

Improving the Outcome of Patients With Toxic Epidermal Necrolysis and Stevens-Johnson Syndrome

TOXIC EPIDERMAL necrolysis (TEN) and Stevens-Johnson syndrome (SJS) are perhaps the most dramatic and severe adverse cutaneous reactions to drugs.¹ Both of these related mucocutaneous disorders have associated high rates of morbidity and mortality.² In this issue of the ARCHIVES, the group from Hôpital Henri Mondor in Créteil, France, presents the results of a retrospective study of the effect of the early withdrawal of causative drugs on the survival of patients with TEN and SJS.³ Because of the seriousness of these conditions and the lack of definitively effective treatment, there is a large body of literature advocating a variety of treatments, some of which are clearly beneficial, some of which are more likely to be harmful than helpful, and some of which are of great interest but still of unproven benefit.

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The article by Garcia-Doval et al³ provides a straightforward message. If there is a strong suspicion that a patient may have SJS or TEN, prompt withdrawal of drug treatment will reduce the risk of death by about 30% per day. These data certainly indicate that any drug that is not life-sustaining should be withdrawn when the substantial suspicion of SJS or TEN occurs. If at all possible, all drug therapy should be stopped in a patient who develops blisters or substantial epidermal erosions with fever that are otherwise unexplained and are suspected to be drug related. Less clear is the extent to which these findings should change the rationale for drug withdrawal among patients who lack the signs and symptoms suggestive of early SJS or TEN, but who present with signs and symptoms consistent with atypical morbilliform (so-called maculopapular eruptions) and lack symptoms except pruritus. For every individual who ultimately develops SJS or TEN, there will be hundreds and perhaps thousands of individuals who will develop less serious skin eruptions that may resolve if drug therapy is continued. In many cases, the initial presentations of patients with self-limited and severe skin eruptions are indistinguishable.^{4,5} Clearly, given the effect of stopping a medication on outcome, the clinical challenge is to differentiate more and less serious reactions as early as possible in their evolution.¹ Fortunately, for most patients, it is usually feasible and straightforward to temporarily stop taking a medication or change to a drug that is unlikely to cross-react with the suspect medication. Unfortunately, this is not always the case, making the deci-

sion to stop, switch, or continue a medicine sometimes difficult, with the “correct” answer often only available in retrospect.

Garcia-Doval et al also indicate that SJS and TEN caused by drugs with a long half-life are more likely to result in a fatal outcome than reactions caused by drugs with a short half-life. This is especially interesting because some drugs with a long half-life are also apparently more likely to induce these reactions than drugs with a short half-life, even though they are from the same chemical family.⁶ Therefore, one needs to be especially concerned about the prognosis of an individual whose drug eruption is serious and likely to be caused by a drug with a long half-life.⁶

The cornerstone of treatment for patients with TEN and so-called transitional SJS-TEN (ie, 10%-30% skin loss) is meticulous skin care, fluid management, nutritional support, and surveillance for and aggressive treatment of infection.⁷ Eye care is often crucial for these individuals, as it is for those with less severe cutaneous involvement.^{8,9} When individuals develop substantial skin necrosis, individual care is best provided in burn units or intensive care units before the detachment of blisters and necrotic skin occurs.^{10,11} A less logical and less clearly beneficial treatment is the surgical debridement of non-necrotic skin and the application of artificial dressings, as is practiced at some medical centers. In my opinion, it seems more logical to try to use naturally covering skin for as long as possible before relying on artificial or xerographic covering. Rather than removing the separated but still-covering skin, every effort should be made to limit trauma to this skin and preserve this natural covering. Debridement is most appropriate for detached skin that can no longer serve as a biological barrier or when infection is suspected in that area.

Treatments intended to halt the progression of skin detachment are more controversial. Both common sense and the findings of Garcia-Doval et al suggest that for such active measures to have any chance of success, they must be used early in the course of the disease. Given that full skin involvement in these conditions typically occurs within 4 days or less, agents meant to halt disease progression and decrease the extent of skin detachment are unlikely to have substantial effect if used more than a few days after disease onset. The short duration of this “window of opportunity” makes rapid diagnosis essential, the effective use of disease-altering treatments more difficult, and the conduct of clinical trials that can rigorously evaluate these treatments very difficult.

Of the various treatments advocated to modify the extent of skin detachment, the one that remains the most controversial is the use of systemic steroids.¹¹⁻¹³ To my knowledge, no well-controlled trials have been conducted whose findings support the beneficial effects of these agents; good data that exclude the benefits of these agents are also lacking. Because systemic steroids are widely used and relatively practical, and their substantial potential benefits cannot be excluded with existing data, well-controlled trials to measure their effectiveness should be among the highest priorities for clinical research concerning TEN and SJS. The literature also suggests that a variety of other agents and therapies may successfully treat TEN and SJS, including plasmapheresis and immunosuppressive therapy.^{14,15} In my opinion, scientific data that support a substantial clinical benefit for plasmapheresis and most immunosuppressive treatments are at best weak. These therapies are not without substantial risk or cost.

In 1998, a Swiss group published an important study demonstrating that human intravenous immunoglobulin (IVIG) may be used in the treatment of SJS and TEN.¹⁶ These investigators provide a good scientific rationale for this approach, but given the open and uncontrolled nature of their study, human IVIG therapy should be considered a promising experimental treatment. The data presented by Viard et al¹⁶ are not sufficient to make human IVIG the standard of therapy for TEN, especially given the limited data available and the high cost of this treatment. If human IVIG is adopted as the standard of therapy without the benefit of robust clinical data, its use might exclude the evaluation of corticosteroid therapy and slow the recognition of other new therapies that may have greater benefit in the treatment of TEN than human IVIG.

We now know that stopping drug therapy sooner does make a difference for patients with SJS or TEN. Continued epidemiologic research to identify causative drugs and better methods for early diagnosis (before the signs and symptoms of SJS or TEN are obvious) will facilitate early withdrawal of causative agents. Scrupulous skin and eye care and supportive treatment are also essential to optimize outcome. The most important therapeutic questions relevant to the treatment of SJS and TEN that could be addressed now are the relative benefits of therapy with oral corticosteroids and IVIG. These vital questions can

only be answered from well-controlled, cooperative trials that will need to be international in scope.

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