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Unveiling risks: Navigating adverse drug reactions in leflunomide therapy

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ABSTRACT
We report a case of a 55-year-old female patient who developed oral ulcer, headache, and hepatomegaly after she started therapy with leflunomide. It was about nine years back that she was diagnosed with Rheumatoid Arthritis. Her earlier history states that she was on tablet Leflunomide 10mg 4years back and she had stopped it.Later decided to continue leflunomide as the part of treatment protocol. After the starting of treatment, she was presented with mouth ulcers in one month of time. She had hepatomegaly, grade 2 fatty liver, cystitis, umblical hernia on USG. She showed features suggestive of acute left pyelonephritis on CT abdomen. She was treated with IV fluid's antibiotics with supportive measures. She stopped leflunomide after discharge and showed significant improvement in mouth ulcer, Withdrawal of leflunomide for a month resulted in 50% healing, these ulcers are induced by folate deficiency due to the leflunomide.In conclusion, though leflunomide is still a cornerstone of the treatment for RA and other autoimmune disorder, its usage is associated with a range of adverse effects that require vigilant monitoring and proactive management.

Keywords: Leflunomide, Rheumatoid Arthritis, Mouth Ulcers, Hepatomegaly

I .INTRODUCTION:

Rheumatoid arthritis is an autoimmune inflammatory disease that affects the joints, causing pain and swelling, stiffness and finally joint destruction. Rheumatoid arthritis is a chronic disease that occurs in 0.8 % of the people. Nonsteroidal anti-inflammatory drugs reduce the pain and inflammation of RA and improve mobility but do not how the progression of joint damage. Disease modifying antirheumatic drugs which limit potentially irreversible joint damage, may influence the course of disease progression.[1]

Leflunomide is classified as a drug under the category DMARDs, and is FDA approved as an active mode of treatment in rheumatoid and psoriatic arthritis. These diseases occur and are prevalent among Indian populations, and the control over the symptoms is achieved through using leflunomide, which only slows the rate at which these autoimmune diseases progress. Psoriatic arthritis (PsA) is an inflammatory arthritis that occurs in some patients with psoriasis - a chronic autoimmune skin condition responsible for painful, bright red and scaly patches. Apart from that, there are off-label approvals for Indian patients with other autoimmune conditions, such as SLE and ankylosing spondylitis, under the guidance of a doctor. Oral ulcers are a recognized association with rheumatoid arthritis and are considered multi-factorial in origin, related to rheumatoid vasculitis and due to an increased susceptibility to trauma caused by changes.[2]

Leflunomide is an immunomodulatory agent that inhibits dihydroorotate dehydrogenase; suppression of de novo pyrimidine synthesis through this mechanism may account for the ability to inhibit T-cell proliferation. The drug has been shown to be effective in decreasing disease activity and improving clinical outcomes in patients with RA. Teriflunomide is the biotransformation from leflunomide to its active metabolite, which means there are two isoforms of the drug achieved from within the living organism. Adverse events for patients with RA who were administered leflunomide consisted of diarrhoea, elevated liver enzymes, alopecia, and rash, Other adverse events occurring in frequency >5% consisted of allergic reaction, asthenia, abdominal pain, back pain, and hypertension, among others, thus leflunomide can be administered in selected patients. However, product labelling is such that concomitant monitoring of liver enzymes should occur on a monthly basis until steady state is achieved. Other labeled warnings include risk of immunosuppression and increased risk of fetal death or teratogenic effects in pregnant women. But as with all drugs, the side effects of

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leflunomide cannot be overlooked; these include gastrointestinal disturbances, hepatotoxicity, and dermatologic reactions. Headache is one of the less frequently documented adverse effects in leflunomide therapy and there are very few literature reports on this topic.[2,3]

Initiation of leflunomide as monotherapy is now recommended in patients with rheumatoid arthritis of all durations of disease and levels of disease activity, regardless of poor prognostic features. Leflunomide when given as monotherapy or in combination with other disease modifying anti-rheumatic drug agents significantly increases incidence of hepatotoxicity. The risk factors of drug-induced liver injury or leflunomide-induce liver injury includes age, gender, pregnancy, alcohol intake, concomitant hepatotoxic agent, obesity, and current smoker.[1] Pre-existing liver disease, pre-existing or concurrent illness or comorbidity, heart failure infection/sepsis, pulmonary failure, pancreatitis, and other possibly hepatotoxic co-medication possibly leading to poorer outcome are among the complications in leflunomide-induced liver injury. Apart from that, Disease-modifying anti rheumatic drugs account for 5% of all hospital admissions and 50% of acute liver failures. drug-induced liver injury can mimic various forms of liver diseases and its principal presentation remains systemic symptoms, jaundice, elevated ALT and ALP.[4]

Oral ulcers" are recorded in 3-5% of leflunomide-medicated rheumatoid arthritis patients showing adverse events, but may also be a manifestation of various oral diseases, including oral candidiasis and herpetic infection which could be present in those patients. Leflunomide was approved for the use in the treatment of rheumatoid arthritis in 1998. Post-marketing surveillance, case reports and observational studies have brought to notice less common or unexpected adverse events.Therefore, it is quite appropriate that we examine the benefit-risk profile of leflunomide after widespread use for 10 years. In this connection, an extensive-based literature search has been undertaken to compose this review.[2]

II. CASE REPORT

A 55-year-old female who had been complaining of burning micturition associated with lower abdomen pain, increased frequency of micturition associated with reduced flow (eight episodes /day), incomplete emptying, and chills on and off for 15 days.

History of Present Illness:

The patient was treated in nearby hospital given by antibiotics and stopped Tab Leflunomide before admitted here. She suffered from rheumatoid arthritis, diagnosed nearly nine years back. She had a spine surgery done nearly 20 years back.

Past History:

According to her past medication history, she has been under the treatment of Rosuvastatin (Rosuvas)20mg, Glimepiride (Azulix)1mg, Pantoprazole(pan) 40mg, and Metformin hydrochloride sustained release tablets (Glyciphage SR)1gm since the past one year. From her past history it was elicited that she was on tablet Leflunomide 10mg 4months back and stopped it due to the development Urinary tract infection. The patient came to the hospital; her vitals were normal.

Systemic examination:

Her abdomen presented left loin tenderness. Loin pain in general occurs in UTI due to extension of infection from bladder to kidneys or can occur as an initial infection to the kidneys itself.

Investigation:

Her USG revealed hepatomegaly with grade 2 fatty liver, anterior myometrial fibroid, cystitis, umblical hernia -omentum as content bladder wall thickened -9mm, low level internal echoes within bladder. She had pain in the abdomen and a CT abdomen was done. CT abdomen feature showing suggestive acute left pyelonephritis -no hydronephrosis. Report echocardiography showing RHD with mild MR, trivial AR, adequate LV systolic functional diastolic dysfunction, mild PAH with trivial TR.

Treatment:

The patient was treated with IV fluids, antibiotics, antipyretics, antiemetics, antihistamines, antimetabolites, vitamin supplements, and other supportive measures. Tablet. Rosuvastatin for dyslipidemia was continued. On day three Clinical examination revealed an irregularly shaped ulcer covered by fibrin purulent membrane and partly surrounded by a firmly attached white plaque on the ventral surface of the right side of the upper lips. Analgesics were given for a history of oral ulcer - a topical ointment ZYTEE is applied locally to the ulcer. She also had headache. The patient described

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these headaches as bilateral, throbbing in nature and associated with photophobia and phonophobia. These headaches had significantly affected her daily activity and quality of life Examination did not reveal any focal neurological defects or increased intracranial pressure. A diagnosis of leflunomide-induced headache was suspected on account of the temporal relationship between the beginning of the initiation of therapy with leflunomide and the beginning of headache. Inj Para was administered. Tablet methotrexate 10mg was prescribed alone but Tablet. Methotrexate should be given along with Tablet folic acid as supplementation. After 5 days her creatinine level was reduced (0.4mg/dl) and blood Urea(11mg/dl) was also decreased. Red blood cells(3.9/ul) were relatively lowered and monocytes(14.5%) were significantly elevated.

TABLE 1 Shows the Investigations of the patient.

INVESTIGATIONS	**RESULTS**
HAEMOGLOBIN	10.00 g/dl
WBC	$12.55*10^3$/UL
RBC	$4.03*10^6$/UL
EPITHELIAL CELLS	6-8
LYMPHOCYTES	9.2%
EOSINOPHILS	0.5%
POLYMORPHS	80.8%
HBA1C	7.0%
RBS	340mg/dl
COLOUR OF THE URINE	Yellow
ELEMENTS FOUND IN URINE	Present
GLUCOSE	+++
PROTEINS	Trace
BACTERIA	Present
SPECIFIC GRAVITY	1.031

III. RESULTS:

Her symptoms improved and her condition was good and afebrile. So, she was planned for discharge. After one week of her discharge she stopped the Tablet. Leflunomide that healed 50% of complaints.

IV .DISCUSSIONS:

Statistics show that oral ulcers are less common but, nonetheless, occur in 1-5% of the patients treated with leflunomide. Hepatomegaly manifested as an enlarged liver occurs in up to 10% of the patients, and the liver function tests should be monitored closely during the treatment period. Her headaches began two weeks after she initiated her treatment regimen of leflunomide for her RA. Headaches is one common adverse effect occurring in the range of 10-15% in patients treated with leflunomide. Apart from above adverse effects, leflunomide can also causes gastrointestinal symptoms like diarrhea in around 15-20% of patients. Skin manifestations in the form of rash and hair loss occur in about 5-10% cases. In our case the discontinuation of drug for a period of a month showed less than 50% healing,these ulcers are caused by the drug causes folate deficiency.[7]

They are caused by the long-existing effect of drug and non-drug-induced folate deficiency on DNA synthesis and cellular maturation mechanisms because methotrexate mainly inhibits the enzyme dihydrofolate reductase and other enzymes in the folate pathway, leading to a disruption of purine and pyrimidine synthesis and also a halt in cell cycle. Intact pathways for purine and pyrimidine synthesis are essential to successful immune responses: the elucidation of genetic diseases that are accompanied by profound deficiencies of T- and B-lymphocytes Teriflunomide was approved in 2012 and appears to be associated with a lower frequency of liver injury than leflunomide. In one case report the recovery was complete and occurred very early after the diagnosis of teriflunomide-induced DILI, whereas in the case of a single patient from the Indian series, death from myocarditis occurred long after recovery from liver and skin injury. Leflunomide-induced liver injury tends to be predominantly hepatocellular and is more frequently an injury pattern in women. In India, it is predominantly in females, is often complicated by severe skin injury and is highly fatal. The differences in presentation and outcomes between

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subjects from India and those from the US are striking, raising a possible role for previously unidentified genetic or environmental factors in the pathogenesis of leflunomide-induced liver injury.[8,12]

We studied the causality of reported ADRs by two different scales of causality assessment: viz. World Health Organization′s ADR probability scaleand Naranjo′s scale. Considering all the relevant data into the account, four reactions were considered probable and one possible for leflunomide by both the scales. The pathogenesis of DHS is not known. These patients exhibit partially inherited increased susceptibility to the toxic effects of oxidative drug metabolites.

V. CONCLUSION:

From the series of reported cases with associated headaches, oral ulcers, and hepatomegaly due to adverse effects from leflunomide, it is established that these presentations can occur with varying frequencies between individuals. Although administered widely in treatment for rheumatoid arthritis and other autoimmune diseases, it must be appreciated that adverse effects of the drug are not intrinsic to the specific nature of the drug but rather across the class of leflunomide and related drugs. The authors of the literature report a higher incidence of adverse effects with leflunomide, including headache, oral ulcer, and hepatomegaly in the present study. But, that such adverse effects thus recognized are not unique to one drug in the class, but rather, attributed as a potential class effect of leflunomide and some other DMARDs. Interestingly, in certain cases, once the patient was switched on to another DMARD within the same class, the adverse effects persisted, making a case that the incidence of such manifestations might not be drug-specific but more relevant to mechanism of action or the general physiological activity it imposes on the body. Such patients may present with headache, oral ulceration, and hepatomegaly, which might not be taken seriously or may be attributed to some other cause. Thus, increased alertness among health workers in the diagnosis and management of such patients is needed, especially among the long-term therapy with leflunomide.

Lastly, something that should be noted is the management of adverse effects of the drug, among which headache, oral ulcer, and hepatomegaly are reported, in order for leflunomide to be an effective treatment for autoimmune conditions. Healthcare providers who care for patients on therapy with leflunomide should continue to monitor for adverse effects and consider alternatives or changes in medication regimen if adverse effects occur. It is a relatively safe drug with proven efficacy in the management of RA. Its clinical use has been rather limited by the historic parallel development of other agents, including methotrexate, which has become the synthetic DMARD of choice and biological DMARDs that have superior efficacy.

Declaration of Patient Consent:

The Authors certify that they have obtained all appropriate patient consent forms. In the form the patient Consent for her images and other clinical information to be reported in the journal. The patient understand that her name and intials will not be published and due efforts will be made to conceal her identify, but anonymity cannot be guaranteed.

Conflicts of Interest:

There are no Conflicts of Interests.

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