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Efficacy of Leflunomide as Alternative Treatment of Refractory Adult Onset Still's Disease in Two Patients from a Resource-Limited Setting

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Short Communication

The treatment of Adult Onset Still's Disease (AOSD) is empirical, but biological Disease-Modifying Antirheumatic Drugs (bDMARDs) appear to be the best drugs in refractory cases [1,2]. In developing countries where these drugs are largely unavailable, effective alternatives are of utmost importance. We report Leflunomide (LEF)-induced remission in two refractory AOSD patients from sub-Saharan Africa.

The first is a lady diagnosed with AOSD in 2008 at the age of 35 years. Her initial treatment was pulse methylprednisolone followed by oral prednisone (60 mg/day) and methotrexate (MTX 10 mg/week). Due to a polycyclic rheumatic course, MTX was increased up to 17.5 mg and sulfasalazine added. At ninth month, MTX and sulfasalazine were switched to LEF due to inefficacy and side effects (alanine aminotransferase 62 UI/L, normal range 5-45 UI/l). Since then, no new flare has been noted, even after complete withdrawal of corticosteroids in 2011 (Figure 1).

The second patient is a lady diagnosed with AOSD in 2013 at the age of 29 years. Her initial treatment was pulse methylprednisolone followed by oral prednisone (60 mg/day) and MTX (10 mg/week). Due to a polycyclic systemic course and complications developed by the patient (macrophage activation syndrome, ischemic heart disease and corticosteroid-induced diabetes) together with the lack of improvement of inflammatory markers despite continuous increase of MTX up to 17.5 mg/week, MTX was switched to LEF at the twelfth month, leading to clinical and biological (Figure 2) remission. But side effects (abdominal pain, cutaneous rash and increased ALAT 81 UI/l) developed under a maintenance dose of 10 mg/day leading to LEF discontinuation one year later. Aside from well controlled diabetes, she has not yet reached remission despite combination of MTX 20 mg/week with prednisone 5 mg/day (reintroduced almost two years ago during a scleritis flare of the right eye).

Considering the consensus, these patients were good candidates for bDMARDs. The efficacy of bDMARDs in refractory AOSD is due to the reduction of the number of flares and their steroid-sparing effect [1]. In the absence of bDMARDs as well as other effective immunosuppressors, LEF treatment was tried and the patients' health improved. But it was prematurely stopped due to its side effects.

LEF is a synthetic DMARD used for Rheumatoid Arthritis (RA) treatment for over two decades [3]. Available studies show similar efficacy of monotherapy with LEF and MTX for RA, psoriatic arthritis and psoriasis [4,5], chronic inflammatory disorders with pathogenic

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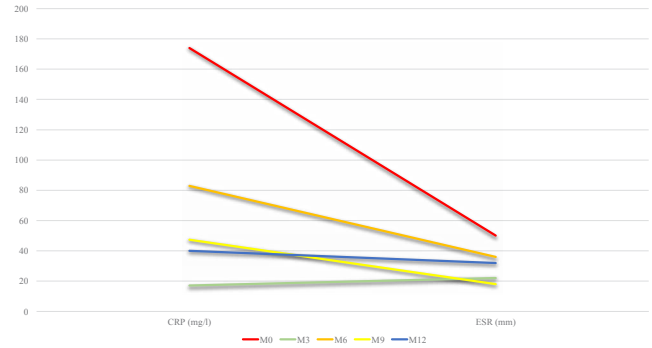

Figure 1: Evolution of inflammatory parameters under initial MTX treatment during one year of follow up. Curves showing persistently elevated values of C-reactive Protein (CRP) and Erythrocyte Sedimentation Rate (ESR) during one year of methotrexate treatment.

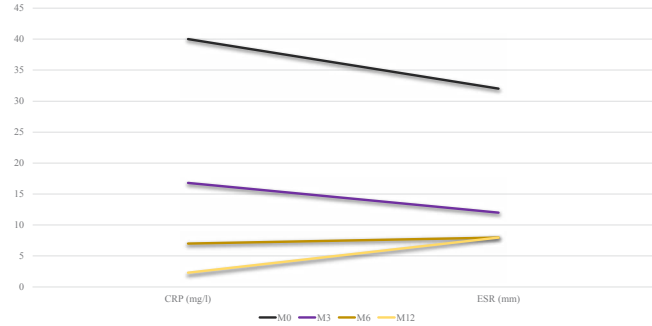

Figure 2: Evolution of inflammatory parameters under LEF treatment during one year of follow up. Curves showing resolution of biological inflammatory syndrome by the sixth month of treatment with leflunomide.

mechanisms comparable to AOSD. This stems from indirect inhibition of T cell clonal expansion by LEF via reduced pyrimidine synthesis. Additionally, a significant LEF-related steroid-sparing effect is documented, as observed in the first patient [3]. By contrast, LEF use in systemic inflammatory diseases is mainly limited by its adverse hepatic effects. Indeed, it is more than MTX associated with elevated liver enzymes despite a broadly similar safety profile [4]. LEF recommended fixed daily dose of 10 to 20 mg in RA treatment is based on this knowledge [6,7]. Its application in AOSD failed to improve LEF safety in the second patient.

Extrapolating from data on RA [6] together with these observations, LEF (10 to 20 mg/day maintenance dose) could be at least as effective as MTX in AOSD patients and hence, a convenient alternative drug for low socioeconomic refractory AOSD patients, providing good tolerance. To implement more inclusive cost-effective treatments, long term powered trials testing LEF (daily 10 to 20 mg maintenance dose, with or without loading dose) superiority/non-inferiority versus MTX (7.5 to 17.5 mg weekly dose) and bDMARDs in AOSD patients are needed.

Abbreviations: AOSD: Adult Onset Still's Disease; bDMARDs: Biological Disease-Modifying Antirheumatic Drugs.

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