

# Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis: Assessment of Medication Risks with Emphasis on Recently Marketed Drugs. The EuroSCAR-Study

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Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare but severe cutaneous adverse reactions (SCAR) related to a variety of medications. They have a significant public health impact because of high mortality and morbidity. A multinational case–control study conducted in Europe between 1997 and 2001 evaluated the risk of medications to induce SCAR. Cases were actively detected through a hospital network covering more than 100 million inhabitants. Three hospitalized patients per case matched on age, gender, and date of interview were enrolled as controls. After validation by an expert committee blinded to exposures, 379 SCAR cases and 1,505 controls were included. Among drugs recently introduced into the market, strong associations were documented for nevirapine (relative risk (RR) >22) and lamotrigine (RR >14), and weaker associations for sertraline (RR = 11 [2.7–46]), pantoprazole (RR = 18 [3.9–85]), and tramadol (RR = 20 [4.4–93]). Strong associations were confirmed for anti-infective sulfonamides, allopurinol, carbamazepine, phenobarbital, phenytoin, and oxycam-NSAIDs, with some changes in relative numbers of exposed cases. Thus, many cases were still related to a few “old” drugs with a known high risk. Risk was restricted to the first few weeks of drug intake. The use of such drugs as first-line therapies should be considered carefully, especially when safer alternative treatments exist. A number of widely used drugs did not show any risk for SJS and TEN.

*Journal of Investigative Dermatology* (2008) **128**, 35–44; doi:10.1038/sj.jid.5701033; published online 6 September 2007

## INTRODUCTION

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe cutaneous adverse reactions (SCARs) to drugs, characterized by extensive detachment of epidermis

and erosions of mucous membranes (Roujeau and Stern, 1994; Becker, 1998). There is growing evidence that SJS and TEN are a single disease with common causes and mechanisms (Auquier-Dunant *et al.*, 2002). The principal difference is the extent of detachment, limited in SJS and more widespread in TEN (Bastuji-Garin *et al.*, 1993). Even though rare (two cases/million population/year), SJS and TEN have a significant impact on public health because of high mortality (20–25%), frequent lasting disability, and reluctance of survivors and their physicians to subsequent use of medications (Rzany *et al.*, 1996). In 1995, a first case–control study (SCAR-study) assessed the risks of SJS and TEN related to medications (Roujeau *et al.*, 1995). High relative risks (RRs) were observed for anti-infective sulfonamides (especially cotrimoxazole), carbamazepine, phenytoin, phenobarbital, non-steroidal anti-inflammatory drugs (NSAIDs) of the oxycam type, allopurinol, chlormezanone, aminopenicillins, cephalosporins, quinolones, and cycline antibiotics. These results contributed to several decisions of regulatory agencies, for example, withdrawal of chlormezanone from the market, restricted indications for cotrimoxazole and phenobarbital.

Since the completion of the prior study, many new medications have been marketed. For some of them, alerts were raised by case reports of SJS or TEN. This concerned

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Abbreviations: ACE, angiotensin converting enzyme; AED, antiepileptic drug; mvRR, multivariate relative risk; NSAID, non-steroidal anti-inflammatory drug; RR, relative risk; SCAR, severe cutaneous adverse reaction SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis uvRR, univariate relative risk

Received 12 May 2006; revised 19 April 2007; accepted 19 April 2007; published online 6 September 2007

lamotrigine (Sachs *et al.*, 1996), nevirapine (Warren *et al.*, 1998), terbinafine (Rzany *et al.*, 1994), fluoxetine (Bodokh *et al.*, 1992), sertraline (Jan *et al.*, 1999), atorvastatin (Pfeiffer *et al.*, 1998), nimesulide (GISED, 1993), leflunomide (Fischer *et al.*, 2003), and cyclooxygenase 2 inhibiting NSAIDs (Friedman *et al.*, 2003). The European Study of SCAR (EuroSCAR-study) was designed as an international multi-center study aiming at an ongoing surveillance of medication risks for SJS and TEN based on a case-control methodology (Slone *et al.*, 1977).

## RESULTS

### Description of the study population

Out of 513 potential cases and 1,763 potential controls, 379 “community” cases of SJS and TEN (i.e., patients who developed the adverse reaction outside the hospital and who were admitted because of symptoms of SCAR) and 1,505 controls, all with a determined index-day and adequate information on exposures, were accepted.

Cases, aged one to 95 years (median 50, with interquartile range (28–68), included 134 SJS, 136 SJS/TEN-overlap and 109 TEN, 234 females (62%), 174 patients from Germany, 130 from France, and 75 from other participating countries. Most cases (93%) had erosions of at least one mucosa. Six weeks after admission the mortality rate was 22%. Cases differed from controls by more frequent HIV infection (6.6 vs 0.2%, multivariate RR (mvRR) = 12 [2.4–59]), collagen vascular disease (7.1 vs 1.5%, mvRR = 2.2 [0.9–5.0]), recent cancer (10.6 vs 1.9%, mvRR = 2.7 [1.3–5.7]), recent X-ray therapy (4.2 vs 0.5%, mvRR = 2.1 [0.5–9.0]), or acute infection in the past 4 weeks (43.5 vs 24.7%, mvRR = 1.7 [1.2–2.3]).

### Recently marketed drugs

Table 1 presents the results for recently marketed drugs. Among medications with prior alerts, two were highly associated with SJS or TEN: nevirapine and lamotrigine. Both shared the overall pattern of “highly suspected” drugs (recent onset of use and infrequent co-medication with another “highly suspected” drug).

A lower but still significant mvRR was found for sertraline, a serotonin re-uptake inhibitor. In this class of antidepressants no other drug including fluoxetine was found to be associated with SJS or TEN.

Pantoprazole was also associated with a significant univariate RR (uvRR), but without a clear pattern of “highly suspected” drugs in terms of timing and co-medication. No association was observed with other proton pump inhibitors. For statins, no significant risk was documented. For other medications with prior alerts, such as terbinafine, fluconazole, cyclooxygenase 2 inhibitors, and leflunomide, numbers of exposed cases and controls were too small for valuable risk estimation.

### Medications with previously demonstrated risks

As shown in Table 2, a risk was confirmed for all previously suspected drugs, with the exception of valproic acid (uvRR = 9.4 [3.9–23], mvRR = 2.0 [0.6–7.4]).

### Risk modification with duration of treatment

Most “highly suspected” drugs are usually taken on a long-term basis. Among cases exposed to these drugs, 85–100% had initiated their treatment less than 8 weeks before the reaction (Table 2). The median time latency (interquartile range) between start of intake and index-day was less than 4 weeks (carbamazepine: 15 days (12–20), phenytoin: 24 days (16–33), phenobarbital: 17 days (9–40), allopurinol: 20 days (14–32)), whereas it was much longer for drugs with no associated risk (above 30 weeks for valproic acid, angiotensin converting enzyme (ACE) inhibitors and calcium channel blockers). For allopurinol, 56 of 66 exposed patients were recent users, in contrast to only one of 27 controls. The uvRR for recent use was 261 [36–infinite] versus a mvRR of 0.9 [0.3–2.4] for long-term use. In general, no significant risk persisted after 8 weeks of use.

### Analgesics

As shown in Table 3, we observed an association for acetaminophen (paracetamol) with a mvRR of 1.9 [1.2–2.8]. Despite great disparity in rates of exposures among controls (from 4.1% in Germany to 22.5% in France), the mvRRs were not significantly different ( $P=0.09$ ); 4.0 [1.9–8.7] in Germany, 2.4 [1.4–4.1] in France, and 1.1 [0.4–3.0] in other countries).

The association with acetaminophen did not change substantially when the analysis was restricted to patients not exposed to any “highly suspected” drug (mvRR = 2.4 [1.5–3.7]) or to any “suspected drug” (mvRR = 1.9 [0.7–5.0]). It neither changed with indication (fever or pain). On the other hand, the mvRR decreased to 0.8 (0.5–1.3) when only patients who took that drug at least four days before index-day were considered exposed. This change resulted in a higher decrease in the number of exposed cases (from 88 to 59) than of the number of exposed controls (from 223 to 216). That reflected a peculiar pattern of exposure in cases, often beginning less than four days before the index-day (Figure 1e).

Tramadol showed a high uvRR for recent use, but a high percentage of co-medication with “highly suspected” drugs (57%), suggesting potential confounding by co-medication.

### Corticosteroids

Many cases had been exposed to steroid therapy before the onset of SJS and TEN (14.8 compared with 2.1% of controls), but for 55% of them in conjunction with a “highly suspected” medication. Despite frequent co-medication, the mvRR was significantly elevated (4.5 [2.4–8.7]) and did not change substantially when the analysis was restricted to cases not exposed to any “highly suspected” drug (5.1 [2.5–10.5]). The timing of exposure to corticosteroids showed some aggregation of cases in the same period as for associated drugs (Figure 1f).

### Drugs of common use without association

A large number of drugs of common use, including sulfonamide-related diuretics and sulfonyleurea antidiabetics, were not associated with a detectable risk of SJS or TEN (Table 4, and additional data available online).

**Table 1. Evaluation of SCAR risk for drugs recently introduced into the market**

Drug Duration of use	Case patients, n=379 (%)	Control patients, n=1,505 (%)	Univariate RR (95% CI)	Multivariate RR (95% CI)	Number of cases (%) with use of other "highly suspected" drugs started within 8 weeks
<i>Confirmation of prior alerts</i>					
Nevirapine	21 (5.5)	0	>22	n.d.	0
≤8 weeks	20	0	>22		0
>8 weeks	1	0	>0.1		0
Lamotrigine	14 (3.7)	0	>14	n.d.	1 (7%)
≤8 weeks	14	0	>14		1 (7%)
>8 weeks	0	0	n.d.		0
Sertraline	6 (1.6)	5 (0.3)	4.8 (1.5–16)	11(2.7–46)	2 (33%)
≤8 weeks	4	1	16 (1.8–144)	n.d.	0
>8 weeks	2	4	2.0 (0.4–11)	n.d.	2 (50%)
<i>Alert from this study needing further confirmation</i>					
Pantoprazole	9 (2.4)	2 (0.1)	18 (3.9–85)	n.d.	5 (56%)
≤8 weeks	5	0	>3.7		2 (40%)
>8 weeks	4	2	8.0 (1.5–44)		3 (75%)
<i>Non-significant risk</i>					
Fluoxetine	5 (1.3)	10 (0.7)	2.0 (0.7–5.9)	0.8 (0.1–5.4)	4 (80%)
Other serotonin re-uptake inhibitors <sup>1</sup>	5 (1.3)	18 (1.2)	1.1 (0.4–3)	0.8 (0.2–3.6)	2 (40%)
Other proton pump inhibitors <sup>2</sup>	25 (6.6)	34 (2.3)	3.1 (1.8–5.2)	1.5 (0.7–3.2)	9 (36%)
HMG-CoA reductase, statins <sup>3</sup>	12 (3.2)	43 (2.9)	1.1 (0.6–2.1)	0.4 (0.2–1.1)	8 (67%)
<i>Not assessable</i>					
Terbinafine	0	1 (0.1)	0 (0–155)	n.d.	0
Fluconazole	1 (0.3)	0	>0.1	n.d.	0
Cox2 inhibitors <sup>4</sup>	1 (0.3)	1 (0.1)	4 (0.3–64)	n.d.	0
Leflunomide	2 (0.5)	0	>0.7	n.d.	0

CI, confidence interval; Cox2, cyclooxygenase 2; RR, relative risk; SCAR, severe cutaneous adverse reactions.

<sup>1</sup>Includes paroxetine (3 cases, 13 controls), citalopram (1 case, 4 controls), fluvoxamine (1 case, 1 control).

<sup>2</sup>Includes omeprazole (23 cases, 24 controls) and lansoprazole (2 cases, 10 controls).

<sup>3</sup>Includes simvastatin (5 cases, 19 controls), atorvastatin (4 cases, 10 controls), pravastatin (0 case, 10 controls), fluvastatin (2 cases, 3 controls), and cerivastatin (1 case, 1 control).

<sup>4</sup>Includes rofecoxib (1 case, 0 control) and celecoxib (0 case, 1 control).

n.d. means not done, because of <3 cases or controls.

### Signals with limited evidence

In univariate analyses, we detected statistically significant associations for a total of 22 medications not listed in the tables. Multivariate analyses were not feasible because of few exposed controls. Long-term use and/or high prevalence of co-medication with a "highly suspected" drug suggested that none was actually a strong risk factor (data available online). Most anti-HIV medications were among these drugs. Their frequent combination with nevirapine suggested that none of these anti-retroviral agents was a risk factor by itself (Barreiro *et al.*, 2000; Fagot *et al.*, 2001).

### DISCUSSION

Our study allowed an up-to-date evaluation of the risk of medications to induce SJS or TEN. Two drugs introduced into the market in recent years and previously suspected from case reports and clinical trials, joined the group of "highly suspected" drugs, namely anti-infective sulfonamides, anti-epileptic drugs (AEDs), oxicam-NSAIDs, and allopurinol.

First, the non-nucleoside anti-retroviral agent nevirapine accounted for most cases in HIV-infected persons (Fagot *et al.*, 2001). Surprisingly, the proportion of HIV-infected persons

**Table 2. Evaluation of SCAR risk for drugs in the market for many years**

Drug Duration of use	Case patients, n=379 (%)	Control patients, n=1,505 (%)	Univariate RR (95% CI)	Multivariate RR (95% CI)	Number of cases (%) with use of other “highly suspected” drugs started within 8 weeks
<i>Confirmation of high risk</i>					
Cotrimoxazole	24 (6.3)	1 (0.1)	102 (14–754)	n.d.	4 (17%)
≤8 weeks	19	0	>20		0
>8 weeks	5	1	21 (2.3–172)		4 (80%)
Other anti-infect. Sulfonamides <sup>1</sup>	13 (3.4)	1 (0.1)	53 (7.0–410)	n.d.	0
≤8 weeks	13	1	53 (7.0–410)		0
> 8 weeks	0	0	n.d.		0
Allopurinol	66 (17.4)	28 (1.9)	11 (7.0–18)	18 (11–32)	7 (11%)
≤8 weeks	56	1	261 (36–∞)	n.d.	2 (4%)
>8 weeks	10	27	1.4 (0.7–3.0)	0.9 (0.3–2.4)	5 (50%)
Carbamazepine	31 (8.2)	4 (0.3)	33 (12–95)	72 (23–225)	1 (3%)
≤8 weeks	29	0	>32	n.d.	0
>8 weeks	2	4	2.0 (0.4–121)	n.d.	1
Phenytoin	19 (5.0)	3 (0.2)	26 (7.8–90)	17 (4.1–68)	3 (16%)
≤8 weeks	17	0	>17	n.d.	2 (12%)
>8 weeks	2	3	2.7 (0.4–16)	n.d.	1
Phenobarbital	20 (5.3)	5 (0.3)	17 (6.2–45)	16 (5.0–50)	3 (15%)
≤8 weeks	17	1	71 (9.4–532)	n.d.	2 (12%)
>8 weeks	3	4	3 (0.7–13)	2.4 (0.2–23)	1 (33%)
Oxicam-NSAIDs <sup>2</sup>	11 (2.9)	7 (0.5)	6.4 (2.5–17)	16 (4.9–52)	1 (9%)
≤8 weeks	11	3	15 (4.1–54)	50 (12–211)	1 (9%)
>8 weeks	0	4	0 (0–6.2)	n.d.	0
<i>Significant but lower risk</i>					
Acetic acid NSAIDs <sup>3</sup>	27 (7.1)	21 (1.4)	5.4 (3.0–10)	5.6 (2.6–12)	7 (26%)
≤8 weeks	24	11	9.2 (4.5–19)	13 (5.2–31)	7 (29%)
>8 weeks	3	10	1.2 (0.3–4.4)	0.7 (0.1–3.3)	0
Macrolides <sup>4</sup>	18 (4.8)	10 (0.7)	7.5 (3.4–16)	6.8 (2.6–18)	8 (44%)
Quinolones <sup>5</sup>	13 (3.4)	5 (0.3)	10.7 (3.8–30)	6.9 (1.8–27)	6 (46%)
Cephalosporins <sup>6</sup>	19 (5.0)	7 (0.5)	11.3 (4.7–27)	7.3 (2.4–22)	12 (63%)
Tetracyclines <sup>7</sup>	7 (1.9)	5 (0.3)	5.6 (1.8–18)	6.3 (1.6–25)	1 (14%)
Aminopenicillins <sup>8</sup>	18 (4.8)	18 (1.2)	4.1 (2.1–8.0)	2.4 (1.0–5.9)	10 (56%)

CI, confidence interval; NSAID, non-steroidal anti-inflammatory drug; RR, relative risk; SCAR, severe cutaneous adverse reaction.

<sup>1</sup>Includes sulfasalazine (5 cases, 1 control), sulfadiazine (5 cases, 0 control), sulfadoxine (2 cases, 0 control), and sulfafurazole (2 cases, 0 control).

<sup>2</sup>Includes meloxicam (2 cases, 2 controls), piroxicam (6 cases, 4 controls), and tenoxicam (3 cases, 1 control).

<sup>3</sup>Includes diclofenac (21 cases, 17 controls), indomethacin (1 control, 2 cases), lonazolac (2 cases, 0 control), etodolac (1 case, 1 control), aceclofenac (1 control, 0 case), sulindac (1 control, 0 case), and ketorolac (0 case, 1 control).

<sup>4</sup>Includes azithromycin (3 cases, 1 control), clarithromycin (4 cases, 5 controls), and erythromycin (3 cases, 0 control), midecamycin (0 case, 1 control), pristinamycin (1 case, 0 control), roxithromycin (4 cases, 2 controls), and spiramycin (3 cases, 1 control).

<sup>5</sup>Includes ciprofloxacin (6 cases, 2 controls), grepafloxacin (1 case, 0 control), levofloxacin (1 case, 0 control), norfloxacin (4 cases, 2 controls), and ofloxacin (1 case, 1 controls).

<sup>6</sup>Includes cefaclor (0 case, 2 controls), cefalexin (3 cases, 0 control), cefapirin (1 case, 0 control), cefatrizine (2 cases, 0 control), cefixime (3 cases, 2 controls), cefonicide (1 case, 2 controls), cefotiam (2 cases, 0 control), cefpodoxime (0 case, 2 controls), ceftibutem (0 case, 1 control), ceftriaxone (3 cases, 0 control), and cefuroxime (5 cases, 0 control).

<sup>7</sup>Includes doxycycline (3 cases, 5 controls), metacycline (1 case, 0 control), and minocycline (3 cases, 0 control).

<sup>8</sup>Includes amoxicillin (17 cases, 18 controls) and bacampicillin (1 case, 0 control).

n.d. means not done, because of <3 cases or controls.

**Table 3. Evaluation of SCAR risk for drugs with high potential for confounding by indication**

Drug Duration of use	Case patients, n=379 (%)	Control patients, n=1,505 (%)	Univariate RR (95% CI)	Multivariate RR (95% CI)	Number of cases (%) with use of other "highly suspected" drugs started within 8 weeks
Acetaminophen (paracetamol)	88 (23.2)	216 (14.4)	1.8 (1.4–2.4)	1.9 (1.2–2.8)	35 (40%)
Pyrazolones <sup>1</sup>	18 (4.8)	15 (0.9)	5.0 (2.5–9.9)	3.1 (1.2–7.7)	8 (44%)
Acetylsalicylic acid	46 (12.1)	97 (6.5)	2.0 (1.4–2.9)	1.6 (0.9–2.7)	21 (46%)
<i>Tramadol</i>	10 (2.6)	2 (0.1)	20 (4.4–93)	n.d.	5 (50%)
≤8 weeks	7	1	28 (3.5–230)		4 (57%)
>8 weeks	3	1	12 (1.2–116)		1 (33%)
<i>Nimesulide</i>	5 (1.3)	3 (0.2)	6.7 (1.6–28)	6.0(1.0–38)	1 (20%)
≤8 weeks	3	3	4.0 (0.8–20)	5.0 (0.7–36)	1 (33%)
>8 weeks	2	0	>0.8	n.d.	0
<i>Ibuprofen</i>	10 (2.6)	24 (1.6)	1.7 (0.8–3.5)	0.9 (0.3–2.6)	5 (50%)
<i>Corticosteroids</i>	56 (14.8)	31(2.1)	8.2 (5.2–13)	4.5 (2.4–8.7)	31 (55%)
≤8 weeks	41	7	26 (12–58)	17 (6.3–46)	26 (63%)
>8 weeks	15	24	2.5 (1.3–4.9)	1.0 (0.4–2.5)	5 (33%)
<i>Dexamethasone</i>	25 (6.6)	1 (0.01)	106 (14–786)	n.d.	19 (76%)
≤8 weeks	19	0	>20		16 (84%)
>8 weeks	6	1	24 (2.9–201)		3 (50%)
<i>Prednisone group<sup>2</sup></i>	29 (7.7)	24 (1.6)	5.1 (2.9–8.9)	3.9 (1.9–8.2)	10 (34%)
≤8 weeks	20	5	17 (6.2–45)	16 (5.0–51)	8 (40%)
>8 weeks	9	19	1.9 (0.9–4.2)	1.0 (0.3–2.9)	2 (22%)

CI, confidence interval; RR, relative risk; SCAR, severe cutaneous adverse reaction.

<sup>1</sup>Includes metamizole (12 cases, 9 controls), propyphenazone (4 cases, 5 controls), and phenazone (2 cases, 1 control).

<sup>2</sup>Includes prednisone (19 cases, 15 controls), prednisolone (6 cases, 4 controls), and methylprednisolone (5 cases, 5 controls); one case is exposed to both, prednisone and prednisolone.

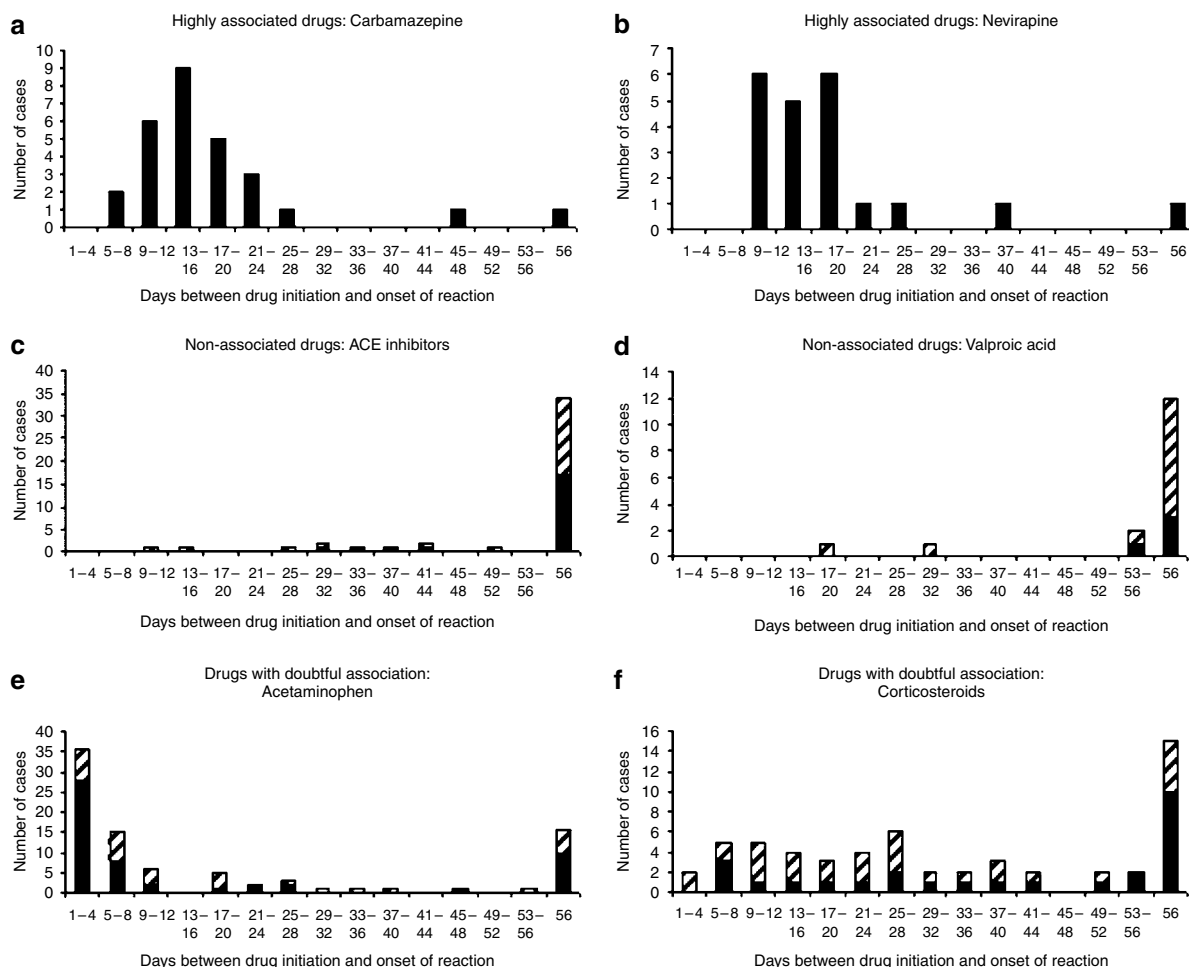
n.d. means not done, because of <3 cases or controls.

among cases of SJS or TEN was the same in this study as that observed a decade ago (Roujeau *et al.*, 1995), only the causative drugs changed. With the decreasing incidence of opportunistic infections and large use of anti-retroviral therapy, nevirapine replaced anti-infective sulfonamides as the leading cause of severe skin reactions in HIV-infected patients.

Second, the AED lamotrigine was associated with a high risk for SJS and TEN. Less frequently used than other AEDs, lamotrigine has indications restricted to certain disorders and age groups. This appears in the prevalence of exposure to various AEDs among controls. However, the overall use of lamotrigine increased substantially between 1997 and 2001, leading to a higher amount of incident users compared with other AEDs known to induce SCAR (Mockenhaupt *et al.*, 2005). Because of insufficient statistical power, we were not able to determine whether the risk

linked to lamotrigine was different from that of carbamazepine, phenytoin, or phenobarbital. Further surveillance of this drug is clearly needed, especially if larger populations are likely to use this medication for other diseases. A dose dependency in relation to the occurrence of SCAR has been suggested for lamotrigine (Sachs *et al.*, 1996) and nevirapine (Barreiro *et al.*, 2000), with recommendation of lead-in periods, which might reduce the risk of skin reactions. For both drugs, recommendations for dose escalation were followed in most cases included in our study, suggesting that a slow titration neither abrogated the risk nor had an effect on the severity of SCAR.

Sertraline, a selective serotonin re-uptake inhibitor introduced within the past 10 years for the treatment of depression, has been suspected of inducing SCAR in case reports (Jan *et al.*, 1999). In our study with six exposed cases



**Figure 1.** Distribution of the number of days between beginning of drug use (drug initiation) and onset of the adverse reaction for selected drugs. (a and b) Highly associated drugs, (c and d) non-associated drugs, and (e and f) drugs with doubtful association. Dashed lines indicate cases with co-medication with another “highly suspected” drug initiated within less than 8 weeks before the onset of the reaction.

**Table 4.** Examples of drugs of common use probably not associated with SCAR

Drug	Case patients, n=379 (%)	Control patients, n=1,505 (%)	Univariate RR (95% CI)	Multivariate RR (95% CI)	Number of cases (%) with use of other “highly suspected” drugs started within 8 weeks
Beta-blockers	37 (9.8)	122 (8.1)	1.2 (0.8–1.8)	0.9 (0.5–1.5)	19 (51%)
ACE inhibitors	44 (11.6)	120 (8.0)	1.5 (1.1–2.2)	0.9 (0.5–1.5)	23 (52%)
Calcium channel blockers	45 (11.9)	104 (6.9)	1.8 (1.3–2.6)	1.4 (0.8–2.4)	24 (54%)
Thiazide diuretics	26 (6.9)	80 (5.3)	1.3 (0.8–2.1)	0.7 (0.4–1.4)	17 (65%)
Furosemide	41 (10.8)	49 (3.3)	3.6 (2.3–5.5)	1.8 (0.9–3.4)	24 (59%)
Propionic acid NSAIDs	16 (4.2)	35 (2.3)	1.9 (1.0–3.4)	1.5 (0.6–3.4)	8 (50%)
Sulfonylurea antidiabetics	11 (2.9)	35 (2.3)	1.3 (0.6–2.5)	0.8 (0.3–2.4)	5 (45%)
Insulin	10 (2.6)	22 (1.5)	1.8 (0.9–3.9)	1.0 (0.3–3.3)	6 (60%)

CI, confidence interval; NSAID, non-steroidal anti-inflammatory drug; RR, relative risk; SCAR, severe cutaneous adverse reaction.

and five controls, we found an increased mvRR of 11 (2.7–46) and a timing pattern compatible with a risk. Due to small numbers, the statistical power is rather low. Nevertheless, this drug needs to be closely monitored.

In the same class of antidepressants, fluoxetine has also been suspected (Bodokh *et al.*, 1992), but there was no evidence of risk in our study, neither for other selective serotonin re-uptake inhibitors.

Pantoprazole, a proton pump inhibitor not previously suspected to induce SCAR, was associated with a high univariate risk. In the absence of multivariate analysis, we cannot discard a risk, but the frequent co-medication with a “highly suspected” drug and a non-convincing timing are not suggestive of a risk.

Terbinafine and fluconazole, two antifungals of different chemical structure, have been reported to induce SCAR (Gussenhoven *et al.*, 1991; Rzany *et al.*, 1994). Due to limited exposure among cases and controls in our study, we were unable to provide accurate risk estimates, but the very low number of exposed cases does not suggest a major public health problem.

Among classes of recently marketed drugs widely used, anti-hyperlipidemia statins were not associated with an increased risk. Also for dozens of drugs with common use, there was neither evidence of an elevated risk for SJS or TEN in the present EuroSCAR-study, nor in the prior SCAR-study. Interestingly, none of the sulfonamide-related diuretic or antidiabetic agents appeared to be associated with a significant risk for SCAR.

Case-control studies do certainly have their limitations and the choice of appropriate controls is crucial for their validity. Conceptually, controls should represent the study base from which cases are drawn, and should be similar to the cases in all relevant aspects. *A posteriori*, we made several quality checks on the control population included in EuroSCAR. For the following diseases the prevalence in our control group was similar to that expected (according to known prevalence) in a group of the same age and gender distribution: diabetes mellitus, asthma, psoriasis, and rheumatism. We also checked the rate of exposure to several antibiotics. We found the disparity in the level of use among controls from different countries that was expected from published prescription data (Cars *et al.*, 2001). Hospital controls did not differ from the “normal population” on the criteria that were analyzed.

In addition, the appropriate multivariate model is of major importance for the robustness of the analysis and the validity of results. In the population of 379 cases, we never used more than a dozen covariables (i.e., age, gender, country, recent cancer (yes or no), HIV infection (yes or no), collagen vascular disease (yes or no), exposure to any “highly suspected” drug (yes or no), exposure to a “low risk” drug (yes or no).

When we looked at specific drugs, the robustness of the model was highly variable. For drugs of common use, there were enough cases and controls exposed to guarantee the robustness of the multivariate analysis. For most “highly suspected” drugs, exposure among controls was found rarely and the multivariate analysis was not performed, if less than three controls were exposed. Although the point estimates of univariate risks were high enough to show unquestionable associations, we provided information on the proportion of cases also exposed to “highly suspected” drugs. When this percentage is low (e.g., less than 15%), it can be assumed that multivariate analysis would not substantially change the lower bound of the RRs. Actually, it seems reasonable to

believe that it can be approximated by the univariate lower confidence interval bound estimated among the patients not exposed to “highly suspected” drugs (more than 85% of the cases and almost 100% of the controls).

Looking at the duration of treatment for “highly suspected” drugs, we found that the risk was mostly confined to recent start of drug use. The duration of treatment is of dramatic relevance for drugs used for long-term medication such as allopurinol, AEDs, or NSAIDs. For allopurinol the numbers were large enough to provide estimates of RRs for recent and long-term use, showing that an overall risk of 18 was a combination of a non-significant association in long-term use and an RR of 261 (36–infinite) in recent use. More precise evaluation of time relationship strongly suggests that SJS and TEN most often begin more than four and up to 28 days after the initiation of the responsible medication. We advise to integrate these figures in the algorithms used for assessing the causality of medications in individual cases.

Some drug classes deserve special comments because of controversies on drug-related or class-related risk, or because of high suspicion of an association with “highly suspected” drugs.

Concerning AEDs, the RR for valproic acid was remarkably reduced after multivariate adjustment and statistical significance was lost. Furthermore, the timing of exposure to valproic acid did not fit with the pattern observed for “highly suspected” drugs and rather reflected that of non-associated drugs. We believe that associations reported previously (Roujeau *et al.*, 1995; Rzany *et al.*, 1999) had been confounded by co-medication with other AEDs. The results of this study suggest that valproic acid should not be considered a “highly suspected” drug to induce SJS and TEN.

Several antibiotics (non-sulfonamide anti-infectives) and acetic acid NSAIDs such as diclofenac, which is widely used in Europe, were found to be associated with significant but lower risks for SJS and TEN.

Concerning NSAIDs there were variable levels of risks. As already suspected, oxamic derivatives were associated with a high risk and acetic acid derivatives with a lower risk for SCAR (Mockenhaupt *et al.*, 2003), whereas for propionic acid derivatives including ibuprofen we did not find a significant risk. Other anti-rheumatic agents like cyclooxygenase 2 inhibitors and leflunomide were introduced soon before the end of our study. We did not obtain enough data to provide risk estimates. Only rofecoxib (VIOXX<sup>®</sup>) and celecoxib (Celebrex<sup>®</sup>) had been used by large numbers of persons. The observation of a single case indirectly suggests that these two agents were probably not associated with a very high risk for SCAR. However, further surveillance of cyclooxygenase 2 inhibitors is necessary.

For analgesics and antipyretics, this study confirmed the huge disparity of exposure rates in different countries. Multivariate analyses showed a weak association of acetaminophen (paracetamol), which did not vary significantly between countries, probably due to the lack of power to detect a difference. Patients often took an analgesic or

antipyretic agent to treat unspecific symptoms such as fever or pain, which might be early signs of the adverse reaction or indicate an infection. In order to better control for confounding by indication, we restricted the analysis to patients who took that drug at least 4 days before the onset of the adverse reaction (index-day). The previously observed association disappeared, suggesting a high potential for confounding by indication, since SJS and TEN often begin with pain or fever, which cannot always be retained as a marker of the index-day in the absence of more specific signs. Therefore, we doubt any causal relationship. For similar reasons we also doubt causal association for pyrazolone analgesics, tramadol, and nimesulide.

This study confirms that a rather high proportion of SJS and TEN occurred in patients taking systemic steroids, especially dexamethasone, often in the context of brain tumor and co-medication with AEDs. Even though the mvRR was not very high, the risk persisted when analyses were restricted to cases without co-medication with “highly suspected” drugs. The time latency between beginning of use and onset of the reaction is also compatible with a risk. Furthermore, we looked for potential confounding in terms of steroid use. Thorough checks of indications for steroid intake revealed that they were not used for the treatment of prodromal symptoms of SJS and TEN. Because of small numbers, we were not able to address the question of a possible interaction between dexamethasone and AEDs. We cannot conclude whether corticosteroids are a direct cause of SJS or TEN, a risk factor by modifying the immune response, or a confounder.

In addition to demonstrating that nevirapine and lamotrigine are associated with very high risks, and triggering some alerts for a few other recently marketed drugs, our study documents the persistence of many cases of SJS and TEN related to “old” drugs with a known high risk. We observed some differences in exposure to these drugs, that is, absence of cases related to chlormezanone, decreases in cases exposed to phenobarbital and oxicam-NSAIDs, and a higher percentage of cases taking allopurinol. These variations probably reflect changing population exposure to drugs in relation to interventions from regulatory agencies, evolving markets, or prescription habits. Nevertheless, the total numbers of cases attributable to these “highly suspected” drugs remained high. The use of such drugs as first-line therapies should be considered carefully, especially when safer alternative treatments exist.

The absolute risk has been estimated in previous studies by calculating excess risks based on the RR, the etiologic fraction (also based on RR), and the incidence of SJS and TEN (Roujeau *et al.*, 1995). Thus, the estimation of the excess risk is depending to a large extent on RR estimates, which we could not calculate for a number of “highly suspected” drugs. We decided not to use the median unbiased estimate, which was done in previous studies, because this method is prone to criticism.

Since SJS and TEN are rare conditions, the absolute risks remain low even for users of drugs with the highest RR (1/1,000 to 1/100,000). The results of this study, however, could help regulatory agencies, drug companies and other specialists in the field to prepare recommendations for the

**Table 5. Practical recommendations and take-home messages for physicians**

A few medications are associated with high risks of SJS or TEN. Prescribing one of them requires thorough evaluation of expected benefits.

Nevirapine

Lamotrigine

Carbamazepine

Phenytoin

Phenobarbital

Cotrimoxazole and other anti-infective sulfonamides

Sulfasalazine

Allopurinol

Oxicam-NSAIDs

A delay of 4–28 days between beginning of drug use and onset of the adverse reaction is the most suggestive timing supporting drug causality in SJS or TEN.

In cases of exposure to several medications with high expected benefits, the timing of administration is important to determine which one(s) must be stopped and if some may be continued or re-introduced.

The risks of various antibiotics to induce SJS and TEN are within the same order of magnitude, but substantially lower than the risk of anti-infective sulfonamides.

Valproic acid does not seem to be a major risk factor by itself.

Sulfonamide-related diuretics and antidiabetics do not appear to be risk factors.

NSAID, non-steroidal anti-inflammatory drug; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

use of “highly suspected” drugs integrating both effectiveness and adverse effects of alternative therapies.

Several practical recommendations and take-home messages for physicians can be derived from our results. They are summarized in Table 5.

## MATERIALS AND METHODS

Basically the methods were identical to those of prior epidemiological studies of rare and severe drug reactions (Slone *et al.*, 1977; Kelly *et al.*, 1995; Roujeau *et al.*, 1995).

### Design and data collection

EuroSCAR was conducted in six countries (Austria, France, Germany, Israel, Italy, and The Netherlands) between April 1997 and December 2001. Cases were actively detected in a network of about 1,800 hospitals covering more than 100 million inhabitants. Cases were patients admitted to hospital with a diagnosis of SJS or TEN (i.e., the reaction occurred in the community), whereas patients developing SCAR during hospitalization for another condition were not included. For each case, three controls were matched on age, gender, region, and date of interview, among patients hospitalized for acute conditions including infections (e.g., pneumonia), trauma (e.g., fractures), and abdominal emergencies (e.g., appendicitis, ruptured ovarian cyst, strangulated hernia) that have not occurred as a complication of an underlying chronic disease. To maximize recall, controls could not be enrolled if, at the time of interview, the hospital stay had exceeded 2 weeks. If sufficient controls with the

preferred diagnoses were not available, alternative non-acute conditions judged to have been unrelated to prior drug use were selected (e.g., hernia, hallux valgus, deviated nasal septum). Thus, we enrolled controls as representative as possible of the same population as cases (Kelly *et al.*, 1995). After obtaining informed consent, trained investigators interviewed cases and controls, using a structured questionnaire to collect clinical data, medical history, and drug exposure. The study has been approved by the ethical committee and institutional review board of each center participating in the EuroSCAR-project in the 6 countries.

### Validation of cases and controls

A group of experts with no information on exposures reviewed all collected cases using clinical data, available photographs (93% of the cases), and histopathology (75% of the cases), and determined the date of onset of the disease (index-day). Controls were also checked for eligibility and date of onset of their acute condition.

### Data quality

Questionnaires were reviewed for internal consistency with automated checks and random comparisons with data forms. Check for homogeneity between data collected by different investigators revealed several abnormalities in the characteristics of controls interviewed by one investigator. Inquiry revealed inadequate work. The full set of controls from this investigation was withdrawn.

### Analyses

Whenever a patient started a drug, he was considered exposed only if this drug was still taken in a “window” of 7 days preceding the index-day. For drugs with long elimination half-lives, the exposure window was extended to 14 days (oxicam-NSAIDs, allopurinol) or 21 days (phenobarbital).

First, an unmatched analysis used data from all validated cases and controls, including controls for potential cases not validated (379 cases, 1,505 controls); second, a matched analysis was restricted to cases with matched controls (326 cases, 838 controls). Due to high consistency between the two analyses, we present only the results that derived from the whole data set. However, results of the matched analysis are available online.

uvRRs and their 95% confidence interval were estimated in terms of odds ratios with standard methods (Slone *et al.*, 1977; Kelly *et al.*, 1995). When there was no exposed control or case, exact methods were used to estimate 95% confidence limits (StatXact-5<sup>®</sup>, Cytel software). In that case, only 95% confidence interval limits are reported. mvRRs were estimated with unconditional logistic regression only when at least three cases and controls were exposed to the risk factor considered. Adjustment was performed on country, gender, age, exposure to any “highly suspected” drug (allopurinol, anti-infective sulfonamides, carbamazepine, lamotrigine, nevirapine, oxicam-NSAIDs, phenobarbital, phenytoin), any other “suspected” drug (aminopenicillins, tetracyclines, quinolones, cephalosporins, macrolides, diclofenac and related NSAIDs, corticosteroids, acetaminophen, pyrazolones, acetylsalicylic acid), any other drug, and any suspected non-drug confounding risk factor (infection with HIV, other infections, recent cancer, recent radiotherapy, collagen vascular disease). We also present in tables the

number of cases concomitantly exposed to a recently introduced different “highly suspected” drug.

### Further ways of risk evaluation, when calculation of mvRR was not feasible

Two criteria were evaluated as a possible help: (1) frequency of concomitant exposure to a “highly suspected” drug, (2) delay between beginning of drug use and onset of the adverse reaction. Both were explored in two subsets of drugs, those with a strong and confirmed high risk and those with a confirmed absence of a detectable association. In less than 20% of the cases, high-risk medications were concomitantly used with another “highly suspected” drug. In contrast, 50–60% of case patients taking drugs without significant risk had been exposed to at least one “highly suspected” drug in parallel. The time pattern of exposure was also very different. For “highly suspected” drugs, beginning of exposure aggregated between 32 and 4 days before onset of the adverse reaction, when there was no similar aggregation for non-associated drugs. This time relationship is exemplified in Figure 1 showing examples of different time latency between beginning of drug use and onset of the adverse reaction for drugs with a definite association (1a and b), non-associated drugs (1c and d), and medications with doubtful association (1e and f).

We, therefore, included these two criteria in our evaluation, when a significant univariate risk could not be validated by multivariate analysis because of lack of controls, and also when we had a strong suspicion of confounding by indication, that is, for medications often prescribed for early unspecific symptoms of the reaction.

### CONFLICT OF INTEREST

The authors state no conflict of interest.

### ACKNOWLEDGMENTS

We are indebted to all the patients whose participation made this study possible. In addition, we thank all the collaborating hospitals and colleagues for their enthusiastic support.

We also thank the following institutions/companies for funding the project (unrestricted grants): ADIR & Cie, Bayer Pharma/AG/Vital, Boehringer Ingelheim, Cassenne, Ciba Geigy/Novartis, Cilag GmbH, Dr Willmar Schwabe, Goedecke Parke Davis, Glaxo Wellcome/GlaxoSmithKline, Hoechst AG/Hoechst Marion Roussel/Aventis, Hoffmann-La-Roche, IRIS Servier, Jouveinal Lab., LEO, LILLY, MSD Sharp & Dohme, Pfizer, Rhone Poulenc Rorer, Sanofi Winthrop/Sanofi Synthelabo GmbH, Schering AG; Funding from Pharmaceutical Companies in France were managed through contract with INSERM (Institut National de la Santé et de la Recherche Médicale), French Ministry of Health (PHRC AOM 98027).

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### SUPPLEMENTARY MATERIAL

**Table S1.** Matched analyses.

**Table S2.** Alerts.

**Table S3.** Drugs used by at least 1.5% of controls (multivariate, unmatched analysis).

**REFERENCES**

- Auquier-Dunant A, Mockenhaupt M, Naldi L, Correia O, Schröder W, Roujeau JC (2002) Correlations between clinical patterns and causes of erythema multiforme majus, Stevens-Johnson syndrome, and toxic epidermal necrolysis: results of an international prospective study. *Arch Dermatol* 138:1019-24
- Barreiro P, Soriano V, Casas E, Estrada V, Tellez M, Hoetelmans R *et al.* (2000) Prevention of Nevirapine-associated exanthema using slow dose escalation and/or corticosteroids. *AIDS* 14:2153-7
- Bastuji-Garin S, Rzany B, Stern RS, Shear NH, Naldi L, Roujeau J-C (1993) A clinical classification of cases of toxic epidermal necrolysis, Stevens-Johnson syndrome and erythema multiforme. *Arch Dermatol* 129:92-6
- Becker DS (1998) Toxic epidermal necrolysis. *Lancet* 351:1417-20
- Bodokh I, Lacour JP, Rosenthal E, Chichmanian RM, Perrin C, Vitetta A *et al.* (1992) Lyell syndrome or toxic epidermal necrolysis and Stevens-Johnson syndrome after treatment with fluoxetine. *Therapie* 47:441
- Cars O, Mostad S, Melander A (2001) Variation in antibiotic use in the European Union. *Lancet* 357:1851-3
- Fagot JP, Mockenhaupt M, Bouwes-Bavinck JN, Naldi L, Viboud C, Roujeau J-C (2001) Nevirapine and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis: preliminary results of a case-control study. *AIDS* 15:1-6
- Fischer TW, Bauer HI, Graefe T, Barta U, Elsner P (2003) Erythema multiforme-like drug eruption with oral involvement after intake of leflunomide. *Dermatology* 207:386-9
- Friedman B, Orlet HK, Still JM, Law E (2003) Toxic epidermal necrolysis due to administration of celecoxib (Celebrex). *South Med J* 96:1213-4 (comment in: *South Med J*. 96:320-321).
- GISED (1993) Cutaneous reactions to analgesic-antipyretics and non-steroidal anti-inflammatory drugs. Analysis of reports to the spontaneous reporting system of the Gruppo Italiano Studi Epidemiologici in Dermatologia. *Dermatology* 186:164-9
- Gussenhoven MJE, Haak A, Peereboom-Wynia JDR (1991) Stevens-Johnson syndrome after fluconazole. *Lancet* 338:120
- Jan V, Toledano C, Machet L, Machet MC, Vaillant L, Lorette G (1999) Stevens-Johnson syndrome after sertraline. *Acta Derm Venereol* 79:401
- Kelly JP, Auquier A, Rzany B, Naldi L, Bastuji-Garin S, Correia O *et al.* (1995) An international collaborative case-control study of severe cutaneous adverse reactions (SCAR). Design and methods. *J Clin Epidemiol* 48:1099-108
- Mockenhaupt M, Kelly JP, Kaufman D, Stern RS (2003) The risk of Stevens-Johnson syndrome and toxic epidermal necrolysis associated with non-steroidal antiinflammatory drugs: a multinational perspective. *J Rheumatol* 30:2234-40
- Mockenhaupt M, Messenheimer J, Schlingmann J, Tennis P (2005) Risk of Stevens-Johnson syndrome and toxic epidermal necrolysis in new users of anti-epileptics. *Neurology* 64:1134-8
- Pfeiffer CM, Kazenoff S, Rothberg HD (1998) Toxic epidermal necrolysis from atorvastatin. *JAMA* 279:1613-4
- Roujeau J-C, Stern RS (1994) Severe cutaneous adverse reactions to drugs. *N Engl J Med* 331:1272-85
- Roujeau J-C, Kelly JP, Naldi L, Rzany B, Stern S, Anderson T *et al.* (1995) Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. *N Engl J Med* 333:1600-7
- Rzany B, Correia O, Kelly JP, Naldi L, Auquier A, Stern R (1999) Risk of Stevens-Johnson syndrome and toxic epidermal necrolysis during first weeks of anti-epileptic therapy: a case-control study. *Lancet* 353:2190-4
- Rzany B, Mockenhaupt M, Baur S, Schröder W, Stocker U, Mueller J *et al.* (1996) Epidemiology of erythema exsudativum multiforme majus (EEMM), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) in Germany (1990-1992). Structure and results of a population based registry. *J Clin Epidemiol* 49:769-73
- Rzany B, Mockenhaupt M, Gehring W, Schöpf E (1994) Stevens-Johnson syndrome after terbinafine therapy. *J Am Acad Dermatol* 30:509
- Sachs B, Ronnau AC, Ruzicka T, Gleichmann E, Schuppe HC (1996) Lamotrigine and toxic epidermal necrolysis. *Lancet* 348:1041
- Slone D, Shapiro S, Miettinen O (1977) Case control surveillance of serious illnesses attributable to ambulatory use of drugs. In: *Epidemiological Evaluation of Drugs*. (Colombo F, Slone D, Shapiro S, Tognoni G, eds) Amsterdam: Elsevier North Holland Biomedical Press
- Warren KJ, Boxwell DE, Kim NY, Drolet BA (1998) Nevirapine-associated Stevens-Johnson syndrome. *Lancet* 351:567