**ABSTRACT**

**Objectives:** To evaluate the efficacy and safety of tacrolimus (TAC) as switching maintenance therapy in patients with established rheumatoid arthritis (RA) in remission after receiving combination therapy with tumor necrosis factor inhibitor (TNFi) and methotrexate (MTX).

**Methods:** This 24-week, open-label, equivalence trial included patients who received TNFi and MTX at stable doses for ≥24 weeks and patients with low disease activity (LDA) on Disease Activity Score-28 (DAS28) for ≥12 weeks. Patients chose between two arms: maintenance (TNFi plus MTX) or switched arm (TAC plus MTX). The primary outcome was the difference in the proportion of patients who maintained LDA at week 24, which was assessed a using logistic regression model.

**Results:** In efficacy analysis,34and 80 patients were included in the maintenance and switched arms, respectively, which was less than planned. At week 24, LDA was maintained in 91% and 99% of patients in maintenance and switched arms, respectively (odds ratio, 0.14; 95% confidence interval, 0.01–1.59). Drug-related adverse event (AE) was commoner in the maintenance arm compared with the switched arm (20.9% vs. 7.1%, respectively, *P* = 0.0501). Half of AEs related to TAC were abdominal pain.

**Conclusions:** This controlled study tested a novel treatment strategy of switching from TNFi to TAC in patients with RA with sustained LDA demonstrated that 91% of patients maintained LDA over 24 weeks after discontinuing TNFi.

**Keywords:** rheumatoid arthritis; tacrolimus; tumor necrosis factor inhibitors; maintenance; low disease activity

**INTRODUCTION**

Rheumatoid arthritis (RA) is an autoimmune disease with progressive joint damage and deformities, which eventually result in functional disability.[[1](#_ENREF_1" \o "Lee, 2001 #1)] Thanks to early diagnosis, treat-to-target strategy, and effective disease-modifying anti-rheumatic drugs (DMARDs), remission is achievable, which can prevent or reduce the progression of joint damage and inflammation-related comorbidities.[[2-5](#_ENREF_2" \o "Landewé, 2002 #2)] Over the last three decades, targeted DMARDs have revolutionized RA therapeutics. The targets include several cytokines, specific lymphocyte subsets, cell-surface receptors, and signaling pathways. The first biological DMARDs (bDMARDs) inhibited tumor necrosis factor-α (TNF-α) from binding to its receptors. TNF-α is a central cytokine in the inflammatory cascade against infection and malignancies that promotes pannus formation and bone erosion in RA.[[6](#_ENREF_6" \o "Blüml, 2012 #65)] Since TNF-α inhibitors (TNFi) were developed in the 1980s, five drugs with proven therapeutic efficacy and safety in RA are used clinically.[[7-9](#_ENREF_7" \o "Klareskog, 2004 #67)]

Recent updates on RA management permit tapering TNFi with dose reduction or prolonged intervals in combination with conventional synthetic DMARDs (csDMARDs).[[10](#_ENREF_10" \o "Smolen, 2020 #107)] However, potential side effects of TNFi, such as serious infections,[[11](#_ENREF_11" \o "Atzeni, 2012 #106)] concerns of malignancies,[12](#_ENREF_12)[13](#_ENREF_13) inconvenience of injections, and economic burden[[14](#_ENREF_14" \o "Fautrel, 2011 #79)] prevent their long-term use. Complete discontinuation of TNFi is not recommended because of high rate of recurrence.[[15-17](#_ENREF_15" \o "Ghiti Moghadam, 2018 #81)]

It is unclear if TNFi can be discontinued when flare-ups of RA can be managed with csDMARDs. Tacrolimus (TAC) is an immunosuppressive drug previously used to prevent rejection following organ transplantation and treat other autoimmune diseases, such as lupus nephritis and myasthenia gravis.[[18](#_ENREF_18" \o "Spencer, 1997 #103)] It is effective in RA and used as a conventional DMARD, mainly, in the Asia-Pacific region.[[19-21](#_ENREF_19" \o "Lau, 2019 #70)] The efficacy of TAC on arthritis in RA is via blocking of the calcineurin pathway in T-lymphocytes and inhibiting their proliferation and cytokine production.[[22](#_ENREF_22" \o "Kitahara, 2007 #93)] An *in vitro* study demonstrated that TAC decreases the levels of inflammatory cytokines, such as interleukin (IL)-15 and TNF-α in synoviocytes.[[23](#_ENREF_23" \o "Cho, 2002 #94)] Additionally, its therapeutic effects have been reported in the treatment of interstitial lung disease (ILD); therefore, it is an option in RA with ILD.[[24-26](#_ENREF_24" \o "Yamano, 2018 #71)] However, no prospective studies have investigated switching from bDMARDs to csDMARDs in patients with sustained remission. Studies that investigated de-escalating TNFi in patients with RA suggest that a constant degree of immunomodulation is not always required to maintain remission.[[27-31](#_ENREF_27" \o "Kuijper, 2015 #97)] The aim of this prospective, non-randomized, active control, parallel group, open-label study was to investigate the potential of stopping TNFi and adding TAC in patients with stable low disease activity (LDA).

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**Competing interests**

 All authors have no conflict of interest regarding the contents of this article.

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