 DOI 10.1111/j.1365-2133.2007.08156.x

Risk factors for acute generalized exanthematous pustulosis (AGEP)—results of a multinational case–control study (EuroSCAR)

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Summary

Background Acute generalized exanthematous pustulosis (AGEP) is a disease characterized by the rapid occurrence of many sterile, nonfollicular pustules usually arising on an oedematous erythema often accompanied by leucocytosis and fever. It is usually attributed to drugs.
Objectives To evaluate the risk for different drugs of causing AGEP.
Patients and methods A multinational case–control study (EuroSCAR) conducted to evaluate the risk for different drugs of causing severe cutaneous adverse reactions; the study included 97 validated community cases of AGEP and 1009 controls.
Results Strongly associated drugs, i.e. drugs with a lower bound of the 95% confidence interval (CI) of the odds ratio (OR) > 5 were pristinamycin (CI 26–∞), ampicillin/amoxicillin (CI 10–∞), quinolones (CI 8·5–∞), (hydroxy)chloroquine (CI 8–∞), anti-infective sulphonamides (CI 7·1–∞), terbinafine (CI 7·1–∞) and diltiazem (CI 5·0–∞). No significant risk was found for infections and a personal or family history of psoriasis (CI 0·7–2·2).
Conclusions Medications associated with AGEP differ from those associated with Stevens–Johnson syndrome or toxic epidermal necrolysis. Different timing patterns from drug intake to reaction onset were observed for different drugs. Infections, although possible triggers, played no prominent role in causing AGEP and there was no evidence that AGEP is a variant of pustular psoriasis.

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Accepted for publication
28 May 2007

Key words
acute generalized exanthematous pustulosis, drug eruptions, pharmacoepidemiology

Conflicts of interest
None declared.

Acute generalized exanthematous pustulosis (AGEP) is a pustular reaction that has been given a number of different designations in the literature such as toxic pustuloderma,[1] pustular drug rash,[2] pustular psoriasiform eruption with leucocytosis,[3] or that has been classified as pustular psoriasis[4] or other diseases.

The reaction is characterized by the sudden occurrence of dozens to hundreds of sterile, nonfollicular pinhead sized pustules arising on an oedematous erythema. The rash is commonly accentuated in the main folds. Additional skin symptoms can comprise oedema of the face and unspecific lesions such as purpura, 'atypical' targets, blisters or vesicles.[5–7] Mucous membrane involvement is rare, usually mild, and is in general restricted to one site (mostly oral). Cutaneous manifestations are often accompanied by systemic symptoms such as fever and leucocytosis. Histology shows subcorneal and/or intraepidermal pustules, a sometimes pronounced oedema in the papillary dermis and perivascular infiltrates consisting of neutrophils and sometimes some eosinophils.[8] Psoriasiform changes are usually not present.

A very characteristic feature of this skin reaction is its clinical course. Skin symptoms usually arise rapidly (within a few hours) and resolve quickly (within a few days) without treatment. Complications are rare[9,10] and occur mostly in elderly people or patients of poor general medical condition.

Up to now AGEP has been attributed to a variety of causes such as viral infections[11–14] or hypersensitivity to mercury[7,15]

but it is primarily an adverse reaction to drugs. Based on reports of individual cases and short series, dozens of medications have been suspected of causing AGEP.

Because the pustules clinically and histologically resemble the lesions of pustular psoriasis, and because in a number of reports patients had a history of plaque psoriasis, some authors assume that AGEP is nothing more than an acute exacerbation of psoriasis caused by a variety of exogenous triggers. To better characterize AGEP and its risk factors a multinational case–control study was designed.

Patients and methods

The EuroSCAR project

EuroSCAR was designed as a multinational ongoing case–control study covering a population base of 100 million people in six countries and devoted to severe cutaneous adverse reactions (SCAR), including AGEP. The study was conducted following the rules of the ethics committees in the participating countries and Declaration of Helsinki protocols were followed. The study was designed and analysed independently from the multiple sources of funding (public and various pharmaceutical companies).

The EuroSCAR network—detection of cases

AGEP cases and controls were actively recruited by a network of hospitals in five countries (Austria, France, Israel, Italy and the Netherlands, whereas in Germany AGEP cases were not systematically ascertained). Hospitals were asked to report cases of acute pustular skin reactions (at least dozens of pustules) to the network. If a telephone contact did not suggest another clear diagnosis the patients were regarded as potential cases of AGEP. They were then seen and interviewed by trained investigators with the help of a specific questionnaire asking for detailed information on the clinical course of the disease, previous medical history and suspected causative factors including infections and medications. Drug intake in the month before hospital admission was recorded in a systematic way including reading a list of brand names and indications. Clinical pictures were taken and when available histological slides or reports were collected.

Case ascertainment—reviewing process

All interviewed cases were reviewed by a multinational expert committee of dermatologists blinded for information on risk factors. Clinical photographs were viewed together with clinical information from the case record forms and histological information (slides or reports). Clinical photographs were considered 'relevant' when their quality and timing in relation to the reaction provided helpful information to the retrospective confirmation of the diagnosis. Cases were ascertained with the help of a scoring system published previously.[6] This scoring system is based mainly on clinical criteria such as type and distribution of cutaneous and mucous membrane manifestations, the presence of leucocytosis, histological findings, and the course/timing of the reaction. Thereby patients could either be excluded from the study or classified as definite, probable or possible cases. Only definite and probable cases entered the analyses. For the analyses of risk factors a 'definite index-day', i.e. the day of the onset of the disease, was determined by the occurrence of first pustules. To take into account the fact that the reaction might have started before the occurrence of pustules a 'probable index-day' was defined by occurrence of skin rash or mucocutaneous symptoms within 3 days before pustules or fever within 2 days before pustules (not explained by other conditions).

Between April 1997 and December 2001 a total of 150 patients hospitalized for possible AGEP were evaluated. Among them 97 were classified as definite or probable cases (see Table 1).

Table 1 Flowchart of inclusion

AGEP cases	Controls
Potential community cases = 150	Potential controls = 1147
Validated community cases = 97	Validated controls = 1009

AGEP, acute generalized exanthematous pustulosis.

Controls

Three control patients were obtained for each AGEP case. Controls were patients admitted to the same hospital also for an acute disease but not suspected of resulting from drug use. Acceptable reasons for hospitalization were: acute infection (e.g. pneumonia), acute condition (e.g. trauma and appendicitis) or elective surgery (e.g. cataract extraction). Patients with chronic disorders were eligible only when admitted for an unrelated acute disease, but not if admitted for an acute exacerbation of a chronic disease. These rules had been designed for obtaining controls as representative as possible of the population to which the cases belonged[16] and has proven to be adequate in comparable investigational settings to be representative of the general population. Controls were interviewed within 2 months of hospitalization of matched case patients. As this study was part of an international case–control study on other drug-induced severe cutaneous reactions [Stevens–Johnson syndrome or toxic epidermal necrolysis (SJS/TEN)],[17] the number of controls could be extended to get a better estimate of exposure to infrequently used medications in the population and therefore enhance the statistical power of the study. Admission and discharge diagnoses, without information on medication use, were reviewed to determine the eligibility of the controls. The day of the first symptom in cases with an acute condition, or the day of admission for elective procedure, was defined as the index-day. Among 1147

controls who were interviewed, 1009 were considered eligible and entered into the analyses.

Quality checks

In each participating country, one monitor was responsible for the quality of interviews performed by the national investigators. All completed clinical report forms were sent to the data study centre in France and were managed centrally. Quality checks were performed when coding the data, when computerizing the data (online automated checks) and after completion of the database (further logical checks).

Statistical analysis

Based upon the hypothesis that a drug or its metabolites do not induce an adverse reaction when no longer present in the body, the analysis window for drug exposure was restricted to 1 week before the index-day. When appropriate, single agents were grouped into coalitions according to their therapeutic and pharmacological class (e.g. anti-infective sulphonamides, calcium channel blockers and thiazide diuretics).

Data were analysed using standard case–control methods. Crude relative risks were estimated with odds ratios (OR). Multivariate models (conditional and unconditional logistic regression) were also used because of probable confounding. Adjustment factors were age (three categories: < 30 years of age, 30–60 years, > 60 years), sex, country (France and others), and exposure to highly suspected drugs excluding, when appropriate, the one analysed. Drugs with a lower bound of the 95% confidence interval of the OR > 5 were considered 'highly suspected' [pristinamycin, ampicillin/amoxicillin, quinolones, (hydroxy)chloroquine, anti-infective sulphonamides, terbinafine and diltiazem]. Multivariate ORs were calculated when more than three cases and three controls were exposed. To ensure the quality of matching, two sets of analyses were performed: one using only the controls matched to the AGEP cases and another using the total population of controls. As we observed no substantial difference, only the results of the second set are presented.

Results

A flowchart of inclusion and demographic characteristics of the study population are given in Tables 1 and 2. Patients with AGEP were slightly more often women and their mean age (56 years) was higher than for other SCARs as indicated by the mean age of the population of all controls. Multivariate ORs (calculated where possible) revealed a number of drugs that were highly associated with the development of AGEP. Table 3 shows all the drugs or drug coalitions that can be considered 'highly suspected' with a lower bound of the 95% confidence interval (CI) of the OR > 5. Table 4 lists drugs that showed slightly elevated risks in the multivariate analysis. Table 5 presents various drugs that are of special interest, either because they are widely used, or because they are known to be causative agents for other drug reactions (like allopurinol for SJS/TEN). The last column of Tables 3–5 provides information on the percentage of cases with recent concomitant use of another 'highly suspected' drug, i.e. a drug with a high risk to induce AGEP.

Table 2 Demographic data

	AGEP cases (n = 97)	Controls (n = 1009)
Age, mean (SD)	56 (21)	48 (24)
Sex, male/female ratio	0·80	0·73
Inclusion by country		
France	78	738
Israel	11	108
Austria, Italy, the Netherlands	8	163
Skin biopsy available	90	n/a
Relevant[a] photographs available	90	n/a

[a]Quality and data appropriate enough to provide help for the diagnosis (see Patients and methods).
AGEP, acute generalized exanthematous pustulosis; n/a, not applicable.

Pristinamycin[7,18]

Of the 97 patients with AGEP, 13 had an intake of macrolide antibiotics in the week before occurrence of the skin reaction (excluding the index-day). Ten of these cases were associated with the intake of pristinamycin, a macrolide that—in our study—was marketed only in France. A very interesting finding is that the cutaneous reaction occurred after only 1 day of intake in nine and after 2 days in one case. As no control was exposed to pristinamycin, no multivariate OR could be provided, but the high lower bound of the univariate CI (26) together with the small percentage of cases with the recent concomitant intake of a highly suspected drug suggest a high risk of AGEP associated with pristinamycin. As shown in Table 4 other macrolide antibiotics were also associated with a probably lower but significant risk.

Aminopenicillins

For ampicillin and amoxicillin, which are often reported causes for AGEP,[5,7,19–22] there was a multivariate OR of 23 (CI 10–54). Exposure time was < 15 days in all cases and often very short.

Quinolones[23–25]

These antimicrobial agents were associated with a high risk in our study: multivariate OR of 33 (CI 8·5–127) with nine cases and five controls exposed. In seven out of nine cases drug intake started < 15 days before the reaction.

Table 3 Drugs highly associated with AGEP

Drug or coalition	AGEP (n = 97) n (%)	Controls (n = 1009) n (%)	OR[a]	95% CI		% of cases with recent use of other 'highly suspected' drugs[b]
Pristinamycin	10 (10)	0	∞	26	∞	10
Aminopenicillins	18 (19)	17 (2)	23	10	54	17
Quinolones	9 (9)	5 (0·5)	33	8·5	127	33
(Hydroxy)chloroquine	7 (7)	2 (0·2)	39	8·0	191	0
Sulphonamides	4 (4)	0	∞	7·1	∞	0
Terbinafine	4 (4)	0	∞	7·1	∞	25
Diltiazem	7 (7)	10 (1)	15	5·0	48	0

[a]Multivariate OR if at least three cases and three controls exposed, otherwise univariate; [b]recent use of other 'highly suspected' drugs (i.e. any other drug listed in the table).
AGEP, acute generalized exanthematous pustulosis; OR, odds ratio; CI, confidence interval.

Table 4 Other drugs with less strong associations with AGEP

Drug or coalition	AGEP (n = 97) n (%)	Controls (n = 1009) n (%)	Multivariate OR	95% CI		% cases with recent use of other 'highly suspected' drugs[a]
Corticosteroids	18 (19)	24 (2)	12	4·6	31	56
Macrolides[b]	4 (4)	8 (1)	11	2·7	48	25
Oxicam NSAIDs[c]	3 (3)	7 (1)	8·4	1·7	42	33
Antiepileptic drugs[d]	5 (5)	9 (1)	7·6	1·6	36	40

[a]Recent use of other 'highly suspected' drugs (i.e. any other drug listed in Table 3); [b]other than pristinamycin; one patient took both pristinamycin and josamycine; [c]exposure window extended to 2 weeks; [d]excluding valproic acid (see text for details).
AGEP, acute generalized exanthematous pustulosis; NSAIDs, nonsteroidal anti-inflammatory drugs; OR, odds ratio; CI, confidence interval.

Table 5 Drugs of common use or known to be risk factors for SJS/TEN with no significant association with AGEP

Drug or coalition	AGEP (n = 97) n (%)	Controls (n = 1009) n (%)	Multivariate OR	95% CI		% cases with recent use of other 'highly suspected' drugs[a]
Acetaminophen	34 (35·1)	196 (19·4)	1·1	0·6	2·2	50
Benzodiazepines	22 (22·7)	131 (13·0)	1·5	0·7	3·2	60
ACE inhibitors	9 (9·2)	81 (8·0)	0·8	0·3	2·3	56
Beta-blockers	6 (6·2)	77 (7·6)	0·7	0·2	2·1	33
Acetylsalicylic acid	11 (11·3)	76 (7·5)	1·0	0·4	2·6	55
Ca channel blockers[b]	10 (10·3)	59 (5·9)	1·9	0·7	5·3	70
Thiazide diuretics	4 (4·1)	54 (5·4)	0·7	0·2	2·9	50
Sartans	4 (4·1)	18 (1·8)	3·4	0·9	13	50
Allopurinol	3 (3·1)	13 (1·3)	2·7	0·5	14	33
Cephalosporins	3 (3·1)	6 (0·6)	0·4	0·0	5·8	0

[a]Recent use of other 'highly suspected' drugs (i.e. any other drug listed in Table 3); [b]excluding diltiazem.
SJS/TEN, Stevens–Johnson syndrome or toxic epidermal necrolysis; AGEP, acute generalized exanthematous pustulosis; OR, odds ratio; CI, confidence interval; ACE, angiotensin-converting enzyme.

Antimalarial drugs

A total of seven cases vs. two controls were exposed to chloroquine or hydroxychloroquine leading to a univariate OR of 39 with a lower bound of the 95% CI of 8·0. None of these cases was exposed to another highly suspected drug suggesting a risk of AGEP associated with these antimalarial drugs.

Anti-infective sulphonamides[26,27]

Four out of 97 patients had taken anti-infective sulphonamides. The lack of exposed controls does not allow calculating an OR but the lower bound of the confidence interval of 7·1 suggests a high risk for these drugs. In all four cases no co-medication with another drug with a high risk of causing AGEP was present.

Terbinafine[3,28–37]

In our study all four cases associated with antimycotic drugs had taken terbinafine. Onset of the reaction was 26, 13, 11 and 9 days after beginning of intake of the drug. Only one patient also took another highly suspected drug. The lower bound of the univariate CI (7·1) suggests a high risk of AGEP associated with terbinafine.

Calcium channel blockers[38–47]

As a whole this medication class was present in 17 cases and 69 controls [multivariate OR 3·5 (CI 1·7–7·4)]. Because of several prior reports of AGEP attributed to diltiazem, we looked specifically at this agent. A total of seven cases and 10 controls had been exposed to diltiazem [multivariate OR 15 (CI 5·0–48)]. No other single calcium channel blocker was associated with a significant risk and the multivariate OR for the class excluding diltiazem was 1·9 (CI 0·7–5·3). No patient exposed to diltiazem had been simultaneously exposed to another high-risk drug.

Corticosteroids

A total of 18 patients and 24 controls had systemic corticosteroid treatment before onset of the skin reaction. The rate of co-medication was high (12 of 18 cases had also been exposed to another highly suspected drug in contrast to only two of 24 controls), but the multivariate analysis resulted in an OR of 12 (CI 4·6–31) all the same.

Oxicam nonsteroidal anti-inflammatory drugs

Nonsteroidal anti-inflammatory drugs of the oxicam type are also typical triggers for SJS/TEN-type reactions[48] and may play some role in AGEP. Exposure in three cases and seven controls led to a multivariate OR of 8·4 (CI 1·7–42).

Antiepileptic drugs

Antiepileptic drugs, with the exception of valproic acid, are known to be highly associated with the development of drug rashes. In our study five cases and nine controls had been exposed to antiepileptics (excluding valproic acid), leading to a multivariate OR of 7·6 (CI 1·6–36). This group is very heterogeneous with regard to type of drug, duration of intake and co-medication. In detail, the numbers of cases and controls exposed to antiepileptics were: lamotrigine, two vs. zero; carbamazepine, two vs. four; phenobarbital, two vs. five; and phenytoin, one vs. one.

Allopurinol

Allopurinol[49–51] is known to have a very high risk of causing severe cutaneous adverse reactions.[48] This seems to be different for AGEP as only three cases (one recent user) were associated with the intake of allopurinol compared with 13 controls. This leads to a multivariate OR of 2·7 (CI 0·5–14).

Other drugs

No elevated relative risk could be detected for any other drug or coalition than those detailed above. Nevirapine, an anti-HIV (human immunodeficiency virus) drug, which in the analysis of other EuroSCAR data was shown to have a high risk of causing SJS/TEN, had not been taken by any AGEP cases or controls. There was only one patient who developed AGEP (1·0%) in whom we detected no drug intake in the month before admission to hospital (in contrast with 14·9% of the controls).

Timing of the reaction in relation to the onset of causative medications

As shown in Figure 1 (a and b), two different patterns were observed when looking at the duration of treatment before onset of reaction in all patients exposed to a 'high-risk' drug. For all exposures to antibiotics (41 cases), including sulphonamides, the median treatment duration was 1 day. In contrast, for all other associated drugs the median was 11 days. Further exploration of data did not provide an explanation for these different delays. For example among the 18 cases exposed to aminopenicillin only two reported a prior skin reaction to the same drug and one to an unknown antibiotic. So a role of prior sensitization for the rapid development of AGEP could not be demonstrated.

Infections

Cases of AGEP due to infections have been published repeatedly in the literature.[7,11–14,52,53] The restrictions of a questionnaire survey did not allow for comprehensive diagnosis of infection, but questions on recent infections were part of the case record forms. Analysis of these data, though, did not reveal a significant association of infections with AGEP. No case patient was known to be HIV infected, vs. one control. More generally 36 patients (37%) and 151 controls (15%) reported having had an infection in the 4 weeks before the index-day. That led to a crude OR of 3·4 (CI 2·1–5·2). But the OR decreased to 1·2 (CI 0·7–2·2) in multivariate analysis.

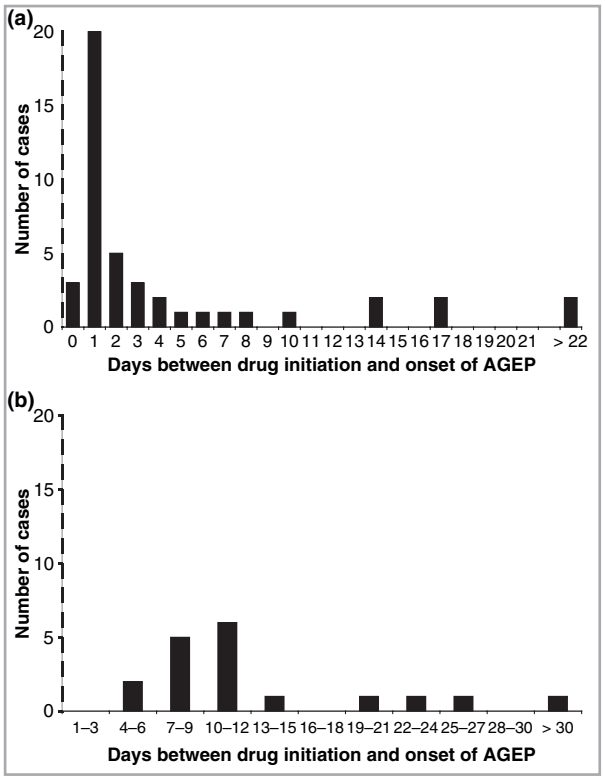

Fig 1. (a) Delay (days) between beginning of drug intake and onset of reaction: 'highly suspected' anti-infectious drugs (pristinamycin, aminopenicillins, quinolones and antibacterial sulphonamides). (b) Delay (days) between beginning of drug intake and onset of reaction: other 'highly suspected' drugs [diltiazem, terbinafine and (hydroxy)chloroquine].

Psoriasis

Due to its clinical similarities with generalized pustular psoriasis of the von Zumbusch type, AGEP is sometimes interpreted as a variant of psoriasis. In our questionnaires we asked for personal history of psoriasis, family history of psoriasis or psoriasis treatment. In the group of AGEP cases the numbers of positive answers were seven, four and five of 97 (7%, 4% and 5%). In the control group the numbers were 34 (3%), 41 (4%) and 33 (3%), respectively. For none of these three criteria did the cases differ significantly from the controls.

Discussion

This study is the first evaluation of risk factors for AGEP using a case–control methodology. Within the limits of a relatively small number of included cases, it confirms the predominant role of drugs in the induction of this reaction, does not find a relevant association with infections, and strongly suggests that AGEP is different from psoriasis.

Concerning the role of medications the study detected strong associations with a limited number of drugs. Many of those, such as pristinamycin, aminopenicillins, terbinafine, diltiazem or (hydroxy)chloroquine, have been previously suspected, while others have not (i.e. quinolones).[18]

For many drugs of frequent use no evident association could be found, although for some an elevated risk cannot be ruled out if one considers that the upper bound of the confidence interval was sometimes above 10.

Another interesting finding of the study is that while some drugs provoke the reaction after a time lag quite comparable to other drug reactions (1–2 weeks), some cases of AGEP occurred very soon after the first intake of the drug, especially pristinamycin or amoxicillin. This very rapid onset could suggest a re-challenge with a drug patients had already been sensitized to, but we did not find any evidence for that. Yet, this obvious peculiarity in the dynamics of the reaction may suggest different pathomechanisms, which have to be further elucidated by laboratory investigations as these questions cannot be answered by an epidemiological study.

Another noteworthy result of our study is that AGEP probably has a different spectrum of causative drugs than SJS/TEN. While antibiotic agents appear to be culprit drugs for both reactions some important triggers for SJS/TEN like allopurinol, antiepileptic drugs or nevirapine do not seem to play a major role in AGEP. On the other hand terbinafine, diltiazem and pristinamycin are more likely to be found in AGEP than in SJS/TEN. In our series of 379 SJS/TEN cases the numbers were terbinafine, no case vs. one control; diltiazem, four cases vs. 11 controls; and pristinamycin, one case vs. no control exposed (unpublished observation).[17]

In contrast to prior case reports of AGEP and with what is suspected for other types of drug eruptions we did not find any stringent evidence that infection played a role in causing the reaction. The significant association observed in univariate analysis totally disappeared in the multivariate model. This strongly suggests that preceding infections led to the prescription of anti-infective drugs which were the cause of AGEP.

Whether AGEP is or is not an entity distinct from pustular psoriasis can also be discussed in the light of the present results. AGEP as a form of pustular psoriasis would suggest a much higher percentage of personal and family history of psoriasis in the AGEP group. Our data show that this percentage is only slightly higher than in the control group (which reflects very well the prevalence of psoriasis in the general population). This slight elevation could either reflect some residual confusion in the clinical definition of AGEP or be a hint in the direction that patients with a pustular form of psoriasis and patients who develop a pustular drug reaction may share a common genetic background which directs them towards reacting with neutrophil-attracting mechanisms (e.g. production of interleukin-8). In this discussion it should also be mentioned that many drugs that had been recognized as inducers of psoriasis, e.g. beta-blockers or angiotensin-converting enzyme (ACE) inhibitors, were not associated with AGEP.

The EuroSCAR network allowed the detection of 97 patients with symptoms that fit the clinical and histopathological features of AGEP. Although it might be given other denomina-

tions, this type of reaction is quite characteristic in terms of cause (i.e. drugs), clinical appearance and course. Its recognition is of clinical relevance as discontinuation of the causative agent is the most important treatment measure. The spectrum of drugs that causes AGEP is different from that of SJS/TEN with pristinamycin, ampicillin/amoxicillin, quinolones, (hydroxy)chloroquine, anti-infective sulphonamides, terbinafine and diltiazem being associated with the highest risks and, for example, allopurinol playing no significant role. Furthermore, because with some drugs (e.g. pristinamycin) the reaction arises so rapidly after intake, it may be assumed that different mechanisms may be involved in the development of this clinical type of reaction. These mechanisms have to be elucidated further by immunological studies whereas ongoing pharmaco-epidemiological surveillance will help to deepen the knowledge on risks for existing drugs and to detect the potential risk of drugs that have been marketed recently.[54–59]

Due to the characteristic clinical features, the pathogenesis, and the clinical course and consequences with respect to treatment it makes sense for the clinician to regard AGEP as an independent entity, at least until its pathomechanisms have been clarified.

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, Glaxo Wellcome/GlaxoSmithKline, Goedecke Parke Davis, 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, Dr Willmar Schwabe. Funding from pharmaceutical companies in France was managed through contract with INSERM (Institut National de la Santé et de la Recherche Médicale), French Ministry of Health (PHRC AOM 98027).

Other participants are as follows: *Austria*: Elisabeth Kowald, Dennis Linder, Gudrun Ratzinger; *France*: Fabienne Bazin, Hélène Bocquet, Laure Dangoumaud, Yves Dorleans, Alain Dupuy, Jean-Paul Fagot, Catherine Paoletti, Annie-Claude Paty, Sylvie Rodriguez, Bruno Sassolas, Patricia Thion, Loïc Vaillant; *Germany*: Konrad Bork, Uwe-Frithjof Haustein, Olaf Hering, Klaus Kitta, Brigitte Loleit, Oliver Pfeiffer, Thekla Renker, Birgit Schneck, Werner Schröder, Esra Tas, Dieter Vieluf; *Israel*: Arnon D. Cohen, Sara Weltfreund; *Italy*: Laura Atzori, Grazia Manfredi, Davide Melandri, Annalisa Pinna; *the Netherlands*: Christianne Bearda Bakker-Wensveen, Joost Govaert, Viña Williams-Snijders.

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