Teriflunomide-induced Raynaud's phenomenon: A serious adverse event, previously unreported

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To the Editor,

Teriflunomide, sold under the brand name Aubagio®, is an immunomodulatory drug inhibiting pyrimidine de novo synthesis by blocking the enzyme dihydroorotate dehydrogenase. It has been approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of patients with remitting relapsing multiple sclerosis (rrMS) (1). This drug exhibits a favourable safety profile and is well tolerated by most patients (2). Most common adverse events include hair thinning, mild lymphocytopenia and headache (2). We report the first case of teriflunomide-associated Raynaud`s phenomenon.

A woman in her late thirties with a medical history of Hurtle Cell Thyroid carcinoma treated with a partial thyroidectomy came to the MS clinic because of subacute sensory disturbances located at her lower limbs. She denied previous focal deficits. Neurologic examination revealed a marked hypoesthesia for light touch and vibration from her feet up to her iliac crests. A spinal MRI showed a gadolinium-enhanced inflammatory lesion at thoracic level. A cranial MRI evidenced multiple T2-enhanced lesions involving both periventricular and juxtacortical territories. An extended blood profile ruled out other inflammatory diseases. With a working diagnosis of rrMS, the patient was treated with intravenous methylprednisolone (1000mg per day for 5 days), followed by disease modifying treatment with daily teriflunomide (14mg).

Two weeks after teriflunomide initiation, the patient stopped it as she began with progressive circulatory disturbances affecting both hands and feet, with colour changes and finger swallowing consistent with Raynaud´s phenomenon (RP). At this point, any known triggers of RP, including physiological ones, were ruled out. Specifically, she

denied other symptoms suggestive of connective tissue disease except for nonspecific asthenia and mild alopecia prior to the diagnosis of thyroid disease. Her blood tests showed no cytopenias and both the acute phase reactants and urine tests were normal. Antinuclear antibodies and complement levels were also normal. Nail fold capillaroscopy showed some mild non-specific changes.

Treatment with physical measures and calcium channel blockers was started. After experiencing a mild improvement of the cutaneous symptoms, and since a clear causality relationship had not been proved, teriflunomide was reintroduced. Ten days after drug reintroduction cutaneous manifestations markedly worsened, including the appearance of painful digital sores (Figure 1A-B), leading to teriflunomide cessation and to accelerated drug elimination with cholestyramine. Ten days later, teriflunomide blood level was 0.06mg/L, and RP had completely disappeared (Figure 1C).

RP is an exaggerated vascular response to cold temperature or emotional stress. It induces colour changes of the skin of the digits. It can be either primary or idiopathic (affecting usually females from 15 to 30 years) but secondary cases must be always ruled out. These, include rheumatologic conditions (scleroderma, systemic lupus erythematosus), occupational and environmental factors and certain medications including chemotherapeutic agents, interferon, estrogen, sympathomimetic agents, ergotamines, nicotine, and narcotics (3;4). In the literature, a few isolated cases of RP have been published associated to the use leflunomide (4), an immunosuppressor agent used for the treatment of patients with rheumatoid arthritis which has a mechanism of action similar to teriflunomide. In the present case, causality between teriflunomide exposure and RP is highly supported by both the initial temporal

sequence and the marked worsening after drug reintroduction, as well as the absence of other secondary causes.

To the best of our knowledge, this is the first case reporting RP associated to teriflunomide treatment. Although a direct causal relationship cannot be fully confirmed, it is supported by both the initial temporal sequence and the marked worsening after drug reintroduction. Therefore, clinicians should consider this very rare, and previously unreported adverse event, when seeing patients with multiple sclerosis, particularly those at high risk of peripheral vascular complications.

FIGURE LEGEND

A-B. After teriflunomide reintroduction the patient experimented a marked Raynaud's phenomenon (RP) consisting in: i) digital colour changes, ii) finger swallowing and iii)painful digital sores. **C**. Accelerated drug elimination with cholestyramine resulted in a rapid resolution of RP

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