Sphingosine-1-Phosphate and Its Signal Modulators Alleviate Psoriasis-Like Dermatitis: Preclinical and Clinical Evidence and Possible Mechanisms

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Background: Psoriasis is an autoimmune skin disease associated with lipid metabolism. Sphingosine-1-phosphate (S1P) is a bioactive lipid that plays a key role in the development of autoimmune diseases. However, there is currently a lack of comprehensive evidence of the effectiveness of S1P on psoriasis.

Objective: To assess the efficacy and possible mechanism of S1P and its signal modulators in the treatment of psoriasis-like dermatitis.

Methods: Six databases were searched through May 8, 2021, for studies reporting S1P and its signal modulators. Two reviewers independently extracted information from the enrolled studies. Methodological quality was assessed using SYRCLE’s risk of bias tool. RevMan 5.3 software was used to analyze the data. For clinical studies, the Psoriasis Area and Severity Index score were the main outcomes. For preclinical studies, we clarified the role of S1P and its regulators in psoriasis in terms of phenotype and mechanism.

Results: One randomized double-blind placebo-controlled trial and nine animal studies were included in this study. The pooled results showed that compared with control treatment, S1P receptor agonists [mean difference (MD): −6.80; 95% confidence interval (CI): −8.23 to −5.38; p<0.00001], and sphingosine kinase 2 inhibitors (MD: −0.95; 95% CI: −1.26 to −0.65; p<0.00001) alleviated psoriasis-like dermatitis in mice. The mechanism of S1P receptor agonists in treating psoriasis might be related to a decrease in the number of white blood cells, topical lymph node weight, interleukin-23 mRNA levels, and percentage of CD3+ T cells (p<0.05). Sphingosine kinase 2 inhibitors ameliorated psoriasis in mice, possibly by reducing spleen weight and cell numbers (p<0.05).
INTRODUCTION

Psoriasis is characterized by demarcated erythema covered with silvery-white scales and often accompanied by varying degrees of itching (1). The global prevalence of psoriasis reportedly varies from 0% to 2.1% in children and 0.91% to 8.5% in adults (2). In addition to the high prevalence of psoriasis, comorbidities such as metabolic syndrome (3), hyperuricemia (4), chronic obstructive pulmonary disease (5), and cardiovascular disease (6) cause great burdens for patients with psoriasis. Psoriasis is considered an autoimmune skin disease, and the classic pathogenesis involves an interleukin-17/interleukin-23 (IL-17/IL-23) immune axis disorder. Therefore, biological agents targeting the IL-17/IL-23 signaling axis have been developed, including IL-17 inhibitors, interleukin 12 (IL-12)/IL-23 inhibitors, and tumor necrosis factor-alpha (TNF-α) antagonists (7). Compared with traditional therapies, although biological agents have good curative effects, the risk of recurrence is increased. A recently published meta-analysis showed that anti-IL-23 drugs are likely to cause a series of immunological and non-immunological adverse events, while their long-term use may cause mental illness (8). Therefore, dermatologists are always seeking better treatment options.

Since several studies have reported that patients with psoriasis have comorbid dysfunctional lipid metabolism (9, 10), dermatologists have developed great interest in studying lipid metabolism in patients with psoriasis. S1P is a bioactive lipid produced by the metabolism of sphingolipids and generated by another sphingolipid metabolite, ceramidase (11, 12). Extracellular S1P is synthesized by two sphingosine kinase subtypes 1 and 2 (SPHK1 and SPHK2) and cleaved by S1P lyase, S1P phosphatase 1, and S1P phosphatase 2 (13). S1P signaling reportedly plays a pivotal role in the development of autoimmune diseases. In 2010, two phase III clinical studies published in The New England Journal of Medicine reported that fingolimod, an S1PR agonist, was more effective than interferon in the treatment of multiple sclerosis and reduced the recurrence rate by more than 50% (14). In 2018, it became the only multiple sclerosis drug approved to treat children. In the brains of patients with multiple sclerosis, S1PR1 and S1PR3 levels are significantly increased (15); in patients with psoriasis, the serum S1P concentration is also significantly increased (16). A phase II trial showed that ponesimod, a drug targeting S1P signaling, has therapeutic potential for psoriasis (17). Compared with the classical treatment of psoriasis, both immunosuppressants and biologics can aggravate metabolic disorders in patients with psoriasis, and S1P signaling pathway modulators may be a new treatment for psoriasis (18). However, the efficacy and mechanisms of S1P and its signaling modulators in psoriasis have not been fully elucidated. Hence, here we reviewed previous literature, including clinical and preclinical studies on treatment of psoriasis with S1P and its signaling modulators and quantitatively analyzed their therapeutic effects. Furthermore, we quantitatively and qualitatively analyzed the possible therapeutic targets in terms of phenotype and mechanism.

METHODS

Literature Search Strategy

The PubMed, Embase, Cochrane, Chinese National Knowledge Infrastructure (CNKI), China Biology Medicine disc (CBMdisc), and Wan Fang databases were electronically searched for relevant articles published through May 8, 2021. A combination of subjects and free words was used for the search. Studies reporting the role of S1P or S1P signaling modulators in animal models of psoriasis were identified. The search terms included “psoriasis”, “S1P”, “sphingosine-1-phosphate”, “fingolimod”, and “animal”. These terms were also translated into Chinese and used to search the Chinese databases. The OpenGery database (http://www.opengery.eu/), Chinese Clinical Trial Registry (http://www.chictr.org.cn/), and ClinicalTrials.gov (https://clinicaltrials.gov/) databases were also searched. This review is conducted in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (19).

Study Selection

Any studies that met the following criteria were included in this systematic review: (1) randomized controlled trials comparing S1P or S1P signaling modulators with any other drugs; (2) psoriasis animal model; and (3) interventions including S1P or S1P signaling modulators. The control conditions were the same amount of non-functional liquid or no treatment. The exclusion criteria were as follows: (1) reviews, case reports, and observational studies; (2) studies without an in vivo model; (3) studies without a control group; and (4) duplicate articles. Two reviewers (H.-J.L. and Y.-Q.Z.) independently screened the titles and abstracts according to the inclusion and exclusion criteria. Any differences in opinions were resolved through discussion.

Data Extraction

Two authors (S.Z. and M.-Z.J.) independently extracted the following information: (1) first author and publication year;
animal species, age (weeks), sex; (3) type of psoriasis model; (4) type of intervention, including different S1P-related drugs, control drugs, and administration route; and (5) main outcome measures. Data are presented as mean ± standard deviation. If the data were not provided in the study, we attempted to contact the authors for the original data or used the publicly available WebPlotDigitizer 4.2 (20) (https://automeris.io/WebPlotDigitizer) to extract the data (21).

Quality Assessment
SYRCLE’s risk of bias tool for animal studies, which was developed by the Systematic Review Centre for Laboratory Animal Experimentation and based on the Cochrane Collaboration risk of bias tool, was used to conduct the quality assessment (22). The SYRCLE tool covers selection bias, performance bias, detection bias, attrition bias, reporting bias, and other sources of bias. Each term was divided into three grades: a judgment of “Yes” implies low risk, a judgment of “No” implies high risk, and an unclear risk implies insufficient details to assess the risk of bias (22). Two reviewers (L.L. and J.W.) independently assessed the risk of bias. In cases of disagreement, a third reviewer (X.L.) joined the discussion to reach consensus.

Statistical Analysis
RevMan software (version 5.3) was used to analyze continuous data using the mean difference (MD) and 95% confidence intervals (CIs). The I² statistic was used to assess the interstudy heterogeneity. A random-effects model was used if the I² was >50%, and a subgroup analysis was performed to avoid heterogeneity.

RESULTS
Characteristics of the Included Studies
A total of 499 relevant studies were identified in the six databases. After the removal of duplicates, 434 articles were subjected to title and abstract screening, which eliminated 405. The remaining 29 studies were subjected to full-text review, which eliminated 17 for having irrelevant research objectives or including incomplete information. Finally, 10 (17, 23–31) studies, including one clinical study and nine preclinical studies, were eligible for inclusion in the qualitative analysis (Figure 1).

The characteristics of the included studies are listed in Table 1 and Supplementary Table 1. The clinical study, a randomized double-blind placebo-controlled phase 2 trial, investigated the efficacy and doses of oral ponesimod in the treatment of patients with chronic plaque psoriasis (17). For preclinical studies, four types of experimental mice were used in all studies; BALB/c, C57BL/6, Kunming, and Guinea pigs. Two studies (27, 30) used male mice, one study did not specify the sex of the mice (28), and the fourth study used female mice. Three modeling methods have been used to create psoriasis-like dermatitis, including imiquimod (23, 24, 26–31), propranolol (25, 29) and diethylstilbestrol (25) modeling methods. The interventions consisted of S1P, FTY720 (fingolimod), Syb930, IMMH002, S1P lyase-specific inhibitor (SLI), Ceranib-2, MP-A08, PF-543, ABC294640, and HWG-35D.

Study Quality
The risk of bias of the preclinical studies was assessed using the SYRCLE risk of bias tool, and one study mentioned generating sequences by weight (26), which indicated a high risk of bias, while the other randomly assessed the outcome (29). Two studies randomly grouped and housed the mice (25, 26); in another two studies, the outcomes were assessed by independent observers blinded to the intervention (28, 29). Attrition and other biases were low risks for the nine studies because they reported the outcome indicators in detail. However, it is difficult to evaluate baseline characteristics because none of the studies provided baseline data. None of the studies described allocation concealment or blinding methods for performance or detection bias (Supplementary Table 2).

Outcomes
Clinical Trial
Vaclavkova et al. (17) performed a randomized double-blind placebo-controlled phase II trial to evaluate the efficacy, safety, and tolerability of the S1PR agonist ponesimod for the treatment of patients with chronic plaque psoriasis. They found that after treatment with ponesimod for 16 weeks, patients who received a 20 mg dose reached at least a 75% reduction in Psoriasis Area and Severity Index (PASI75) score with a lower risk of adverse events (AEs) than those in the 40 mg and placebo groups. The main AEs were dyspnea and increased liver enzyme concentrations.

Preclinical Research
Phenotype
S1PR. A meta-analysis of five studies (23, 25, 26, 29, 31) evaluated the efficacy of S1PR agonists for treating psoriasis-like dermatitis. Overall, S1PR agonists improved psoriasis-like dermatitis in mice (MD: −6.80; 95% CI: −8.23, −5.38; p<0.00001) (Supplementary Figure 1). After intervention with agonists, ear swelling (MD: −0.06; 95% CI: −0.09 to −0.03; p<0.0001), skin erythema (MD: −0.89; 95% CI: −1.22 to −0.57; p<0.00001), thickness (MD: −0.65; 95% CI: −0.97 to −0.34; p<0.001), and total PASI scores (MD: −2.21; 95% CI: −2.88 to −1.54; p<0.00001) of psoriatic mice were significantly decreased. When analyzing the hematoxylin-eosin (HE)-stained sections of the skin lesions, the epidermal thickness (MD: −27.24; 95% CI: −48.59 to −6.16; p=0.01), pathological score (MD: −1.91; 95% CI: −2.52 to −1.30; p<0.00001), and number of proliferating cell nuclear antigen (PCNA)-positive cells (MD: −19.16; 95% CI: −36.55 to −1.76; p=0.03) in mice with psoriatic dermatitis were substantially lower (Table 2 and Supplementary Figure 1).

SPHK1/2
Shin et al. (27) reported that both Ceranib-2 and MP-A08 improved the severity of psoriasis-like skin lesions with reduced PASI scores, erythema, scaling, and epidermal thickness and upregulated cellular proliferation. In particular,
the effect of the topical application of a specific SPHK2 inhibitor on imiquimod (IMQ)–induced skin disease was more significant than that of the SPHK1 inhibitor (27, 30). We found that the SPHK2 inhibitor significantly reduced the skin erythema (MD: −0.80; 95% CI: −1.02 to −0.58; p<0.00001), epidermal thickness (MD: −0.92; 95% CI: −1.22 to −0.62; p<0.00001), and total PASI scores (MD: −1.73; 95% CI: −2.90 to −0.56; p=0.004), while skin scales (MD: −0.80; 95% CI: −1.70 to 0.11; p=0.09) were not significantly changed after treatment with a topical SHPK2 inhibitor (Table 2 and Supplementary Figure 2).

**SL1**

Jeon et al. reported that the S1P lyase inhibitor SL1 alleviated psoriatic lesions and reduced epidermal thickness and mean PASI scores (28).

**Mechanisms**

**S1PR**

We first analyzed the inflammatory state of ear lesions in psoriasis-like mice, and the meta-analysis showed that IL-23 mRNA levels in the ear lesions of psoriatic mice were significantly decreased (MD: −4.35; 95% CI: −7.64 to −1.06; p=0.009, Supplementary Figure 3) in the S1PR agonist group, while the ear inflammatory cell influx (Supplementary Figure 4) and IL-17 mRNA production did not change markedly (p>0.05, Supplementary Figure 5). In addition, after the S1PR agonist intervention, lymph node weight was reduced (MD: −2.49; 95% CI: −4.05 to −0.93; p=0.002; Supplementary Figure 6), while the cell count did not change significantly (p=0.10; Supplementary Figure 7). Moreover, there was almost no change in the number of lymphocytes in the blood after S1PR agonist treatment.
TABLE 1 | Characteristics of the included preclinical studies.

| Study | Author and Year | Drug(s) | Species | Sex/Age/Weight | Psoriasis Model | Intervention Group | Control Group | Administration Route | Outcomes |
|-------|------------------|---------|---------|----------------|----------------|--------------------|---------------|---------------------|----------|
| Schaper et al., 2013 [23] | FTY720 | BALB/c | Female/6–8 w | 50 mg, 5% IMQ | 1. IMQ +FTY720 | IMQ +vehicle | Intraperitoneal | HE (ET, PCNA), ICI, EE, IL-17, IL-23, LNW, LNCC, WBC, Lymphocytes | S1p |
| Sun, 2017 [24] | FTY720 | BALB/c | Female/6–8 w | 62.5 mg, 5% IMQ | 1. IMQ +FTY720 | IMQ +vehicle | Intraperitoneal | HE (ET, PCNA), ICI, EE, IL-17, IL-23, LNW, LNCC, WBC, Lymphocytes, ES | HE |
| Ji et al., 2018 [25] | Syl930 Vehicle | Guinea pigs | Female | 5% (m/v) propranolol ethanol solution containing azone and diethylstilbestrol | 1. FTY720 | Vehicle | Oral | Mitotic index; Body weight | PASI, scaling, skin thickness, FN, PC, Sw, IL-17A, K6, K16 |
| Shin et al., 2019 [27] | Ceranib-2/MP-A08 | C57BL/6 | Male | 8 w | 50 mg, 5% IMQ | 1. IMQ +Ceranib-2 | IMQ +vehicle | Topical | HE, PCNA, ICI, EE, IL-17, IL-23, LNW, LNCC, WBC, Lymphocytes | Eta, CD3+ T cells |
| Qin and Zheng, 2019 [26] | FTY720 | C57BL/6 | Female | 10 mg/d IMQ | 1. IMQ +FTY720 | IMQ +PBS | Intraperitoneal | HE (ET), PASI (erythema, scaling, skin thickness), FN, PC, Sw, IL-17A, K6, K16 |
| Jeon et al., 2020 [29] | SLI | BALB/c | Male/8 w | 83 mg, 5% IMQ | 1. IMQ +SLI | IMQ +PBS | Subcutaneous | HE (ET), PASI (erythema, scaling, skin thickness), Eta, CD3+ T cells |
| Jing et al., 2020 [29] | FTY720 | IMMH002 | Female | 50 mg, 5% IMQ | 1. IMQ +FTY720 | IMQ | Oral | PASI (erythema, scaling, skin thickness), Eta, CD3+ T cells |
| Shin et al., 2020 [30] | HWG-35D | BALB/c | Male/8 w | 83 mg, 5% IMQ | 1. IMQ +HWG-35D | IMQ +PBS | Topical | PASI (erythema, scaling, skin thickness), FN, PC, Sw, IL-17A, K6, K16 |
| Okura et al., 2021 [31] | Fingolimod (FTY720) | BALB/c | Female | 30 mg, 5% IMQ | 1. IMQ +Fingolimod | IMQ +PBS | Intraperitoneal | HE, PCNA, Eta, CD3+ T cells |

CLAI, cutaneous lymphocyte-associated antigen; DC, dendritic cells; Eta, ear thickness; EE, edema ear; ES, ear swelling; ET, epidermal thickening; HE, hematoxylin-eosin staining; ICI, inflammatory cell influx; IMQ, imiquimod; LC, Langerhans cell; LNCC, lymph node cell count; LNW, lymph node weight; PCNA, proliferating cell nuclear antigen; PS, pathology score; S1P, sphingosine-1-phosphate; SL1, S1P lyase-specific inhibitor; SpCC, spleen cell count; SpW, spleen weight; WBC, white blood cell; w, weeks.

(p=0.10; Supplementary Figure 8). However, in the peripheral tissues, the percentage of CD3+ T lymphocytes (including in the ears, blood, and spleen) decreased significantly after treatment with S1PR agonists (MD: −10.35; 95% CI: −15.19 to −5.51; p<0.0001; Supplementary Figure 9). We also found that the number of white blood cells (WBCs) was markedly reduced (MD: −1.67; 95% CI: −3.20 to −0.15; p<0.03; Supplementary Figure 10) relative to the control group. The details are listed in Table 3.

**SPHK1/2**

Shin et al. (27) reported that, after treatment with Ceranib-2 or MP-A08, IL-17A, IL-17F, and TNF-α levels were significantly decreased (p<0.05) compared with those in IMQ-induced skin inflammation. Levels of keratinocyte hyperproliferation markers K6 and K16 were also significantly suppressed (p<0.05). A meta-analysis showed that SPHK2 inhibitors reduced spleen weight (MD: −0.03; 95% CI: −0.06 to −0.00; p=0.03; Supplementary Figure 11) and spleen cell numbers (MD: −24.88; 95% CI: −35.27 to −14.48; p<0.00001; Supplementary Figure 12). However, the number of lymph nodes did not significantly decrease (p>0.05; Supplementary Figure 13). The details are listed in Table 3.

**DISCUSSION**

To our knowledge, this is the first systematic review and meta-analysis of clinical and preclinical animal studies to evaluate the efficacy and mechanism of S1P and its signal modulators for treating psoriasis and psoriasis-like mice (Figure 2). This study mainly included literature of clinical and preclinical research. In the preclinical research section, we subdivided the basic research of S1P and its modulators for psoriasis into phenotypes and mechanisms for the meta-analysis. In this study, we classified intervention drugs into S1PR agonists, SPHK inhibitors, and S1P lyases according to their different roles in the S1P signaling pathway. The S1PR agonists in this systematic review included...
SIP, FTY720, Sy930, and IMMH002. FTY720, also known as fingolimod, is an analog of SIP derived from the structure-modified extract of *Cordyceps sinensis*. It is the first S1PR modulator approved by the US Food and Drug Administration for the treatment of relapsing multiple sclerosis (32). FTY720 binds to four of S1PRs (S1PR1, S1PR3, S1PR4, S1PR5) to reduce the number of lymphocytes in the blood and inhibit the infiltration of inflammatory cells (13). Sy930 and IMMH002, developed by a Chinese team, are selective S1PR1 modulators, such as FTY720, that regulate the distribution of lymphocytes by inducing lymphocyte homing to treat psoriasis (29).

In patients with psoriasis, the serum concentration of SIP increases (16). Shin et al. used Ceranib-2, a ceramidase inhibitor, and MP-A08, an SPHK1/2 inhibitor, to prevent SIP synthesis. They found that topical inhibition of SIP production improves inflammation in psoriasis-like mice, possibly by blocking Th17 cell differentiation (27). In particular, SPHK2 inhibitors such as ABC294640 and HWG-35D have the greatest inhibitory effect on S1P synthesis (27, 30). Several studies have reported that SIP induces keratinocyte differentiation (33, 34). Jeon et al. used an SLI to inhibit SIP lyase activity in human keratinocytes and observed the same phenomenon. In addition, the severity of psoriasis-like dermatitis in mice is alleviated (28). Our findings point to the improvement of psoriasis by inhibiting SIP expression or synthesis. Only clinical study to date has reported on the clinical efficacy and safety of S1PR. It is recommended that 20 mg

### TABLE 2 | Phenotypes of S1P signal modulators for treating psoriasis.

| Study or subgroup | Experiment | Control | Mean difference [95% CI] | I² | P value |
|-------------------|------------|---------|--------------------------|----|---------|
| **1. S1PR agonists** |            |         |                          |    |         |
| 1.1 PASI scores   |            |         |                          |    |         |
| Jing et al., 2020-1 (29) | 5.26 ± 1.14 | 10 | 7.26 ± 1.14 | 10 | -2.00 [-3.00, -1.00] | 0% | <0.00001 |
| Okura et al., 2021 (31) | 4.95 ± 1.25 | 5  | 7.60 ± 1.25 | 5  | -2.65 [-4.20, -1.10] | 0% | <0.00001 |
| Subtotal (95% CI) | 25          |        | 25                      |    |         |
| 1.2 PASI-Erythema |            |         |                          |    |         |
| Shin et al., 2020-1 (29) | 1.21 ± 0.45 | 10 | 1.99 ± 0.45 | 10 | -0.78 [-1.17, -0.39] | 0% | <0.00001 |
| Subtotal (95% CI) | 20          |        | 20                      |    |         |
| 1.3 PASI-Thickness |            |         |                          |    |         |
| Shin et al., 2020-1 (29) | 2.17 ± 0.50 | 10 | 2.82 ± 0.50 | 10 | -0.66 [-1.11, -0.21] | 0% | <0.00001 |
| Subtotal (95% CI) | 20          |        | 20                      |    |         |
| 1.4 Ear swelling   |            |         |                          |    |         |
| Schaper et al., 2013-2 (23) | 0.09 ± 0.02 | 6  | 0.15 ± 0.03 | 6  | -0.06 [-0.09, -0.03] | 0% | <0.00001 |
| Subtotal (95% CI) | 12          |        | 12                      |    |         |
| 1.5 HE pathology score |          |         |                          |    |         |
| Jing et al., 2020-3 (29) | 0.89 ± 0.34 | 8   | 2.26 ± 0.46 | 8   | -1.37 [-1.77, -0.97] | 0% | <0.00001 |
| Subtotal (95% CI) | 21          |        | 21                      |    |         |
| 1.6 HE Epidermal thickness |        |         |                          |    |         |
| Jing et al., 2020-3 (29) | 80.30 ± 8.12 | 10 | 108.27 ± 7.22 | 8  | -27.97 [-35.50, -20.44] | 84% | <0.00001 |
| Okura et al., 2021 (31) | 138.14 ± 28.46 | 5 | 228.87 ± 28.46 | 5 | -90.73 [-128.01, -55.45] | 0% | <0.00001 |
| Schaper et al., 2013-1 (23) | 62.22 ± 4.68 | 6  | 68.25 ± 5.65 | 6  | 3.97 [2.02, 9.96] | 0% | <0.00001 |
| Schaper et al., 2013-2 (23) | 53.57 ± 9.36 | 6  | 58.25 ± 5.65 | 6  | -4.68 [-13.51, 4.15] | 0% | <0.00001 |
| Subtotal (95% CI) | 33          |        | 33                      |    |         |
| 1.7 HE PCNA positive cells |           |         |                          |    |         |
| Jing et al., 2020-4 (29) | 56.25 ± 1.47 | 8   | 79.41 ± 1.10 | 8   | -23.16 [-24.43, -21.89] | 97% | 0.01 |
| Schaper et al., 2013-1 (23) | 33.46 ± 2.57 | 8   | 40.01 ± 1.09 | 8   | -6.54 [-8.22, -4.86] | 0% | <0.00001 |
| Schaper et al., 2013-2 (23) | 23.12 ± 1.70 | 6   | 24.68 ± 4.68 | 6   | -1.56 [-5.54, 2.42] | 0% | <0.00001 |
| Subtotal (95% CI) | 21          |        | 21                      |    |         |
| 2. SPHK2 inhibitor |            |         |                          |    |         |
| 2.1 PASI scores   |            |         |                          |    |         |
| Shin et al., 2019 (27) | 1.86 ± 0.55 | 5   | 3.03 ± 0.55 | 5   | -1.17 [-1.85, -0.49] | 0% | <0.00001 |
| Shin et al., 2020 (30) | 5.13 ± 0.74 | 6   | 7.50 ± 0.74 | 6   | -2.37 [-3.29, -1.45] | 0% | <0.00001 |
| Subtotal (95% CI) | 10          |        | 10                      |    |         |
| 2.2 PASI-Erythema |            |         |                          |    |         |
| Shin et al., 2019 (27) | 2.03 ± 0.28 | 5   | 2.93 ± 0.28 | 5   | -0.90 [-1.25, -0.55] | 76% | 0.004 |
| Shin et al., 2020 (30) | 2.25 ± 0.23 | 5   | 2.99 ± 0.23 | 5   | -0.74 [-1.03, -0.45] | 0% | <0.00001 |
| Subtotal (95% CI) | 10          |        | 10                      |    |         |
| 2.3 PASI-Thickness |            |         |                          |    |         |
| Shin et al., 2019 (27) | 2.30 ± 0.37 | 5   | 3.08 ± 0.37 | 5   | -0.78 [-1.24, -0.32] | 0% | <0.00001 |
| Shin et al., 2020 (30) | 1.81 ± 0.32 | 5   | 2.83 ± 0.32 | 5   | -1.02 [-1.42, -0.62] | 0% | <0.00001 |
| Subtotal (95% CI) | 10          |        | 10                      |    |         |
| 2.4 PASI-Scale    |            |         |                          |    |         |
| Shin et al., 2019 (27) | 1.77 ± 0.64 | 5   | 3.12 ± 0.64 | 5   | -1.35 [-2.14, -0.56] | 0% | <0.00001 |
| Shin et al., 2020 (30) | 1.67 ± 0.13 | 5   | 2.08 ± 0.13 | 5   | -0.41 [-0.57, -0.25] | 81% | 0.09 |
| Subtotal (95% CI) | 10          |        | 10                      |    |         |
| Total (95% CI) | 40          |        | 40                      |    |         |

CI, confidence interval; HE, hematoxylin and eosin; PASI, Psoriasis Area and Severity Index; PCNA, proliferating cell nuclear antigen; S1PR, sphingosine-1-phosphate receptor; SPHK2, sphingosine kinase 2.
ponesimod orally can achieve good efficacy with fewer adverse reactions. However, a recent meta-analysis reported that patients receiving S1P modulators were at an increased risk of infection and transient cardiovascular events (35). As these modulators can be considered potential drugs for the treatment of psoriasis, future large-scale clinical research on different dosage forms and chemical modifications to reduce toxicity can be pursued. Additionally, S1P signaling plays a complex role in different cells, and further studies are needed to explain the mechanism underlying psoriasis.

This systematic review has some limitations. First, the methodological quality of the enrolled animal studies was low, and most had a high risk of selection bias. Second, because there are few studies on the mechanism of S1P and its signal modulators for psoriasis, the number of articles included was limited, which reduced our ability to reach a definitive conclusion. Third, the PASI score, the gold standard method for evaluating improvement in psoriasis, was not used in all studies.

| Study or subgroup | Experiment | Control | Mean difference [95%CI] | I² | P value |
|------------------|------------|---------|-------------------------|----|---------|
| **1. S1PR agonists** | | | | | |
| **1.1 Ear lesions** | | | | | |
| **1.1.1 Ear-inflammatory cell influx** | Schaper et al., 2013-1 (23) 2.3 0.6 6 | Schaper et al., 2013-2 (23) 1.7 0.7 6 | -0.10 [-0.78, 0.58] | 27% | 0.20 |
| | Total (95%CI) 12 | 12 | -0.38 [-0.97, 0.20] | | |
| **1.1.2 IL-17** | Schaper et al., 2013-1 (23) 21 6 3 | Schaper et al., 2013-2 (23) 59 20 3 | -27.00 [-48.47, -5.53] | 75% | 0.61 |
| | Total (95%CI) 6 | 6 | -9.60 [-46.70, 27.51] | | |
| **1.1.3 IL-23** | Schaper et al., 2013-1 (23) 7 6 6 | Schaper et al., 2013-2 (23) 5 3 6 | -3.00 [-8.77, 2.77] | 0% | 0.009 |
| | Total (95%CI) 12 | 12 | -4.35 [-7.64, -1.06] | | |
| **1.2 White blood cells** | Schaper et al., 2013-1 (23) 5.8 1.7 6 | Schaper et al., 2013-2 (23) 6.9 4.0 6 | -1.67 [-3.20, -0.15] | 0% | 0.03 |
| | Total (95%CI) 12 | 12 | -1.26 [-2.64, 0.23] | | |
| **1.3 Lymph node** | | | | | |
| **1.3.1 Lymph node weight (mg)** | Schaper et al., 2013-1 (23) 4.2 0.8 6 | Schaper et al., 2013-2 (23) 4.9 1.5 6 | -2.80 [-4.90, -0.70] | 0% | 0.002 |
| | Total (95%CI) 12 | 12 | -2.49 [-4.06, -0.93] | | |
| **1.3.2 Lymph node cell count (*10⁶)** | Schaper et al., 2013-1 (23) 6.4 1.7 6 | Schaper et al., 2013-2 (23) 7.4 3.3 6 | -1.83 [-4.01, 0.38] | 0% | 0.10 |
| | Total (95%CI) 12 | 12 | -1.28 [-2.64, 0.23] | | |
| **1.4 Lymphocytes in blood** | Schaper et al., 2013-1 (23) 2.0 0.9 6 | Schaper et al., 2013-2 (23) 3.5 1.9 6 | -1.80 [-2.71, -0.89] | 60% | 0.10 |
| | Total (95%CI) 12 | 12 | -1.21 [-2.64, 0.23] | | |
| **1.5 CD3⁺T cells in peripheral tissues** | Qin and Zheng, 2019 (26) 6.63 0.54 6 | Jin Jing et al., 2020-2 (29) 3.75 0.92 10 | -10.35 [-15.19, -5.51] | 97% | <0.0001 |
| | Jin Jing et al., 2020-2-1 (29) 24.47 2.93 10 | Jin Jing et al., 2020-2-1 (29) 24.47 2.93 10 | -10.35 [-15.19, -5.51] | 97% | <0.0001 |
| | Total (95%CI) 26 | 26 | -10.35 [-15.19, -5.51] | | |
| **2. SPHK2 Inhibitor** | | | | | |
| **2.1 Spleen weight (g)** | Shin et al., 2019 (27) 0.12 0.01 5 | Shin et al., 2020 (30) 0.14 0.02 5 | -0.02 [-0.03, -0.01] | 78% | 0.03 |
| | Total (95%CI) 10 | 10 | -0.03 [-0.06, -0.00] | | |
| **2.2 Spleen cell number (*10⁶)** | Shin et al., 2019 (27) 90.83 14.16 5 | Shin et al., 2020 (30) 52.60 10.41 5 | -30.05 [-47.60, -12.50] | 0% | <0.00001 |
| | Total (95%CI) 10 | 10 | -22.08 [-34.98, -9.18] | | |
| **2.3 Lymph node cell number (*10⁵)** | Shin et al., 2019 (27) 368.16 70.41 5 | Shin et al., 2020 (30) 2.43 2.36 5 | -149.41 [-236.89, -62.13] | 90% | 0.33 |
CONCLUSION

Our findings indicate that psoriasis can be treated by blocking S1P activity by competitively binding to S1PR and inhibiting S1P synthase activity (SPHK2 inhibitor) using a mechanism that is related to decreased immune responses and inflammatory factor levels. These drugs improve psoriatic dermatitis by decreasing the number of immune cells including lymphocytes, and downregulating the secretion of inflammatory factors.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding authors.

AUTHOR CONTRIBUTIONS

XL and BL proposed and designed the study. They also obtained funding support. JW, SZ, S-tC, H-jL, and X-yS retrieved and selected the data. Y-qZ and M-ZJ extracted the data. YinL and YR assessed the quality of all studies. LL, YiL, DY, and Y-qZ performed the statistical analysis of all data. LL and JW drafted the manuscript, and XL revised it.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2021.759276/full#supplementary-material
Supplementary Figure 1 | Meta-analysis of the phenotype of psoriasis-like dermatitis after treatment with an S1PR agonist. 95% CI, 95% confidence interval; S1PR, sphingosine-1-phosphate receptor.

Supplementary Figure 2 | Meta-analysis of phenotype in psoriasis-like dermatitis after treatment with an SPHK2 inhibitor. 95% CI, 95% confidence interval; SPHK2, sphingosine kinase 2.

Supplementary Figure 3 | Meta-analysis of IL-23 levels in psoriasis-like dermatitis, after treatment with an S1PR agonist. 95% CI, 95% confidence interval; IL-23, interleukin-23; S1PR, sphingosine-1-phosphate receptor.

Supplementary Figure 4 | Meta-analysis of IL-17 levels in psoriasis-like dermatitis after treatment with an S1PR agonist. 95% CI, 95% confidence interval; IL-17, interleukin-17; S1PR, sphingosine-1-phosphate receptor.

Supplementary Figure 5 | Meta-analysis of ear inflammatory cell influx in psoriasis-like dermatitis after treatment with an S1PR agonist. 95% CI, 95% confidence interval; S1PR, sphingosine-1-phosphate receptor.

Supplementary Figure 6 | Meta-analysis of lymph node weight in psoriasis-like dermatitis after treatment with an S1PR agonist. 95% CI, 95% confidence interval; S1PR, sphingosine-1-phosphate receptor.

Supplementary Figure 7 | Meta-analysis of lymph node cell counts in psoriasis-like dermatitis after treatment with an S1PR agonist. 95% CI, 95% confidence interval; S1PR, sphingosine-1-phosphate receptor.

Supplementary Figure 8 | Meta-analysis of lymphocytes in blood in psoriasis-like dermatitis after treatment with an S1PR agonist. 95% CI, 95% confidence interval; S1PR, sphingosine-1-phosphate receptor.

Supplementary Figure 9 | Meta-analysis of CD3+ T cells in psoriasis-like dermatitis after treatment with an S1PR agonist. 95% CI, 95% confidence interval; S1PR, sphingosine-1-phosphate receptor.

Supplementary Figure 10 | Meta-analysis of white blood cells in psoriasis-like dermatitis after treatment with an SPHK2 inhibitor. 95% CI, 95% confidence interval; SPHK2, sphingosine kinase 2.

Supplementary Figure 11 | Meta-analysis of spleen weight in psoriasis-like dermatitis after treatment with an SPHK2 inhibitor. 95% CI, 95% confidence interval; SPHK2, sphingosine kinase 2.

Supplementary Figure 12 | Meta-analysis of spleen cell numbers in psoriasis-like dermatitis after treatment with an SPHK2 inhibitor. 95% CI, 95% confidence interval; SPHK2, sphingosine kinase 2.

Supplementary Figure 13 | Meta-analysis of lymph node cell numbers in psoriasis-like dermatitis after treatment with an SPHK2 inhibitor. 95% CI, 95% confidence interval; SPHK2, sphingosine kinase 2.

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