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Editorial

Severe Cutaneous Adverse Reactions Caused by Anti-Tubercular Drugs

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▸ See the article "Severe Cutaneous Adverse Reactions to Anti-tuberculosis Drugs in Korean Patients" in volume 13 on page 245.

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Tuberculosis (TB) is still a major health problem worldwide. It is estimated that about a quarter of the world's population is infected with *Mycobacterium tuberculosis.* There are about 7 million new incident cases and about 1.6 million TB-related death annually.[1] For successful treatment and control of TB, treatment adherence is very important. However, in the treatment of TB and latent TB infection, adverse reactions to antitubercular drugs (ATD) frequently occur, interfering with the scheduled drug treatment and treatment success.[2,3] Certain types of adverse reactions to ATD may threaten life requiring discontinuation of medication and hospitalization for the management of illness. These severe adverse drug reactions to ATD include liver injury and immediate or delayed hypersensitivity reactions.[4]

Severe cutaneous adverse reactions (SCAR) refer to several serious conditions involving the skin.[5] They include Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), acute generalized exanthematous pustulosis (AGEP), and drug reaction with eosinophilia and systemic symptoms (DRESS), also known as drug-induced hypersensitivity syndrome (DIHS). While ATD has not been considered a common causative drug of SCAR,[6,7] an increasing number of reports have shown that ATD could induce DRESS (or DIHS),[8-11] SJS/TEN,[12,13] and AGEP.[14] In this issue of the *Allergy, Asthma & Immunology Research*, Jin *et al.*[15] reported demographic and clinical characteristics of 56 cases of ATD-related SCAR (42 cases of DRESS and 12 cases of SJS/TEN) selected from the Korean registry of SCAR. In the analysis of the causative drugs of SCAR cases enrolled in the Korean registry, isoniazid and rifampin were listed in the top 15 causative drugs.[16] It is noteworthy that ATD-related SCAR more frequently present as DRESS rather than as SJS/TEN or AGEP compared with other causative drugs of SCAR. Compared with SJS/TEM, the clinical presentation of DRESS is more diverse and complex. Thus, the diagnosis of DRESS depends on collective features of clinical manifestations of adverse reactions and laboratory tests without the use of the confirmation tests.[17] Major features of adverse reactions included in the diagnostic criteria for DRESS are fever, skin rash, eosinophilia, involvement of internal organs, such as liver injury. However, each of these adverse reactions to ATD frequently occurs solely or with other adverse reactions in the treatment with ATD. In addition, since 3 or more drugs are prescribed and taken at the same time for the treatment of TB, different adverse reactions to multiple drugs can occur simultaneously or overlap. In this case, the diagnosis of DRESS can be made mistakenly. Therefore, it is recommended that the diagnostic criteria for DRESS should be applied more strictly and objective tests for drug allergy should be used in the diagnosis of ATD-related DRESS.

Regarding the characteristics of ATD-related SCAR, the study by Go *et al.*[18] showed that subjects with ATD-induced SCAR are older compared with those with other drugs-related SCAR. They also stated that since there are no data regarding risk factors of developing SCAR in patients taking ATD, it is not certain whether old age is a risk factor for ATD-induced SCAR. It is more likely that TB patients on treatment are relatively old, given that nearly half of the incident cases occurred in elderly population in Korea. For the same reason, worse clinical outcomes of ATD-related SCAR could be related to old age of TB patients. Furthermore, most mortality occurred in cases of SJS and TEN. ATD-induced DRESS was not different in severity from DRESS caused by other drugs.[19]

Isoniazid, rifampin, ethambutol, and pyrazinamide are recommended as the first-line ATD by the WHO and national guidelines. These drugs have frequently been implicated as the causative drugs of ATD-induced SCAR in the previous reports and a study by Jin *et al.*,[15] while the frequency of the culprit drugs differed among studies. The inconsistency of the results on causative drugs reflects the absence of valid and effective tests for causality in ATD-induced SCAR. Even though patch test[11,20] and lymphocyte transformation test[21] have been used to confirm the causative drugs of ATD-induced SCAR, they have not been validated and commercially available. Although rechallenge is usually discouraged in the management of SCAR due to the possible serious risks, previously prescribed ATD has been readministered in cases of ATD-related DRESS.[10,11] Since the treatment of TB requires long-term medication and the second-line drugs are less effective than the first-line ATD, rechallenge with ATD can be considered in finding the culprit drug and in administering the other ATDs to patients with adverse reactions including hepatotoxicity.[22] In the study of Jin *et al.*,[15] 14 cases of ATD-induced SCAR had rechallenge of ATD. They argued that rifampin was the most common causative drug and that 42.9% of the cases of ATD-induced SCAR (6 of 14) were induced by 2 or more drugs. However, their argument can be misleading, since a positive response to the rechallenge test does not necessarily mean that the response to each rechallenge meets diagnostic criteria for DRESS. Instead, it is more likely that clinical manifestations of the suspected cases of ATD-induced DRESS might be a summation of various adverse reactions to multiple drugs. Considering that several drugs are administered simultaneously in the treatment of TB, the diagnosis of DRESS and the identification of causative drugs should be made more carefully.

Several genetic variants have been found to be related to ATD-induced liver injury and maculopapular eruption.[23-25] Also, the association between human leukocyte antigen and ATD-induced DRESS has been reported in the Korean population.[9] This association and discovery of other genetic variations need to be validated in different populations and ethnic groups. To find strong genetic markers to predict SCAR in patients receiving ATD, pharmacogenetic studies would be required using confirmed cases of ATD-induced DRESS, SJS, or TEN, of which one single causative drug is detected by using immunological tests and rechallenge. In the treatment of TB, the prevention, diagnosis, and management of SCAR to ATD is crucial. A novel strategy is urgently needed to manage patients with suspected SCAR caused by ATD in the treatment of TB.

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REFERENCES

1. World Health Organization. Global tuberculosis report 2020. Geneva: World Health Organization; 2020.
2. Kim SH, Lee BH, Lee KD, Park JS, Kim YS, Jee YK, et al. The prevalence of adverse drug reactions to a short course anti-tuberculosis regimen. Korean J Med 2007;73:496-502.
3. Chung SJ, Lee H, Koo GW, Min JH, Yeo Y, Park DW, et al. Adherence to nine-month isoniazid for latent tuberculosis infection in healthcare workers: a prospective study in a tertiary hospital. Sci Rep 2020;10:6462.
PUBMED | CROSSREF
4. Kwon H, Lee SH, Kim SE, Lee JH, Jee YK, Kang HR, et al. Spontaneously reported hepatic adverse drug events in Korea: multicenter study. J Korean Med Sci 2012;27:268-73.
PUBMED | CROSSREF
5. Bellón T. Mechanisms of severe cutaneous adverse reactions: recent advances. Drug Saf 2019;42:973-92.
PUBMED | CROSSREF
6. Mockenhaupt M. The current understanding of Stevens-Johnson syndrome and toxic epidermal necrolysis. Expert Rev Clin Immunol 2011;7:803-13.
PUBMED | CROSSREF
7. Jeung YJ, Lee JY, Oh MJ, Choi DC, Lee BJ. Comparison of the causes and clinical features of drug rash with eosinophilia and systemic symptoms and stevens-johnson syndrome. Allergy Asthma Immunol Res 2010;2:123-6.
PUBMED | CROSSREF
8. Ditto AM, Story RE. Drug rash with eosinophilia and systemic symptoms (DRESS) secondary to anti-tuberculosis therapy with features of isoniazid toxicity. J Allergy Clin Immunol 2004;113:S309.
CROSSREF
9. Kim SH, Lee SK, Kim SH, Park HW, Chang YS, Lee KW, et al. Antituberculosis drug-induced hypersensitivity syndrome and its association with human leukocyte antigen. Tuberculosis (Edinb) 2013;93:270-4.
PUBMED | CROSSREF
10. Allouchery M, Logerot S, Cottin J, Pralong P, Villier C, Ben Saïd B, et al. Antituberculosis drug-associated DRESS: a case series. J Allergy Clin Immunol Pract 2018;6:1373-80.
PUBMED | CROSSREF
11. Jung HY, Park S, Shin B, Lee JH, Lee SJ, Lee MK, et al. Prevalence and Clinical features of drug reactions with eosinophilia and systemic symptoms syndrome caused by antituberculosis drugs: a retrospective cohort study. Allergy Asthma Immunol Res 2019;11:90-103.
PUBMED | CROSSREF
12. Jung SO, Cho MJ, Park DI, Kim SY, Kim JO, Jung SS, et al. Stevens-Johnson Syndrome and hypothermia associated with anti-tuberculosis medication in a patient with heart failure. Chin Med J (Engl) 2015;128:2837-8.
PUBMED | CROSSREF
13. Bomb BS, Purohit SD, Bedi HK. Stevens-Johnson syndrome caused by isoniazid. Tubercle 1976;57:229-30.
PUBMED | CROSSREF
14. Szatkowski J, Schwartz RA. Acute generalized exanthematous pustulosis (AGEP): A review and update. J Am Acad Dermatol 2015;73:843-8.
PUBMED | CROSSREF
15. Jin HJ, Kang DY, Nam YH, Ye YM, Koh YI, Hur GY, et al. Severe cutaneous adverse reactions to anti-tuberculosis drugs in Korean patients. Allergy Asthma Immunol Res 2021;13:245-55.
CROSSREF
16. Kang DY, Yun J, Lee SY, Koh YI, Sim DW, Kim S, et al. A nationwide study of severe cutaneous adverse reactions based on the multicenter registry in Korea. J Allergy Clin Immunol Pract. Forthcoming 2020.
PUBMED | CROSSREF
17. Kardaun SH, Sidoroff A, Valeyrie-Allanore L, Halevy S, Davidovici BB, Mockenhaupt M, et al. Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist? Br J Dermatol 2007;156:609-11.
PUBMED | CROSSREF
18. Go U, Park M, Kim UN, Lee S, Han S, Lee J, et al. Tuberculosis prevention and care in Korea: evolution of policy and practice. J Clin Tuberc Other Mycobact Dis 2018;11:28-36.
PUBMED | CROSSREF

19. Sim DW, Yu JE, Jeong J, Jung JW, Kang HR, Kang DY, et al. Variation of clinical manifestations according to culprit drugs in DRESS syndrome. Pharmacoepidemiol Drug Saf 2019;28:840-8.
PUBMED | CROSSREF

20. Lee SW, Yoon NB, Park SM, Lee SM, Um SJ, Lee SK, et al. Antituberculosis drug-induced drug rash with eosinophilia and systemic symptoms syndrome confirmed by patch testing. J Investig Allergol Clin Immunol 2010;20:631-2.
PUBMED

21. Ye YM, Hur GY, Kim SH, Ban GY, Jee YK, Naisbitt DJ, et al. Drug-specific CD4$^+$ T-cell immune responses are responsible for antituberculosis drug-induced maculopapular exanthema and drug reaction with eosinophilia and systemic symptoms syndrome. Br J Dermatol 2017;176:378-86.
PUBMED | CROSSREF

22. Saukkonen JJ, Cohn DL, Jasmer RM, Schenker S, Jereb JA, Nolan CM, et al. An official ATS statement: hepatotoxicity of antituberculosis therapy. Am J Respir Crit Care Med 2006;174:935-52.
PUBMED | CROSSREF

23. Kim SH, Kim SH, Bahn JW, Kim YK, Chang YS, Shin ES, et al. Genetic polymorphisms of drug-metabolizing enzymes and anti-TB drug-induced hepatitis. Pharmacogenomics 2009;10:1767-79.
PUBMED | CROSSREF

24. Kim SH, Kim SH, Lee JH, Lee BH, Yoon HJ, Shin DH, et al. Superoxide dismutase gene (SOD1, SOD2, and SOD3) polymorphisms and antituberculosis drug-induced hepatitis. Allergy Asthma Immunol Res 2015;7:88-91.
PUBMED | CROSSREF

25. Kim SH, Kim SH, Yoon HJ, Shin DH, Park SS, Kim YS, et al. NAT2, CYP2C9, CYP2C19, and CYP2E1 genetic polymorphisms in anti-TB drug-induced maculopapular eruption. Eur J Clin Pharmacol 2011;67:121-7.
PUBMED | CROSSREF