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Who should support the costs of severe adverse drug reactions?

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Even if adverse drug reactions (ADRs) occur frequently, those that threaten life are rare. A serious ADR, whatever its type or the organ involved, was shown to occur in 2.1% (95% confidence interval [CI], 1.9–2.3%) of in-hospital patients in the USA and to result in the death of 0.19% (95% CI, 0.13–0.26%) of all hospitalized persons [Lazarou *et al.* 1998].

Epidermal necrolysis is a particularly striking example of a very rare, but very severe ADR. Owing to a more or less disseminated destruction of epithelia of the skin and mucous membranes, the disease evolves in two stages: an acute phase lasting 3–4 weeks and a chronic phase related to sequelae that may last forever. When considering the full spectrum, including the less-severe (Stevens–Johnson syndrome [SJS]) and the most-severe forms (toxic epidermal necrolysis [TEN]), the incidence is about two cases per million per year [Rzany *et al.* 1996] and the death rate during hospital stay for SJS or TEN is 20–25% [Schneck *et al.* 2008]. That is followed by 5–10% delayed mortality in the following weeks. Sequelae affecting nearly all survivors may progress with time and often impair daily life. Thus, less than 20% of persons suffering from SJS/TEN survive without resulting harm for the rest of their lives. These figures completely support the denomination of 'victims' used by patients' associations.

Two large-scale multinational case–control studies have demonstrated that about one half of all SJS/TEN cases are related to a dozen of 'frequently associated' medications, but also that a substantial proportion of cases (up to 40%) cannot be attributed clearly to a specific drug [Roujeau *et al.* 1995; Mockenhaupt *et al.* 2008]. Even for 'frequently associated' medications, the magnitude of risk is in the range of 1–2 per 100,000 users [Gimnig *et al.* 2006]. In most instances, when drug causality is evident, there was no medical error in the prescription of these medications.

The occurrence of the reaction remains totally unpredictable. A few years ago, advances in pharmacogenetics raised hope for the development of predictive tests [Chung *et al.* 2004]. Unfortunately, further investigations strongly suggested that such tests would be useful only for a very limited number of drugs in specific population groups [Lonjou *et al.* 2008].

The costs of SJS/TEN are high

The costs of hospital stay during the acute phase of disease vary from a few thousand US dollars for the milder cases of SJS to more than US$100,000 for the most severe and complicated cases of TEN. In France, hospital re-imbursements within a diagnosis-related group (DRG) system can reach €90,000 for the most severe cases of TEN. Hospital costs are usually covered by health insurance. The costs of care for chronic sequelae have never been evaluated to the best of the authors' knowledge but are likely to reach very high figures when including eye surgery,

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psychological support or even lung transplantation. The frequency and nature of sequelae have been poorly recognized up to now. For many of these sequelae, coverage of costs by health insurance is very limited.

Many others costs should be added to the direct health expenses. Losses of opportunities in professional, social and personal life are linked to incapacitation induced by sequelae affecting the eyes and many other organs. These latter costs should be taken into account, as suggested by the World Health Organization with the introduction of the concept of a disability-adjusted life year (DALY). The prejudice linked to sequelae of SJS/TEN has never been evaluated scientifically, but it is noteworthy that courts in the US attributed settlements up to US$4,500,000 for SJS victims (www.sjs-lawyers.com).

What is the present status of compensation?

In most developed countries, civil law enables patients who have suffered SJS/TEN and/or their families to sue the physician who prescribed the drug, the pharmacist who delivered it or the manufacturer. However, to seek compensation through law courts has many pitfalls. The first is the difficulty in proving causation. A substantial number of cases of SJS/TEN (30–40%) cannot be linked with certainty to just one drug. The drug origin of the reaction is likely in most of these cases, but no specific and unique 'culprit' can be definitely identified. Another flaw is that it must be shown that a fault was committed, which is unlikely in most cases. A fault in prescription or delivery is rare. A fault attributed to insufficient information about the risk from the manufacturer or the prescriber is the most frequent reason for court decisions in favour of patients. However, even when this lack of information is proven, patients are awarded damages to the level of an estimated and specific 'loss of chance' to avoid injuries and their consequences. This 'loss of chance' does not automatically cover 100% of the damages, e.g. when it is estimated that the information would not have prevented the medication to be taken but would have accelerated the diagnosis.

As a result, the mention of a risk of SJS/TEN in the *summary* of *product* characteristics (SPC) or in the patient leaflet is used (and abused) by pharmaceutical companies as legal protection. Another side effect of increasing litigations related to adverse effects of medicines is to force physicians towards 'defensive medicine' with superfluous investigations, excessive record taking and distribution to patients of endless lists of precautions and side effects.

Compensation schemes for victims of severe unavoidable ADRs (where no fault was committed, i.e. 'no fault systems') have been introduced successively in Sweden (1975), New Zealand, Japan, Taiwan and France (2002). In Japan, the Relief Services for Adverse Health Effects, a branch of the Pharmaceuticals and Medical Devices Agency (PMDA), the Japanese drug regulatory agency, provides medical expenses, disability pensions and bereaved family pensions for people who have suffered from severe illness and disabilities caused by ADRs. However, activity figures reported by several of the agencies mentioned above strongly suggest that only a small proportion of victims of severe ADRs actually received financial compensation. As an example, PMDA in Japan reported allowance of compensation concerned 113 cases in 2008, i.e. about 50% of the number of expected cases of SJS/TEN in Japan annually and therefore a much lower proportion of all severe ADR cases. A similar trend had been suspected in New Zealand [Smith, 1982]. Reasons for poor coverage were not investigated but some are likely the same as for lawsuits: ignorance of their rights by many patients and more importantly difficulty in proving causality.

In summary, compensatory damages awarded by law courts or by existing 'no fault systems' do not appear to provide adequate answers to victims of SJS/TEN.

Who should take the responsibility for compensation of victims and other costs?

Does risk disclosure either on a drug package leaflet or given by a practitioner provide a sufficient level of information to declare a patient duly informed and fully responsible when taking a medicine?

First, we strongly doubt that disclosure of very rare risks is meaningful and explicit enough for patients or even for prescribing physicians. For many medications that mention a risk of SJS/TEN in their SPC, this risk is of the same magnitude or even lower than the risk of severe injury during air travel. Would it make sense to mention such risks on airplane tickets?

Second, relying on full information of medicine users ignores the fact that many illnesses put patients in the position of being dependant consumers and that only very few have the possibility to discuss their practitioner's opinion or even to oppose it.

Marketing of new drugs is regulated, which is a serious hint that the responsibility is not only that of the pharmaceutical company but is also *de facto* endorsed by the public authorities. The FDA and EMA deliver marketing authorizations based on prior demonstration by the manufacturer in clinical trials that the drug is effective and safe. Obviously, neither effectiveness nor safety can be 100% guaranteed. What is evaluated by agencies is a collective benefit–risk balance. In order to authorize a drug, this balance has to be positively evaluated at the scale of a population. However, it is only based on data available at a specific date and needs periodic re-evaluation. More importantly, this collective benefit–risk balance should not be mistaken for the individual one. When a drug is authorized, it means theoretically that most users will benefit from the new medicine, some at the price of mild adverse effects, but sometimes, for a very (unhappy) few, at the price of rare and severe adverse effects such as SJS or TEN. For individual victims of such severe reactions, however, the individual benefit–risk balance is infinitely negative. Do they alone have to pay the price of a hazardous accident while a hundred thousand other users gain a benefit?

In a regulated market, agencies in charge of the benefit–risk balance evaluation should deliver Marketing Authorizations associated with solid and extensive risk management plans as scheduled by the European Union (article 8 of Directive 2001/83/EC). Such plans have still to be precisely defined but should contain many practical and likely expansive measures. This might involve options, including the following:

1. strategies (epidemiological studies through, e.g. ADR registries) for adequate measurement of risks that are too rare for being detected in premarketing studies such as SJS/TEN;
2. periodic re-evaluation of the benefit–risk balance according to the above-mentioned measurements;
3. identification and monitoring of measures capable of mitigating the risk (populations at higher risks, comedications, environmental factors, etc.) and of curtailing its impact (promotion of research on severe ADRs as a tool that should in the long term reduce the burden of rare but very severe reactions).

Where the SPC specifically mentions potentially severe risks, granting of Marketing Authorization should perhaps also be linked to provision by the holder of authorization of funds for compensation plans for victims of severe adverse effects and coverage of medical costs linked to such ADRs (these costs are actually covered either by public and private health insurance plans or by the victims themselves).

The costs linked to the risk management of rare life-threatening ADRs would be included in the price of the drug by the marketing authorization holder. If the costs are being distributed among a large population of users, it should not increase the drug's price significantly as long as the risk is rare. Should the opposite occur, it would be a possible incentive for patients and healthcare institutions to consider using safer and/or cheaper alternative medications. That might also encourage pharmaceutical companies to reduce the enormous disequilibrium between the investments on efficacy and those on safety during the development of drugs.

The visibility given by this mechanism on the risk's real cost should result progressively in a better perception and management of the risk and a decrease in severe ADR cases. Since a higher drug price would be balanced by covering ADR medical costs by the above-mentioned fund, the financial impact on healthcare institutions is expected to be limited. On the other hand, this kind of mechanism would make a huge difference for victims.

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Conflicts of interest statement

Jean-Claude Roujeau has provided paid expertise for many pharmaceutical companies on cases of severe cutaneous adverse reactions. He has been recently and/or is still a member of advisory boards on safety for Boehringer-Ingelheim, OM Pharma, Pfizer, Roche, Servier and Vertex.

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