CORRESPONDENCE

Leflunomide: Is It the Game Changer in Musculoskeletal Chronic Graft Versus Host Disease?

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Musculoskeletal involvement in chronic graft versus host disease (cGVHD) can be extremely crippling. Manifestations of musculoskeletal cGVHD are varied and can include fasciitis, myositis, weakness, cramping, joint stiffness and contractures. Pathogenetically, in musculoskeletal GVHD there is accumulation of alloimmune donor T-cells in the muscles, joints, and soft tissues. Release of cytokines by these activated T-cells results in fibroblast proliferation and activation. Cross talk between these alloimmune T-cells with macrophage will further augment the fibrosis. Alloimmune donor T cells also activate B-cells resulting in the production of auto antibodies directed against joints and muscular tissues [1]. Thus, pathophysiology of musculoskeletal GVHD closely mimics many autoimmune disorders. Though systemic steroids may improve clinical manifestations of musculoskeletal GVHD, prolonged usage of steroids is associated with several long term complications and predisposition to infections. Steroid sparing agents like Cyclosporine, Tacrolimus, Sirolimus, Mycophenolate mofetil, Etanercept, Low dose Methotrexate have been used with variable success. Olivieri et al. [2] described the role of Imatinib in chronic GVHD associated with fibrotic changes. Many of these drugs are associated with adverse effects like reactivation of infections, organ toxicities and some of them are costly. Leflunomide with its anti-T cell proliferative action has shown to be useful in rheumatoid arthritis [3]. Leflunomide has been shown to be effective in prevention

and treatment of GVHD in various animal models [4, 5]. We describe our patient with Musculoskeletal GVHD who responded to single agent Leflunomide.

A 46 year old female with Myelodysplastic syndrome (RAEB2) with progression to acute myeloid leukemia underwent haploidentical stem cell transplant with her 8/10 HLA matched son. Her baseline comorbidities included remote hepatitis B infection for which she was on prophylaxis with lamivudine. Her conditioning regimen was reduced intensity with fludarabine, and treosulfan. GVHD prophylaxis consisted of cyclosporine (CsA), mycophenolate mofetil (MMF) and post-transplant cyclophosphamide. Her immediate post-transplant period was complicated by febrile neutropenia, voriconazole induced visual hallucinations and CsA related headache. She engrafted on day + 11 and developed engraftment related fever needing low dose steroids for few days. MMF was stopped on day + 36 and CsA tapering was started from day + 91. On Day + 125 her liver enzymes were found to be mildly elevated on routine blood workup. Virology testing did not show any seroconversion. HBV DNA and HCV RNA PCR were negative. She was continued on lamivudine. Suspecting liver GVHD, cyclosporine tapering was withheld temporarily. Her liver enzymes showed a declining trend by day + 130. On day + 133 she started having bilateral shoulder pain with some restriction of movements. This worsened gradually and 2 weeks later (day + 144), she had severe restriction of movements, increased pain, joint stiffness in small joints of hand and difficulty in getting up from sitting position. MRI of shoulder joints ruled out avascular necrosis. A clinical diagnosis of musculoskeletal GVHD was made. Her baseline PROM score was 21 and NIH joint score was 2. Since her manifestations resembled rheumatoid arthritis, she was started on oral leflunomide (100 mg once a day for first 3 days followed by 20 mg

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once a day) along with physiotherapy. CsA was continued. Within 2 weeks of start of leflunomide (by day + 158), her symptoms had improved by 50–60%. CsA was stopped on day + 165. One month following start of leflunomide (by day + 172 of transplant), the PROM score improved to 24 and NIH joint score became 0. By end of 3 months of start of leflunomide, the PROM score had improved to 25. She is currently 2 years post-transplant, without any manifestations of musculoskeletal GVHD. She is continued on leflunomide therapy (20 mg once a day). She has had no adverse effects of leflunomide therapy so far.

Leflunomide (*N*-(4-trifluoromethylphenyl)-5-methylisoxazol-4-carboxamide), is a low molecular weight (270), synthetic isoxazol derivative. Leflunomide gets converted into its active metabolite, A77 1726 in the gut, which exerts majority of its action (3). Leflunomide has a variety of actions on immune system, most common of which is the inhibition of Dihydro-orotate dehydrogenase enzyme. Inhibition of this enzyme results in depletion of pyrimidine in actively multiplying lymphocytes. This explains the anti-proliferative effect of leflunomide on T and B cells. Déage et al. [6] showed that leflunomide suppresses the cross talk between activated T cells and monocytes resulting in inhibition of pro-inflammatory and matrix destructive factors. Leflunomide may also exert immune-modulation by inhibition of cytokine synthesis (IL-2, IL-3, IL-4), tyrosine kinase inhibition, and suppression of IL2 and transferrin receptor expression [7]. T cell dependent B cell formation of auto-antibodies, including IgA and IgG isotypes, is also inhibited by A77 1726 [8]. Thus Leflunomide interferes with several major pathways of the immune system which play a role in the pathogenesis of chronic GVHD. Schorlemmer et al. [4] and Morwka et al. [5] demonstrated the role of; eflunomide in the prevention and treatment of GVHD in animal models. To date there is no data of Leflunomide use in human beings in GVHD. Leflunomide with its anti-rheumatoid and proposed anti-GVHD effect was thus beneficial in our patient. Leflunomide being a cheap drug with an excellent

safety profile has a significant potential as a steroid sparing agent. It needs to be prospectively studied in the setting of chronic musculoskeletal GVHD.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Research Involving Human Participants This is not a clinical trial or research project. This is a case report highlighting the use of a drug routinely used in rheumatoid arthritis (an autoimmune disorder). The patient was treated at the discretion of the treating clinician.

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