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Immune modulation by rebamipide in a mouse model of Sjogren's syndrome via T and B cell regulation

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ABSTRACT

Rebamipide is a gastroprotective drug used widely in the treatment of gastritis and gastric ulcers. It has also been shown to improve dry eye and dry mouth, two major symptoms of Sjogren's syndrome (SS). However, little is known about the effects of rebamipide on T and B cell regulation in SS. In this study, we used a NOD/ShiLtJ mouse model of SS to examine the ability of rebamipide to ameliorate disease development by modulating T and B cells. Our results show that the oral administration of rebamipide suppressed SS progression and the level of inflammatory cytokines, including interleukin (IL)-6, tumor necrosis factor-α, and IL-17, in the salivary glands and spleen of NOD/ShiLtJ mice. Rebamipide treatment also increased the number of *ex vivo* CD19 + CD25 + Foxp3 + regulatory B cells and CD19 + CD5 + CD1d + IL-10 + cells in NOD/ShiLtJ mice. *In vitro*, rebamipide suppressed IL-6 and IL-17 production by Th17 cells in splenic CD4 + cells from the mice. Thus, rebamipide may be effective in controlling the immune imbalance between pathogenic immune cells and regulatory cells, resulting in fundamental improvement in patients with SS.

1. Introduction

Sjögren's syndrome (SS) is a systemic autoimmune disease characterized by the infiltration of lymphocytes into the salivary and lacrimal glands, which leads to destruction of the glands and therefore dysfunctional glandular secretion. Ocular dryness (keratoconjunctivitis sicca) and oral dryness (xerostomia) are the major clinical manifestations of SS [1]. The extraglandular complications of SS include chronic fatigue, musculoskeletal symptoms, and symptoms involving the peripheral nervous system [2]. Moreover, SS patients are at a higher risk of developing malignancies, particularly non-Hodgkin's lymphomas, which are a significant cause of morbidity [3].

Although the pathogenesis of SS has yet to be fully elucidated, lymphocytic infiltration of the exocrine glands is known to be a major cause of disease development. In ectopic lymphoid structures such as the salivary and lacrimal glands, T cells act directly to induce tissue destruction and transmit signals to B cells that are essential for the latter's clonal selection and affinity maturation [4,5]. The hyperactivated B cells produce autoantibodies, including anti-SSA/Ro and anti-SSB/La, directed against small RNA molecules and rheumatoid factors, respectively [6,7].

Rebamipide is a gastroprotective agent used in the treatment of gastritis and gastric ulcers. Its mechanism of action involves the enhanced biosynthesis of gastric endogenous prostaglandins E2 and I2 and epithelial mucin, which in turn acts as an oxygen-free radical scavenger [8,9]. The various anti-inflammatory properties of

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rebamipide include suppressing the production of inflammatory cytokines from monocytes and gastric mucosal cells [10]. In a previous study, we showed that rebamipide ameliorates the severity of rheumatoid arthritis and spondyloarthritis through the modulation of T and B cells [11–13]. However, whether rebamipide also acts on T and B cells in SS is unknown.

Thus, in the present study we investigated the ability of rebamipide to alleviate SS progression by acting on disease-induced T and B cells in NOD/ShiLtJ mice, a murine model of SS. Our results show that rebamipide administration suppressed both the severity of SS and the levels of inflammatory cytokines in the salivary glands and spleen of the mice. Specifically, rebamipide increased the number of *ex vivo* regulatory B (Breg) cells and interleukin (IL)-10-producing B cells while decreasing the number of IL-17-producing T (Th17) cells and the production of inflammatory cytokines, such as IL-6 and IL-17. In addition, in splenic CD4 + cells from NOD/ShiLtJ mice, rebamipide increased the number of regulatory T (Treg) cells *in vitro*.

2. Materials and methods

2.1. Animals

Female 7-week-old NOD/ShiLtJ mice were purchased from the Jackson Laboratory (Bar Harbor, ME, USA) and maintained under specific pathogen-free conditions at the Institute of Medical Science of the Catholic University of Korea. The mice were fed a gamma ray-sterilized diet (TD 2018S; Harlan Laboratories, Inc., Madison, WI, USA) and provided with autoclaved R/O water. All experimental procedures were evaluated according to the Laboratory Animals Welfare Act, the Guide for the Care and Use of Laboratory Animals, and the Guidelines and Policies for Rodent Experiments, provided by the Institutional Animal Care and Use Committee of the School of Medicine and subsequently approved. The procedure conformed to all National Institutes of Health (USA) guidelines (permit number: CUMC-2019-0095-01).

2.2. Rebamipide treatment

Rebamipide was dissolved in 0.5% carboxylmethylcellulose (CMC). Seventeen-week-old NOD/ShiLtJ mice were orally administered 3 mg of rebamipide/kg daily for 6 weeks. Control mice were administered vehicle (0.5% CMC).

2.3. Measurement of saliva secretion from NOD/ShiLtJ mice

Saliva secretion was stimulated in anesthetized mice by an intraperitoneal injection of pilocarpine (Sigma-Aldrich, St. Louis, MO, USA) at a dose of 5 mg/kg body weight. Saliva was collected from the oral cavity for 7 min beginning 90 s after the injection and using a micropipette. The volume of saliva in the sample was determined gravimetrically (μl/g/min).

2.4. Histopathologic examination and immunohistochemistry

The salivary glands of the mice were fixed in 4% paraformaldehyde and embedded in paraffin. Sections (5 μm thick) were prepared and stained with hematoxylin and eosin. Histopathologic indexes were enumerated as described previously [14]. The salivary glands and spleen were incubated overnight at 4 °C with primary antibodies against IL-6, IL-17, and tumor necrosis factor (TNF)-α, followed by incubation with biotinylated secondary antibodies and the addition of a streptavidin-peroxidase complex. After 1 h of incubation, the colored products were developed using the chromogen DAB (Dako, Carpinteria, CA, USA) as the substrate. The sections were then examined under a light microscope (Olympus, Tokyo, Japan).

2.4.1. Isolation and stimulation of splenocytes

CD4 + cells were purified from the spleens of the mice using a MACS Isolation Kit (Miltenyi Biotec, Inc., Bergisch Gladbach, Germany). The splenocytes were cultured in RPMI 1640 medium (Gibco, Grand Island, NY, USA) supplemented with 5% fetal bovine serum. Murine CD4 + T cells were treated with soluble anti-CD3 (0.5 μg/ml) and anti-CD28 (1 μg/ml) (BD Pharningen, San Diego, CA, USA) antibodies. The cells were also pretreated for 2 h with rebamipide at concentrations of 100, 300, and 900 μM and then stimulated under the required conditions. Three days later, the cells were analyzed by flow cytometry. Supernatants were used to determine cytokine levels.

2.5. FACS analysis

CD4 + cells were stimulated with 25 ng/ml of phorbolmyristate acetate/ml (Sigma-Aldrich) and 250 ng/ml of ionomycin/ml and treated with GolgiStop (BD Biosciences, Franklin Lakes, NJ, USA). They were also stained with Percp-conjugated anti-CD4, PCy7-conjugated anti-CD19, and allophycocyanin (APC)-conjugated anti-CD25 (BD Pharmingen) antibodies or phycoerythrin (PE)-conjugated anti-CD1d and FITC-conjugated anti-CD5 (eBiosciences, San Diego, CA, USA) antibodies. Surface marker staining was followed by staining with APC-conjugated anti-interferon-γ, PE-conjugated anti-IL-4, FITC-conjugated anti-IL-17 or PE-conjugated anti-Foxp3 or APC-conjugated anti-IL-10 (eBiosciences) antibodies. The cells were fixed and permeabilized using the Cytofix/Cytoperm buffer set (BD Biosciences). All samples were analyzed on a FACsCalibur (BD Pharmingen) and the data were processed using FlowJo software (Tree Star, Ashland, OR, USA).

2.6. Enzyme-linked immunosorbent assay (ELISA)

The level of interferon (IFN)-γ, IL-6, and IL-17 in the culture supernatants were determined by a sandwich ELISA (Duoset; R&D Systems, Lille, France). Streptavidin-conjugated horseradish peroxidase was used for color development. The absorbance at 450 nm was measured using an ELISA microplate reader (Molecular Devices, Sunnyvale, CA, USA).

2.7. Statistical analysis

Statistical analyses were performed using GraphPad Prism 5 software. The data were analyzed using a two-tailed paired *t*-test and one-way ANOVA (grouped). In all analyses, P-values < 0.05 were considered to indicate statistical significance.

3. Results

3.1. Rebamipide reduces SS progression in NOD/ShiLtJ mice

The ability of rebamipide to alter the progression of SS *in vivo* was examined by measuring the saliva flow rate in NOD/ShiLtJ mice orally administered the drug or treated with vehicle. The results show that saliva secretion was higher in the rebamipide-treated NOD/ShiLtJ mice than in the vehicle-treated mice (Fig. 1A). The infiltration of inflammatory cells into the salivary glands was also lower in the rebamipide group than in the vehicle control group (Fig. 1B).

3.2. Rebamipide decreases the level of inflammatory cytokines in NOD/ShiLtJ mice

The effect of rebamipide on the level of inflammatory cytokines was determined in salivary gland sections stained immunohistochemically for IL-6, TNF-α, and IL-17. The levels of all three cytokines were markedly lower in the salivary glands of the treated mice (Fig. 2). Compared with the vehicle-injected group, the expression of IL-6, TNF-α, and IL-17 in the spleen was lower in mice injected with rebamipide

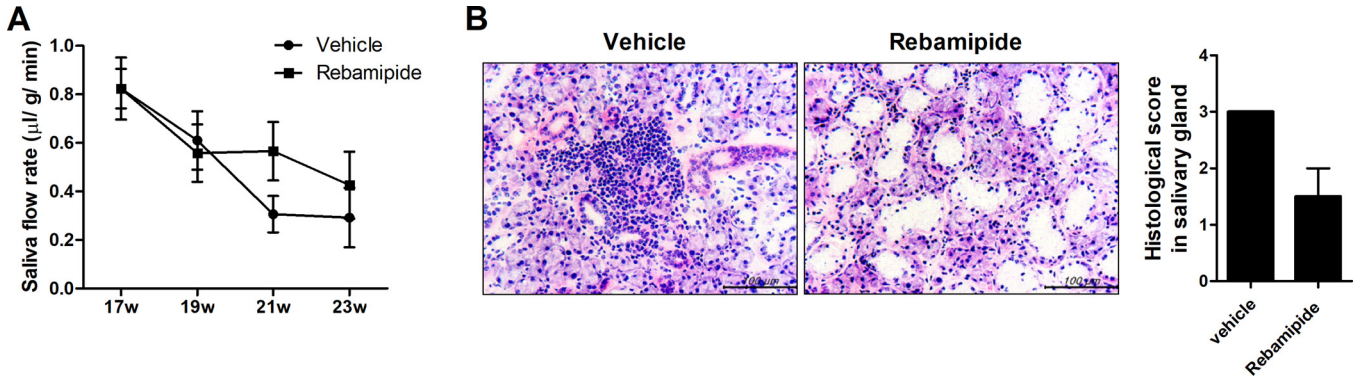

Fig. 1. Rebamipide attenuates the severity of SS in NOD/ShiLtJ mice. Seventeen-week-old female NOD/ShiLtJ mice were orally administered 3 mg of rebamipide/kg daily for 6 weeks (n = 3). (A) The saliva flow rate was measured for 7 min at weeks 17, 19, 21, and 23. (B) Five weeks after the oral administration of rebamipide to the mice, salivary gland sections were prepared and stained with hematoxylin and eosin. Representative histological features are shown. The graph shows the histologic grade. The values represent the mean ± standard deviation (SD).

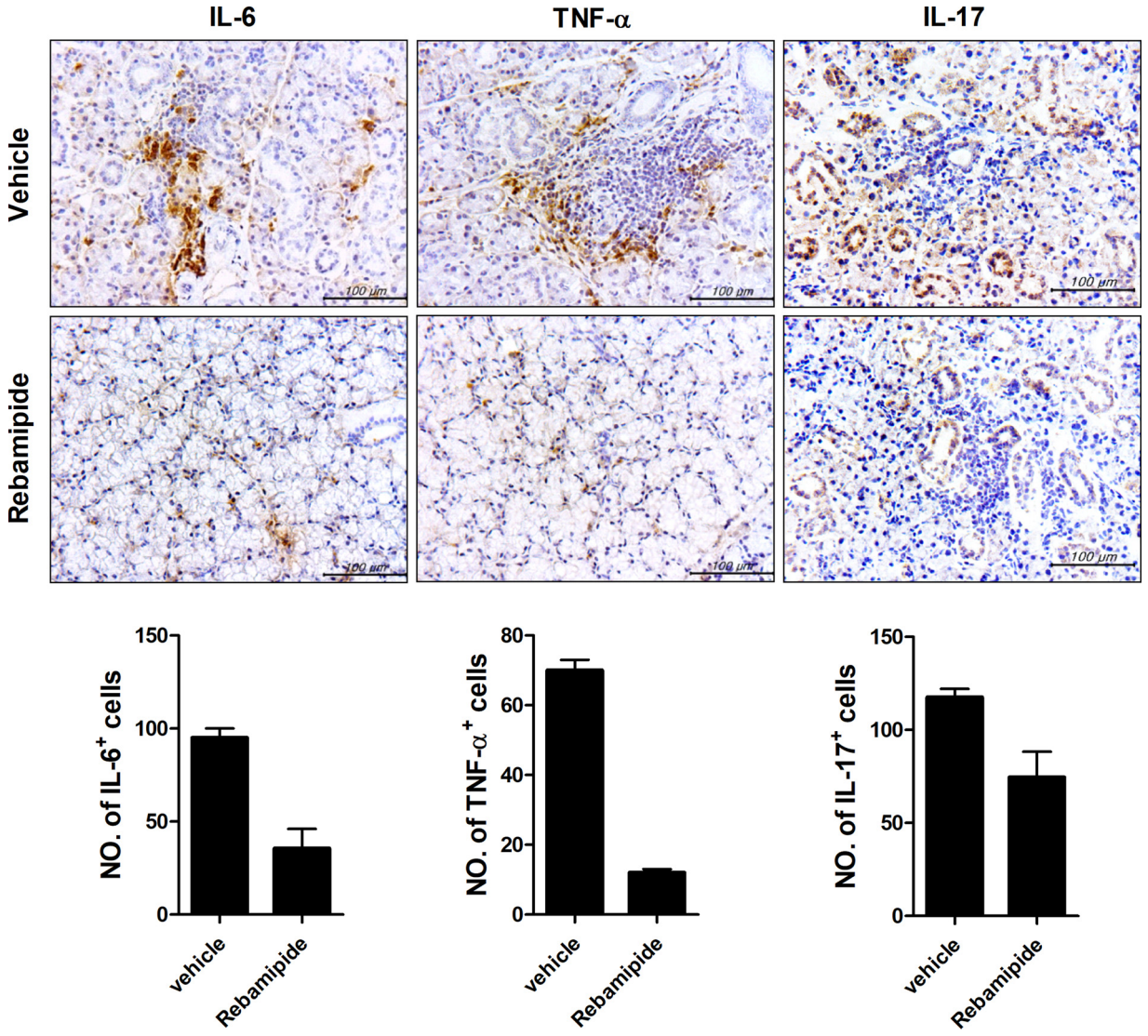

Fig. 2. Rebamipide treatment decreases the levels of inflammatory cytokines in the salivary glands of NOD/ShiLtJ mice. Seventeen-week-old female NOD/ShiLtJ mice were orally administered 3 mg of rebamipide/kg daily for 6 weeks (n = 3). Five weeks later, tissue sections prepared from the salivary glands of the mice were stained with antibodies against IL-6, TNF-α, and IL-17. Representative histological features are shown. Scale bar = 100 μm. The graph shows the number of antibody-positive cells. $^{*}P < 0.05$ and $^{**}P < 0.01$ *vs.* the vehicle-treated group. The values represent the mean ± SD.

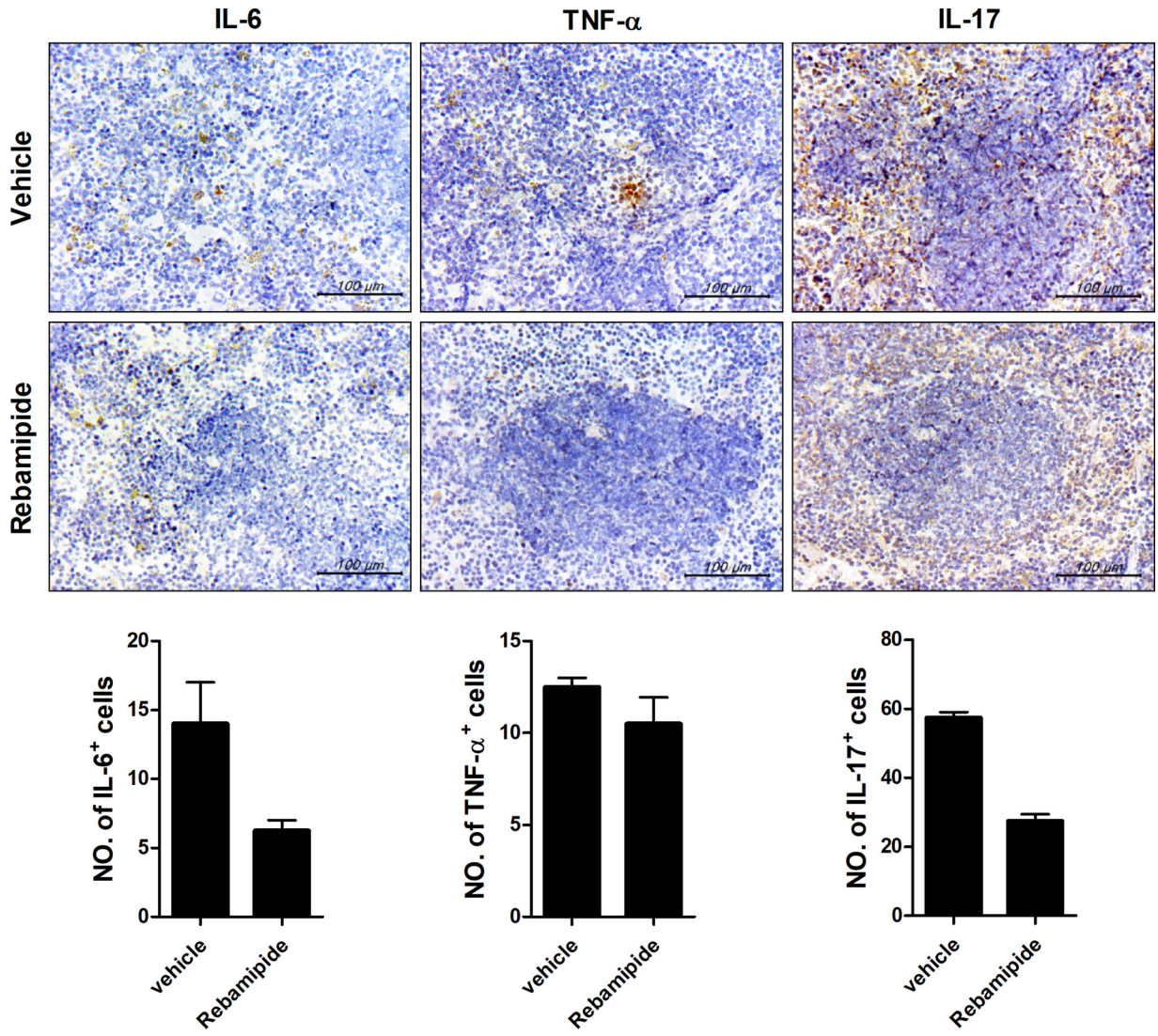

Fig. 3. Rebamipide treatment decreases the level of inflammatory cytokines in the spleen of NOD/ShiLtJ mice. Seventeen-week-old female NOD/ShiLtJ mice were orally administered 3 mg of rebamipide/kg daily for 6 weeks (n = 3). Five weeks later, tissue sections prepared from the spleens of the mice were stained with antibodies against IL-6, TNF-α, and IL-17. Representative histological features are shown. Scale bar = 100 μm. The graph shows the number of antibody-positive cells. $^{*}P < 0.05$ and $^{**}P < 0.01$ *vs*. the vehicle-treated group. The values represent the mean ± SD.

(Fig. 3).

3.3. Rebamipide administration promotes the proliferation of Breg cells in NOD/ShiLtJ mice

Because B cell hyperactivation is a major feature of SS [15], we examined whether rebamipide could be used to control the B cell-mediated inflammatory response. Thus, *ex vivo* cells were isolated from spleens and the number of CD19 + CD25 + Foxp3 + Breg cells and of CD19 + CD1d + CD5 + IL-10 + B cells was analyzed by flow cytometry. Compared to the vehicle-treated mice, larger numbers of Breg and IL-10-producing B cells were obtained from the rebamipide-treated NOD/ShiLtJ mice (Fig. 4A-B).

3.4. Rebamipide controls the number of NOD/ShiLtJ mouse effector T cells in vitro

The regulation of T cells by rebamipide was examined in CD4 + T cells isolated from the spleens of NOD/ShiLtJ mice and stimulated with anti-CD3 and anti-CD28 in the presence or absence of rebamipide. Treatment with rebamipide suppressed Th1 and Th17 cell numbers but dose-dependently increased the number of Treg cells (Fig. 5A). Decreases in the production IFN-γ, IL-6, and IL-17 were also detected in the supernatants prepared from cultures of these cells (Fig. 5B). However, no phenotypic changes were observed in LPS-stimulated CD19 + cells isolated from NOD/ShiLtJ mice treated with rebamipide (data not shown).

4. Discussion

Our results show that rebamipide is able to ameliorate the development of SS by enhancing the number of regulatory B and T cells while reducing both the number of Th17 cells and the production of inflammatory cytokines. In addition, in NOD/ShiLtJ mice, rebamipide suppressed the severity of SS and the level of inflammatory cytokines in the salivary glands and spleen compared with vehicle-treated NOD/ShiLtJ mice. Rebamipide-treated NOD/ShiLtJ mice also had higher numbers of Breg and IL-10-producing B cells in the spleen. In splenic CD4 + cells isolated from NOD/ShiLtJ mice and treated with rebamipide *in vitro*, Th1 and Th17 cell levels as well as the production of IL-6 and IL-17 were suppressed.

Rebamipide has been widely prescribed as a mucosal protective

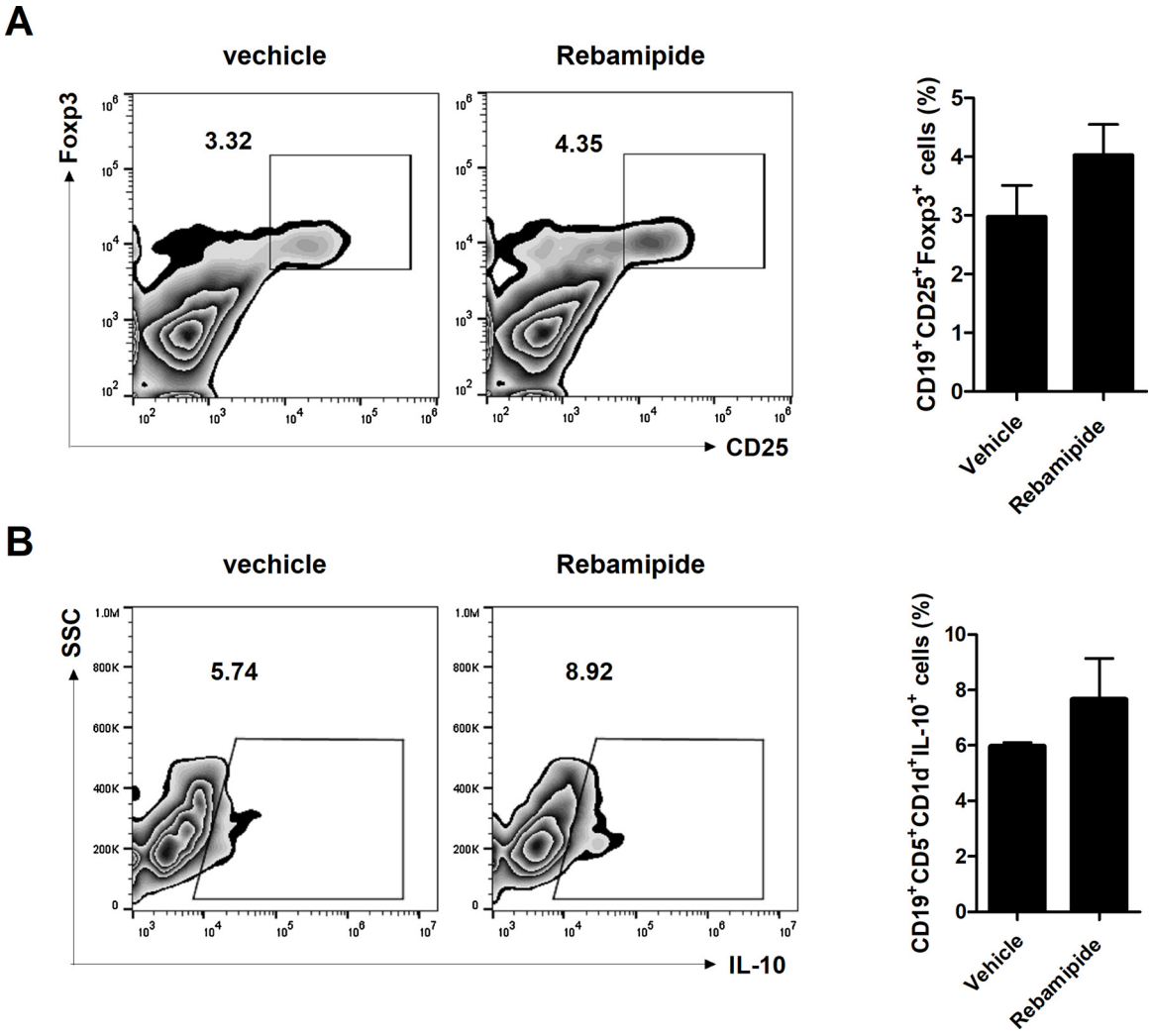

Fig. 4. Rebamipide promotes the number of *ex vivo* Breg cells in NOD/ShiLtJ mice. Seventeen-week-old female NOD/ShiLtJ mice were orally administered 3 mg of rebamipide/kg daily for 6 weeks (n = 3). Five weeks later, *ex vivo* splenocytes were cultured with PMA, ionomycin, and GolgiSTOP for 4 h and then immunostained with antibodies against CD19 + CD25 + Foxp3 + Breg cells (A) and CD19 + CD1d + CD5 + IL-10 + B cells (B). The cells were analyzed by flow cytometry. Representative dot-plot images are shown. The values represent the mean ± SD.

agent for patients with gastritis and gastric ulcers. The drug also exhibits mucin secretagogue and anti-inflammatory activities as well as antibacterial effects [8,10,16]. The efficacy of rebamipide in controlling SS progression and in the treatment of dry eye, a major feature of SS, has been described in several reports. In thymectomized NFS/*sld* mice administered rebamipide eye drops, tear secretion was increased and injuries to the corneal epithelium improved [17]. In clinical studies, SS patients who used rebamipide eye drops had a complete reversal of corneal erosion [18] and improvements in keratoconjunctivitis sicca [19]. Other studies of the therapeutic efficacy of rebamipide in the development of SS determined that the oral administration of the drug to thymectomized NFS/*sld* mice, an alternative murine model of SS, decreased the activation of CD4 + cells, IL-2 and IFN-γ production, and NFκB activity [20]. Rebamipide treatment was also shown to reduce the number of TUNEL + apoptotic duct cells in salivary and lacrimal glands and to inhibit the levels of autoantibodies, IgM, and IgG1 in serum [20]. Our results also showed *in vitro* reductions in Th1 cell numbers and the production of IFN-γ following the exposure of splenic CD4 + cells from NOD/ShiLtJ mice to rebamipide. In a clinical study, patients who received 100 mg of oral rebamipide three times a day reported improvements in dry mouth and increased salivary secretion; however, the results were not significantly different from those of patients who received the placebo [21]. Nonetheless, taken together, these findings demonstrate the potential therapeutic efficacy of rebamipide in patients with SS.

To our knowledge, this is the first study to examine the effects of rebamipide on the regulation of Th17 cells and Breg cells. Rebamipide increased the number of Breg cells and IL-10-producing B cells with an immunomodulating function, while decreasing the number of Th17 cells involved in SS disease development. The inflammatory cytokines produced and released by Th17 cells, including IL-17A, IL-17 F, and IL-21, have been shown to play key roles in rheumatoid arthritis, psoriasis, and other autoimmune diseases [22,23]. Treg cells, by contrast, act to control excessive inflammatory responses and hinder the activity of Th17 cells [24]. In previous reports, we showed that the intraperitoneal injection of rebamipide into a mouse model of spondyloarthritis, established by curdlan injection into SKG ZAP-70^{W163C} mice, improved disease severity, increased the number of Treg cells, and decreased the number of Th17 cells compared to the control group [13]. In addition, rebamipide treatment of splenic CD4 + cells from DBA/1 J mice expressing Th17 cells reduced IL-17 production and decreased the mRNA levels of Th17-associated factors by suppressing the phosphorylation of STAT3, an essential transcription factor in Th17, thus activating Nrf2/hemeoxygenase 1 and increasing the number of Treg cells [12].

In SS, the hyperactivity of B cells leads to the formation of autoantibodies and an ectopic lymphoid structure; both are key events in

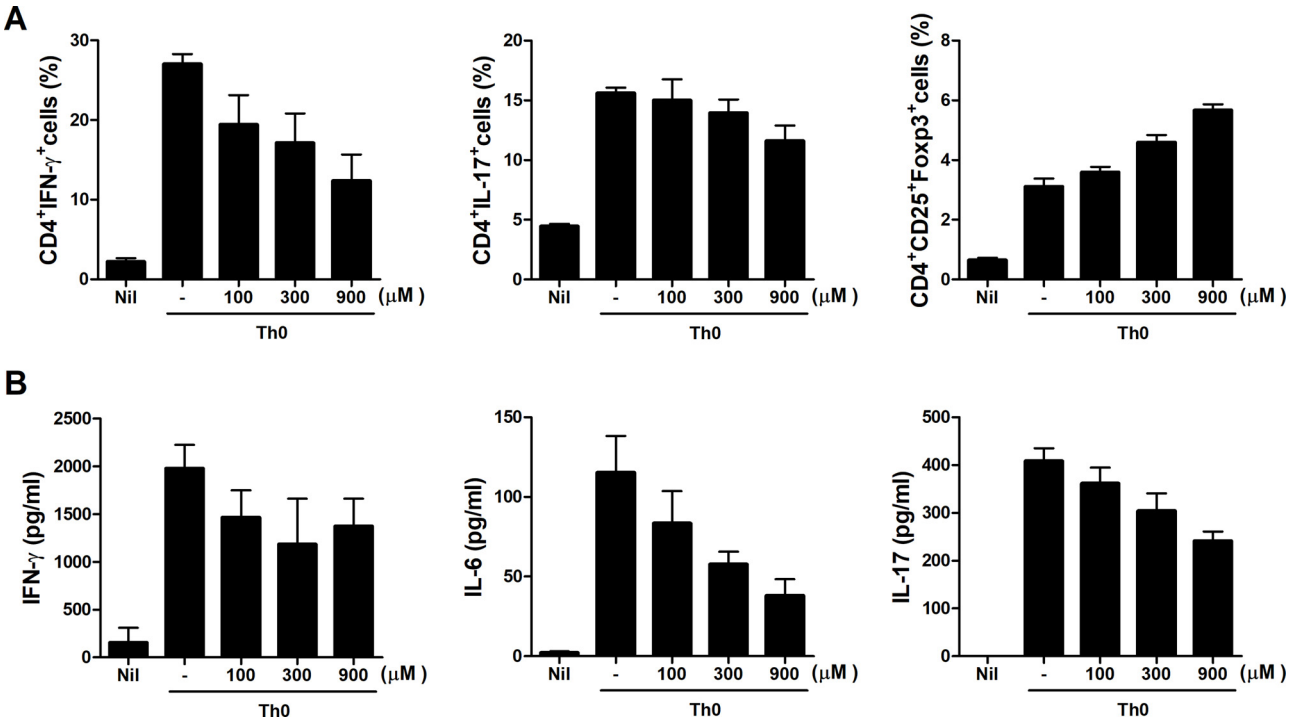

Fig. 5. Rebamipide controls the number of effector T cells *in vitro* in NOD/ShiLtJ mice. Splenic CD4+ cells were isolated from NOD/ShiLtJ mice and then cultured for 72 h with anti-CD3 and anti-CD28 in the presence or absence of rebamipide (100, 300, 900 μM). (A) The cells were stained for CD4+IFN-γ+ (Th1 cells), CD4+IL-17+ (Th17 cells), and CD4+CD25+Foxp3+ (Treg cells) positivity and analyzed by intracellular flow cytometry. (B) The production of IFN-γ, IL-6, and IL-17 in the culture supernatants of the rebamipide-stimulated CD4+ cells in (A) was measured by ELISAs. The values represent the mean ± SD.

the pathogenesis of SS [15]. Therefore, a therapeutic strategy aimed at controlling hyperactive B cells may be effective in SS patients.

In previous studies, we demonstrated that intraperitoneal rebamipide administered to zymosan-injected SKG mice increased the number of *ex vivo* CD19+CD25+Foxp3+ Breg cells and CD19+CD1d + CD5+ cells while reducing serum IgG1 and IgG2a levels [11]. In addition, a decrease in the number of germinal center B cells and an increase in the number of Breg cells were found in LPS-stimulated CD19+ cells isolated from the spleens of SKG mice and treated with rebamipide [11]. In the present study, rebamipide administration to NOD/ShiLtJ mice increased the number of *ex vivo* Breg cells and IL-10-producing B cells compared with vehicle-treated NOD/ShiLtJ mice. Taken together, these results suggest that rebamipide enhances Breg cell activity to control B cell hyperactivation. However, *in vitro*, rebamipide had no effect on LPS-stimulated CD19+ cells from NOD/ShiLtJ mice. Additional studies are needed to determine the direct effect of rebamipide on the regulation of immune-mediated B cells by altering the conditions leading to B cell stimulation.

In conclusion, our study is the first to demonstrate the regulatory effects of rebamipide on Th17 cells and Breg cells in a NOD/ShiLtJ mouse model of SS. Since the overactivity of T and B cells in SS plays an important pathogenic role in oral and ocular dryness, which is the major clinical manifestation of SS, application of rebamipide may be meaningful for the improvement of SS through balancing the immune responses.

Ethics approval and consent to participate

Animals

The procedures were approved by the Animal Research Ethics Committee of the Catholic University of Korea, and conformed to the National Institutes of Health of the United States guidelines (permit number: CUMS- 2019-0095-01)

Consent for publication

Not applicable.

Availability of data and material

All data are available in the manuscript or upon request to the authors.

Competing interests

The authors declare that they have no competing interests.

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Authors' contribution

J.S.P. and S.H.H. designed the experiments, analyzed the data, and wrote the manuscript. S.C.Y., K.A.*J. and J.*W.C. performed the experiments. S.H.P. and M.L.C. conceived and designed the study, analyzed the data, and prepared the manuscript.

Declaration of Competing Interest

All the authors state that they have no conflicts of interest.

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None.

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