Background: An increase in immune activation and turnover of CD4 T cells is considered to be a primary mechanism of HIV pathogenesis. Leflunomide is an immunomodulatory agent approved for use in rheumatoid arthritis that acts by decreasing turnover of activated lymphocytes via inhibition of dihydroorotate dehydrogenase, the rate-limiting enzyme in the de novo synthesis of pyrimidines.

Methods: We performed a randomized, double-blind, controlled trial (ALETHIA) to evaluate the safety and effect of leflunomide on CD4 cell turnover in HIV-1-infected subjects. Subjects with CD4 counts ≥350 cells/µL who were not receiving ART were treated with either leflunomide 20 mg/day or placebo for 28 days. On day 28, the treatment arm was unblinded to allow patients who received leflunomide to undergo wash-out treatment with cholestyramine. Toxicity data, CD4 and CD8 T cell counts, and viral load were followed. Ki67 expression, BRDU incorporation and activation markers on T cells were examined by flow cytometry. Sign and Wilcoxon rank-sum tests were used for comparisons. Final results are reported here.

Results: We randomized 12 subjects to receive leflunomide, and 6 subjects to receive placebo. There were no differences between groups in median age (39.5 vs 39.0 years), baseline CD4 count (637 vs 434 cells/µL), viral load (3.87 vs 4.31 log_{10} copies/mL), or expression of Ki67 on CD4 T cells (4.3 vs 5.6%). The median leflunomide level in the treated group was 21.5 mg/L. A significant decrease in Ki67 expression was seen in the leflunomide group after 28 days of treatment (-0.8%; p = 0.02) and was not seen in the placebo group (-0.05%; p = 1). The between-group comparison was not significant for change in CD4 expression of Ki67 (p = 0.55), however, there was a significant difference between the 2 groups in change in BRDU incorporation in CD4 (-0.0785% vs 0.085%; p = 0.03). Additionally, the percentage of CD8 cells expressing CD38 and HLA-DR decreased in the leflunomide group (-5%; p = 0.02). Although HIV viral load decreased at day 15 in the leflunomide group (-0.152 log_{10} copies/mL; p = 0.02), a significant decrease was not seen at day 29 (-0.124 log_{10} copies/mL; p = 0.34). There were no grade 3 or 4 adverse events seen in the leflunomide group.

Conclusions: Leflunomide given for 28 days was safe and well tolerated in HIV-infected subjects who were not receiving ART. Additionally, it was effective in decreasing the turnover of CD4^+ T cells.