

Epidermal Necrolysis, Ocular Complications, and “Cold Medicines”



Jean-Claude Roujeau, MD^a, Ariane Dunant, MS^b, and Maja Mockenhaupt, MD^c Créteil and Villejuif, France; and Freiburg, Germany

In the present issue of *The Journal of Allergy and Clinical Immunology: In Practice*, Lee et al¹ report severe ocular complications in patients surviving epidermal necrolysis (EN), also known as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), attributed to nonsteroidal anti-inflammatory drugs (NSAIDs) or “cold medicines.”

THAT REPORT IS IMPORTANT FOR SEVERAL REASONS

After 60 years of efforts, recent evidence for the first time supports that a “specific” therapeutic intervention (cyclosporine A) added to complex supportive measures in specialized settings is able to decrease current high death rates of EN.²⁻⁴ That indicates that from now on the objective in the management of patients with EN should not only be survival but “survival without major disabilities” as well. Ocular lesions are actually the most frequent severe sequelae of EN. They can remain active for years and too often result in severe disabilities including blindness.

With decreasing mortality in the acute phase of EN, efforts should now focus on risk factors, mechanisms, prevention, and treatment of sequelae, especially those affecting the eyes.

One of the co-authors of the present *JACI: In Practice* article, Mayumi Ueta, is an eminent member of one of the best ophthalmology teams working on EN ocular lesions in the world. Her team at Kyoto University was the source of important advances regarding ocular complications of EN. Those include the use of a simple scale for grading the severity of acute eye lesions⁵ now used worldwide,⁶ recommendations for the

management of acute ocular lesions,⁷ chronic sequelae,⁸ and initiation of an international campaign “no more blindness from EN” that we support with enthusiasm.

The same team was the first to report that young patients with EN attributed to “cold medicines” had more severe eye lesions and that, in Japanese population, the risk was associated with HLA-A*02:06 and HLA-B*44:03, and with polymorphism of enzymes implicated in the “prostaglandin cascade” (references 4, 6-8 in the publication by Lee et al¹).

The present publication also reports, in another population, that more severe chronic ocular complications are observed among EN cases attributed to NSAIDs or “cold medicines.” It does not include investigation of possible HLA associations.

STRONG DOUBTS ON THE CAUSATIVE ROLE OF “COLD MEDICINES”

We do not contest the most important findings of present and prior publications: existence of a higher risk of severe ocular complications among younger patients with, at least in Japan, an HLA association that remains to be confirmed in other populations.

What we strongly challenge is the interpretation that “cold medicines” had been the causes of EN in most of these patients.

For drug-induced diseases in general, especially for the most severe such as EN, appropriate determination of causality is essential in many respects. Patients must be protected from the risk of re-exposure. Drug companies and regulatory agencies need correct estimation of the risk for evaluating the “benefit/risk” ratio of medications. *In vitro* deciphering of drug-specific immunological cytotoxicity leading to widespread apoptosis of epithelial cells is only feasible after the identification of the most likely inducing compound. All recent advances on HLA associations with the risk of EN (eg, carbamazepine and HLA B*15:02 in Southeast Asia, allopurinol, and B*58:01 worldwide) required appropriate determination of the causative drug.

For more than 30 years, we have contributed several extensive studies to the evaluation of drug causality in EN. In 1984, in an early series of 50 cases, the 3 drugs most often taken by the patients before hospital admission were phenylbutazone (PBZ), sulfamethoxazole (SMX), and acetyl-salicylic acid (ASA).⁹ Prior reports had suggested that PBZ and SMX could induce EN, but that was not the case for salicylates. There was also a strikingly different pattern of exposures to these medications before onset of the disease. The median duration of exposure was 15 days for PBZ and SMX but less than 3 days for ASA. The authors proposed the hypothesis that ASA might be an innocent bystander, used because of early symptoms such as fever or pain preceding full-blown disease. The authors were rediscovering a phenomenon well known by epidemiologists: “protopathic bias,” the bias that occurs when a

^aUniversité Paris-Est Créteil, Créteil, France

^bBiostatistics and Epidemiology Unit, Gustave Roussy, Villejuif, France

^cDepartment of Dermatology Universitätsklinikum/Medical Center and Faculty of Medicine, University of Freiburg, Freiburg, Germany

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Corresponding author: Jean-Claude Roujeau, MD, Université Paris-Est Créteil, 61 Avenue du Général de Gaulle, Créteil, 94000 France. E-mail: jean-claude.roujeau@wanadoo.fr.

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pharmaceutical agent is prescribed for an early manifestation of a disease that has not yet been diagnostically detected.¹⁰ The authors were later sensitized toward that bias when collaborating with professional methodologists in case-control studies.

One of the first requests from the methodology team was the use of strict criteria for the definition of disease onset, blinded to any information on exposure to medications.¹¹

A *definite index-day* was defined as the day of objective lesions: blisters or erosions of the skin or mucous membranes.

A *probable index-day* was defined as the day of first symptom(s) affecting the skin or mucous membranes (erythema, pain, burning, etc.) and later followed by objective sign(s) on the same site. Fever was accepted as a marker of probable index-day if preceding the above symptoms by no more than 1 day (principle of a continuum).

An *earlier possible index-day* was occasionally proposed in a small percentage of cases with more ambiguous or more prolonged initial symptoms.

Analyses of drug exposures were all performed using the *probable index-day* as the date of disease onset. Comparisons with the use of *earlier possible index-day* were done only for “sensitivity analyses” of the methods and never resulted in substantial differences.

With such stringent definitions of onset, 2 large case-control studies conducted in Europe^{12,13} demonstrated clearly that allopurinol, sulfamethoxazole, phenobarbital, phenytoin, carbamazepine, lamotrigine, nevirapine, and oxicam NSAIDs were strongly associated with EN.

Concerning “cold medicines,” no evidence of association was found for salicylates, with a relative risk (RR) of 1.3 [0.7-2.4], or ibuprofen, RR of 0.9 [0.3-2.6]. The status of acetaminophen (paracetamol) was a little less clear: on all cases the RR of 1.9 [1.2-2.8] was still compatible with a low risk, but it decreased to 0.8 [0.5-1.3] when only patients who took the drug at least 4 days before the index-day were considered exposed.¹⁵

A re-evaluation of acetaminophen risk among EN cases reported to the French Pharmacovigilance was recently performed using an EN-specific algorithm, ALDEN.¹⁴ The conclusion was: “This rigorous individual analysis of a large pharmacovigilance series did not find an obvious SJS/TEN risk related to the use of acetaminophen.”¹⁵

We suggest that the attribution of many cases to “cold medicines” in the present Korean series resulted in part from not rigorous enough use of the ALDEN criterion related to timing of the reaction. The authors considered as suggestive of causality a delay of 4 days or more between initiation of a medication and “onset of EN.” The ALDEN paper made it very clear that it should be the date of FIRST SYMPTOMS (“probable index-day”) and not the date of OBJECTIVE SIGNS (“definite index-day”). The difference (median 2 days in our experience) is precisely the time when nonspecific symptoms are often treated with “cold medicines.”

In a recent unpublished analysis of several hundred new cases of EN validated by the RegiSCAR group, 17% were considered as not drug-related and labeled as “idiopathic” cases.

IS THIS DEBATE MEANINGFUL?

We agree on the probable existence of a large overlap between “idiopathic” cases and “cold medicine-related” cases. However, we strongly prefer the label of “idiopathic” for the following important reasons.

- (1) We consider it unjustified to create reluctance to using drugs without a real risk of EN.
- (2) We disagree with the too often used sentence that “any drug may induce EN.” Actually, a dozen “high-risk” medications are responsible for the majority of cases. Recommendations for usage restricted to adequate indications should focus on these medications.
- (3) For “idiopathic” cases, we strongly suspect the role of nondrug causes, especially infections. *Mycoplasma pneumoniae* (MP) likely contributes to some but not all of such cases. We recommend investigations for recent MP infection in all cases without exposure to “high risk medications.” We also suggest that structured investigations for other causes in “not drug-related cases” should become a priority in research on EN.
- (4) We are afraid that too easy attribution of idiopathic cases to “cold medicines” may result in delaying investigations of the real causality of such cases.

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