

Efficacy and safety of tacrolimus in 101 consecutive patients with rheumatoid arthritis: a possible alternative treatment to methotrexate?

Evaluation of: Kitahama M, Okamoto H, Koseki Y *et al.*: Efficacy and safety of tacrolimus in 101 consecutive patients with rheumatoid arthritis. *Mod. Rheumatol.* DOI: 10.1007/s10165-010-0319-1 (2010) (Epub ahead of print). Although the use of biologic agents combined with methotrexate has been reported to be effective in the treatment of patients with rheumatoid arthritis, a proportion of rheumatoid arthritis patients do not experience disease remission, partly because of their complications or background factors. In this context, tacrolimus treatment might be effective and safe for such patients. In the study being evaluated, the authors provide additional useful information for treating physicians. However, further studies regarding the long-term efficacy and safety of tacrolimus treatment in a larger number of active rheumatoid arthritis patients are necessary in order to draw valid conclusions.

KEYWORDS: disease-modifying antirheumatic drug • rheumatoid arthritis • tacrolimus

Hiroshi Tanaka

Department of Pediatrics,
Hirosaki University Hospital,
Hirosaki 036-8563, Japan
Tel.: +81 172 395 070
Fax: +81 172 395 071
hirotana@cc.hirosaki-u.ac.jp

Tacrolimus (Tac) is a T-cell-specific calcineurin inhibitor that prevents activation of helper T cells, thereby inhibiting transcription of the early activation genes of IL-2, and suppressing the production of TNF- α , IL-1 β and IL-6. Considering its effects, Tac is expected to have clinical benefits in the treatment of patients with active rheumatic diseases. Indeed, to date, several papers have described the efficacy and safety of Tac treatment for patients with rheumatoid arthritis (RA) [1-5], lupus nephritis [6,7] and systemic-onset juvenile idiopathic arthritis [8].

In the paper being evaluated, the authors have attempted to demonstrate the efficacy and safety of Tac treatment in patients with active RA in a hospital-based prospective observational setting [1]. On the basis of the result of the study, the authors appear to provide further useful information regarding Tac treatment for treating physicians. The authors have used information drawn from a database (the IORRA database) of the authors' academic center (The Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan), which was established in October 2000. Using this database, data sets of patient clinical variables before and after Tac treatment were collected from a prospective observational cohort of patients with active RA. Thus, most of the information appears to pertain to ordinary Japanese RA patients in a clinical setting.

A total of 7512 patients were registered in the database, in which patients selection bias appears to be very small. Of these patients, 101 consecutive patients with active and disease-modifying

antirheumatic drug (DMARD)-resistant RA were treated with Tac using an initial average dose of 1.62 mg/day. Clinical and laboratory assessments were performed at baseline, month 4 and month 12. The study was conducted in accordance with the following: a hospital-based prospective observational study using last observation carried forward methodology; and the variables included the European League Against Rheumatism improvement criteria using the Disease Activity Score (DAS)28 scale and the American College of Rheumatology preliminary criteria for improvement (ACR20). The results were compared with 5867 patients with RA from the 13th phase of the IORRA cohort (from October 2006 in the database).

When compared with the IORRA database as the control group, the Tac-treated patients were of a similar average age (62 years old) and had a similar disease duration (13 years). However, these patients had received higher doses of methotrexate (MTX; 8.59 mg/week) and prednisolone (6.92 mg/day), and had used nonsteroidal anti-inflammatory drugs more frequently, indicating that Tac was preferentially prescribed to RA patients with higher disease activity [1]. Comorbidities (i.e., respiratory disease, hyperlipidemia and Type 2 diabetes mellitus) were frequently observed in 26 patients (25.7%) of the Tac-treated group at baseline. Thus, the average daily dose of Tac at entry was relatively low at 1.62 mg/day, which resulted in an average whole blood Tac concentration of 4.3 ng/ml approximately 12 h post-dosing.

future
medicine part of fsg

Of the 101 Tac-treated patients, 44 patients (43.6%) had discontinued Tac at 12 months, mainly because of side effects ($n = 18$), insufficiency ($n = 16$), financial reasons ($n = 2$) or other reasons ($n = 10$). Regarding side effects, renal dysfunction ($n = 5$), defined as an increased serum creatinine level greater than 30% at baseline, gastrointestinal signs ($n = 3$), respiratory disease ($n = 2$), infection ($n = 2$) and deterioration of diabetes mellitus ($n = 2$) were documented in the clinical records. Regarding efficacy, in the analysis using the last observation carried forward methodology and the Kruskal–Wallis test, compared with baseline, the DAS28 score, C-reactive protein (CRP) level and matrix metalloproteinase-3 level were significantly improved both at month 4 and month 12. When the efficacy of Tac was evaluated using the European League Against Rheumatism response criteria, 57.4% of the Tac continuation patients ($n = 54$) achieved a good or moderate response, whereas 14.2% of patients in the ‘insufficiency’ subgroup ($n = 14$) and 22.2% patients in the ‘side effect’ subgroup ($n = 18$) achieved a moderate response. From the study, Tac blood concentration was significantly correlated with improvement in CRP level, but not MTX or prednisolone use. Thus, Tac treatment resulted in an overall improvement in DAS28, CRP levels and matrix metalloproteinase-3 levels, as well as a significant clinical improvement. Furthermore, Tac continuation rates were calculated and analyzed using Kaplan–Meier curves, and compared with those of other DMARDs in the IORRA cohort. With respect to the continuation rate of DMARDs in the IORRA cohort, the Tac continuation rate was, unexpectedly, lower than that of MTX, infliximab and etanercept, and was similar to that of sulfasalazine and bucillamine. The authors speculated that this was due to the background of the Tac group patients, who had more comorbidities, as described earlier. On the other hand, the discontinuation rate for insufficiency in the Tac group was similar to that in the MTX group, even though the Tac group had higher disease activity.

In conclusion, the authors confirmed the relative efficacy and safety of a 12-month course of Tac treatment for patients with active and DMARD-resistant RA. Tac may accordingly represent a suitable therapeutic strategy for RA patients who are unable to use biologic agents or to tolerate high-dose MTX because of their complications or background factors [1].

Although MTX is considered to be the most effective DMARD as a first-line drug in RA, a proportion of patients with active RA exhibit resistance or intolerance to MTX [2]. In this context, Tac is reportedly effective and relatively safe for treating active RA patients who respond inadequately to DMARDs, including MTX [1–5]. On the other hand, the safety of Tac treatment is an important concern because of its potent nephrotoxicity. Indeed, some patients with RA have reportedly experienced an increase in baseline serum creatinine levels following Tac treatment [1,2]. Although these patients did not necessarily always have high Tac blood levels [3], the development of an optimal Tac treatment strategy for RA, with the administration of a dose of Tac as low as possible, is sought to minimize treatment toxicity while maintaining treatment efficacy. In this context, in Japan, Tac is usually administered once daily for patients with RA or lupus nephritis, since once-daily administration of Tac is the government-approved procedure [1,3–5,7]. Kawai and Yamamoto reported the safety of Tac treatment when 1.5–3.0 mg was administered as a single daily dose for the treatment of RA even in the elderly [4]. Although further studies, including a histologic evaluation following Tac treatment, are needed, we consider that a once-daily administration Tac treatment protocol could shorten the exposure to the drug, is more cost beneficial than the conventional twice-daily protocol and may improve treatment compliance. Further, Tac has been reported to stimulate glucocorticoid receptor transactivity through its ligands [9], which may explain the tendency to exacerbate glucose intolerance in selected patients who received Tac [1].

It has recently been reported that Tac may overcome treatment unresponsiveness through the blockade of the drug exclusion effect of P-glycoprotein, leading to restoration of intracellular therapeutic levels of corticosteroids and clinical improvement [10]. These laboratory and clinical observations suggest that this might be another of Tac’s beneficial mechanisms of action, which would warrant its use in the treatment of patients with active and DMARD-resistant RA. We suspect that this mechanism may represent a mode of action of Tac different from that of MTX. Moreover, Tac may be useful for selected RA patients who are refractory to the conventional treatment, including TNF inhibitors [11], although we cannot confirm at present whether Tac is at least as effective as biologic agents for active RA patients.

Finally, the weaknesses of the study should be considered. First, the treatment duration (12 months) was relatively short. Further evaluation is needed to confirm the clinical findings, and also the efficacy and safety, particularly the possible oncogenic risks, of long-term Tac administration. Second, radiographic progression or regression in the study participants was not examined. Further studies regarding this issue are needed accordingly. Despite these limitations, Tac can be considered for patients with active RA who respond inadequately to or cannot tolerate DMARDs, including MTX. Although this study appears to be somewhat anecdotal and remains preliminary, the

authors provide additional useful information for treating physicians regarding Tac treatment for RA patients with complications or background factors.

Financial & competing interests disclosure

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Executive summary

- In a clinical setting, tacrolimus can be considered for patients with active rheumatoid arthritis who respond inadequately to or cannot tolerate disease-modifying antirheumatic drugs, including methotrexate.
- Moreover, tacrolimus may accordingly represent a suitable therapeutic strategy for rheumatoid arthritis patients who are unable to use biologic agents or to tolerate high-dose methotrexate because of their complications or background factors.

Bibliography

- 1 Kitahama M, Okamoto H, Koseki Y *et al.*: Efficacy and safety of tacrolimus in 101 consecutive patients with rheumatoid arthritis. *Mod. Rheumatol.* DOI: 10.1007/s10165-010-0319-1 (2010) (Epub ahead of print).
- 2 Lee Y, Woo JH, Choi S, Ji J, Bae SC, Song G: Tacrolimus for the treatment of active rheumatoid arthritis: a systemic review and meta-analysis of randomized controlled trials. *Scand. J. Rheumatol.* 39(4), 271–278 (2010).
- 3 Suzuki K, Kameda H, Amano K *et al.*: Single center prospective study of tacrolimus efficacy and safety in treatment of rheumatoid arthritis. *Rheumatol. Int.* 29(4), 431–436 (2009).
- 4 Kawai S, Yamamoto K: Safety of tacrolimus, an immunosuppressive agent, in the treatment of rheumatoid arthritis in elderly patients. *Rheumatology (Oxford)* 45(4), 441–444 (2006).
- 5 Kawai S, Hashimoto H, Kondo H, Murayama T, Kiuchi T, Abe T: Comparison of tacrolimus and mizoribine in a randomized, double-blind controlled study in patients with rheumatoid arthritis. *J. Rheumatol.* 33(11), 2153–2161 (2006).
- 6 Mok CC, Tong KH, To CH, Siu YP, Au TC: Tacrolimus for induction therapy of diffuse proliferative lupus nephritis: an open-labeled pilot study. *Kidney Int.* 68(2), 813–817 (2005).
- 7 Tanaka H, Oki E, Tsugawa K, Nonaka K, Suzuki K, Ito E: Effective treatment of young patients with pediatric-onset, long-standing lupus nephritis with tacrolimus given as a single daily dose: an open-label pilot study. *Lupus* 16(11), 896–900 (2007).
- 8 Tanaka H, Tsugawa K, Suzuki K *et al.*: Treatment of difficult cases of systemic-onset juvenile idiopathic arthritis with tacrolimus. *Eur. J. Pediatr.* 166(10), 1053–1055 (2007).
- 9 Davies TH, Ning YM, Sanchez ER: Differential control of glucocorticoid receptor hormone-binding function by tetratricopeptide repeat (TPR) proteins and immunosuppressive ligand FK506. *Biochemistry* 44(6), 2030–2038 (2005).
- 10 Suzuki K, Saito K, Tsujimura S *et al.*: Tacrolimus, a calcineurin inhibitor, overcomes treatment unresponsiveness mediated by P-glycoprotein on lymphocytes in refractory rheumatoid arthritis. *J. Rheumatol.* 37(3), 512–520 (2010).
- 11 Yokota K, Akiyama Y, Asanuma Y, Miyoshi F, Sato K, Mimura T: Efficacy of tacrolimus in infliximab-refractory progressive rheumatoid arthritis. *Rheumatol. Int.* 29(4), 459–461 (2009).