Abstract Background: Programmed cell death-1 (PD-1) is an immunoreceptor that negatively regulates antigen receptor signaling and plays a critical role in the immunoregulation of autoimmune diseases. Aim of the work: This study aimed to measure the plasma and synovial fluid levels of soluble programmed death-1(sPD-1) in rheumatoid arthritis (RA) patients and to correlate them with the clinical and laboratory characteristics, disease activity, functional status and radiological severity. Patients and methods: We measured sPD-1 in the plasma (n = 60) and synovial fluid (SF) samples (n = 24) from 60 RA patients and in the plasma from healthy control (n = 30). In the patients, disease activity score using 28 joint counts (DAS28) and the health assessment questionnaire (HAQ) score were assessed; immunoglobulin-M rheumatoid factor (IgM-RF) titer, anti-cyclic citrullinated peptide (anti-CCP) antibodies titer and C-reactive protein (CRP) levels were measured and total Sharp score calculated. Results: In RA patients both plasma and SF sPD-1 levels (1416.9 ± 1037.9 pg/ml and 1503.9 ± 1129.48 pg/ml respectively) were highly significantly increased compared to its plasma level in the healthy control (165 ± 26.11 pg/mL) (p < 0.001). In RA patients, the plasma and SF levels of sPD-1 significantly correlated with DAS28 (r = 0.52 and 0.58 respectively, p < 0.05), HAQ scores (r = 0.48 and 0.51 respectively, p < 0.05) and anti-CCP titers (r = 0.55 and 0.58 respectively, p < 0.05). Conclusions: Rheumatoid arthritis patients have significantly elevated plasma and synovial levels of sPD-1 that remarkably correlated with the DAS28 suggesting that it could be a useful marker to reflect RA disease activity. The considerable association of sPD-1 with autoantibodies production implies a possible role in the pathogenesis of RA.