Severe Cutaneous Adverse Reactions (SCARs): How do they mark the Portuguese national pharmacovigilance system?

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INTRODUCTION & AIM

Severe Cutaneous Adverse Reactions (SCARs) are drug-induced reactions that encompass delayed type hypersensitivity reactions involving the activation of T cells, such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug-reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP) and generalized bullous fixed drug eruptions (GBFDE)^{1 2}.

Early identification, management and treatment are crucial for improving patient outcomes due to the seriousness of these reactions, that may be fatal^{1 2}. This study aims to assess Individual Case Safety Reports (ICSRs) focusing to find the more frequently medicinal products suspected to induce SCARs in the Portuguese population.

MATERIALS & METHODS

Retrospective analysis of ICSRs reported to the Portuguese national pharmacovigilance system between September 1st, 2012 and December 31th, 2022, containing at least one of the following MedDRA preferred terms: Stevens-Johnson syndrome; Toxic epidermal necrolysis; Drug reaction with eosinophilia and systemic symptoms; Acute generalised exanthematous pustulosis; Generalised bullous fixed drug eruption; SJS-TEN overlap. Patients' demographic data, suspected medicinal product (International Nonproprietary Names [INN] applied), seriousness and predictability were assessed.

International Nonproprietary Names (INN)	Frequency	Percentage (%)	INN	Frequency	Percentage (%)
Allopurinol	36	18.7%	Allopurinol	19	19.0%
Amoxicillin + Clavulanic acid	12	6.2%	Phenytoin	6	6.0%
Sulfamethoxazole + Trimethoprim	8	4.1%	Carbamazepine	4	4.0%
Lamotrigine	7	3.6%	Paracetamol	4	4.0%
Phenytoin	7	3.6%	Sulfametoxazol + Trimetoprim	4	4.0%
Azithromycin	6	3.1%	Etoricoxib	3	3.0%
Ibuprofen	5	2.6%	Amoxicillin + Clavulanic acid	2	2.0%
Paracetamol	5	2.6%	Azithromycin	2	2.0%
Carbamazepine	4	2.1%	Ciprofloxacin	2	2.0%
Ciprofloxacin	4	2.1%	Diclofenac	2	2.0%
Drug-reaction with eosinophilia and systemic symptoms (n=258)			Acute generalized exanthematous pustulosis (n=43)		
INN	Frequency	Percentage (%)	INN	Frequency	Percentage (%)
INN Allopurinol	Frequency 91	Percentage (%) 24.7%	INN Amoxicillin + Clavulanic acid	Frequency 9	Percentage (%) 15.8%
INN Allopurinol Carbamazepine	Frequency 91 38	Percentage (%) 24.7% 10.3%	INN Amoxicillin + Clavulanic acid Amoxicillin	Frequency 9 5	Percentage (%) 15.8% 8.8%
INN Allopurinol Carbamazepine Amoxicillin	Frequency 91 38 15	Percentage (%) 24.7% 10.3% 4.1%	INN Amoxicillin + Clavulanic acid Amoxicillin Ciprofloxacin	Frequency 9 5 4	Percentage (%) 15.8% 8.8% 7.0%
INN Allopurinol Carbamazepine Amoxicillin Vancomycin	Frequency 91 38 15 15	Percentage (%) 24.7% 10.3% 4.1% 4.1%	INN Amoxicillin + Clavulanic acid Amoxicillin Ciprofloxacin Diltiazem	Frequency 9 5 4 3	Percentage (%) 15.8% 8.8% 7.0% 5.3%
INN Allopurinol Carbamazepine Amoxicillin Vancomycin Amoxicillin + Clavulanic acid	Frequency 91 38 15 15 14	Percentage (%) 24.7% 10.3% 4.1% 4.1% 3.8%	INN Amoxicillin + Clavulanic acid Amoxicillin Ciprofloxacin Diltiazem Flucloxacillin	Frequency 9 5 4 3 3	Percentage (%) 15.8% 8.8% 7.0% 5.3% 5.3%
INNAllopurinolCarbamazepineAmoxicillinVancomycinAmoxicillin + Clavulanic acidPhenytoin	Frequency 91 38 15 15 14 14	Percentage (%) 24.7% 10.3% 4.1% 4.1% 3.8%	INN Amoxicillin + Clavulanic acid Amoxicillin Ciprofloxacin Diltiazem Flucloxacillin Azithromycin	Frequency 9 5 4 3 3 3	Percentage (%) 15.8% 8.8% 7.0% 5.3% 5.3%
INNAllopurinolCarbamazepineAmoxicillinVancomycinAmoxicillin + Clavulanic acidPhenytoinPiperacillin + Tazobactam	Frequency 91 38 15 15 14 14 10	Percentage (%) 24.7% 10.3% 4.1% 3.8% 3.8% 2.7%	INN Amoxicillin + Clavulanic acid Amoxicillin Ciprofloxacin Diltiazem Flucloxacillin Azithromycin Piperacillin + Tazobactam	Frequency 9 5 4 3 3 3 2	Percentage (%) 15.8% 8.8% 7.0% 5.3% 5.3% 3.5%
INNAllopurinolCarbamazepineAmoxicillinVancomycinAmoxicillin + Clavulanic acidPhenytoinSulfamethoxazole + Trimethoprim	Frequency 91 38 15 15 14 14 14 10 9	Percentage (%) 24.7% 10.3% 4.1% 3.8% 3.8% 2.7% 2.4%	INN Amoxicillin + Clavulanic acid Amoxicillin Ciprofloxacin Diltiazem Flucloxacillin Azithromycin Piperacillin + Tazobactam Aciclovir	Frequency 9 5 4 3 3 3 2 2	Percentage (%) 15.8% 8.8% 7.0% 5.3% 5.3% 3.5%
INNAllopurinolCarbamazepineAmoxicillinVancomycinAmoxicillin + Clavulanic acidPhenytoinPiperacillin + TazobactamSulfamethoxazole + TrimethoprimValproic Acid	Frequency 91 38 15 15 14 14 10 9 8	Percentage (%) 24.7% 10.3% 4.1% 3.8% 3.8% 2.7% 2.4% 2.4%	INN Amoxicillin + Clavulanic acid Amoxicillin Ciprofloxacin Diltiazem Flucloxacillin Flucloxacillin Azithromycin Piperacillin + Tazobactam Aciclovir Terbinafine	Frequency 9 5 4 3 3 3 2 2 2 2	Percentage (%) 15.8% 8.8% 7.0% 5.3% 5.3% 3.5% 3.5%

RESULTS

Our search retrieved a total of 494 ICSRs (51.6% females [n=255]; median age= 59,0 years; interquartile range=34,5), corresponding to 511 SCARs. The most reported SCAR was DRESS (n=258), followed by SJS (n=132), TEN (n=75), AGEP (n=43) and GBDFE (n=3). 16 ICSRs were related to SJS/TEN overlap and 1 to SJS/DRESS overlap. From the total of ICSRs 5.7% (n=28) had a fatal outcome. Allopurinol was the most reported medicinal product for SJS (n=36), TEN (n=19) and DRESS (n=91), while Amoxicillin + Clavulanic acid was the most reported for AGEP (n=9). Paracetamol, Etoricoxib, Naproxen and Diclofenac were reported for GBDFE one time each. SJS, TEN and DRESS were listed in the Summary of Products Characteristics of all the respective medicinal products unlike CRDEE.

Generalized bullous fixed drug eruptions (n=3)

INN	Frequency	Percentage (%)
Paracetamol	1	25.0%
Etoricoxib	1	25.0%
Naproxen	1	25.0%
Diclofenac	1	25.0%

Table 1: Most frequent medicinalproducts suspected to induce SCARsreported to the PortuguesePharmacovigilance National System.from 01.09.2012 to 31.12.2022. pertype.

CONCLUSION

The results of our work show that even if SCARs are a well-known risk of several medicinal products, continuous monitoring of these life-threatening conditions is crucial, in order to identify new potential safety issues, allowing more informed decisions by healthcare professionals and helping to prevent further harm to patients.

all the respective most reported medicinal products, unlike GBDFE.



fatal outcome

(n=28)

associated with

SCARs (n=148)

LITERATURE

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