—Review—

A Review of the Active Treatments for Toxic Epidermal Necrolysis

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Toxic epidermal necrolysis (TEN) is a severe adverse drug reaction associated with the separation of skin and mucous membranes at the dermal-epidermal junction. Although it is rare, many treatments have been trialed because of its high mortality rate. Active interventions performed to date include the use of systemic corticosteroids, intravenous immunoglobulins (IVIg), cyclosporine, plasmapheresis, anti-tumor necrosis factor drugs and N-acetylcysteine, but none has been established as the most effective therapy. IVIg and short-term high-dose corticosteroids were regarded as the most promising treatments for TEN in a comprehensive review of all reported TEN cases from 1975–2003. When used with an appropriate dose and timing, the beneficial effects of IVIg can be maximized. Although no randomized controlled trials have been conducted, cyclosporine and plasmapheresis are considered to be beneficial. As no gold standard for active intervention for TEN has been established, the choice of treatment relies partly on the available guidelines and the experience of the dermatologist. There is still much to be investigated regarding the pathogenesis of TEN, and new findings may contribute to the identification of an effective active intervention strategy. (J Nippon Med Sch 2017; 84: 110–117)

Key words: treatment, corticosteroids, toxic epidermal necrolysis, cyclosporine, intravenous immunoglobulins

Introduction

Toxic epidermal necrolysis (TEN) is a severe adverse drug reaction associated with the separation of skin and mucous membranes at the dermal-epidermal junction[1]. Although it is rare, many treatments have been trialed because of its high mortality rate. Active interventions performed to date include the use of systemic corticosteroids, intravenous immunoglobulins (IVIg), cyclosporine, plasmapheresis, anti-tumor necrosis factor drugs and N-acetylcysteine, but none has been established as the most effective therapy[2].

The evidence for each of these treatments will be reviewed and evaluated in this paper.

Systemic Corticosteroids

Systematic corticosteroids, first reported in 1976, have been the lonest used treatment for TEN. The therapeutic effects on TEN are inconclusive (**Table 1**)[3–8]. There have been no randomized controlled trials to determine their effects, but overall, their use has declined primarily due to concern about detrimental side effects, and the increased use of other interventions, especially IVIg. In a study in 1986, the treatment outcomes of 30 consecutive patients with Stevens-Johnson syndrome (SJS)/TEN in a single burn center were compared. The mortality rates of 15 patients treated with systemic corticosteroids and 15 patients treated only with supportive care were compared. The former group had a survival rate of 33%, whereas the latter had a survival rate of 66%. The latter group also had a lower incidence of gastrointestinal ulcers and candida sepsis[4]. Thus, from this study, the association between systemic corticosteroid use and the increased risk of gastrointestinal problems and infection emerged. This use also led to increased mortality, prompting the author of this study to suggest that the use of steroids for the treatment of TEN should be contraindicated[9,10]. IVIg may have contributed to this decline because it was reported relatively soon thereafter, in 1998, to have a plausible mechanism for the treatment of TEN[11]. Indeed, in a systematic review of the treatment efficacy for TEN patients in burn centers, until 2011, the number of patients treated with corticosteroids was 30%,

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Table 1 Summary of systemic corticosteroids studies in TEN [4–8]

Author	Year	Type of study	Details of treatment	Reported benefit
Halebian et al.[4]	1986	Case control	Hydrocortisone 240–1,000 mg/day	Ineffective
Kardaun et al.[5]	2007	Case series	First 4 patients: IV dexamethasone 100 mg ×3 days plus 500 mg cyclophosphamide Other patients: 1.5 mg/kg IV dexamethasone ×3 days	Effective
Schneck et al.[6]	2008	Case series	Median steroids dose 250 mg prednisolone equivalent (Interquartile range 100–500 mg) Median of 4 days	Ineffective
Hirahara et al.[7]	2013	Case series	Methylprednisolone 1,000 mg ×3 days±oral predinisolone 0.8–1 mg/kg/day or methylprednisolone 500 mg ×2 days	Effective
Roongpisuthipong et al.[8]	2014	Case series	A mean dose of dexamethasone <15 mg × mean of 5 days	Ineffective

TEN, toxic epidermal necrolysis

compared with 40% for IVIg[3].

In contrast to the negative reports on corticosteroid use, there are other reports suggesting their beneficial effects. It was suggested that therapy should be high dose, short term and preferably initiated within 48 hours of extensive epidermal detachment. Two retrospective studies indicated the benefits of early pulse therapy. In 2007 and 2013, intravenous corticosteroids were given in the studies, and the actual mortality rate was lower than the score of the TEN (SCORTEN) predicted mortality rate[5,7]. The study in 2007 was conducted over 10 years, and 12 consecutive SJS/TEN patients were treated with dexamethasone pulse therapy. The first 4 patients were given dexamethasone 100 mg within 30–60 minutes for 3 consecutive days, with one dose of cyclophosphamide 500 mg only on the first day. The rest of the patients were given dexamethasone 1.5 mg/kg body weight for 3 consecutive days. SCORTEN predicted a fatal outcome for 4 patients but only 1 patient died[5]. The study in 2013 treated 8 SJS/TEN patients with methylprednisolone pulse therapy. Methylprednisolone 1,000 mg/d for 3 consecutive days was administered. SCORTEN predicted a fatal outcome of 1.6 patients but none of the patients died. Seven of the 8 patients had a reduction of epidermal detachment as well. Sepsis, a severe side effects that could be attributed to corticosteroids, was seen in 3 patients in the 2013 study[7].

Discouraging outcomes in the past may have been due to an inadequate dose, duration, and timing. Measures against negative effects, especially infection and gastrointestinal problems, may have been insufficient when compared to present day medicine[9,12]. However, a large cohort study, mainly in France and Germany, did not find an improved survival rate with any treatment, including corticosteroids in SJS/TEN patients, compared to supportive care. In a study conducted in 2008, the odds ratio (OR) for deaths compared to supportive therapy was favorable, but had no statistical significance. For corticosteroid treatment, the OR in France was 0.4 (95% CI 0.1–1.7), and that in Germany was 0.3 (95% CI 0.1–1.1). The differences in the tendency toward corticosteroid treatment, in France, where it is less common and done with a lower dose, could have affected the results[6]. A recent retrospective study in Thailand also was unable to prove the benefits of corticosteroid use. The study was conducted over 10 years, and the mortality rates of SJS/TEN patients treated with corticosteroids from 2003–2007 and 2008–2012 were compared. In the former group, 8 patients (22.2%) were treated with corticosteroids. The mean SCORTEN score was 1.7, and the actual mortality rate was 25%. In the latter group, in 2008–2012, 39 patients (76.5%) were treated with corticosteroids. The mean SCORTEN score was 2.1, and the actual mortality rate was 13%. A mean dose of less than 15 mg/day of dexamethasone was given for a mean duration of approximately 5 days for both groups. Patients given treatment for more than 6 days decreased from 50.7% to 33.3% in the latter group. The latter group, with better mortality, had more patients on corticosteroids and short-term therapy. Despite that, the difference in the actual mortality rates between the two groups showed no statistical significance[8].

Intravenous Immunoglobulins

IVIg became a popular choice for treatment for TEN in 1998 (**Table 2**)[11,13–22]. The proposed mechanism of action of IVIg was that it contained anti-Fas antibodies that inhibited the Fas/Fas ligand (FasL) interaction, preventing further apoptosis of keratinocytes, and arresting the progression of TEN. Ten TEN patients were enrolled in an

Table 2 Summary of IVIg studies in TEN [11, 13–21]

Author	Year	Type of study	Details of treatment	Reported benefit
Viard et al.[11]	1998	Case series	0.2–0.75 g/kg IVIg ×4 days	Effective
Mangla et al.[13]	2005	Case series	IVIg 0.05–0.1 mg/kg ×5 days	Not applicable
Yeung et al.[14]	2005	Case series	3 g/kg IVIg ×3 days	Effective
French et al.[15]	2006	Literature review	IVIg >2 g/kg	Effective
Del Pozzo-Magana et al.[16]	2011	Systematic review	IVIg 0.25–1.5 g/kg ×5 days	Effective
Firoz et al.[17]	2011	Case series	4 g/kg IVIg ×3 days	Ineffective
Huang et al.[18]	2012	Systematic review	0.2–2 g/kg IVIg	Ineffective
Zhu et al.[19]	2012	Case series	Initial dose of methylprednisolone 1.5 mg/kg ×5 days and/or 2 g/kg IVIg ×5 days	Effective
Lee et al.[20]	2013	Case series	Cumulative dosage IVIg 2.4±0.8 g/kg over a mean of 4 days	Ineffective
Barron et al.[21]	2015	Systematic review	Cumulative dosage IVIg 1.6–3.85 g/kg	Effective

TEN, toxic epidermal necrolysis; IVIg, intravenous immunoglobulin

open, non-controlled trial, and treated with IVIg at 0.2 to 0.75 g/kg body weight for four consecutive days. In all 10 patients, the disease progression halted within 2 days, and healing of the skin started[22]. Although details about the patients are not known, this trial triggered the recognition of the potential of IVIg as an effective treatment for TEN, and to date there have been reports of both favorable and poor outcomes with IVIg[9,12,22]. IVIg and short-term high-dose corticosteroids were regarded as the most promising treatments for TEN in a comprehensive review of all reported TEN cases from 1975–2003[23].

When used with the appropriate dose and timing, the beneficial effect of IVIg may be maximized. A literature review in 2006 analyzed 8 studies of TEN treated with IVIg, each study with more than 9 TEN patients enrolled. Six studies suggested the effectiveness of IVIg, and 5 of the 6 used an IVIg dose of more than 2 g/kg. Patients who received total doses of 2 g/kg or more had a 59% reduction when the mortality predicted by SCORTEN was compared with the actual mortality rate. The predicted mortality was 34±4%, and the actual mortality rate was 14±8%. Patients who received less than 2 g/kg had a 3% reduction of the predicted, which was 31±7%, while the actual mortality rate was 30±19%. Because this was a literature review, there was no unified treatment regimen with variable doses and durations, or unified diagnosis, making the results less reliable[15]. In addition to the dose, the timing of administration may affect mortality. Four to six days after the initial skin symptoms, epidermal detachment occurs in the acute stage of TEN. It is reasonable to think that the best timing for IVIg intervention is before this detachment occurs, and the earlier the better to limit further apoptosis of keratinocytes and arrest progression of the disease. A study in 2005 demonstrated the effect of timing. One g/kg IVIg was given for 3 consecutive days. Of the 6 TEN patients, 1 died, and this was the only patient to have been given IVIg on the 7th day. The 5 surviving patients were given IVIg within the first 4 days[14]. However, in 2 recent retrospective studies, with either dosage regimes or both dose and timing considered, IVIg had no impact on mortality. Both studies were single-center studies presumably treating the patients without differences, allowing the effectiveness of IVIg to be analyzed[17,20]. In a study in 2012, all the patients received 4 g/kg IVIg within 72 hours after admission to a burn unit, over a 3 day period, but there was no improvement in survival. Of the 82 TEN patients, 24 died and the observed mortality rate was 29%. The mortality predicted by SCORTEN was 26% (22 patients), and there was no significant difference between the two (p=0.61). Age could have made the risk of mortality higher, because the mean age of the patients was 45.1 years, and it was reported in one study that age greater than 40 years had an OR of 4.57 (95% CI 1.58–13.2) for mortality[17]. In a study in 2013, 64 SJS/TEN patients were given a mean dose of 2–4 g/kg IVIg. The mortality rates of the patients who received a high dose (≥3 g/kg/day) and those receiving a low dose (<3 g/kg/day) did not significantly differ, with the observed mortality being 31% (n=13) for the high-dose group, and 26% (5) for the low-dose group (p=0.71). More than half of the patients were Chinese, and the mean age was 57 years old. Such factors could have affected the results[20]. What can be said for both the studies discussed above is that, considering the incidence rate of TEN reported throughout the world, the number of patients reported seems very high. It could be that the

Table 3 Summary of cyclosporine studies in TEN [24–27]

Author	Year	Type of study	Details of treatment	Reported benefit
Valeyrie-Allanore et al.[26]	2010	Case series	Initial dose of 3 mg/kg ×10 days cyclosporine	Effective
Reese et al.[25]	2011	Case series	Initial dose of cyclosporine 5 mg/kg	Effective
Singh et al.[24]	2013	Case control	Cyclosporine 3 mg/kg ×7 days, tapered for 7 days	Effective
Kirchhof et al.[27]	2014	Case series	Average dose of 3–5 mg/kg ×3–5 days orally or 7 days IV	Effective

TEN, toxic epidermal necrolysis

diagnosis of TEN was not accurate, affecting the results. In addition, a systematic review of observational studies published before 2011 revealed no difference in mortality when TEN was treated with IVIg. At least 8 patients were treated in the studies, and the pooled OR for mortality was 1.00 (95% CI 0.58–1.75). Favorable outcomes were achieved, though there was no significant difference between the high-dose and low-dose treatments. The pooled OR for mortality in patients treated with a high dose of IVIg was 0.63 (95% CI 0.27–1.44) compared to those who only received supportive care. The adjusted OR of mortality between patients treated with high dose (total dose of IVIg ≥2 g/kg) and low dose (total dose of IVIg <2 g/kg) was 0.494 (95% CI 0.106–2.300)[18]. A factor that can influence the effect of IVIg may be whether the IVIg is from a single batch. Anti-Fas activity depends upon the batch because the antibody concentrations differ[15]. In another systematic review in 2015, evaluating whether IVIg affects the standardized mortality rate (SMR) in patients with SJS or TEN, IVIg at a dose of greater than 2 g/kg was suggested to improve mortality. There were 13 studies in the review. In the 8 studies where a control group of patients who did not receive IVIg was included, the SMR difference was −0.322 (95% CI −0.766–0.122), favoring IVIg but this was not statistically significant. For all 13 studies the overall SMR point estimation was 0.814 (95% CI 0.617–1.076). Of the 13 studies used, when 2 studies with an IVIg dose of less than 2 g/kg were removed from the meta-analysis, there was a significant reduction in the SMR. Meta regression demonstrated a strong inverse correlation.

Combination of IVIg with a corticosteroid may reduce the mortality rate. An initial dose of 1.5 mg/kg/day of methylprednisolone combined with a total dose of 2 g/kg IVIg was given to 39 patients within a 5-day period. In a retrospective study between 2002 and 2010, that combination resulted in a lower mortality rate than predicted by SCORTEN compared with corticosteroid use alone. The mortality rate with corticosteroid therapy was 31% (5 of 16 patients), while that with combination therapy was 13% (5 of 39 patients). The progression of the disease was arrested earlier, although there was no statistical significance. This reduction in mortality could have been due to the IVIg, but the dose and duration of steroids varied, the number of TEN patients seemed to be more than the reported incidence rates, and there were more SCORTEN 1 and 2 patients than those with scores of 3 or more, which could have affected the results[19].

Cyclosporine

Cyclosporine inhibits the activation of CD4+ and CD8+ T cells, and the subsequent release of granulysin, granzyme and perforin. Nuclear factor-κB (NF-κB) is thereby inhibited, working against apoptosis. Although there have been no randomized controlled trials done, cyclosporine tends to be beneficial for the treatment of TEN (**Table 3**)[24–27]. The doses (3–10 mg/kg/day) and durations vary but have been reported to arrest the disease progression and promote re-epithelialization[9,12]. A limitation in the active use for the treatment of TEN is that the full therapeutic effect takes more than 1 month. There are also concerns over the renal and hepatic toxicity of cyclosporine[23]. In an open phase II trial for this drug, 26 of 29 TEN patients completed the treatment. Ten days of 3 mg/kg/day cyclosporine was administered, and tapered over a one month period. The SCORTEN predicted mortality was 2.75 but there were no deaths. Three patients had to stop treatment early due to side effects such as leukoencephalopathy, transitory neutropenia, and severe infection. Overall, the side effects were tolerable, making the use of cyclosporine compatible. However, the mean age of the patients was 34 years[26]. In a review of a case series in 2011, 4 patients with SJS/TEN were treated in a single burn unit with cyclosporine (5 mg/kg/day). These patients had rapid clinical improvement, with arrest of skin eruptions within 24 hours. In this study, all the patients were in their 20s and 30s, with a SCORTEN of only 1 or 2[25], which might have influenced the results.

Table 4 Summary of plasmapheresis studies in TEN [28–33]

Author	Year	Type of study	Details of treatment	Reported benefit
Kamanabroo et al.[28]	1985	Case series	Plasma exchange 31 ×1–3 sessions	Effective
Bamichas et al.[29]	2002	Case series	Plasma exchange 6.6–17.6 mL ×2–5 sessions	Effective
Lissia et al.[31]	2005	Case series	IVIg 1 g/kg ×3 days+IVIg 0.5 g/kg ×3 days+plasma exchange 31 ×3 sessions	Effective
Yamada et al.[30]	2007	Literature review	Plasma exchange ×1–6 sessions Double filtration plasmapheresis ×1–6 sessions	Effective
Szczeklik et al.[32]	2010	Case series	Plasma exchange 3.51 ×8 sessions	Effective
Kostal et al.[33]	2012	Case series	Plasma exchange one body fluid ×3–8 sessions	Effective

TEN, toxic epidermal necrolysis

Cyclosporine is suggested to be more effective for the treatment of TEN, than systematic corticosteroids or IVIg, with fewer side effects. There have been 2 studies, each comparing outcomes with cyclosporine to either corticosteroids or IVIg. In a comparative study in 2013, the efficacies of cyclosporine and corticosteroids were evaluated. Eleven TEN patients were treated with cyclosporine, and 6 TEN patients were treated with a corticosteroid. Cyclosporine was administered at 3 mg/kg over 7 days, and then tapered. Dexamethasone followed by oral prednisolone ≥1 mg/kg/day was administered to the comparative group. In the cyclosporine group, the SCORTEN predicted mortality was 1.11 but there were no deaths. In contrast, in the corticosteroid group, SCORTEN predicted mortality was 0.51 but there were 2 deaths. The mean hospital stay (18.09 days vs. 26 days) and the mean duration until re-epithelialization (14.54 days vs. 23 days) were shorter in the patients treated with cyclosporine. Not just the effectiveness but how well cyclosporine was tolerated was noted. Only 1 patient suffered from a side effect of cyclosporine, developing corneal ulceration[24]. In a retrospective cohort study comparing a total of 71 patients treated with IVIg and cyclosporine between 2001 and 2011, there was a benefit to the usage of cyclosporine in the treatment of SJS/TEN. The average dose of IVIg was 1 g/kg/day for 3 days whereas the dose for cyclosporine varied between 3 and 5 mg/kg/d orally or intravenously for an average of 7 days. The standardized mortality ratio of cyclosporine was 0.42, compared with the use of IVIg, which had a standardized mortality ratio of 1.43[27].

Plasmapheresis

Plasmapheresis is thought to be effective by clearing the drugs, drug metabolites, FasL and cytokines circulating in the body that trigger TEN. Overall, although there is no randomized controlled trial, the results have been beneficial for TEN patients (**Table 4**)[28–33]. There have been case reports and series showing improvement of disease progression. It seems relatively safe, with no harmful side effects[9,12,28,29,31,32,34]. In a case series of 4 patients, after unsuccessful IVIg and/or corticosteroid treatment, plasmapheresis was performed, improving their condition. The initiation of double filtration plasmapheresis corresponded with a halt in the progression of skin and mucous membrane lesions and healing began. The number of sessions ranged from 3 to 8. Side effects of the procedure included paresthesia, a decrease in blood pressure, and allergic skin reactions, but the 4 patients in this study had no major side effects. Prior steroid and IVIg treatments, and the age of the patients (3 of them were 18–25 years old) may have affected the results[33].

In a literature review of TEN cases treated in Japan until 2006, 47 patients underwent plasmapheresis. Of these, 25 had simple plasma exchange (PE), 13 double filtration plasmapheresis (DFPP), 1 both PE and DFPP, 4 PE and continuous hemodiafiltration (CHDF), 1 DFPP and CHHP, and the remaining 3 other treatments. The number of plasmapheresis sessions ranged from 1 to 6 with the mean number of sessions being 3.1. Thirty cases had excellent outcomes, with 41 experiencing some effect and 5 cases no effect. The rate of effectiveness was 80.9% and the mortality rate was 23.4% with 11 deaths. Thirty-six of the patients had used corticosteroids prior to plasmapheresis but without effect. Side effects during treatment included sepsis and liver dysfunction but all patients recovered. Combination therapy with IVIg or steroids before and/or after plasmapheresis, and the variable treatment regimen may have affected the results[30]. To date there seems to be no consensus on the appropriate number of sessions, frequency or type of plasmapheresis. The number of sessions varies and both PE and DFPP

Table 5 Summary of anti-TNF therapy studies in TEN [35–38]

Author	Year	Type of study	Details of treatment	Reported benefit
Wolkenstein et al.[35]	1998	Randomised controlled trial	Thalidomide 400 mg ×5 days	Ineffective
Zarate-Correa et al.[36]	2013	Case series	Infliximab 300 mg ×1	Effective
Paradis et al.[37]	2014	Case series	Etanercept 50 mg ×1	Effective
Scott-Lang et al.[38]	2014	Case report	Infliximab 5 mg/kg ×1	Effective

TEN, toxic epidermal necrolysis; TNF, tumor necrosis factor

Table 6 Summary of N-acetylcysteine studies in TEN [39-42]

Author	Year	Type of study	Details of treatment	Reported benefit
Claes et al.[39]	2004	Case report	IVIg 400 mg/kg ×3 days+NAC 300 mg/kg ×1 day	Effective
Velez et al.[40]	2012	Case series	NAC 300 mg/kg	Effective
Paquet et al.[41]	2014	Case series	NAC 150 mg/kg ±infliximab 5 mg/kg	Ineffective
Yavuz et al.[42]	2014	Case report	IVIg 0.4 g/kg ×5 days+NAC 300 mg/kg ×1+150 mg/kg ×1	Effective

TEN, toxic epidermal necrolysis; NAC, N-acetylcysteine

are used. In the future, it will be important to determine the most effective treatment regimen to avoid confusion.

Anti-TNF Therapy

TNF-α increases in TEN and, although the exact mechanism is unknown, it is generally acknowledged it largely contributes to the pathogenesis of TEN (**Table 5**)[35–38]. As treatments for TEN were sought, the effect of thalidomide, an inhibitor of TNF, was evaluated in a double-blind randomized placebo controlled study[35]. A total of 22 patients were in the trial, with 12 actually treated and 10 receiving a placebo. Treated patients were given 200 mg of thalidomide twice daily for 5 days. The primary endpoint was the measurement of the progression of skin detachment after seven days, but the trial was terminated due to a high mortality rate. Those who were being treated had a mortality rate of 83% compared to 30% in the placebo group (relative risk 2.78, 95% CI 1.04−7.40). The overall mortality was thus 59% higher than the known mortality. Thalidomide was not effective for the treatment of TEN and, on the contrary, raised the mortality rate of patients. The reason for the rise in mortality is unclear but it was noted that TNF-α concentrations in plasma fluid increased in patients treated with thalidomide. Anti-TNF-α may have a protective effect during TEN, as in septic shock, and thalidomide may have paradoxically increased the production of TNF. Because of this trial, thalidomide is firmly contraindicated for SJS/TEN[9,12]. Infliximab and etanercept reportedly show beneficial results[9,12,36–38]. Infliximab has been administered at 3–5 mg/kg intravenously, and etanercept has been administered at 50 mg subcutaneously[36–38]. In the largest case series of TEN patients treated with etanercept in 2014, 10 consecutive patients were administered 50 mg of etanercept in a single subcutaneous injection. All patients promptly responded to treatment, achieving complete re-epithelialization without complications or side effects. The median time to healing was 8.5 days. Even though thalidomide, etanercept and infliximab are all anti-TNF-α drugs, the reason why there is a difference in their effects is still unclear. Differences in administration could perhaps be one of the causes. Compared to thalidomide, etanercept and infliximab may have other mechanisms besides being anti-TNF such as blocking lymphotoxin-α, which has been reported to be involved in the pathogenesis of graft-versus-host disease[37]. The advantage of infliximab and etanercept compared to IVIg and corticosteroids is that only 1 or 2 administrations are required, and they work rapidly. Also, unlike IVIg, they are more likely to be found easily in the dermatology department due to their increased use against psoriasis.

N-acetylcysteine

N-acetylcysteine (NAC), a precursor of glutathione, has been used because an increase of glutathione enhances the detoxification of drugs (**Table 6**)[39–42]. It has been used orally for pulmonary disorders as an expectorant and intravenously for acetaminophen overdose. NAC 300 mg/kg was given intravenously, and had positive results[9,12,39,40]. In a recent case report, a child with TEN who

was unresponsive to a steroid and IVIg was treated with NAC[42]. NAC is a non-toxic drug, inexpensive and quite safe, with a long half-life of 1−2 days in patients with normal liver function[39,42], and probably still works after cessation of the drug[39]. It acts to inhibit the production of cytokines, TNF-α, and IL1, and expression of skin homing receptor cutaneous lymphocyte associated antigen, working to suppress apoptosis[42]. However, in another recent study in 2014, NAC treatment did not reverse the evolving TEN process. Ten patients were given NAC 150 mg/kg alone or in combination with the anti-TNF-α antibody infliximab. The mean mortality rate with only NAC was 20%, and with the combination it was 40%. The predicted SCORTEN mortality rates were 20.4% in the former group and 21.4% in the latter[41]. The actual mortality rate with only NAC had no significant decrease compared to the predicted mortality. The actual mortality with the combination was higher than predicted, which could have been due to the combination with infliximab. Although NAC is thought to inhibit TNF-α, it is possible that together with infliximab the anti-TNF effect weakened.

Conclusion

As no gold standard for the active intervention for TEN has been established, the choice of treatment relies partly on the available guidelines and the experience of the dermatologist. There is still much to be investigated regarding the pathogenesis of TEN, and new findings may contribute to the identification of an effective active intervention strategy[43]. Although difficult to perform, randomized controlled trials for available active interventions should be performed to better clarify their potential efficacy.

Conflict of Interest: None declared.

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