Pharmaceutical Medicine

Severe cutaneous adverse reactions (SCAR) syndromes

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Idiosyncratic drug reactions are unpredictable reactions that can cause significant morbidity and mortality. The causal mechanisms continue to be unclear and because of the lack of consensus regarding the definition of these syndromes, reports, and therefore epidemiological data, are often unreliable.

Severe idiosyncratic drug reactions are often characterized by fever and internal organ involvement. They also frequently involve the skin, which amount to less than 5% of the reported drug reactions in hospitalized patients, and probably more than 90% of these are related to an unpredicted effect mediated by a drug that activates the immune response. The clinical presentation is highly variable, from the most common transient and benign erythema that occurs six to nine days after the introduction of a new drug in 1% to 3% of users, to the most severe forms that fortunately affect less than 1/10,000 users[1].

In order to establish a common criteria to refer to these entities, the RegiSCAR-group proposed the denomination of severe cutaneous adverse reactions (SCAR) for the very rare disorders that are severe and often associated with significant morbidity and mortality, non-predictable or idiosyncratic, and most frequently caused by drugs[2].

Acute generalized exanthematous pustulosis (AGEP)

Acute generalized exanthematous pustulosis (AGEP) was described as an entity in the 1980's as an extensive pustular eruption similar to pustular psoriasis, usually taking place as a drug reaction in patients without a history of psoriasis; the mortality rate has been consistently reported in the medical literature as 5%[3].

The diagnosis criteria include acute pustular eruption, fever above 38°C, neutrophilia with or without a mild eosinophilia, subcorneal or intraepidermal pustules on skin biopsy, and spontaneous resolution in less than 15 days[4].

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)

Stevens-Johnson syndrome (SJS) is characterized by acute onset and rapid progression of painful skin and mucous membranes lesions. The skin lesions are widespread and predominate on the trunk, with a tendency to become confluent, leading to a restricted detachment of epidermis on less than 10% of the body surface area.

Toxic epidermal necrolysis (TEN), described in 1956 by Lyell (Lyell's syndrome), is characterized by the same lesions as SJS but with the detachment of large epidermal sheets on more than 30% of the body surface area.

Based on the results of a large case control study, the RegSCAR group suggested that SJS and TEN can be considered as severity variants of a single disease[5].

A severity-of-illness score that estimates the risk of death in toxic epidermal necrolysis[6] has been developed and validated. The authors identified seven independent risk factors for predicting an outcome of death in TEN cases:

1. Age > 40 years
2. Heart rate > 120 beats per minute
3. Cancer or hematologic malignancy
4. Involved body surface area > 10%
5. Blood urea nitrogen level > 10 mmol/L (28 mg/dL)
6. Serum bicarbonate level < 20 mmol/L (20 mEq/L)
7. Blood glucose level 14 mmol/L (252 mg/dL)

Mortality rates based on the number of positive criteria are as follows:

- 0 to 1 factor = 3%
- 2 factors = 12%
- 3 factors = 35%
- 4 factors = 58%
- 5 or more factors = 90%

The opinion regarding the usefulness of specific treatments varies, since some results show no benefit from using intravenous immunoglobulin and a strong (but not significant) potential reduction of mortality with the use of corticosteroids[7].

Drug rash with eosinophilia and systemic symptoms (DRESS syndrome)

Drug rash with eosinophilia and systemic symptoms (DRESS syndrome) was defined by the triad of skin eruption, haematological involvement, and internal organ involvement according to Bocquet's diagnosis criteria

in 1996[8], in order to differentiate it from drug-induced pseudo lymphoma, and comprises the following criteria:

1. Cutaneous drug eruption
2. Hematologic abnormalities: eosinophilia **or** presence of atypical lymphocytes
3. Systemic involvement:
   Adenopathies ≥ 2 cm in diameter
   or hepatitis (liver tronsaminases values ≥ 2 N)
   or interstitial nephritis
   or interstitial pneumonitis
   or carditis

It has been estimated to occur in about 1 in 10,000 exposures to drugs such as antiepileptics and sulfonamides. It typically begins two to six weeks after first drug use, later than most other skin reactions. Visceral involvement differentiates DRESS syndrome from common exanthematous eruptions[8].

Prominent eosinophilia is common, and a characteristic feature of this reaction is the appearance of atypical lymphocytosis in the circulation. Rash and hepatitis may persist for several weeks after drug withdrawal, and some of the manifestations may be life-threatening, with a mortality rate of about 10%.

The differential diagnosis includes acute viral infections, idiopathic hypereosinophilic syndrome, and lymphoma. Special attention should be paid to human herpesvirus-6 (HHV6), since several publications suggested a possible interaction between DRESS and reactivation of HHV6.

A peculiar feature of this syndrome is its long-lasting clinical course despite withdrawal of the causative drug. There may also be persistent intolerance to other chemically distinct drugs, leading to flare-up reactions months after the initiating drug therapy is stopped. Recently, it has been shown that HHV6 DNA can be found in many patients with this syndrome during the third or fourth week of the disease (but not before), followed by an increase in antibodies to HHV6[9]. Other reports document reactivation of cytomegalovirus infection. The justification is that a drug-induced massive immune stimulation somehow leads to a loss of control of these herpes viruses, which subsequently replicate and possibly contribute to the chronic course and persistent drug intolerance characteristic of this disease[10].

The aromatic antiepileptic agents (phenobarbital, carbamazepine, phenytoïn), minocycline, and allopurinol are the most frequent causes. Sulfonamides, gold salts, and dapsone may also induce this syndrome[11].

Experts agree that the decision of whether an organ is involved by DRESS should rely on two criteria: clinical relevance and absence of other alternative causes. As an example, the liver would be considered involved if alanine aminotransferase levels were at least twice the upper limit of normal values in the absence of another disease.

Japanese authors classify a subset of DRESS as drug induced hypersensitivity syndrome (DIHS) if containing the following features: maculo-papular rash; prolonged clinical symptoms two weeks after discontinuation of the causative drug; fever higher than 38ºC; liver abnormalities (alanine aminotransferase [ALT] > 100 U/L); leukocyte abnormalities, including leukocytosis (> 11 x 10^9 leukocytes/L), atypical lymphocytosis (> 5% lymphocytes), or eosinophilia (> 1.5 x 10^9 eosinophils/L); lymphadenopathies; and HHV6 reactivation. Diagnosis of definite or typical DIHS requires the presence of the seven criteria and might be a more severe expression of DRESS[11].

Clinical aspects and diagnosis

The diagnosis of severe cutaneous drug reactions (SCAR) requires the identification of a skin eruption with high fever and severe constitutional symptoms that might have been caused by a medication and not by another cause. The differential diagnosis includes other cutaneous drug reactions, acute viral infections (e.g., Epstein-Barr virus, hepatitis virus, influenza virus, cytomegalovirus, and human immunodeficiency virus), lymphoma, pseudolymphoma, idiopathic hypereosinophilic syndrome, and angio-immunoblastic lymphadenopathy. In addition, while some medications are "usual suspects" for all types (e.g. anticonvulsants), others are more specific of a given pattern (pristinamycine, hydroxychloroquine, and diltiazem for AGEP; minocycline for DRESS; anti-infectious sulfonamides and allopurinol for epidermal necrolysis). The identification of organ involvement, which differs according to the type of reaction, is another important point for the diagnostic confirmation of SCAR entities.

The "phenotypic" diversity of the final expression drug reactions can be explained by the engagement of a variety of cytokines and inflammatory cells, and by regulatory mechanisms. For example, memory cytotoxic T-cells are key effectors in extensive blisters of epidermal necrolysis.

With this in mind, prognosis can be determined, and recovery after drug withdrawal is usual, but symptoms may persist for several weeks. When internal organ involvement exists, treatment with systemic corticosteroids is often proposed even though the efficacy of corticosteroids has not been proved to be useful for all entities described.

Conclusion

The denomination of severe cutaneous adverse reactions (SCAR) defines very rare disorders that are severe and often associated with significant morbidity; these disorders are idiosyncratic and most frequently caused by drugs, and mortality ranges from 5% to 40%.

For a better understanding of these clinical entities a consensus on the definition will help reliable reporting, and therefore superior epidemiological data will be available.

Recognition is of fundamental importance since recovery after drug withdrawal is usual, but symptoms may persist for several weeks. When internal organ involvement exists, treatment with systemic corticosteroids is often proposed.

It is important to remember that all these entities are associated with drug use, and that the accuracy of adverse reaction reporting, which in turn relies on the recognition of these entities and their diagnoses in the clinical setting, is of paramount importance for the recognition of potential drug-related associations and helps to define the safety profile of drugs.

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