Severe Cutaneous Adverse Reaction (SCAR): Clinical Pharmacologists' Viewpoint

"Skin is Like an Ocean's Surface Which Tells Deep Stories If You Watch Carefully"

Four years ago, one of us received a call from a senior internist in our tertiary medical care, teaching, and research center. The call was for reviewing a case of Drug Reaction, Eosinophilia and Systemic Sclerosis (DRESS). The patient was a middle-aged woman with multi-system involvement and had a history of self-medication with both conventional and complementary and alternative medicines for her rheumatoid arthritis. After bedside review which included assessment of causality, an academic session was planned to discuss the case by the treating unit. Reviewing for the session where inputs of a clinical pharmacologist were required, it was understood by us that there were quite a few unanswered aspects of the condition which warranted a multi-disciplinary approach. Such an addressal was required not only for DRESS but also the broader group of severe cutaneous adverse reactions (SCARs). The three entities, namely, DRESS, Stevens-Johnson Syndrome and/or toxic epidermal necrolysis (SJS/TEN) and acute generalized exanthematas pustulosis (AGEP) which have been included in SCAR have posed a challenge to the community of dermatologists and internists. The challenges revolved around dilemmas in diagnosis, serious and unpredictable nature of the condition, unclear pathogenesis and paucity of evidence for treatment options. Some of these issues were addressed in an editorial in 2011 issue of Indian Journal of Dermatology, Venereology and Leprology (*IJDVL)*.[1] As SCAR continues to be dealt by groups at various levels, we try to revisit it with a clinical pharmacologist's viewpoint this time.

Beyond conventional pharmacovigilance exercise

A typical pharmacovigilance approach would involve exploring pharmacovigilance databases or conducting observational studies for assessing the drugs involved, the nature of the reaction, and causality assessment. While such knowledge is of immense importance, one needs to have a deeper look for getting insight into the problem. Sasidharanpillai *et al*.[2] address the issue of diagnostic dilemma considering two commonly used criteria, that is, RegiSCAR (The European Registry of Severe Cutaneous Adverse Reactions to Drugs and Collection of Biological Samples) and Japanese consensus diagnostic criteria for Drug Induced Hypersensitivity Syndrome/DRESS. Importantly, the authors comment on statistical concordance, it is the discordance which captures the attention. Importantly, the two criteria have very different bases, While RegiSCAR criteria[3] tries to quantify the probability of causality assessment, the Japanese criteria[4] tries to group the cases of SCAR as atypical and typical. With this basic difference in consideration, it needs to be really given a thought whether the constructs for classification make a valid case for comparison. If we scale some published reports of DRESS alone from databases of pharmacovigilance, we are posed with further confusion wherein the classification system for causality assessment is more generic and uses World Health Organization- Uppsala Monitoring Centre(WHO-UMC) criteria. In the absence of publicly available databases, it is difficult for people working in the area to use appropriate data mining and modeling approaches to see whether there is any scope of arriving at a common causality assessment criterion. The thought needs deliberation in a bigger forum of dermatologists and clinical pharmacologists and immunologist/pathologists. The exercise may enable better categorization of the three components of SCAR.

Using pharmacogenetic tools to identify genetic predisposition to SCARs

SCAR is conventionally regarded as unpredictable. However, pharmacogenetic evaluations have been able to reduce the degree of unpredictability in some of the adverse drug reaction (ADR) regarded as unpredictable. For SCAR variations in human leukocyte antigens(HLA) genes have been most commonly evaluated. HLA-B*58:01 has been associated with allopurinol induced SCAR (SJS/TEN and DRESS).[5] Several allelic variants of HLA-A genes have been associated with carbamazepine induced SJS/TEN and DRESS with recommendation in place for HLA-A*15:02 evaluation before initiation of carbamazepine in populations where the variant is common.[5,6] The variant HLA-A*15:02 has also been associated with cotrimoxazole induced SJS/TEN and DRESS. Vancomycin induced SCAR have been associated with HLA-A*32:01.[6] A comprehensive review of the subject may not be captured in the current article. Suffice it to say that such evaluation in diverse ethnicities will be able to throw better light on inherent risk for SCAR. A better understanding of such predisposition could help in identifying persons who may have a higher predisposition to SCAR. A case in example is that of abacavir wherein genomic testing for HLA-B*57:01 variant can help in identifying patients in whom abacavir may present increased risk of hypersensitivity and such a test is commercially available too.[5,6]

Mechanistic studies for identifying targets for intervention

Various pathophysiology has been described to explain the findings of the three conditions listed in SCAR. Briefly,

participation of specific subpopulations of T cells like Cytotoxic T lymphocytes (CTLs), regulatory T cells (Treg), and T-helper type 1 (Th1), Th2, Th17, in delayed hypersensitivity ultimately leads to SCAR. The final phenotypic outcome includes numerous interactions between variety of cell lineages, their products, soluble mediators, environmental, and genetic factors.[7] Histopathological findings may include dendritic cell infiltration, spongiform superficial epidermal pustules, oedema of papillary dermis, and perivascular infiltrates of lymphocytes.[8,9] The present issue of the journal carries an article by Jindal *et al*.[10] which have noted similar histopathological findings. The primary aim of the study was to find out histopathological correlate of clinical severity, the authors conceded that owing to the small sample size they could not come to a definite conclusion. However, previous investigators have identified some histopathological features which may suggest worse outcomes.[8,9]

However, for deeper understanding more information such as metabolic profile of drugs, immunological markers may be needed. While anticonvulsants, specially, carbamazepine have been responsible for majority of cases of SJS/TEN, the groups of agents which have been implicated are structurally diverse[11] as has been highlighted by Manvi *et al*.[12] in the present issue. It is often the metabolites which are the implicated agents. It has been seen that skin expresses different isoforms of CYP enzymes and they handle these drugs differently than liver.[13] Although limited, but there are *in vitro* evidence of carbamazepine producing reactive metabolites by CYP isoforms in the skin which can bind to protein and mediate inflammatory response.[13] Digging further into the metabolomics of carbamazepine, it was found that the capacity of making a structural alteration of the protein binding pocket of HLA B *15:2 is different for the carbamazepine and it is epoxide metabolite (carbamazepine-10,11-epoxide) (EPX). Suggesting an important pathway of immunogenic adverse reactions including SCAR.[14,15] However, near absence of data regarding the role of metabolites in understanding the pathophysiology of the SCAR agents warrants incorporation of metabolomics approach for better insight in the disease process. In developing countries where the use of complementary and alternative medicines (CAM) is common it needs to be paid special attention. In personal communications for such cases, a thorough history often reveals intake of CAM. In many of the cases, these medicines contain arsenic or steroid/steroid-like substances which can lead to severe allergic reactions including SCAR.[16] CAM preparations often operate in grey market and have very little detail of components. Further even less is available in public domains.

Issues around therapeutic agents

Stopping the implicated agents is the mainstay of therapy. It may not be easy to narrow down to one agent particularly if the patient was on multiple therapeutic agents and/or complementary and alternative medicines. Though steroids remain the mainstay of treatment, propensity to subsequent infections remains a major concern particularly so if infections constitute major cause of death. Importantly, a low threshold for initiating antimicrobials is kept in view of susceptibility to infection. However, antimicrobials may themselves contribute to worsening.[17] Recent evidence from Japan proposes efficacy of Intravenous immune globulin (IVIG) treatment along with pulse methylprednisolone or high dose corticosteroids in reducing mortality form SJS and TEN.[18] Immunomodulators and targeted therapies like cyclophosphamide, calcineurin inhibitors, and anti- tumor necrosis factor (TNF) therapies have had inconclusive results.[19,20] Plasmapheresis, in recent years, has shown some benefit but the evidence is at best anecdotal.[17] An important concern with the use of immunosuppressive therapy is long-term sequelae such as immune reactive inflammatory syndrome and polyglandular autoimmune syndrome III.[20] Validation of prognostic markers such as HLA-B*57:01 for guiding therapy may prove to be useful.[6] Although the pathogenesis of SCAR is better understood, new therapeutic targets for drug development are rather conspicuous for their absence. Animal model described for SJS/TEN[21] is an interesting development remain understudied particularly for the development of new drugs.

In conclusion, at any given time, in any given center, the number of cases of SCAR are not likely to exceed 13.6% of the total ADR cases.[22] For deep learning, it is important to adopt a holistic approach and work in a Consortium mode. RegiSCAR was made with similar objectives. It was mainly based in Europe but had participants from Israel, Italy, and the Netherlands (http://www.regiscar.org/). They did propose evaluation of biomarkers for identifying prognostic relationship between SCAR and cytokines. Unfortunately, the last update of the website dates to October 2014. More recently, Council for the International Organizations of Medical Sciences (2020) working group have floated the concept paper regarding various issues of SCAR. This include diagnosis, causality assessment, predictive models, and prevention strategies for SCAR[23] The need of the hour is multicentric, multi-ethnic, and multi-regional registries which not only capture information on clinical and demographic profile but are also supplemented with biobanking facilities for enabling histopathological, genomic, proteomic, and metabolomic evaluation. Supplemented with data mining approaches for generating and evaluating signals, a better understanding will be visible in near future.

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References

1. Grover S. Severe cutaneous adverse reactions. Indian J Dermatol Venereol Leprol 2011;77:3-6.
2. Sasidharanpillai S, Ajithkumar K, Jishna P, Khader A, Anagha KV, Binitha MP, *et al*. RegiSCAR DRESS (drug reaction with eosinophilia and systemic symptoms) validation scoring system and Japanese consensus group criteria for atypical drug induced hypersensitivity syndrome (DiHS): A comparative analysis. Indian Dermatol Online J 2022;13
3. Kim DH, Koh YI. Comparison of diagnostic criteria and determination of prognostic factors for drug reaction with eosinophilia and systemic symptoms syndrome. Allergy Asthma Immunol Res 2014;3:216-21.
4. Jeremic I, Ostojic P. Possible DRESS syndrome in a patient with systemic sclerosis and rheumatoid arthritis during treatment with lamotrigine. Arch Med 2018;10:1-3.
5. Yang S-C, Chen C-B, Lin M-Y, Zhang Z-Y, Jia X-Y, Huang M, *et al*. Genetics of severe cutaneous adverse reactions. Front Med (Lausanne) 2021;8:652091.
6. Chang C-J, Chen C-B, Hung S-I, Ji C, Chung W-H. Pharmacogenetic testing for prevention of severe cutaneous adverse drug reactions. Front Pharmacol 2020;11:969.
7. Ortonne N, Valeyrie-Allanore L, Bastuji-Garin S, Wechsler J, de Feraudy S, Duong TA, *et al*. Histopathology of drug rash with eosinophilia and systemic symptoms syndrome: A morphological and phenotypical study. Br J Dermatol 2015;173:50-8.
8. Bellón T. Mechanisms of severe cutaneous adverse reactions: Recent advances. Drug Saf 2019;42:973-92.
9. Orime M. Immunohistopathological findings of severe cutaneous adverse drug reactions. J Immunol Res 2017;2017:6928363.
10. Jindal R, Chugh R, Chauhan P, Shirazi N, Bisht YS. Histopathological characterization of Drug rash with eosinophilia and systemic symptoms (DRESS) and comparison with maculopapular drug rash (MPDR). Indian Dermatol Online J XX;XX:XX.
11. Chi MH, Hui RC, Yang CH, Lin JY, Lin YT, Ho HC, *et al*. Histopathological analysis and clinical correlation of drug reaction with eosinophilia and systemic symptoms (DRESS). Br J Dermatol 2014;170:866-73.
12. Manvi S, Mahajan VK, Mehta KS, Chauhan PS, Vashist S, Singh R, *et al*. The clinical characteristics, putative drugs, and optimal management of 62 patients with Stevens-Johnson Syndrome and/or toxic epidermal necrolysis: A retrospective observational study. Indian Dermatol Online J XX;XX:XX.
13. Merk HF. Drug skin metabolites and allergic drug reactions. Curr Opin Allergy Clin Immunol 2009;9:311-5.
14. Wolkenstein P, Tan C, Lecoeur S, Wechsler J, Garcia-Martin N, Charue D, *et al*. Covalent binding of carbamazepine reactive metabolites to P450 isoforms present in the skin. Chem Biol Interact 1998;113:39-50.
15. Simper GS, Hò GT, Celik AA, Huyton T, Kuhn J, Kunze-Schumacher H, *et al*. Carbamazepine-mediated adverse drug reactions: CBZ-10,11-epoxide but not carbamazepine induces the alteration of peptides presented by HLA-B*15:02. J Immunol Res 2018;2018:5086503.
16. Witkowski JA, Parish LC. Dermatologic manifestations of complementary therapy. Skinmed 2003;2:175-80.
17. Cho YT, Chu CY. Treatments for severe cutaneous adverse reactions. J Immunol Res 2017;2017:1503709.
18. Hsieh MH, Watanabe T, Aihara M. Recent dermatological treatments for Stevens-Johnson syndrome and toxic epidermal necrolysis in Japan. Front Med (Lausanne) 2021;8:636924.
19. Chen CB, Wu MY, Ng CY, Lu CW, Wu J, Kao PH, *et al*. Severe cutaneous adverse reactions induced by targeted anticancer therapies and immunotherapies. Cancer Manag Res 2018;5:1259-73.
20. Shiohara T, Mizukawa Y. Drug-induced hypersensitivity syndrome (DiHS)/drug reaction with eosinophilia and systemic symptoms (DRESS): An update in 2019. Allergol Int 2019;68:301-8.
21. Saito N, Yoshioka N, Abe R, Qiao H, Fujita Y, Hoshina D, *et al*. Stevens-Johnson syndrome/toxic epidermal necrolysis mouse model generated by using PBMCs and the skin of patients. J Allergy Clin Immunol 2013;131:434-41.e1-9.
22. Jhaj R, Uppal R, Malhotra S, Bhargava VK. Cutaneous adverse reactions in in-patients in a tertiary care hospital. Indian J Dermatol Venereol Leprol 1999;65:14-5.
23. SCARS_CIOMS-16.9.2020. Available from: https://cioms.ch/wp-content/uploads/2021/02/SCARs_CIOMS-16.09.2020 Last accessed on 13/01/2022.

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