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Short Communication

A potential reciprocal emergence of regulatory T cells in oral lichen planus and pemphigus vulgaris: A meta-analysis

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Abstract Oral lichen planus (OLP) and pemphigus vulgaris (PV) are 2 common inflammatory mucocutaneous diseases of immune-based etiology. Evidence indicates regulatory T (Treg) cells maybe play a role in the pathogenesis of OLP and PV, which are caused by aberrant immune responses. In this report, 7 eligible case–control studies containing 517 OLP patients and 261 healthy controls (HC) were identified. The level of Tregs was significantly higher in OLP patients than HC (mean difference: 1.79; 95%CI: 0.99, 2.60). On the other hand, 7 eligible case–control studies containing 169 PV patients and 121 HC were identified. Conversely, the level of Tregs was significantly lower in PV patients than HC (mean difference: −2.49; 95%CI: −3.90, −1.08). Collectively, this analysis for the first time reported reciprocal emergence of Tregs in

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OLP and PV using meta-analysis, and provided an interesting insight into a previously undescribed the linkage of the 2 mucocutaneous diseases.

Introduction

Lichen planus (LP) and pemphigus vulgaris (PV) are 2 relatively common chronic inflammatory mucocutaneous diseases of immune-based etiology. LP is widely acknowledged to mainly affect oral mucosa as oral LP (OLP), and PV is also described to affect over 90% oral mucosa of patients with this disease.[1,2] PV is the most subtype of pemphigus, which is a category of life-threatening autoimmune bullous diseases characterized by intraepithelial blister formation owing to keratinocyte adhesion loss produced by autoantibodies against desmosomal adhesions, desmoglein (Dsg) 3 and/or Dsg1.[3]

Recently, it was found that OLP-like lesions may occur on the oral mucosa of PV patients.[4,5] These reports attracted our attention, because we also observed OLP-like lesions on the oral mucosa of our PV patients occasionally. The investigators appealed to unveil the unknown aspects of the association between the PV and LP in further studies, e.g. T-cell subset study.[4,5] Regulatory T (Treg) cells are a subset of CD4+ T lymphocytes to maintain peripheral immunological tolerance and immune homeostasis by modulating T helper (Th)1/Th2 balance.[6] Hence, Tregs maybe play a role in the pathogenesis of PV and LP, which are caused by aberrant immune responses.

In recent years, several studies have been conducted to evaluate the association of Tregs with PV and OLP, respectively.[7–20] For instance, Sun et al. recently reported that CD4+Foxp3+ Treg cells are increased to modulate OLP disease activity.[13] However, some authors reported a lack of association of Tregs with the pathogenesis of the diseases,[13,18] partially because of their limited sample size and sampling effects. To overcome the limitations of individual study, we quantitatively synthesized the previous results by a meta-analysis. Based on the evidence from case–control studies, this brief paper attempts to interpret 3 issues: i) association of Tregs with the pathogenesis of LP; ii) association of Tregs with the pathogenesis of PV; iii) diagnostic and therapeutic implications of Tregs in LP and PV.

Materials and methods

A comprehensive literature search was conducted on PubMed, Web of Science, and Scopus databases for all relevant publications on the association between Tregs and LP or PV on Jun 25, 2022. We searched electronic databases without any restriction following the Cochrane Collaboration and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The following search terms were used: ("Regulatory T" OR "Tregs") AND ("lichen planus" OR "pemphigus vulgaris"). In addition, the reference lists given in relevant articles and reviews were also considered for eligible studies. All eligible case–control studies comparing the quantity of peripheral blood Tregs between patients with LP or PV and healthy controls (HC) were included. Studies with not available full text and lack of peripheral blood Tregs data, other type of studies such as case reports or conference papers were excluded. Two independent authors (Q. Z. and W. L.) screened the titles, abstracts, and full text of all publications, and subsequently analyzed the eligible studies.

A descriptive analysis was performed on the parameters of included studies. The parameters used to present differences of Tregs were the proportion (%) of Tregs to CD4+ T cells in peripheral blood. The strength of association of Tregs with LP or PV was determined by mean difference (MD) with 95% confidence interval (CI). In this meta-analysis, pooled MD and 95% CI were calculated from combination of the studies on association of Tregs with LP or PV. In addition, subgroup analyses were conducted by subtypes of Tregs. The statistical significance of the pooled MD was evaluated using the Z-test, and the heterogeneity of the ORs was tested by χ^2–based Q-test and I^2 statistics. If the result of heterogeneity test showed $P > 0.05$, MDs were pooled according to the fixed-effects model. Otherwise, the random-effects model was selected. Additionally, the potential publication bias was visually examined by the Begg's funnel plot. All statistical analyses were performed with the software Review manager 5.4 (The Cochrane Collaboration, Oxford, UK) using two-sided P value, and the value of <0.05 was considered as statistically significant.

Results

Association between tregs and LP

According to the flow diagram of the PRISMA (Supplementary Fig. S1), 7 eligible case–control studies containing 517 OLP patients and 261 HC were identified for detailed evaluation (Table 1). There was not relevant study on this issue of cutaneous LP. The subjects in all the studies were Chinese ethnicity. The overall analysis (Fig. 1A) showed that the level of Tregs was significantly higher in OLP patients than HC (mean difference: 1.79; 95%CI: 0.99, 2.60; $P < 0.001$). In the subgroup analysis based on the definition of Tregs, the proportion of CD4+CD25+ Tregs was significantly higher in OLP patients than HC (mean difference: 2.36; 95%CI: 1.02, 3.70; $P < 0.001$); and the level of CD4+CD25+Foxp3+ Tregs was significantly higher in OLP patients than HC (mean difference: 2.29; 95%CI: 1.11, 3.47; $P < 0.001$).

Association between tregs and PV

As presented in Supplementary Figs. S2 and 7 eligible case–control studies were identified for detailed evaluation

Table 1 Characteristics of included studies on regulatory T cells (Tregs) in peripheral blood of patients with lichen planus.

Author, year	Country /Region	Lichen planus			Healthy control			Matched factor	Definition of Tregs
		n	Age (mean, y (range))	F, M	N	Age (mean, y (range))	F, M		
Zhu et al., 2014[7]	China	150	NA	106, 44	102	NA	61, 41	Age, sex	CD4+CD25+Foxp3+
Wang et al., 2016[8]	China	36	47 (32–63)	21, 15	20	44 (33–58)	8, 12	Age, sex	CD4+CD25+Foxp3+
Zhou et al., 2016[9]	China	40	43.5 (20–73)	NA	22	45.6 (35–58)	NA	Age	CD4+CD25+
Jia et al., 2018[10]	China	33	(20–78)	NA	17	NA	NA	NA	CD4+Foxp3+
Wang et al., 2019[11]	China	10	NA	NA	10	NA	NA	NA	CD4+CD25+Foxp3+
Huang et al., 2021[12]	China	65	46.2	32, 33	70	45.1	32 38	Age, sex	CD4+CD25+
Sun et al., 2021[13]	Taiwan	183	54.8 (20–80)	141, 42	20	51.9 (26–71)	16, 4	Age, sex	CD4+Foxp3+

Abbreviations: F, female; M, male; NA, not available.

(Table 2). There were 169 cases of PV and 121 HC from Japan, Romania, India, and China. The overall analysis (Fig. 1B) showed that the level of Tregs was significantly lower in PV patients than HC (mean difference: −2.49; 95%CI: −3.90, −1.08; $P < 0.001$). In the subgroup analysis based on the definition of Tregs, the level of CD4+CD25+ Tregs was significantly lower in PV patients than HC (mean difference: −2.74; 95%CI: −3.00, −2.48; $P < 0.001$); and the proportion of CD4+CD25+Foxp3+ Tregs was significantly lower in PV patients than HC (mean difference: −2.85; 95%CI: −5.20, −0.50; $P = 0.02$). The level of CD4+Foxp3+ Tregs was significantly lower in PV patients than HC (mean difference: −0.40; 95%CI: −0.59, −0.21; $P < 0.001$).

Discussion

Increasing evidence substantially indicates that Th1/Th2 imbalance may greatly participate into the T-cell-mediated immune pathogenesis of OLP.[6] Importantly, Tregs are a subset of CD4+ T lymphocytes to maintain peripheral immunological tolerance and immune homeostasis by modulating Th1/Th2 balance.[6] Although the disclosure on the roles of the specific autoantibodies and autoantigens in the pathogenesis of PV, the possible mechanism begins with the loss of peripheral and central tolerance by the T lymphocytes toward the autoantigens which is attributed to the dysregulation of immune moderators and Treg cells.[3] In addition, Kianfar et al.[5] and De et al.[6] reported 36 and 32 PV patients having OLP-like lesions, respectively. They concluded that these lesions might be considered as the postremission phase of PV or postinflammatory hyperpigmentation. Hence, OLP and PV not only have some clinical similarities but also share certain T-cell subset in the immunopathogenesis.

Accordingly, the evidence suggests that Tregs play a role in the pathogenesis of OLP and PV, respectively. Interestingly, the role of Tregs in OLP and PV is reciprocal. Considering the vital role of Tregs in immune tolerance, investigators and clinicians should be required to become familiar with the reciprocal role of Tregs to proceed with correct implications for the diagnosis and treatment of both diseases. PV is shown to have significant reductions in Tregs quantity and function impairment.[3] The negative regulatory role of Tregs in PV implies that a deficiency of Tregs in their activity could lead to a loss of immune tolerance and impair immune down-regulatory function in the pathogenesis of this disease. Conversely, the quantity and function of Tregs in OLP is positive correlation, in agreement with the results analyzed by Chen et al.[6] Compared to their analysis, we added 3 different studies and update the relevant evidence. The implications of Tregs increased in OLP might augment the immune tolerance and dysregulate the Th1/Th2 imbalance in the pathogenesis of this disease.

The limitations of the meta-analysis included high heterogeneity and publication bias (Supplementary Fig. S3). The number of eligible studies and the sample size of individual studies were small, and there may be sample bias in studies on OLP due to all the subjects being Chinese ethnicity. The clinical manifestation of OLP patients with concomitant PV or PV patients with concomitant OLP-like lesions was not

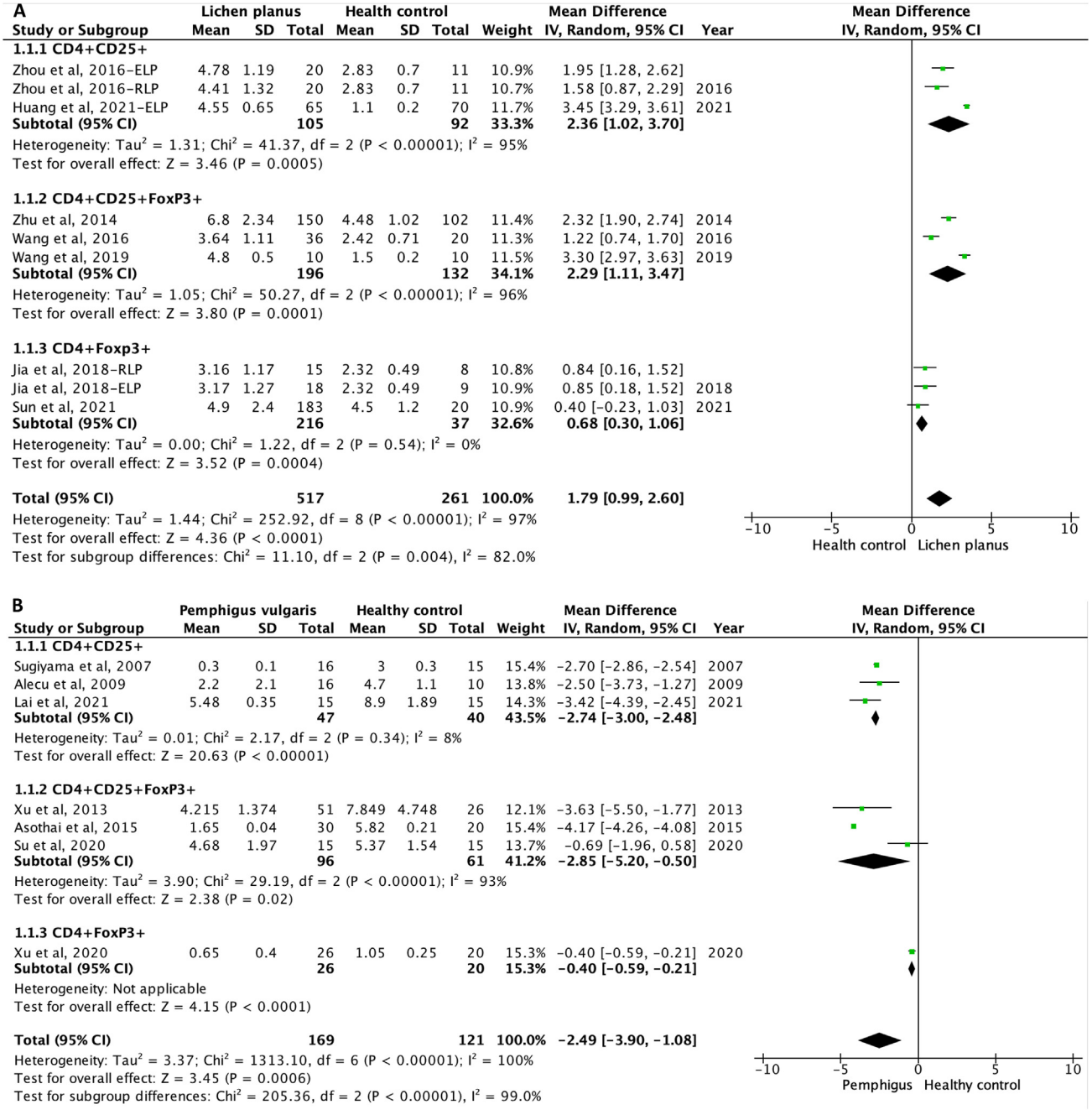

Figure 1 Forest plots of meta-analysis of regulatory T cells in (A) lichen planus (LP) and (B) pemphigus vulgaris compare to heathy control, respectively. CI, confidence interval; SD, standard deviation.

reported in the included studies. Moreover, the function of Tregs in OLP or PV is required to be researched. The distinctive amount of Tregs in peripheral blood may be used to differentially diagnose the diseases, especially coexistence of PV and OLP. After all, anti-Dsg3 and/or anti-Dsg1 against PV have been also detected in OLP patients.[4] Although the exact mechanisms still lurk, effective Treg cell-based immunotherapy could be a future hope for PV or OLP, and could aid in the treatment of immune response based on antigen-Tregs induction or inhibition.

In summary, this analysis for the first time reported reciprocal emergence of Tregs in PV and OLP, and provided an interesting insight into a previously undescribed the linkage of the 2 mucocutaneous diseases based on the clinical observation.[4,5] To obtain a more accurate association of Tregs with the pathogenesis of PV or OLP, additional

Table 2 Characteristics of included studies on regulatory T cells (Tregs) in peripheral blood of patients with pemphigus vulgaris.

Author, year	Country	*Pemphigus vulgaris*			Healthy control			Matched factor	Definition of Tregs
		n	Age (mean (range))	F, M	n	Age (mean (range))	F, M		
Sugiyama et al., 2007[14]	Japan	16	56.7 (37–78)	10, 6	15	54 (29–72)	NA	Age	CD4+CD25high
Alecu et al., 2009[15]	Romania	16	23–71	7, 9	10	25–62	5, 5	Age, sex	CD4+CD25+
Xu et al., 2013[16]	China	51	50.2 (13–81)	23, 28	26	42.4 (20–70)	12, 14	Age, sex	CD4+CD25highFoxp3+
Asothai et al., 2015[17]	India	30	NA	NA	20	NA	NA	NA	CD4+CD25+FOXP3+
Su et al., 2020[18]	China	15	NA	NA	15	NA	NA	NA	CD4+CD25+FOXP3+
Xu et al., 2020[19]	China	26	NA	NA	20	NA	NA	Age, sex	CD4+Foxp3+
Lai et al., 2021[20]	China	15	20–70	NA	15	NA	NA	Age, sex	CD4+CD25high+

Abbreviations: F, female; M, male; NA, not available.

well-designed studies with larger sample size and diverse ethnicities are warranted to validate the findings.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jds.2022.07.009.

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