The Risk of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis Associated with Nonsteroidal Antiinflammatory Drugs: A Multinational Perspective

MAJA MOCKENHAUPT, JUDITH PARSELLS KELLY, DAVID KAUFMAN, ROBERT S. STERN, and the SCAR Study Group

ABSTRACT. ***Objective.*** To quantify the risk of the severe cutaneous adverse reactions Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) associated with use of nonsteroidal antiinflammatory drugs (NSAID).

Methods. Three large data sources were analyzed: an international case-control study on severe cutaneous reactions (SCAR Study), a population based registry in Germany, and the US Food and Drug Administration (FDA) spontaneous reporting system.

Results. In the international case-control study, the oxicams were associated with the greatest increase in risk of SJS and TEN (relative risk 34, 95% confidence interval 11–105). When the risk for only recently initiated use was compared to that for longterm use of these agents (> 8 weeks), the relative risk of SJS and TEN associated with oxicams was significantly increased ($p < 0.05$). German data registry confirm these findings. The incidence of spontaneous US reports of SJS and TEN (per 1,000,000 visits with a prescription) for diflusinal, sulindac, oxaprozin, and etodolac were not significantly lower than that of piroxicam ($p > 0.05$, all comparisons).

Conclusion. Although the absolute risks of SJS and TEN associated with NSAID use are low, these risks should be considered in monitoring patients who recently began therapy. In 3 independent databases, oxicams have higher risk of SJS and TEN than other NSAID widely used on the 2 continents. The FDA spontaneous reporting systems suggest some NSAID not widely used in Europe may have risks comparable to the oxicams. (J Rheumatol 2003;30:2234–40)

Key Indexing Terms:
STEVENS-JOHNSON SYNDROME
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MULTIVARIATE ANALYSIS
CASE CONTROL STUDY

Nonsteroidal antiinflammatory drugs (NSAID) are among the most commonly prescribed drugs in medical practice. Originally available only by prescription, many are now available without a prescription (over the counter). NSAID have been associated with a variety of skin reactions including severe reactions such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)[1-6]. These often life-threatening disorders are characterized by fever, malaise, erythematous macules that blister, and target-like lesions of the skin. Mucosal involvement is frequent[7]. Both SJS and TEN are rare, with an estimated incidence of less than 5 per million person-years in the general population[4-6,8].

Although NSAID have been associated with SJS and TEN in the literature, most reports have been small series or individual case reports. Because these medications may be used for symptomatic relief of the early signs and symptoms of SJS or TEN due to another cause, assigning etiologic responsibility to the drugs is particularly difficult.

We analyzed 2 European data sources to quantify the risks of SJS and TEN associated with NSAID widely used in Europe. The data were from an international case-control study and an enhanced active surveillance program in Germany. We also utilized a third data source to identify NSAID not widely used in Europe but marketed in the United States, for which exists a signal that suggests a risk comparable to that of higher risk NSAID for which quantitative data exist in Europe. We used the US Food and Drug

From the Dokumentationszentrum schwerer Hautreaktionen, Freiburg, Germany; Slone Epidemiology Unit, Boston University School of Medicine; and Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, USA.

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M. Mockenhaupt, MD, Research Dermatologist, University of Freiburg; J.P. Kelly, MS, Epidemiologist, Slone Epidemiology Center; D. Kaufman, ScD, Associate Director, SCD, Slone Epidemiology Center; R.S. Stern, MD, Carl J. Herzog Professor of Dermatology, Harvard Medical School.

Address reprint requests to Dr. R.S. Stern, Beth Israel Deaconess Medical Center, Department of Dermatology, 330 Brookline Ave, GZ 522, Boston, MA 02215. E-mail: rstern@caregroup.harvard.edu

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Administration (FDA) spontaneous reporting system and the National Ambulatory Medical Care survey to identify these NSAID by comparing frequency of spontaneous reports relative to office visits with a prescription for that medication.

MATERIALS AND METHODS

Case-control study. The international case-control study was designed to estimate the risks of SJS and TEN in association with all drugs. The study attempted to ascertain all cases of SJS and TEN occurring in specific regions of France, Italy, Germany, and Portugal. Data collection began in participating countries between February 1989 and March 1992, and ended in 1993 in France and in 1995 in the other countries. The study design and overall results for all drugs of 245 cases and 1147 controls ascertained during the first phase of the study have been reported[9]. For NSAID, only summary results from the first phase have been published.

This report assesses the results of the complete international study, focusing on reactions associated with NSAID. We included as cases only those individuals who were admitted to a hospital for their skin reaction and whose reactions were validated and classified as SJS, TEN, or overlap between these conditions by an expert committee who utilized standardized definitions and who were blinded to the exposures of the cases[10]. Controls were patients admitted to the same hospital for trauma, an acute illness, or for an elective procedure not suspected to be related to drug use. They were matched to cases by age, sex, and date of hospital admission. For all cases and controls an index-day was estimated without knowledge of drug exposures. For cases, this index-day was defined as the day when the skin reaction or other symptom of SJS or TEN first occurred in the patient[11]. We defined exposure to a drug as use within one week before the index-day. On the basis of clinical opinion and earlier results, risk of SJS and TEN appears to be most strongly associated with recently started drugs[9]. Therefore, we also separately considered drugs started within 8 weeks of onset and those used for longer periods.

The German Registry. The German registry for severe skin reactions was started in 1990. Its aim is to record all hospitalized cases of SJS and TEN. A network was established that includes more than 1500 departments that are likely to treat patients with severe skin reactions. Included are departments of dermatology, pediatrics, internal medicine with intensive care facilities, and burn units. Until the end of 1995, the registry operated in the former West Germany and Berlin. Since 1996, the new federal states of the former East Germany have also been included. The structure is that of an enhanced surveillance system, which also cooperates with the spontaneous reporting systems in Germany like the Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM). All cases ascertained by the registry were classified by an independent dermatological expert committee, blinded to possible causes, utilizing the diagnostic classification also used by the International Case-Control Study[10]. Between April 1990 and December 2000, more than 950 cases classified as SJS, SJS/TEN overlap, and TEN were validated by the expert committee. An index-day was estimated by the experts using a procedure similar to that of the International Case-Control Study. A detailed drug history was obtained for each patient with SJS and TEN using the same questionnaire and method of drug inquiry as the International Case-Control Study[12].

Drug exposure was calculated based on prescription data in defined daily doses as published on a yearly basis by the Research Institute of General Health Insurance (Wissenschaftliches Institut der Ortskrankenkassen, WIDO)[13]. The population based case-ascertainment linked to nationwide prescription data allowed a calculation of drug based incidences for certain drugs or drug groups. In addition, a drug was classified as to whether it was the only suspect drug or whether another suspect drug was also administered in the likely etiologic period of 2 weeks prior to the index-day[12].

FDA Spontaneous Reporting System. The spontaneous reporting system maintained by the Division of Epidemiology and Surveillance of the FDA represents a database of spontaneous reports of suspected reactions to drugs or biologics reported by manufacturers, health professionals, and others to the FDA[14]. The majority of these reports originated as reports from health professionals or lay persons to the drug manufacturers and then reported to the FDA, as required by law. Complete reports include the demographic characteristics of the patient experiencing the reaction, the diagnosis (according to the reporter and coded by a standard system), the type of reactions (up to 4 per case), the drugs and biologics to which the patient was exposed, and the degree to which each drug or biologic was suspected as a cause of the reaction. A narrative describing the reaction, care provided to the patient, and the outcome is also included.

In addition to varying with the actual risk of specific adverse events in association with a drug, the number of spontaneous reports would be expected to vary with use of the drug. Also, the total number of reports per year has increased over the study period. To adjust for these factors, we first determined the number of spontaneous reports relative to the use of these medications in ambulatory practice as measured by survey data from the National Ambulatory Medical Care Survey (NAMCS). This survey estimates the number of outpatient visits with a specific drug prescribed or advised in the United States[15]. Since 1980, the NAMCS has provided information on drugs prescribed or mentioned at physicians' office visits. For years when no survey was conducted (1982-84 and 1986-88), we estimated annual outpatient prescriptions by interpolating between years for which survey data were available. The design and methods of the NAMCS have been described[15]. Because prescription data were not available to us for the years before 1980, we limited estimates of incidence of spontaneous reports in relation to number of visits with a prescription to the years 1980 to 1997. We searched the FDA database for all reactions categorized as SJS or TEN reported with NSAID as a suspect drug and which were marketed for at least 3 years in the US between 1980 and 1997[14].

Statistical methods. For the International Case-Control Study, data were analyzed by SPSS (v 4.0). Crude relative risks (RR) were estimated by standard case-control methods[16]. We also calculated relative risk estimates using both unconditional and conditional logistic regression[16]. These models included demographic factors (age, sex, region) and patient reliability and medical factors (radiation, collagen vascular disease, recent herpes simplex eruption, history of herpes simplex, radiation therapy, human immunodeficiency virus infection). Reference categories for relative risk were those not exposed during the week before the index-day.

To provide a basis for quantitative comparison in the international and German studies of NSAID risk with other drug classes, we chose 3 comparator drugs. Carbamazepine is an example of a drug usually used for extended periods of time and shown to be associated with a high risk of SJS and TEN. Allopurinol is used in rheumatologic conditions and recognized as also causing SJS and TEN. Amoxicillin is usually prescribed for short periods and is generally believed to have a lower associated risk of SJS and TEN than carbamazepine or allopurinol[9].

For the German registry and US spontaneous reporting system study, 95% confidence intervals (CI) for incidence rates were calculated using the Poisson distribution. For spontaneous US reports, Poisson regression techniques were used to calculate incidence rate ratios and 95% CI for each NSAID relative to piroxicam, the NSAID with the highest risk in the 2 European studies, which also had substantial use in both Europe and the US. To adjust for the increasing number of reports to the system over time, the model also incorporated the year of report. This Poisson model was analyzed using STATA (v 6)[17]. We then identified all agents whose adjusted incidence of spontaneous reports in the FDA system was not significantly different from that of piroxicam.

RESULTS

Case-control study. A total of 373 cases who developed SJS or TEN as outpatients and 1720 controls are included in the

International Case-Control Study. Of the 373 cases, 112 were exposed to NSAID (excluding aspirin). Among the NSAID, the oxicams (RR 34, 95% CI 11–105) were associated with the greatest increase in risk of SJS and TEN (Table 1). Of the non-oxicam NSAID with sufficient numbers of exposed cases, only diclofenac and ibuprofen had significantly increased risks of SJS and TEN, and the point estimate of their relative risks was moderate (RR 4–5). The risk of SJS and TEN associated with amoxicillin was as high as or higher than that associated with all non-oxicam NSAID (Table 1).

Table 2 provides the data on relative risk for NSAID and

Table 1. International case-control study: crude and multivariate relative risk of SJS and TEN associated with NSAID use*.

Drug	Cases, N = 373, No. (%)	Controls, N = 1720, No. (%)	Multivariate Relative Risk (95% CI)
Oxicams	25 (7)	4 (0.2)**	34 (11–105)
Piroxicam	16 (4)	4 (0.2)	20 (6–67)
Tenoxicam	9 (2)	1 (0.06)	43 (12–145)***
Propionic acids	16 (4)	19 (1)	1.9 (0.7–5.0)
Ibuprofen	5 (1)	6 (0.3)	5.3 (1.2–25)
Ketoprofen	5 (1)	7 (0.4)	1.0 (0.2–5.6)
Other	6 (2)	6 (0.3)	—
Diclofenac	14 (4)	12 (0.7)	4.1 (1.5–11)
Other NSAID	17 (4)	14 (0.8)	—†
Carbamazepine	22 (6)	13 (0.7)	6.3 (2.5–16)
Allopurinol	28 (8)	18 (1)	9.1 (4.5–19)
Amoxicillin	18 (5)	10 (0.6)	11 (4.2–28)

* Use in days 1–7 before the index-day (total: 373 cases, 1720 controls). ** One control took both. *** Crude estimate. † Other NSAID (cases, controls): indomethacin (2, 5); niflumic acid (4, 2); sulindac (2, 0); indobufen (2, 0); feprazone (1, 2); benzydamine (1, 1); ketorolac (1, 0); nimesulide (1, 0); phenylbutazone (1, 0); fentiazac (1, 0); indomethacin + flupirtine (1, 0); meclofenamate (0, 1); mefenamic acid (0, 1); etodolac (0, 1); acemetacin (0, 1).

Table 2. Relative risk of SJS and TEN by duration of use and type of NSAID.

Drug	Cases, n = 373	Controls, n = 1720	RR (95% CI)
Oxicams			
≤ 8 weeks	24	1	118 (19–4871)*
> 8 weeks	1	2	2.5 (0.04–47)*
Unknown	0	1	—
Propionic acid			
≤ 8 weeks	13	13	3.9 (1.3–11)
> 8 weeks	2	6	0.3 (0.03–3.0)
Unknown	1	0	—
Diclofenac			
≤ 8 weeks	8	8	3.3 (0.9–12)
> 8 weeks	4	2	5.6 (0.8–40)
Unknown	2	2	—
Other NSAID			
≤ 8 weeks	12	9	4.5 (1.4–14)
> 8 weeks	3	3	8.2 (1.3–51)
Unknown	2	2	—
Carbamazepine			
≤ 8 weeks	19	0	130 (23–00)**
> 8 weeks	1	12	0.4 (0.3–0.7)*
Unknown	2	1	
Amoxicillin			
≤ 8 weeks	18	10	11 (4.2–28)
> 8 weeks	0	0	—
Allopurinol			
≤ 8 weeks	22	1	109 (63–161)*
> 8 weeks	5	12	2.1 (1.8–2.4)*
Unknown	1	5	—

* Crude; ** median unbiased estimate.

the 3 comparator drugs according to duration of use (≤ 8 weeks, > 8 weeks). When the risk for only recently-initiated use is compared to that for longterm use (> 8 weeks), the relative risk of SJS and TEN associated with oxicams was significantly increased ($p < 0.05$). For all non-oxicam NSAID taken together, the relative risks were not significantly different with short and longterm use ($p > 0.05$), but the power to detect such a difference is limited (Table 2). The increased risk associated with the use of carbamazepine, allopurinol, and amoxicillin was confined to short term use. The point estimates for oxicams, carbamazepine, and allopurinol exceeded 100.

There was no significant difference in risk of SJS and TEN associated with oxicam use for arthritis and joint pain compared to all other indications ($p = 0.1$, exact 2 tailed probability). The risk associated with other NSAID did not vary substantially or significantly with indication for treatment.

Cases and controls exposed to NSAID were similar for distribution of age and sex (data not shown). The proportion of NSAID-exposed cases who were female was similar to that for all other cases not exposed to NSAID (59% vs 55% female, respectively; $p > 0.2$, chi-square test). Cases exposed to propionic acids were significantly younger than cases exposed to other types of NSAID (mean age 39 vs 54 yrs; $p < 0.01$). The proportion of all cases that were more severe (TEN rather than SJS or overlap) among users of oxicams and other NSAID was not substantially different than this proportion for cases associated with other classes of drugs.

The attributable fraction for all cases of SJS and TEN due to oxicams was 6.5% (95% CI 3.9–9.0). Oxicam use was noted in only 0.3% of controls. Even assuming a population incidence of up to 5 cases per million for SJS and TEN combined[12], the excess risk of SJS and TEN during an initial 8 week course of oxicam therapy is about one in 100,000[4-6,8,12]. For non-oxicam NSAID, the excess risk of propionic acid derivatives and diclofenac during the initial 8 weeks of therapy is less than one in a million.

The German Registry. In Germany, one NSAID, diclofenac, accounted for more than half of all prospectively ascertained cases of SJS and TEN occurring in outpatients and associated with NSAID use within 2 weeks of onset (Table 3). However, diclofenac was by far the most frequently used prescription NSAID in Germany as measured by defined daily doses (DDD) sold[13]. Among NSAID with substantial use (> 100 million DDD), the oxicams had the highest point estimates of risk for SJS and TEN (Table 3). The risk of SJS and TEN was significantly higher for oxicams than for diclofenac (RR 2.7, 95% CI 1.3–5.1). The risk of SJS and TEN were also significantly higher for the oxicams than for ibuprofen (RR 2.5, 95% CI 1.1–6.0). Since our data included only prescription and not nonprescription use of ibuprofen (available in Germany since 1989), the risk of ibuprofen is probably even lower compared to oxicams than this ratio. The risk of SJS and TEN calculated for oxicams, carbamazepine, and amoxicillin were not significantly different (RR 0.8, 95% CI 0.4–1.51; RR 1.1, 95% CI 0.5–2.31; and RR 1.1, 95% CI 0.6–2.1, respectively) for oxicams compared to carbamazepine, and amoxicillin and allopurinol, respectively[18].

US spontaneous reports. From 1980 to 1997, the FDA spontaneous reporting system recorded 2840 reactions coded as TEN or SJS with at least one drug listed as a suspected cause. Altogether, 3791 drugs were listed as suspect agents for these 2840 reactions. More than 100 different drugs were listed as suspect agents for these reactions. The NSAID with the most reports coded as SJS or TEN (sulindac, 89 reports) ranked fifth among all drugs on the basis of total reports.

Of 14 NSAID marketed in 1997, we identified 10 that were listed as suspect agents in at least 7 reports of SJS and TEN. Because of the small number of reports, the US-marketed NSAID with fewer than 7 reported reactions (fenoprofen, meclofenamate, ketorolac, and tolmetin) were excluded from our analysis. Together, the 10 NSAID with at least 7 reported cases were suspected in a total of 452 reports of SJS and TEN, which represents slightly more than 10% of all cases in the FDA database we analyzed. For all 10 of these NSAID, the NAMCS estimates exceeded 5,000,000 visits to physicians with prescriptions for these agents between 1980 and 1997.

Overall, the number of SJS and TEN reports per year was significantly higher ($p < 0.05$ for trend) in later years than earlier years (data not shown). The annual incidence of reports of SJS and TEN per million visits with an NSAID prescription was more than twice as high during the years 1994 to 1997 than the years 1980 to 1985.

Because of its substantial sales in Europe and the US and high risk in the International Case-Control Study and German Registry, we chose piroxicam as the comparator drug. The incidences of spontaneous reports of SJS or TEN (per 1,000,000 visits with a prescription) for diflunisal, sulindac, oxaprozin, and etodolac were not significantly lower than that of piroxicam ($p > 0.05$, all comparisons; data not shown).

DISCUSSION

NSAID are among the most frequently prescribed and used medications in the US and Europe. Between 1980 and 1997, the 10 most frequently prescribed NSAID were recommended or prescribed at more than one-half billion office visits to ambulatory care physicians in the US. Many millions of additional prescriptions were written in non-office settings such as emergency rooms, hospital clinics, neighborhood health centers, and hospitals. Some of these medications are also available without a prescription. However, the relative frequency of use of these medications varies among nations. A number of NSAID widely used in

Table 3. The German Registry. Number of probable and definite cases of SJS and TEN defined daily dose and incidences for the most important NSAID within the German market with use within 2 weeks of onset of SJS/TEN (1992–2000).

Drug	Cases*	Defined Daily Doses (DDD), millions	Incidence***
Oxicams	11	348	0.032
Ibuprofen	10	788	0.013
Diclofenac**	36	3041	0.012
Indomethacin	5	312	0.016
Carbamazepine	38	955	0.040
Allopurinol**	79	2744	0.029
Amoxicillin**	14	468	0.030

* Community cases ascertained prospectively. ** Includes prescription of combination agents. *** Per 1,000,000 DDD.

the US are not widely used in Germany or other countries that participated in the International Case-Control Study. As a result, quantification of the risk of agents largely used in the US is lacking.

Given the high frequency of use of these medications and their use for fever and malaise that can be early symptoms of SJS or TEN, different reaction rates among NSAID are strong evidence that at least some NSAID are true risk factors for the development of SJS and TEN. This finding was common to the 2 studies that provide quantification of the risk of SJS and TEN — a large international case-control study and a German academically based enhanced surveillance system. Piroxicam, a NSAID widely used in both Europe and the US, showed consistently high relative risks in both quantitative studies. To identify NSAID widely used in the US but not Europe that have risks of SJS and TEN comparable to those for piroxicam, we compared spontaneous reporting rates for all NSAID widely prescribed in the US with the rate for piroxicam. We identified 4 NSAID widely used in the US with spontaneous reporting rates comparable to those of piroxicam: diflunisal, sulindac, oxaprozin, and etodolac.

A difference in indications for use or in the characteristics of users is unlikely to account for differences in risk of SJS and TEN among NSAID. In the International Case-Control Study the oxicams, which had the highest risk, were most often used for arthritis and joint pain, indications unlikely to represent the earliest phase of SJS and TEN.

The risk associated with one of the other oxicams marketed only in Europe (tenoxicam) appears comparable to that for piroxicam. Both the International Study and the German Registry data suggest substantially lower risks associated with ibuprofen and diclofenac compared to the oxicams. In both European studies, the risk for ketoprofen, another propionic acid derivative, was not significantly different than that for ibuprofen, the most widely used NSAID in this class. Low prevalence of use observed for other propionic acid derivatives precluded further intraclass comparisons.

The US spontaneous reporting system does not include controls or other means to measure absolute or relative drug exposure in the population. It also lacks uniformity in methods of case-ascertainment, as well as the blinded, standardized review process used in the European studies to confirm the diagnosis. Therefore, quantification of relative risk from this source is likely to be subject to greater error than from the case-control and enhanced surveillance system that we conducted in 5 European countries and Germany, respectively.

Although significantly and substantially elevated relative risks of SJS and TEN are apparent for some NSAID, the excess risk associated with these drugs is low. For oxicams, the International Case-Control Study predicts an excess risk for SJS and TEN of one per 100,000 new users or less during the initial 8 weeks of therapy. The excess risk of SJS and TEN during an initial 8 week period of use for the propionic acid derivatives and diclofenac is probably less than one-tenth as high.

A comparison of the relative risk of NSAID with different usage patterns is difficult. The risk of SJS and TEN appears to be highest for most drugs during the initial weeks of treatment[9]. The German Registry quantifies exposure in defined daily doses. As a result, the relative risk of drugs such as antiepileptics used on a longterm basis are likely to be underestimated relative to drugs such as antibiotics and NSAID that are often used for shorter courses. When these biases are considered, our findings suggest that the risks for SJS and TEN during the initial 8 weeks of oxicam use are likely to be comparable to those for carbamazepine and allopurinol.

The risk of SJS and TEN in association with various NSAID should be considered along with the risk of other toxicities associated with NSAID use. Together, this information is helpful in determining whether the differences in risk of SJS and TEN among NSAID should be a clinically important consideration in determining the optimal NSAID in the individual patient. Data collection for our study was completed before the introduction of the COX-2 specific

inhibitors. For NSAID of the types assessed here, the incidence of ulcer complications and symptomatic gastrointestinal (GI) ulcers 6 months after use is likely to exceed 5%[19,20]. For oxicams, the NSAID with the highest risk, we estimate the risk is about one per 100,000 or less during an 8 week initial course of therapy. In Denmark, only 3% of deaths attributable to NSAID use were dermatological reactions[21]. Therefore, compared to the risks of GI toxicity, the excess risk of SJS and TEN in association with pre-COX-2 specific inhibitors is very low. The risk of SJS and TEN does not increase greatly with age[6], but GI side effects associated with NSAID do increase with age[21]. Although other safety and efficacy considerations should in most cases govern the choice among alternative NSAID, differences in SJS and TEN should also be considered. However, GI risks should be the primary risk consideration in prescribing the NSAID agents assessed in this report, particularly among older persons. Although infrequent, given the severity and life-threatening potential of SJS and TEN and the substantial incidence of other cutaneous side effects of NSAID — including urticaria and morbilliform reactions — patients should be warned to discontinue NSAID should they develop any rash, fever without an alternative explanation, or mucosal symptoms[1,2,7].

APPENDIX

In addition to the authors the following investigators participated in the SCAR Study Group.

Canada: N. Shear, Sunnybrook Health Science Centre, Toronto.

France: J.C. Roujeau, S. Bastuji-Garin, H. Assier, C. Bénabou, Z. El Wady, S. Slimani, Université Paris XII; C. Paoletti, Institut Gustave Roussy, Villejuif; B. Bégaud, A. Chaslerie, V. Legrain, F. Penouil, Université de Bordeaux; B. Sassolas, Université de Brest; I. Alcaraz, H. Bergoend, E. Berteloot, C. Marlier, Université de Lille; B. Ducros, D. Jullien, S. Lyonnet, L. Misery, C. Stamm, Université de Lyon; N. Bassères, J-J. Bonérandi, N. Cnudde, A. Raoux, F. Roudil, Université de Marseille; C. Delavierre, E. Mansat, Université de Nantes; M. Foret, Université de Poitiers; H. Bosser, E. Grosshans, M. Sanchez, Université de Strasbourg; F. Sorbette, Université de Toulouse; N. Julien, J-P. Morère, D. Roger, L. Vaillant, Université de Tours.

Germany: M. Mockenhaupt, E. Schöpf, B. Rzany, B. Loleit, S. Baur, R. Höchstetter, M. Körner, J. Mueller, R. Sinhgraven, U. Stocker, S. Teske, K. Wieck, Dokumentationszentrum schwerer Hautreaktionen, Freiburg; G. Kreutz, Bundesinstitut für Arzneimittel und Medizinprodukte, Berlin; T. Ruzicka, University of Düsseldorf; D. Vieluf, University of Borhum; U. Schwabe, N. Viktor, University of Heidelberg; G. Hopf, K-H. Munter, Arzneimittelkommission der deutschen Ärzteschaft, Köln; U.F. Haustein, University of Leipzig; K. Bork, University of Mainz; B. Przybilla, J. Ring, University of München; H. Heilmaier, Bundesministerium für Forschung und Technologie, München.

Switzerland: R. Bruppacher, University of Basel.

Italy: M. Cavaleri, Hospital of Albenga-Alassio; R. Filotico, University of Bari; F. Cusano, Hospital of Benevento; A. Tosti, C. Misciali, University of Bologna; G. Pasolini, Hospital of Brescia; A. Pinna, University of Cagliari; T. Di Prima, University of Catania; F. Arcangeli, Hospital of Cesena; A. Locatelli, Hospital of Como; S. Moretti, G. Palleschi, University of Firenze; A. Virgili, University of Ferrara; G. Fenizi, Hospital of Foggia; A. Burroni, A. Pestarino, S. Martino and Galliera Hospitals of Genova; F. Rongioletti, University of Genova; G. Cannata, Hospital of Imperia; F. Locati, S. Veraldi, R. Betti, M.M. Polenghi, University of Milano; E. Rossi, E. Gennari, Hospital of Monza; N. Balato, University of Napoli; C. Veller Fornasa, S. Poletto, University of Padova; P. Perno, University of Perugia; A. Fanti, Hospital of Ravenna; S. Gatti, University of Roma; A. Farris, Hospital of Savona; P. Taddeucci, University of Siena; P. Puiatti, C. Solaroli, University of Torino; G. Magaton Rizzi, University of Trieste; D. Schena, University of Verona.

Portugal: M. Gonçalo, F. Neves, University of Coimbra; M. Dias, Hospital Curry Cabral, Lisboa; H. Melo, Hospital Desterro, Lisboa; M. Martins, F. Meneses-Brandão, Hospital St. Maria, Lisboa; C. Lisboa, Hospital S. João, Porto; G. Velho, Hospital St. Antonio, Porto.

USA: D.W. Kaufman, J.P. Kelly, T. Anderson, S. Shapiro, Slone Epidemiology Unit, Boston University School of Medicine; R.S. Stern, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston.

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