Thyroid eye disease: From pathogenesis to targeted therapies

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Abstract:
Thyroid eye disease (TED) is the most common extrathyroidal manifestation of autoimmune Graves’ hyperthyroidism. TED is a debilitating and potentially blinding disease with unclear pathogenesis. Autoreactive inflammatory reactions targeting orbital fibroblasts (OFs) lead to the expansion of orbital adipose tissues and extraocular muscle swelling within the fixed bony orbit. There are many recent advances in the understanding of molecular pathogenesis of TED. The production of autoantibodies to cross-linked thyroid-stimulating hormone receptor and insulin-like growth factor-1 receptor (IGF-1R) activates OFs to produce significant cytokines and chemokines and hyaluronan production and to induce adipocyte differentiation. In moderately severe active TED patients, multicenter clinical trials showed that inhibition of IGF-1R with teprotumumab was unprecedentedly effective with minimal side effects. The emergence of novel biologics resulted in a paradigm shift in the treatment of TED. We here review the literature on advances of pathogenesis of TED and promising therapeutic targets and drugs.

Keywords:
Autoimmune, insulin growth factor-1 receptor, orbital fibroblast, pathogenesis, thyroid eye disease, thyroid-stimulating hormone receptor

Introduction

Thyroid eye disease (TED, synonyms: Graves’ ophthalmopathy, Graves’ orbitopathy, and thyroid-associated ophthalmopathy) is the most frequent extrathyroidal feature of Graves’ disease (GD) but can also be associated with euthyroidism and Hashimoto’s thyroiditis.[¹,²] This is an orbital inflammatory autoimmune disorder, and the incidence of new cases is estimated at 20–50 per 100,000 people per year.[¹] It is reported that 40%–50% of GD patients develop TED with heterogeneous clinical phenotypes. TED is a multifactorial autoimmune disease affected by genetics, environmental factors such as smoking and stress, and immune status. Most common symptoms of TED include eyelid retraction, exophthalmos, restrictive strabismus with diplopia, and dysthyroid optic neuropathy. Thus far, high-dose glucocorticoid and orbital radiation have been a mainstay of treatment focusing on reducing orbital inflammation. These treatments mainly improve clinical activity score (CAS) and diplopia in patients with early, active inflammation. Therapy for chronic inactive TED is primarily surgical for exophthalmos, strabismus, and eyelid retraction. It is difficult to assess and manage TED patients, owing to its heterogeneity and also to predict which patients will progress into severe ophthalmopathy.

Various treatments targeting specific receptors, cytokines, and immune cells have been introduced with promising results. Recent remarkable advances in understanding pathogenesis of TED led to the emergence of a new biologic inhibitor of insulin-like growth factor-1 receptor (IGF-1R), teprotumumab, which gained approval by the US Food and Drug Administration (FDA) in early 2020.[³] This paper will review accumulated knowledge regarding the...
immunopathogenesis of TED by both clinicians and scientists and suggest promising specific drugs, as well as recently approved novel treatment for TED. A systematic search of PubMed was undertaken for studies related to pathogenesis of TED and therapeutic targets.

**Orbital Fibroblast and Fibrocyte**

Human orbital fibroblasts (OFs) are considered as the key target and effector cells in TED pathogenesis [Figure 1]. Studies have characterized why extrathyroidal manifestations of GD occur in the orbit, and it may be because the orbital tissues display a novel phenotype including peculiar sensitivity to cytokines and undergo characteristic remodeling. More robust production of interleukin (IL)-6, IL-8, and monocyte chemotactic protein-1 in response to IL-1β [4,5] and a substantial induction of IL-16 and regulated on activation, normal T-cell expressed and secreted responding to GD-immunoglobulin G (IgG) was noticed in Graves’ OFs but not in OFs from controls without GD. [6] Graves’ OFs also showed enhanced proliferative capacity at baseline and in response to proinflammatory cytokines. [7] A subpopulation of OFs, based on the expression of the surface Thy-1 antigen, was observed with a different molecular response, which explains the heterogeneous clinical course of TED. [8] Perimysial fibroblasts express Thy-1 uniformly and do not undergo adipogenesis, whereas adipose tissue-derived fibroblasts express less Thy-1, undergo adipocyte differentiation, and express high level of peroxisome proliferator-activated receptor γ. Thy-1+ OFs produce higher levels of prostaglandin endoperoxide H synthase-2 and prostaglandin E2 than Thy-1-OFs, whereas Thy-1-OFs produced more IL-8 than Thy-1+ OFs. [8] Khoo et al. reported that Thy-1 mRNA and protein expression was higher in orbital tissue and OFs from TED donors compared to those from controls. [9]

Fibrocytes, bone marrow-derived fibroblast-like progenitor cells expressing CD34, CXCl chemokine receptor 4, and collagen I phenotype, participate in the inflammatory process. [10,11] A significant increase of circulating CD34+ fibrocytes is observed in TED patients. [12] These fibrocytes express thyroid-stimulating hormone receptor (TSHR) and CD40 in substantially higher amounts than in OFs, producing high levels of cytokines and chemokines [12,13] and carrying plasticity to differentiate into adipocytes or myofibroblasts. [14] An assumption has been proposed that circulating CD34+ fibrocytes infiltrate orbital tissues, where they convert into CD34+ OFs mixing with CD34-OFs, all expressing both IGF-1R and TSHR. [11] Evidence shows CD34+/CD34-OFs exhibit distinct molecular functions associated with TED pathogenesis. Dramatic elevation of autoimmune regulator proteins necessary for the expression of thyroid proteins, [15] augmented TSH-induced IL-6 production by CXCL-12 (C-X-C Motif Chemokine Ligand 12), [16] and enhanced expression of tumor necrosis factor-α (TNF-α) by TSH [17] were all shown in CD34+ OFs but not in CD34-OFs. These findings suggest a modulatory role of CD34-OFs by releasing a determining factor that downregulates pathological TSHR signaling. It was recently reported that Slit2 has a distinct role in hyaluronan and cytokine productions in CD34+ fibrocytes and OFs but not in CD34-subsets. [18]

**CD40-CD40 L Interaction**

CD40 plays a pathogenic role in various autoimmune diseases. CD40 is active in regulating B-cell responses

Figure 1: A schematic presentation of the complex cellular and humoral immune responses against autoantigens, thyroid-stimulating hormone receptor (TSH-R), and insulin-like growth factor-1 receptor (IGF-1R) in orbital fibroblasts and the targeted therapy
of the GD susceptibility genes identified.\textsuperscript{[19]} CD40 is characterized as a molecule to active B lymphocytes through the engagement of CD40, by its ligand CD154, presented by activated CD4+ T helper (Th) cells.\textsuperscript{[20]} Like B cells, CD40 is overexpressed in OFs in TED, especially in Thy-1+ OFs,\textsuperscript{[48]} and CD40 L upregulates proinflammatory cytokine and chemokine production and hyaluronan synthesis.\textsuperscript{[4,21,22]} High levels of CD40 are also displayed by fibrocytes,\textsuperscript{[23]} and TSHR-CD40 L protein interaction and co-localization are discovered in fibrocytes.\textsuperscript{[13]} Iscalimab (CFZ533), an Fc-silenced blocking anti-CD40 monoclonal antibody, was proven safe and well tolerated without depletion of leukocytes in a first-in-human randomized controlled study.\textsuperscript{[24]} In an open-label multicenter phase 2 study in GD patients, iscalimab induced euthyroidism in 47%, with a decline of TSHR antibody in all patients with minimal side effects.\textsuperscript{[25]} In a recent pilot study, haplotypes B and C of CD40 single nucleotide polymorphisms (SNPs) were associated with higher CD40 mRNA and clinical response to iscalimab, suggesting a pretreatment screening of SNF genotype.\textsuperscript{[26]} CD40 targeting biologics have not yet been investigated in TED, which could represent a novel therapeutic approach in the disease where CD40-CD40 L interaction has a major role in the immunopathogenesis.

**Thyroid-Stimulating Hormone Receptor and Insulin-Like Growth Factor-1 Receptor Crosstalk**

TSHR is a glycoprotein hormone receptor with a large extracellular domain for binding to the ligand, a seven transmembrane domain, and an intracellular domain bound to G-protein subunits.\textsuperscript{[27]} Several studies have exhibited that TSHR is an autoantigen shared by the orbit and the thyroid gland.\textsuperscript{[28,29]} and significantly higher levels of TSHR transcript and immunoreactivity are demonstrable in Graves’ orbital tissues and early passage of OFs.\textsuperscript{[30]} Adipose tissues from active TED patients express higher levels of TSHR along with proinflammatory cytokines than tissues obtained from inactive patients.\textsuperscript{[31]} Clinical observations demonstrate that persisting high TSHR antibody levels is associated not only with low remission rates of hyperthyroidism but also with a more severe course of ophthalmopathy, independent from smoking and age.\textsuperscript{[32]} A novel TSHR luciferase reporter bioassay with Mc4-CHO cells revealed a strong positive correlation with the clinical activity and severity of TED.\textsuperscript{[33,34]}

Several treatments targeting TSHR have been proposed. Isolation of human monoclonal autoantibody with blocking activity (K1-70) with high affinity resulted in a dose-dependent reduction of fT4 levels and suppressed the stimulating effect of M22 in rats.\textsuperscript{[35,36]} A phase 1 open-label trial is currently obtaining safety and tolerability data in GD patients (ClinicalTrials.gov identifier: NCT02904330). Thyroid-stimulating antibody activity in serum decreased with the improvement of proptosis and inflammation of orbit following administration of K1-70 therapy in a case with follicular thyroid cancer, GD, and orbitopathy.\textsuperscript{[37]} Some of the low-molecular-weight antagonists for TSHR (NIDDK/CEB-52,\textsuperscript{[38]} NCGC00229600\textsuperscript{[39]}) were identified to inhibit the activation of TSHR. NCGC00229600 inhibited TSH and M22 stimulated cAMP, Akt phosphorylation, and hyaluronan production in Graves’ OFs.\textsuperscript{[40]} Nanomolar concentrations of Org 274179-0 eliminated TSH-mediated TSHR activation with little effect on the potency of TSH by an allosteric-binding mechanism.\textsuperscript{[41]} S37a, a highly selective TSHR inhibitor, was discovered to repress TSHR activation with no toxicity and high oral bioavailability in mice.\textsuperscript{[42]} These TSHR antagonists possess the potential to treat TED; however, efficacy and safety have not yet been demonstrated through clinical studies.

A functional crosstalk between G-protein coupled TSHR and a tyrosine kinase receptor, IGF-1R, has been discovered, suggesting the signaling platform containing two receptors leads to synergistic stimulation of cellular responses.\textsuperscript{[43,44]} Co-localization of two receptors in OFs and thyrocytes was demonstrated by immunofluorescence staining for IGF-1R and TSHR.\textsuperscript{[44]} IGF-1R is composed of the ligand binding, extracellular domain, IGF-1Rα, and membrane-spanning β subunit-containing tyrosine phosphorylation site for canonical signaling.\textsuperscript{[45]} IGF-1R levels are considerably higher on Graves’ OFs, and the IGF-1R+T cells are increased in both peripheral blood and orbital connective tissue infiltrates in patients with GD.\textsuperscript{[46,47]} IGF-1R was also upregulated in B cells from GD patients, and IGF-1 synergistically adds to the IgG production by B cells from GD but not from control donors.\textsuperscript{[47]} IGF-1R on OFs, when stimulated with GD-Igs or IGF-1, leads to the expression of T-cell chemoattractants\textsuperscript{[48]} and enhanced synthesis of hyaluronan in Graves’ OFs, which is absent in control OFs.\textsuperscript{[49]} IGF-1 blocking antibody (IH7) attenuated the actions of both TSH and IGF-1 in fibrocytes with the suppression of proinflammatory cytokine production.\textsuperscript{[50]} Two different IGF-1R blocking antibodies, IH7 and AF305, blocked binding of IGF-1 to IGF-1R in Graves’ OFs but only IH7 partially blocked hyaluronan production by M22, a stimulating TSHR antibody similar to the effect of linsitinib, an IGF-1R kinase inhibitor, indicating IGF-1R is activated through TSHR/IGF-1R crosstalk.\textsuperscript{[51]} In a recent study, the crosstalk occurs proximal to the receptors and the distance between is within 40 nm of each other by Proximity Ligation Assay.\textsuperscript{[52]} In this study, the presence of β-arrestin 1 protein was necessary for the TSHR/IGF-1R signaling complex, as knock-down of β-arrestin 1 decreased the receptor co-localization.
Teprotumumab, a fully human IgG1 monoclonal blocking antibody that binds to extracellular α-subunit domain of IGF-1R, was first developed for solid tumors and lymphomas but became the first approved drug for TED based on recent advances in the understanding of the TSH/IGF1R crosstalk as an effective target. Teprotumumab has been shown to decrease TSHR and IGF-1R display and reduce TSH/M22 stimulated cytokines and Akt phosphorylation in Graves’ OFs and fibrocytes.[50,51] In two randomized, multicenter, double-masked, placebo-controlled, phase 2 and 3 clinical trials, published in 2017 and 2020, teprotumumab demonstrated a significant improvement in proptosis beginning at 6 weeks of treatment and over the course of 24 weeks compared to controls, with similar effects to surgical decompression in active moderate-to-severe TED patients.[5,54] At week 24, 83% in teprotumumab group had a reduction of proptosis ≥2 mm compared to 10% in the placebo group, and all secondary outcomes including overall response, CAS, diplopia, and quality of life score were significantly better in the teprotumumab group with minimal side effects.[53] Fifty-five percent in Teprotumumab-treated group achieved proptosis reduction ≥3 mm compared to 8.9% of placebo-treated group.[53] Of the most commonly reported adverse events with teprotumumab, muscle spasm (18%), hearing loss (10%), and hyperglycemia (8%) had the greatest risk difference from placebo. Based on the evidence, FDA approved Teprotumumab in early 2020, as the first drug for TED treatment. Orbital imaging showed decreased extraocular muscle and orbital fat volume and reduced MRI signal intensity ratio of extraocular muscles in post-teprotumumab patients.[56] Some reports demonstrate that teprotumumab is effective in the resolution of optic neuropathy in the early course of teprotumumab[57,58] and significantly reduces the proptosis even in chronic TED patients with low CAS.[59,60]

**T Cells Trafficking to Orbit and Their Cytokines**

T cells have a significant role in the pathogenesis of TED. T cells activate B cells to stimulate the production of autoantibody and OFs through CD40/CD40 L binding. Sensitized T lymphocytes recognizing autologous orbital antigens are demonstrated in the peripheral blood and orbit from TED.[61] OFs secrete chemokines and adhesion molecules which recruit lymphocytes into orbital tissues,[61,62] and further interaction between OFs and T cells occurs. The clinical activity of TED was reported to correlate with T and B lymphocytes infiltration in orbital tissues[63] and with the TH1/Th2 cell ratio in peripheral blood.[64] Th17 cells are newly identified to contribute to the TED pathogenesis. Higher levels of IL-17A and IL-17A producing T cells were detected in the peripheral blood from TED patients,[65,66] and IL-17A enhances more robust production of cytokines in TED fibrocytes than in normal.[67] Furthermore, a positive correlation between the number of Th17 cells and CAS was found.[67]

Activated T cells, primarily CD4+T cells, produce cytokines, aggravating the inflammatory response, adipocyte differentiation, proliferation, and glycosaminoglycan accumulation in OFs.[68,69] A Th1 immune response predominates in the active early phase, leading to the production of interferon (IFN)-γ, TNF-α, IL-1β, and IL-2 that enhance fibroblast proliferation and glycosaminoglycan synthesis, whereas Th2 cytokines are more abundant later.[70] Orbital muscle tissue from TED patients was dominated by Th1 cytokines, while cytokine types varied in orbital adipose tissues, meaning clinical manifestation of TED may be dependent on types of cytokines.[71] Cytokines have been discussed as novel targets for TED. Several case and pilot studies have demonstrated that monoclonal antibody against TNF-α such as infliximab and etanercept is effective in steroid resistant, active TED patients reducing inflammation and visual function.[72,73] Adalimumab, another anti-TNF-α agents, was effective in anti-inflammatory and steroid-sparing effect in TED patients.[74] Tocilizumab, a humanized monoclonal antibody against IL-6, was effective in reducing proptosis and motility restriction with no relapse of TED in a prospective, nonrandomized study.[75] A follow-up double-masked, placebo-controlled trial demonstrated a reduction of at least 2 CAS in 93% of tocilizumab group compared to 59% receiving placebo.[76]

**B Cells and Targeting CD20**

B cells migrate to the orbit and recognize autoantigens expressed on OFs through B cell receptors after immune tolerance. Besides the production of antibodies, B cells have multiple other actions based on B-T cell interactions. B cells produce cytokines, mainly IL-4, IL-6, IL-10, IFN-γ, and TGF-β, and also function as antigen-presenting cells in the early phase of the autoimmune process.[77] In peripheral blood from patients with recent-onset autoimmune thyroid disease, thyroid antigen-reactive B cells are activated expressing CD86, leading to the production of autoantibodies.[78]

Rituximab (RTX) is a chimeric murine/human monoclonal antibody against CD20 antigen located on B cells. It is FDA approved in rheumatoid arthritis, granulomatosis with polyangiitis, chronic lymphocytic leukemia, and non-Hodgkin’s lymphoma. It has also been used in different autoimmune disease as off-label drug.[79] RTX was proposed as a promising drug to treat TED based on reducing autoantibody. Stimulating TSHR Ab was significantly reduced when RTX was combined with antithyroid drugs in hyperthyroid
patients, compared to those administered antithyroid drugs alone.\textsuperscript{79} Salvi \textit{et al.} reported CAS decreased more after RTX than with IV methylprednisolone (7.5 g), and there was no reactivation in RTX group compared to five patients of IV methylprednisolone treated patients.\textsuperscript{80} However, RTX was not effective in another randomized, placebo-controlled trial.\textsuperscript{81} A post hoc analysis of the two trial results has found that the disease duration differed patients between groups and might have been responsible for inconsistent data.\textsuperscript{82} A meta-analysis and systemic review of four randomized trials found a significant reduction of CAS but not proptosis reduction in the RTX group, compared to controls.\textsuperscript{83} Recently, early use of low-dose RTX was reported to be effective to ameliorate inflammatory activity in active, steroid-resistant TED leading to a reduced systemic steroid administration.\textsuperscript{84,85}

The neonatal fragment crystallizable (Fc) receptor (FcRN) has a role to prevent degradation and prolong the half-life of IgG during recycling process of IgG.\textsuperscript{86,87} Multiple FcRN inhibitors have emerged as a potential treatment in antibody-mediated autoimmune disease and currently are in clinical trials for antibody-mediated autoimmune diseases such as myasthenia gravis and immune thrombocytopenia.\textsuperscript{88} IMVT-1401/RVT-1401, a fully human monoclonal antibody against FcRn, developed as a subcutaneous injection, has been studied in a phase 2, multicenter, open-label trial (ASCEND GO-1) and double-blinded, placebo-controlled trial (ASCEND GO-2) for active, moderate-to-severe TED (ClinicalTrials.gov Identifier: NCT03922321, NCT03938545, retrospectively), however, unfortunately, ASCEND GO-2 was terminated due to unexpected elevation of serum cholesterol level.

**Statins and Other Hypolipidemic Drugs with Pleotropic Effects**

Statins are a class of hypolipidemic drug that is traditionally used to lower cholesterol by inhibiting hydroxymethylglutaryl-coenzyme A reductase. In the past recent years, extensive studies have shown that statins also have a pleiotropic anti-inflammatory, antifibrotic, and anti-immune modulatory effect.\textsuperscript{88} Statins can shift proinflammatory Th17/Th1 cells toward regulatory T-cells resulting in decreased T-cell activation and inflammatory cytokine production.\textsuperscript{89} In a longitudinal cohort study of 740 patients with newly diagnosed GD, statin use for ≥60 days was related to a 40% decreased hazard (adjusted hazard ratio [HR], 0.6) but not with nonstatin cholesterol-lowering agents.\textsuperscript{89} A recent epidemiologic report showed statin users were less likely to develop TED with full adjusted HR 0.78 for men and 0.91 for women.\textsuperscript{90} Laboratory evidence regarding therapeutic effect of statin in OFs was studied. Simvastatin inhibited TGF-β induced fibrosis markers in Graves’ OFs through RhoA-mediated Erk and p38 signaling pathways.\textsuperscript{91} Cysteine-rich protein 61, a product of an immediate early gene, is known to act as a proinflammatory factor in many inflammatory diseases and was found overexpressed in OFs and in serum from active TED patients,\textsuperscript{92} and its induction by TNF-α was suppressed by simvastatin through the mediation of FoxO3a signaling.\textsuperscript{93} Simvastatin also downregulated the early and late adipogenic gene and adipogenesis in OFs.\textsuperscript{94} A hypothesis is proposed that statins reduce orbitopathy risk by modulation of both apoptosis and autophagy,\textsuperscript{95} which are found to be involved in the pathogenesis of TED.\textsuperscript{96} In a recent randomized controlled study, addition of oral atorvastatin to an IV glucocorticoid improved TED outcomes at 24 weeks of treatment in patients with moderate-to-severe, active eye disease and hypercholesterolemia (ClinicalTrials.gov Identifier: NCT03110848, protocol ID: STAGO).\textsuperscript{97}

Metformin is a biguanide hypoglycemic drug for Type 2 diabetes and also has been shown to have anti-inflammatory action by blunting secretion of proinflammatory cytokines and inhibition of nuclear factor kappa β signaling.\textsuperscript{98} In a meta-analysis of six randomized placebo-controlled studies, both total and low-density lipoprotein (LDL)-cholesterol levels decreased in metformin-treated patients.\textsuperscript{99} In Graves’ OFs, metformin and phenformin suppressed adipogenesis, proinflammatory cytokine production, and hyaluronan release, providing some evidence of the potential use of biguanide for the treatment of TED.\textsuperscript{100}

Recently, proprotein convertase subtilisin-kexin type 9 (PCSK9) is identified to play a major role in hypercholesterolemia and atherosclerosis through promoting lysosomal degradation of LDL receptors, and the FDA approved two novel antibodies against PCSK9, evolocumab and alirocumab, for lowering LDL-cholesterol.\textsuperscript{101} PCSK9 inhibitors have also shown to have pleotropic effects of anti-inflammation beyond the LDL-lowering effect.\textsuperscript{102} Orbital adipose tissue from TED patients had higher PCSK9 transcript levels than controls and knock-down of PCSK9 blocked proinflammatory cytokine production and adipogenesis in Graves’ OFs, suggesting PCSK9 as a potential promising therapeutic target.\textsuperscript{103}

**Selenium**

While the management of moderate-to-severe and active TED includes high dose intravenous glucocorticoids, orbital radiotherapy, surgery, and other biologics of specific immunologic target, an anti-oxidant trace mineral, selenium, is recommended in patients with mild TED. Selenium has been reported to show more improved quality of life, less eye involvement, and
more improvement of CAS, compared to placebo in a randomized, double-masked, placebo-controlled trial.\footnote{104}

In several in vitro studies, selenium reduces \( \text{H}_2\text{O}_2 \)-induced oxidative stress, proliferation, hyaluronan synthesis,\footnote{105} and proinflammatory cytokine production in OFs.\footnote{106,107} Controversy exists regarding the association of selenium levels with the severity or activity of TED.\footnote{108,109} The value of supplemental selenium on antithyroid drug medication in GD is still debatable in some randomized, controlled trials, especially in a selenium-sufficient cohort of GD.\footnote{110,111}

**Conclusion**

Over the last decades, substantial progress has been made in understanding the pathogenesis of TED, and several potential therapeutic targets have been discovered. Despite the lack of specific animal model for TED, in vitro studies in OFs and fibrocytes from patients with GD (recognizing the importance of IGF1-1R/THSR crosstalk) have been vital to the development of a new drug targeting IGF-1R with a remarkable treatment effect in moderate-to-severe, active TED patients, even replacing surgery in many cases. However, the high cost of the drug is a barrier to uninsured patients’ treatment access and may lead to obstacles in approval in other countries. More results from multicenter, prospective longitudinal studies are needed to understand the long-term effects of teprotumumab compared to the combination of glucocorticoid and radiotherapy, which has still shows some efficacy with lower costs.

With advances in monoclonal antibody technology, there are a number of approaches targeting TSHR, B cells, T cells, and multiple cytokines, especially in the field of GD, which still need to be investigated in TED to provide a proof of efficacy. The efficacy of statins and other hypolipidemic drugs with pleotropic effects also needs verification in clinical trials. Many questions remain to be answered regarding aspects of TED including the unknown molecular pathogenesis associated with heterogeneous clinical phenotypes.

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**Conflicts of interest**

The authors declare that there are no conflicts of interest of this paper.

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