients treated with etanercept. Only one study used infliximab for SJS/TEN therapy; they found only mild sequelae of post-inflammatory hyperpigmentation (PIH) and dry eyes that resolved with viscous neutral eye drops to reduce discomfort.

**DISCUSSION**

Steven Johnson Syndrome and Toxic Epidermal Necrolysis are dermatologic emergencies and acute life-threatening mucocutaneous reactions characterized by extensive necrosis and detachment of the epidermis and mucosal epithelium. Stevens and Johnson firstly discovered this disease in 1922; they reported two cases of disseminated cutaneous eruptions associated with erosive stomatitis and severe ocular involvement. In the following year, in 1956, Lyell described patients with epidermal loss secondary to necrosis.
and introduced the term toxic epidermal necrolysis (TEN). Due to their similar clinical pattern, etiology, risk factor, and histopathologic findings are considered one disease entity with differences only in skin involvement. The clinical manifestations of SJS/TEN mostly begin with non-specific prodromal symptoms such as sore throat, runny nose, cough, headache, fever, and malaise, followed by the appearance of mucocutaneous lesions for 1 to 3 days. The mucocutaneous lesions continue with the appearance of erythematous macules and atypical targets on the blistered skin.1,2

The pathophysiology of SJS/TEN involves an immune-mediated-complex mechanism that happens because of misdirected immune response to medications or infections. It causes CD8+ releases pro-inflammatory cytokines that induce extensive epidermal destruction. The exact pathophysiology of SJS/TEN is still unclear, but studies have proposed that T-cells mediated apoptosis of keratinocytes through Fas/Fas ligand (FasL). The other study also found that granulysin and TNF-α have a role as a key mediator in keratinocyte apoptosis and detachment of the epidermis and mucous membranes in SJS/TEN. The histopathologic findings also found the elevated TNF-α level within blister fluid, serum, and the keratinocyte cell surface in SJS/TEN patients, suggesting the role of TNF-α in the apoptosis of keratinocytes cell.2,4

There is no definitive gold standard treatment of SJS/TEN. Generally, the management includes immediate discontinuation of medication as suspected etiology and supportive therapy such as electrolyte replacement and wound care.2 Based on the pathophysiology mechanism stated above, the use of TNF-α inhibitor gives hope as a therapy to halt the progression of SJS/TEN. In our systematic review, two types of TNF-inhibitors were etanercept and infliximab.4 Etanercept has been approved by the United States Food Drug Administration (US-FDA) to treat rheumatoid arthritis, ankylosing spondylitis, plaque psoriasis, psoriatic arthritis, and juvenile rheumatoid arthritis. At the same time, infliximab is a monoclonal antibody used to treat chronic inflammatory disease. Both etanercept and infliximab are biological tumor necrosis factor that acts as soluble TNF receptor and works specifically to bind and inhibit the activity of TNF-α and TNF-β. TNF-α-induced cytokines involved in inflammation, such as interleukin-1 and interleukin-6, promote leukocyte migration.19,20 In SJS/TEN pathophysiology, TNF-α could increase the activity of the granulysin promoter that regulates granulysin gene expression. The increased expression of granulysin will increase the keratinocytes’ apoptosis. Treatment with etanercept or infliximab helps to neutralize these functional activities of TNF-α, leading to an overall reduction in inflammation and keratinocyte cell death.4

This systematic review aims to evaluate the efficacy of TNF-α inhibitors in SJS/TEN management. Overall, previous studies show good efficacy of etanercept and infliximab. But there is also some crucial point that should elucidate the exclusion criteria of TNF-α-inhibitor usage. As stated by Faris et al., the exclusion criteria of single-dose etanercept administration are active infection or ongoing infection found in the patient, combination with other immunosuppressive agents such as chemotherapy or long-term steroid used and received treatment with cyclosporine or oral or intravenous steroids. Cyclosporine and steroid are potent immunosuppressive and immunomodulatory drugs that, if combined with a TNF-α inhibitor, can cause over immunosuppression that can lead to bacteremia and sepsis.10

Our systematic review found promising effects of etanercept and infliximab as therapy for SJS/TEN that help hasten skin healing, reduce time to re-epithelization, reduce mortality and shorten the length of stay with minimal complications and side effects. Our finding is similar to other systematic reviews such as Zhang et al. and Sachdeva et al., which found an overall positive effect of TNF-α inhibitors with minimal complications and side effects.31,32 The limitation of our systematic review is that we mostly included case reports; only three non-case reports were involved in the analysis due to the limited year of publication we used as inclusion criteria. Due to the limited RCT involved in this study, the efficacy and safety of TNF-α inhibitors for SJS/TEN management cannot be conclusively determined. Nevertheless, our systematic review summarizes the latest literature that supports the use of TNF-α inhibitors in SJS/TEN management.

CONCLUSION

Steven Johnson Syndrome and Toxic Epidermal Necrolysis are dermatologic emergencies with high mortality rates characterized by extensive necrosis and detachment of the epidermis and mucosal epithelium. There is a potential role of TNF-α in inducing the production of granulysin that enhances keratinocyte cell death. The use of TNF-α inhibitors such as etanercept and infliximab is promising in SJS/TEN therapy due to their effect on accelerating skin healing time and re-epithelization, reducing in-hospital duration and mortality rate, and also minimal complications and side effects. Etanercept can be given a single dose or two doses subcutaneously, while infliximab was given a single dose intravenously. TNF-α inhibitors should give quickly after the disease onset, and combination with other immunosuppressive agents should be avoided to prevent excessive immunosuppressive effects that can lead to severe infection.

CONFLICT OF INTEREST

There was no conflict of interest in the writing of this research.

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AUTHOR’S CONTRIBUTION

The author contributed to the writing of this research report, from the stage of proposal preparation, data collection and analysis to the preparation of reports in the form of publications.

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