EDITORIAL

Expanding Field of Dermatological Side Effects of Pharmaceuticals

During the last decades there has been an enormous development of new drugs and therapies. The skin is the organ most frequently affected by drug reactions; it is described in about 40% of drug reactions and may affect up to 10% of hospitalized patients. Today there are 35 different cutaneous drug-reaction patterns described (1).

Different pharmaceuticals may cause identical skin symptoms depending on the pathomechanisms of the reaction. Immediate drug reactions, such as urticaria angioedema or anaphylaxis, can develop within 1 h of the drug intake, while delayed types of reactions have more diverse manifestations. Adverse drug reactions are divided into type A and type B. Type A are predictable, for instance renal toxicity. Type B, drug hypersensitivities (DHR) are unpredictable and are caused by non-immunological or immunological mechanisms (IgE or T-cells mediated) (2).

Teriflunomide is a disease-modifying immunomodulatory drug with anti-inflammatory properties that selectively and reversibly inhibits the mitochondrial enzyme dihydro-orotate dehydrogenase. It inhibits *de novo* pyrimidine synthesis and reduces lymphocyte proliferation, thus curtailing the expansion of activated T and B cells. Teriflunomide is used in relapsing multiple sclerosis (MS). The drug is considered to be well tolerated based on randomized controlled trials and use for long-term treatments (3).

Teriflunomide is the active metabolite of leflunomide, so similar cutaneous side effects could thus be expected. Leflunomide is used as an antirheumatic, disease-modifying drug and subacute cutaneous lupus erythematosus (SCLE) has been reported to be one of the cutaneous side effects following this treatment (4). One case of SCLE has also been described where a patient was treated with teriflunomide for MS. The patient continued the treatment with teriflunomide but was also treated for SCLE with hydroxychloroquine and tofacitinib. Notable is that the patient exhibited positive serum biomarkers for ANA, Ro/SSA, La/SSB, and Ro-52 antibodies (5). Finally, development of pustulosis palmoplantaris has also been described for both leflunomide and teriflunomide (6).

In this issue, Gökçe et al. describe an unusual cutaneous side effect from teriflunomide presented as pruritic scaly, hyperkeratotic, violaceous papules and plaques on the palms and soles. The man had no history of previous dermatological disease. Standard laboratory testing was normal and the results of serological testing for syphilis, autoimmune antibodies, and the hepatitis B and C viruses were negative. Tinea could also be ruled out. Histopathological examination showed hypergranulosis, irregular acanthosis with a saw-tooth-like appearance, apoptotic basal keratinocytes, and a band-like mononuclear cell infiltration with eosinophils. The findings were concordant with the diagnosis of teriflunomide-induced lichenoid drug eruption. This is the second case report with this cutaneous side effect (7).

Even if neurologists are aware of the possibility of various dermatological side effects from teriflunomide, it is proposed that patients with presentations of skin reactions during treatment with teriflunomide are seen by a dermatologist.

In a future perspective, testing for genetic factors might become a standard tool for clinical decisions in pharmacological treatment.

It was recently shown that differences in skin reactions to leflunomide may be related to variations in in CYP2C9* 3 (8).

REFERENCES

1. Del Pozzo-Magaña BR, Liy-Wong C. Drugs and the skin: a concise review of cutaneous adverse drug reactions. Br J Clin Pharmacol 2024; 90: 1838–1855. https://doi.org/10.1111/bcp.15490
2. Zalewska-Janowska A, Spiewak R, Kowalski ML. Cutaneous manifestation of drug allergy and hypersensitivity. Immunol Allergy Clin North Am 2017; 37: 165–181. https://doi.org/10.1016/j.iac.2016.08.006
3. Scott LJ. Teriflunomide: a review in relapsing-remitting multiple sclerosis. Drugs 2019; 79: 875–886. https://doi.org/10.1007/s40265-019-01135-8
4. Goëb V, Berthelot JM, Joly P, Mejjad O, de Quatrebarbes J, Reynaud-Hautin C, et al. Leflunomide-induced subacute cutaneous lupus erythematosus. Rheumatology (Oxford) 2005; 44: 823–824. https://doi.org/10.1093/rheumatology/keh586
5. Xu K, Zhang M, Yang S, Yu G, Zheng P, Qin X, et al. Subacute cutaneous lupus erythematosus as a rare complication of disease-modifying therapy administration in multiple sclerosis: case report. BMC Neurol 2023; 23: 168. https://doi.org/10.1186/s12883-023-03146-1
6. Negrotto L, Correale J. Palmar pustular psoriasis associated with teriflunomide treatment. Mult Scler Relat Disord 2019; 27: 400–402. https://doi.org/10.1016/j.msard.2018.11.020
7. Agharbi FZ, Aasfara J, Oqbani K, Slamti K, Chiheb S. Lichenoid drug eruption induced by teriflunomide. Ann Indian Acad Neurol 2023; 26: 275–277. https://doi.org/10.4103/aian.aian_27_23
8. Devarbhavi H, Ghabril M, Barnhart H, Patil M, Raj S, Gu J, et al. Leflunomide-induced liver injury: differences in characteristics and outcomes in Indian and US registries. Liver Int 2022; 42: 1323–1329. https://doi.org/10.1111/liv.15189

Maria Palmetun Ekbäck
Section Editor of
Acta Dermato-Venereologica

Magnus Lindberg
Co-Editor of
Acta Dermato-Venereologica

Acta Derm Venereol 2024; 104: adv42086.
https://doi.org/110.2340/actadv.v104.42086