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REVIEW

Moderate-to-Severe Refractory Ulcerative Colitis: Focus on Tacrolimus

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Abstract: Tacrolimus, a 23-member macrolide lactone discovered in 1984 from the actinomycete *Streptomyces tsukubaensis*, was the first macrolide immunosuppressant agent. Tacrolimus was first used for patients after liver transplantation to reduce the activity of the patient's immune system and the risk of organ rejection. Oral tacrolimus was recently approved for use in steroid-refractory moderate-to-severe ulcerative colitis in Japan. This review focuses on the clinical efficacy and safety data of tacrolimus in moderate-to-severe refractory ulcerative colitis.

Keywords: tacrolimus (FK506), cyclosporine, ulcerative colitis

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Introduction

Tacrolimus, previously known as FK-506, is a 23-member macrolide lactone discovered in 1984 from the actinomycete *Streptomyces tsukubaensis*[1] (Fig. 1). It was the first macrolide immunosuppressant agent. Tacrolimus was first used for patients after liver transplantation to reduce the risk of organ rejection.[2] Since tacrolimus was approved by the Food and Drug Administration (FDA) in 1994 for use in liver transplantation, its approval has been extended to include kidney, heart, bone marrow, small bowel, pancreas, lung, trachea, skin, cornea, and limb transplants. In terms of inflammatory bowel disease, clinical trials in Crohn's disease (CD) and ulcerative colitis (UC) have been conducted.[3,4] In Japan, oral tacrolimus (Prograf®, Astellas Pharma Inc., Tokyo) was approved by the Ministry of Health, Labour and Welfare in 2009 for remission induction therapy in patients with steroid-refractory moderate-to-severe UC. This review focuses on the clinical efficacy and safety of tacrolimus in moderate-to-severe refractory UC.

Mechanism of Action and Pharmacokinetic Profile

Tacrolimus is a calcineurin inhibitor that suppresses pro-inflammatory cytokine production and T-cell activation (Fig. 2). Tacrolimus binds to an intracellular protein, 12-kDa FK506-binding protein (FKBP12)[5]. A complex of tacrolimus-FKBP12 blocks

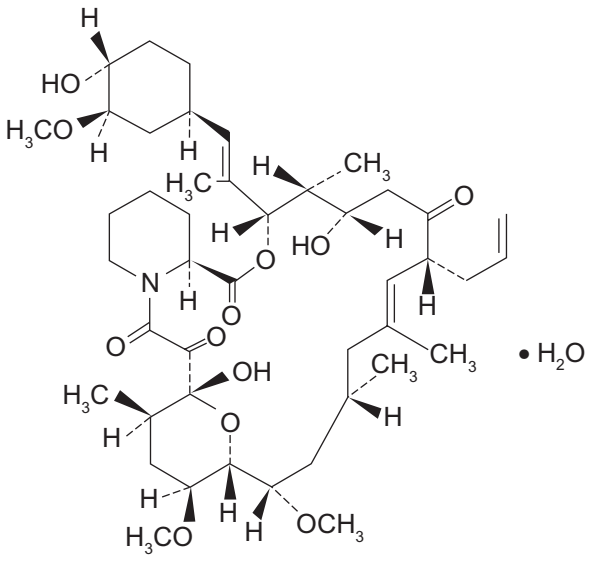

Figure 1. Structure of tacrolimus. The molecular formula is C44H69NO12. The molecular weight is 8040.

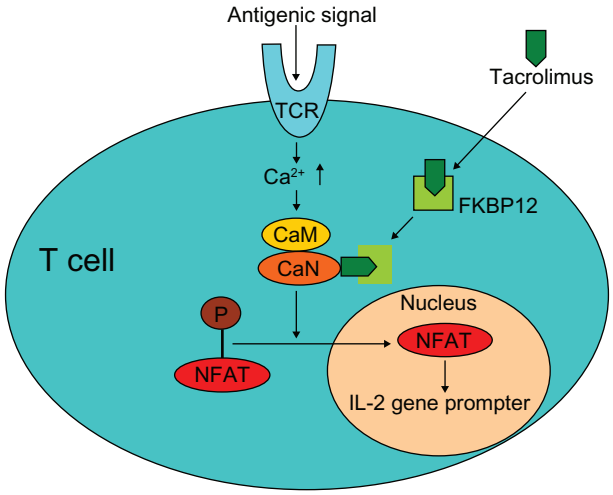

Figure 2. Mechanism of tacrolimus for immunosuppression. Tacrolimus inhibits calcineurin activation, which prevents dephosphorylation and translocation of nuclear factor of activated T-cells (NFAT), which in turn suppresses the NFAT-dependent transcription of cytokines such as interleukin-2. TCR, T cell receptor; FKBP12, 12-kDa FK506-binding protein.
Abbreviations: CaM, calmodulin; CaN, calcineurin.

the phosphatase activity of calcineurin (CaN). This prevents dephosphorylation and translocation of nuclear factor of activated T-cells (NFAT), which suppresses the NFAT-dependent transcription of cytokines such as interleukin (IL)-2, IL-3, IL-4, IL-5, interferon-γ, granulocyte-macrophage colony-stimulating factor, and tumor necrosis factor-α.[6–10] The cascade results in inhibition of T-lymphocyte activation. Tacrolimus also has a local effect at the intestinal lumen via modulation of the expression of local inflammation mediators, which could be of importance in inflammatory bowel disease.[11,12] Tacrolimus is metabolized predominantly to 13-O-demethyltacrolimus in the liver and intestine by cytochrome P450 3A (CYP3A), and it is eliminated mostly with the bile[13].

Cyclosporine A (CyA) is also a calcineurin inhibitor, although it binds to different target molecules from tacrolimus. Both tacrolimus and CyA have immunosuppressive properties, but tacrolimus is approximately 10 to 100 times more potent than CyA *in vitro*.[5] Compared with CyA, tacrolimus has the advantage of more predictable intestinal absorption. CyA needs to be administered intravenously to achieve sufficient, stable levels due to its variable intestinal absorption, whereas tacrolimus has better intestinal absorption and is well-absorbed orally even in severe colitis.

Clinical Studies

One randomized, double-blind, placebo-controlled study and several uncontrolled studies have demonstrated the efficacy of tacrolimus treatment in patients with UC. Ogata et al conducted a randomized, double-blind, placebo-controlled study to determine the effective trough levels of tacrolimus for remission induction therapy in patients with refractory moderate-to-severe UC.[3] The study randomly divided patients into 3 groups according to target blood trough concentrations: a high trough level group (n = 19, 10–15 ng/ml whole blood), a low trough level group (n = 21, 5–10 ng/ml whole blood), and a placebo group (n = 20). Patients received an initial oral dose of 0.05 mg/kg tacrolimus or placebo twice daily. Efficacy was evaluated over the 2-week treatment period based on a disease activity index (DAI) score, which was determined by combining scores of stool frequency, rectal bleeding, endoscopic findings, and physician's global assessment.[14,15] Patients were classified as complete responders (CRs) if all their symptoms disappeared, partial responders (PRs) if all symptoms improved, and non-responders (NRs) if no improvement was observed. Clinical remission was defined as a DAI score ≤2, with no individual subscore >1. Mucosal healing was defined as an endoscopy subscore (≥2 at entry) of 0 or 1. At the end of 2-week treatment, there were no CRs; however, PRs were observed for 68.4% of cases in the high trough level group, 38.1% in the low trough level group, and 10% in the placebo group. There was significant improvement in the high trough level group versus the placebo group. In the high trough level group, 20.0% of patients had clinical remission and 78.9% had mucosal healing. The authors concluded that the optimal target range for remission induction therapy appears to be 10–15 ng/ml in terms of efficacy with 2 weeks of therapy.

Several uncontrolled studies have also evaluated the efficacy of tacrolimus in adult patients with UC[16–21] (Table 1). In terms of children, Bousvaros et al performed an open-label, multicenter study to evaluate the efficacy of oral tacrolimus for remission induction therapy in steroid-refractory severe colitis (including UC, CD, or indeterminate colitis) in children.[22] Patients received tacrolimus, 0.1 mg/kg twice daily, and the dosage was adjusted to achieve blood levels between 10 and 15 ng/mL. Patients who responded by 14 days continued to receive tacrolimus, and 6-mercaptopurine or azathioprine was added as a steroid-sparing agent 4–6 weeks after tacrolimus had been instituted. One patient withdrew after 48 hours. The authors reported that 9 (69%) of 13 patients improved within 14 days of tacrolimus therapy. The short-term responders included 5 (55%) of 9 patients with UC and 4 of 4 patients with indeterminate or Crohn's colitis. They also reported that the initial response rate of oral tacrolimus was similar to that of patients treated with either intravenous CyA or oral CyA. Tacrolimus was continued for 2–3 months in the responders, except for one patient who was given tacrolimus for 11 months. After 12 months of follow-up, 5 (38%) patients were receiving maintenance therapy; the other 4 (28%) responders had undergone colectomy.

Safety Profile

The commonly reported adverse events of tacrolimus are hypomagnesemia, hyperkalemia, hyperglycemia, tremor, paresthesias, headache, diarrhea, hypertension, nausea, and renal dysfunction[16–21] (Table 1). Adverse effects are usually dose-related; most are mild and can be managed by reducing the dose of tacrolimus. Therefore, monitoring blood concentrations of tacrolimus is important. In terms of children, Watson et al retrospectively reviewed the medical records of 46 children with steroid-refractory UC treated with oral tacrolimus.[23] Oral tacrolimus was initiated at a dose of 0.1 mg/kg twice daily and titrated to yield trough levels of 10–15 ng/mL for induction and 5–10 ng/mL once in remission. They reported that the common adverse events noted in the first 3 months of tacrolimus therapy were hypertension (52%), tremor (46%), hyperglycemia (36%), headache (24%), infection (22%), and nephrotoxicity, defined as a creatinine >1.5 × baseline creatinine (11%). They reported that most cases of hand tremor and headache resolved spontaneously or upon routine weaning and cessation of tacrolimus.

Bottiger et al reported that the whole blood concentrations of tacrolimus correlate closely to side effects in renal transplantation recipients.[24] They reported that side effects were noted in connection with 76% of tacrolimus concentrations above 30 ng/ml, with 41% of concentrations within the interval of 20–30 ng/ml, with 26% of concentrations within the

Table 1. Retrospective studies focus on tacrolimus in steroid-refractory adult UC patients.

Author (year)	No. of patients	Disease distribution	Disease duration prior to tacrolimus	Treatment prior to tacrolimus therapy	Dose and trough levels of tacrolimus
Yamamoto[16]	UC: 27	Pancolitis: 22 Left sided: 5	37 mo (2–236) median (range)	Steroid: 25 (93%) 5-ASA or SASP: 27 (100%), Thioprines: 7 (26%) Leucocytapheresis: 16 (59%) Inflixmab: 1 (4%)	Remission induction Initial dose: 0.01 mg/kg/day (iv) 0.1 mg/kg/day (po) Target trough level: 10–15 ng/ml Remission maintainance Target trough level: 5–10 ng/ml
Benson[17]	UC: 32 (CD: 15)	Pancolitis: 12 Extensive: 6 Left-sided: 11 Proctitis: 3	81 mo (1 mo–37 yr) mean (range)	Steroid: 21 (66%) Antimetabolites: 25 (78%) Infliximab: 1 (3%)	Remission induction Initial dose: 0.2 mg/kg/day(po) Target trough level: 10–12 ng/mL Remission maintainance Initial dose: 0.1 mg/kg/day (po)
Ng[18]	UC: 6 (CD: 12) (Pouchitis: 1)	Pancolitis: 1 Extensive: 3 Left-sided: 2	6.8 yr (5–10) mean (range)	Steroid: 6 (100%) 5-ASA: 4 (67%) 6MP: 2 (33.3%) Thioprines: 6 (100%) Leucocytapheresis: 1 (17%) Probiotics: 1 (17%)	Initial dose 0.1 mg/kg/day (po) Target trough level 5–10 ng/ml
Baumgart[19]	UC: 40 (CD: 11) (Pouchitis: 2)	Pancolitis: 23 Left-sided: 12 Colon other: 4 Rectum: 1	4.8 yr (0.04–43.51) median (range)	5-ASA: 40 (100%) Thioprines: 28 (70%) Hydrocortisone foam: 23 (57%) Budesonide: 1 (25%) Methotrexate: 4 (10%) Mycophenolate mofeti: 4 (10%) Cyclosporin A: 4 (10%) Infliximab: 1 (2.5%)	Initial dose: 0.01 mg/kg/day (iv) 0.1 mg/kg/day (po) Target trough level: 4–8 ng/ml
Baumgart[20]	UC: 23 (CD: 6) (Pouchitis: 2)	N.A.	65.6 mo (median)	(including CD and pouchitis) Steroid: 31 (100%) Mesalazine: 31 (100%) Ciprofloxacin: 23 (74%) Loperamide: 20 (65%) Thioprines: 19 (61%) Metronidazole: 19 (61%) Hydrocortisole foam: 17 (55%) Budesonide: 15 (48%) Probiotics: 13 (42%) Infliximab: 5 (16%) Cyclosporin A: 4 (13%) Mycophenolate mofetil: 4 (13%) Octreotide: 3 (10%)	Initial dose: 0.01 mg/kg/day (iv) 0.1 mg/kg/day (po) Target trough level: 4–6 ng/ml

Response to tacrolimus	Steroid wean	No. of patients with colectomy	Duration of tacrolimus therapy	Duration of follow up	Adverse events
Remission: 19 (70.4%) Respond: 2 (7.4%) at 30 days after starting tacrolimus Based on modified Truelove–Witts severity index (MTWSI)	Discontinued: 16/19 (84.2%) Reduced: 2/19 (10.5%)	7 (26.9%) Overall cumulative colectomy-free survival: 62.3% at 65 mo	11 mo (1–39) median (range)	17 mo (2–65) median (range)	Hypomagnesemia: 14 (52%) Tremor: 7 (26%) Creatine rise: 5 (19%) Infectious disease: 4 (15%) Hot flashes: 3 (11%) Hyperkalemia: 2 (7%) Headache: 2 (7%) Epigastralgia: 2 (7%) Nausea: 1 (4%)
Remission: 22 (68.8%) Respond: 3 (9.4%) Based on disease activity index (DAI)	Discontinued: 4/30 (13.3%)	12 (37.5%)	29 wk (<1 wk–4.7 yr, 15 wk) mean (range, median)	Colectomy free follow-up: 92 wk, mean	(including CD patients) Hypomagnesemia: 28 (60%) Headache: 4 (9%) Tremor: 4 (9%) Arthralgia: 3 (6%) Nausea: 2 (4%) Insomnia: 2 (4%) Leukoencephalopathy: 1 (2%)
Remission: 3 (50%) Respond: 1 (16.7%) at 4 wk Based on Truelove-Witts index	Discontinued: 3/6 (50%)	0 (0%)	5 mo (0.5–16) mean (range)	8 mo, mean	(including CD and pouchitis) No side effect: 14 (74%) Severe tremor: 3 (16%) Insomia: 1 (5%) Arthralgia: 1 (5%) Severe malaise: 1 (5%) Creatine rise: 1 (5%)
Remission: 18 (45%) Respond: 13 (32.5%) at 30 days Remission: 27 (67.5%) at the end point Based on modified clinical activity index (M-CAI)	Discontinued: 17/36 (47.2%) Reduced: 16/36 (44.4%)	9 (22.5%) Overall cumulative colectomy-free survival: 56.5% at 43.8 mo	(including CD and pouchitis) 25.2 ± 4.6 mo (0.43–164) mean ± SD (range)	39 ± 4.1 mo (5–164) mean ± SD (range)	(including CD and pouchitis) No side effect: 40 (76%) Tremor: 5 (9%) Paresthesias: 5 (9%) Creatinine rise: 4 (8%) Opportunistic infections: 3 (8%) Hypertension: 1 (2%) Hyperkalemia: 1 (2%)
Remission: 17 (73.9%) Respond: 5 (21.7%) at 1 yr Based on M-CAI	(including CD and pouchitis) Discontinued: 9/23 (39.1%) Reduced: 10/23 (43.5%)	3 (9.7%)	(including CD and pouchitis) 12 mo (1–137) median (range)	(including CD and pouchitis) 18.4 mo (1–61.73) median (range)	(including CD and pouchitis) Creatine rise: 3 (10%) Tremor and/or paraesthesias: 3 (10%) Hypertension: 1 (3%) Hyperkalemia: 1 (3%) Opportunistic infection: 1 (3%)

(*Continued*)

Table 1. (*Continued*)

Author (year)	No. of patients	Disease distribution	Disease duration prior to tacrolimus	Treatment prior to tacrolimus therapy	Dose and trough levels of tacrolimus
Hogenauer[21]	UC: 9	Pancolitis: 5 Extensive: 2 Left-sided: 2	22 mo (4–288) median (range)	Steroid: 9 (100%) 5-ASA or SASP: 7 (78%) Thioprines: 6 (67%) Local budesonide: 1 (11%)	Initial dose: 0.15 mg/kg/day (po) Target trough level: 10–20 ng/ml

interval of 10–20 ng/ml, and with only 5.3% of concentrations lower than 10 ng/ml. They concluded that tacrolimus whole blood trough concentrations should preferably be kept below 20 ng/ml to avoid side effects.

Patient Preference and Dosing

In Japan, oral tacrolimus (Prograf®) is approved for remission induction therapy in patients with steroid-refractory moderate-to-severe UC. Oral tacrolimus is approved to be administered up to 3 months when it is clinically effective, because most responders achieved clinical remission, mucosal healing, and reduction of steroid dose within 3 months of administration (data not published). Tacrolimus for remission maintenance therapy is not approved in Japan, because the efficacy and safety of tacrolimus for remission maintenance therapy is still unclear. If clinical response is not observed after 2 weeks of tacrolimus administration, administration is discontinued.

The initial dose of oral tacrolimus is 0.025 mg/kg twice daily. The target range for tacrolimus trough level is 10–15 ng/ml in the first 2 weeks. After 2 weeks' administration, the target range for tacrolimus trough level is 5–10 ng/ml to help avoid side effects (Fig. 3). As with CyA, the scheduled examination of whole blood trough levels and electrolytes with renal function are important to avoid side effects. The following methods are recommended in Japan (Fig. 4): the whole blood trough level is measured 12 and 24 hours after the first administration of oral tacrolimus, and the dose is adjusted as needed. More than 48 hours after the first dosage adjustment, the whole blood trough level is measured twice and the dose is adjusted as needed. More than 36 hours after the second dose adjustment, the whole blood trough level is measured once and the dose is adjusted as needed. About 1 week after the third dose adjustment, the whole blood trough level is measured and the dose is adjusted as needed. Four weeks after the first administration of oral tacrolimus, the whole blood trough level is measured once or more a month. The maximum dose of tacrolimus is 0.3 mg/kg per day.

Conclusions

With sufficient knowledge of the adverse effects and appropriate monitoring, oral tacrolimus can be used both safely and effectively. Compared with CyA,

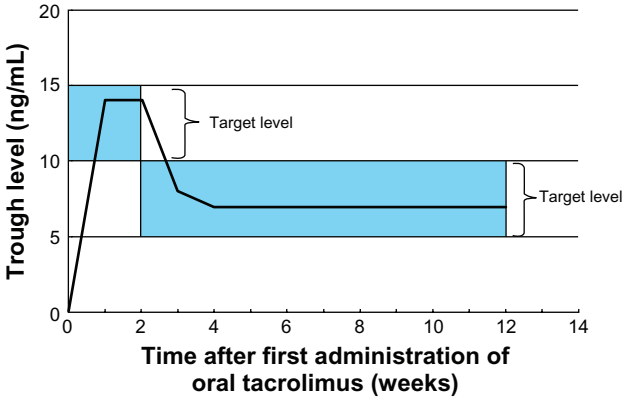

Figure 3. Target trough levels of oral tacrolimus for moderate-to-severe UC. The target range for tacrolimus trough levels is 10–15 ng/ml in the first 2 weeks. After 2 weeks' administration, the target range for tacrolimus trough levels is 5–10 ng/ml to help avoid side effects.

Response to tacrolimus	Steroid wean	No. of patients with colectomy	Duration of tacrolimus therapy	Duration of follow up	Adverse events
Remission: 6 (67%) Respond: 2 (22%), at 12 wk Based on MTWSI	Discontinued or reduced: 9 (100%)	1 (11%)	15 ± 3 wk	21 ± 6 mo mean, SD	Intermittent hypomagnesemia: 9 (100%) Paresthesia: 2 (22%) Thrombopenia with intestinal bleeding: 1 (11%) Bicytopenia: 1 (11%) Creatine rise: 1 (11%) Mild leucopenia: 1 (11%) Mild alopecia: 1 (11%) Verrucae on the finger: 1 (11%)

tacrolimus has the advantage of more predictable intestinal absorption, and it is well-absorbed orally even in severe colitis. Oral tacrolimus is an alternative induction therapy in steroid-refractory moderate-to-severe active ulcerative colitis. Further studies are expected to evaluate the effect of oral tacrolimus as maintenance therapy in addition to induction therapy.

Disclosure

This manuscript has been read and approved by all authors. This paper is unique and is not under

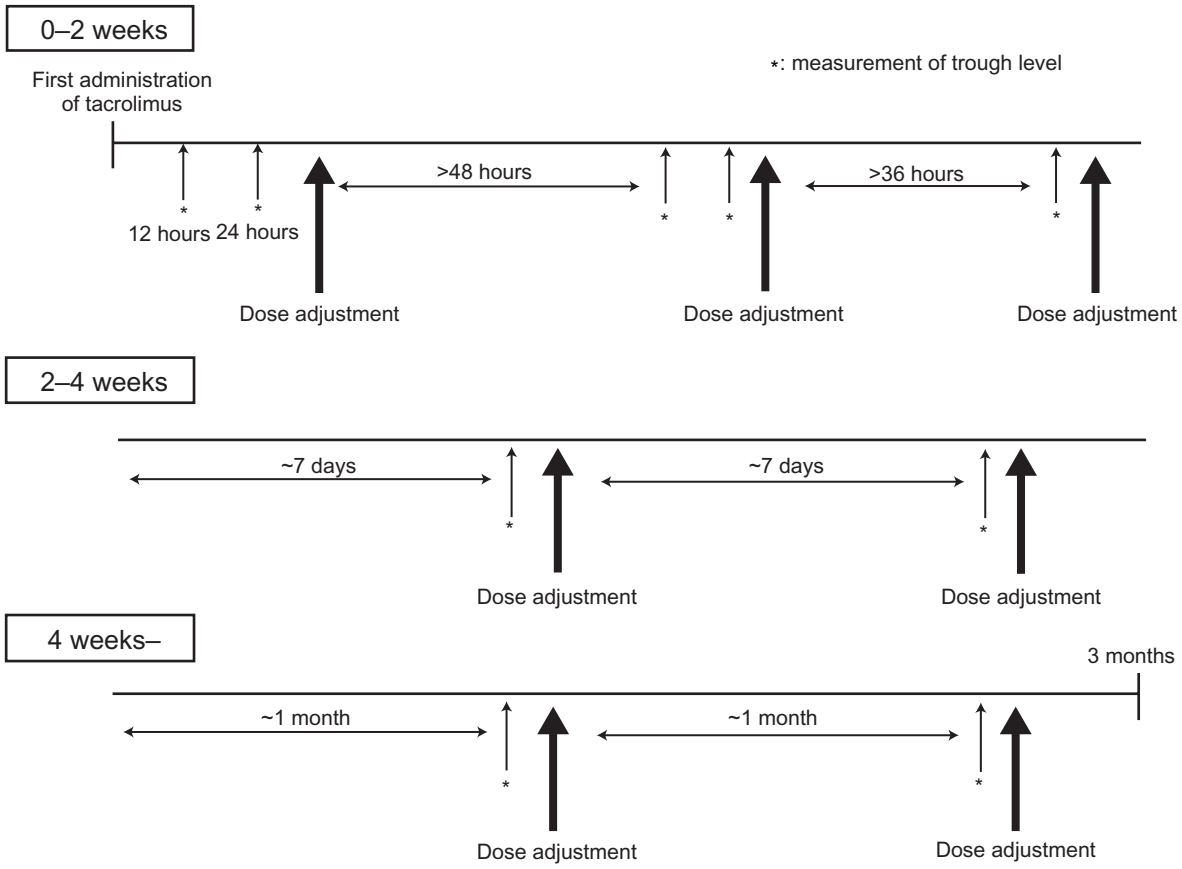

Figure 4. The timing of measurements of whole blood trough levels of tacrolimus for dose adjustments.

consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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