


# The association of Th17/Treg cells expression in peripheral blood and chronic spontaneous urticaria

## A protocol of systematic review and meta-analysis

Qianying Yu, MM<sup>a</sup>, Wenxia Lin, MD<sup>a,b</sup>, Jie Zhang, MD<sup>a,b</sup>, Li Peng, MD<sup>a,b</sup>, Qiaoqiao Kong, MM<sup>c</sup>, Rubin Zhong, MM<sup>d</sup>, Yan Lan, MM<sup>e</sup>, Min Xiao, MD<sup>a,\*</sup>, Mingling Chen, MD<sup>a,\*</sup> 

### Abstract

**Background:** The pathogenesis of chronic spontaneous urticaria (CSU) is not clear, but its occurrence is closely related to the immune state of the body, that is, the balance of T cell subsets. Previous studies have confirmed that the dynamic imbalance of Th1/Th2 cells in CD4+T cell subsets of T cell subsets is closely related to the pathogenesis of CSU, but there are few studies on the relationship between the dynamic imbalance of Th17/Treg cells in CD4+T cell subsets and the pathogenesis of CSU. The purpose of this study is to evaluate the relationship between Th17/Treg cells expression in peripheral blood and CSU, so as to provide a reference basis for the pathogenesis of CSU.

**Methods:** PubMed, Embase, CENTRAL, Web of Science, China Biology Medicine Database, China National Knowledge Database, Wan Fang Database, and Chongqing VIP Database will be searched to collect case-control studies and cohort studies evaluating the relationship between Th17/Treg cells expression in peripheral blood and CSU. The search time limits will be from the establishment of the database to December 2020. The meta-analysis will be carried out with the RevMan V.5.3 statistical software. The quality of all included studies will be evaluated by the Newcastle-Ottawa scale.

**Results:** The results of this study will comprehensively evaluate the Th17/Treg cells expression levels in peripheral blood of patients with CSU, and provide a reference basis for the pathogenesis of CSU.

**Conclusion:** The findings of this study may provide new evidence for the relationship between Th17/Treg cells balance in peripheral blood and CSU.

**OSF registration number:** DOI 10.17605/OSF.IO/S8MYW

**Abbreviations:** CSU = chronic spontaneous urticaria, OSF = open science framework, Treg = regulatory T-cells.

**Keywords:** chronic spontaneous urticaria, systematic review, Th17/Treg

### 1. Introduction

Urticaria is a condition characterized by the development of wheals (hives), angioedema or both, including chronic spontaneous urticaria (CSU) and inducible urticaria.<sup>[1]</sup> The CSU refers to

those with spontaneous appearance of wheals, angioedema, or both for >6 weeks due to known or unknown causes. The incidence of CSU is 0.5% to 0.1%, the course of the disease is prolonged, and the recurrence rate is high, which seriously affects

WL and QY contributed to the work equally and should be regarded as co-first authors.

This study was supported by the project of science and technology development fund of TCM Hospital of Sichuan Province/Hospital of Chengdu University of Traditional Chinese Medicine (Grant No. 18PY17).

Ethics and dissemination: Original data will not be collected, and no ethical approval will be required.

The authors have no conflicts of interest to disclose.

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

<sup>a</sup> Department of Dermatology, Hospital of Chengdu University of Traditional Chinese Medicine, <sup>b</sup> Chengdu University of Traditional Chinese Medicine, Chengdu,

<sup>c</sup> Department of Dermatology, Honghe Hani-Yi Autonomous Prefecture TCM Hospital, Honghe Hani-Yi Autonomous Prefecture, Yunnan Province, <sup>d</sup> Department of Dermatology, Guangzhou Zengcheng District Hospital of Traditional Chinese Medicine, Guangzhou, Guangdong Province, <sup>e</sup> Department of Dermatology, Jianyang Chinese Medicine Hospital, Jianyang, Sichuan Province, P.R. China.

\* Correspondence: Mingling Chen, Min Xiao, Department of Dermatology, Hospital of Chengdu University of Traditional Chinese Medicine, No. 39 Shi-er-qiao Road, Chengdu 610072, Sichuan Province, P.R. China (e-mail: cml1388@sina.com, 16401917@qq.com).

Copyright © 2020 the Author(s). Published by Wolters Kluwer Health, Inc.

This is an open access article distributed under the Creative Commons Attribution License 4.0 (CCBY), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

How to cite this article: Yu Q, Lin W, Zhang J, Peng L, Kong Q, Zhong R, Lan Y, Xiao M, Chen M. The association of Th17/Treg cells expression in peripheral blood and chronic spontaneous urticaria: A protocol of systematic review and meta-analysis. *Medicine* 2020;99:36(e22014).

Received: 26 July 2020 / Accepted: 31 July 2020

<http://dx.doi.org/10.1097/MD.00000000000022014>

the quality of life of the patients and aggravates the economic burden of the patients.<sup>[2]</sup>

The pathogenesis of CSU is not clear, but its occurrence is closely related to the balance of T cell subsets, that is, the immune state of the body. In recent years, many studies have confirmed that the pathogenesis of CSU is closely related to the dynamic imbalance of Th1/Th2 cytokines,<sup>[3–5]</sup> but there are few studies on the relationship between Th17/Treg immune imbalance and the pathogenesis of CSU. In the occurrence and development of most autoimmune diseases and inflammatory diseases, the destruction of Th17/Treg balance plays an important role,<sup>[6]</sup> which is related to the occurrence of many autoimmune diseases, such as anaphylactoid purpura, atopic dermatitis, systemic lupus erythematosus, hashimoto thyroiditis, rheumatoid arthritis, and so on.<sup>[7–11]</sup> The CSU is a multifactor autoimmune disease with the disorder of human autoimmune function as the core.<sup>[12]</sup> The immune imbalance of Th17/Treg may play a key role in the pathogenesis of CSU.

## 2. Methods

### 2.1. Study registration and ethics

This protocol has been registered at the Open Science Framework (OSF). Original data will not be collected, and no ethical approval will be required. This protocol will adhere to the preferred reporting items for systematic reviews and meta-analysis protocols statement.<sup>[13]</sup>

### 2.2. Inclusion criteria

**2.2.1. Type of study.** Case-control studies and cohort studies that evaluate the relationship between Th17/Treg cells expression in peripheral blood and CSU.

**2.2.2. Participants.** Patients in the case group should be diagnosed as CSU, regardless of race, sex, age, and course of the disease. People in the control group should be without CSU.

**2.2.3. Exposure factors.** The expression levels of Th17/Treg cells in peripheral blood will be regarded as exposure factors.

**2.2.4. Types of outcomes.** The outcome measurements include the expression levels of Th17 and Treg cells in peripheral blood.

### 2.3. Exclusion criteria

The exclusion criteria will be as follows: duplicate literature, literature with incomplete data, and animal experiments.

### 2.4. Electronics searches search strategy

We will comprehensively search the literature sources of the PubMed, Embase, CENTRAL, Web of Science, China Biology Medicine Database, China National Knowledge Database, Wan Fang Database, and Chongqing VIP Database. All case-control studies and cohort studies evaluating the relationship between the expression of Th17/Treg cells in peripheral blood and CSU will be searched. The search time limits from the establishment of the database to December 2020. The searches will be carried out using the Medical Subject Headings and all synonyms for Chronic Spontaneous Urticaria, Th17, Treg, case-control studies, and cohort studies.

### 2.5. Data extraction

Two authors (QY and WL) will independently extract data from the included studies. We will resolve discrepancies through discussion with a third researcher (MC). Data abstracted will include the first author, title, year of publication, sample size, study design, diagnostic criteria, and outcome measurement data.

### 2.6. Data synthesis and analysis

We will use RevMan V.5.3 (Copenhagen, The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) statistical software for meta-analysis. The standardized mean difference will be used for continuous variables, and the odds ratio will be used for dichotomous data. The 95% confidence interval will be given for the results of each outcome indicator.

**2.6.1. Measures for heterogeneity.** The chi-square test will be used to evaluate the statistical heterogeneity of the result of each study ( $\alpha=0.1$ ), and  $I^2$  will be used to quantitatively judge the size of heterogeneity. If the  $I^2 < 50\%$  and  $P > .1$ , the fixed-effects model will be used for meta-analysis. If the  $I^2 > 50\%$  and  $P \leq .1$ , the random-effects model will be used for meta-analysis. The obvious clinical heterogeneity will be treated by subgroup analysis, sensitivity analysis, or descriptive analysis.

**2.6.2. Subgroup analysis.** Subgroup analysis will be performed based on the study types, the detection methods of Th17 and Treg cells.

**2.6.3. Sensitivity analysis.** We will use the sensitivity analysis to check the reliability and stability of the outcome data. The weak studies will be removed from the robust studies, and meta-analysis will be conducted again to determine whether there is a significant difference in the effect size before and after the removal of the weak studies.

**2.6.4. Reporting bias.** If there are sufficient studies, the funnel plot will be applied to check the reporting bias.

### 2.7. Quality assessment

The quality of each study will be evaluated by the Newcastle-Ottawa scale.<sup>[14]</sup> Each study could obtain a maximum of 9 points,<sup>[15]</sup> which categorized into 3 groups: very high risk of bias (0–3), high risk of bias (4–6), and low risk of bias (7–9).<sup>[16]</sup>

## 3. Discussion

Several studies had paid attention to the Th17/Treg imbalance in peripheral blood of patients with CSU.<sup>[17–20]</sup> While a few articles had summarized the existing evidence. In this study, a comprehensive literature search will be conducted to systematically evaluate the relationship between the expression levels of Th17/Treg cells in peripheral blood and the pathogenesis of CSU. The results of the present study will summarize the latest evidence of the relationship between the Th17/Treg balance in peripheral blood and CSU. This study will not only provide helpful evidence for both patients and clinicians but also provides a theoretical basis for the pathogenesis of CSU.

However, there may be several limitations to this systemic review. First, the included studies and sample size are limited, which may affect the accuracy of the results. Second, this systematic review only searches the literature in Chinese and English, so the results are not globally representative. Third, this

study excludes non-Chinese and English literature, there may be reporting bias. Fourth, we will include 2 types of studies, which may lead to heterogeneity of the results. We hope that this systematic review and meta-analysis can provide reliable evidence for the association between the Th17/Treg balance in peripheral blood and CSU.

### Author contributions

**Conceptualization:** Qianying Yu, Min Xiao, and Mingling Chen.

**Investigation:** Qianying Yu and Wenxia Lin.

**Supervision:** Wenxia Lin, Min Xiao, and Mingling Chen.

**Writing – original draft:** Qiaoqiao Kong, Rubin Zhong, and Yan Lan.

**Writing – review & editing:** Jie Zhang and Li Peng.

### References

- [1] Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA<sup>2</sup>LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. *Allergy* 2018;73:1393–414.
- [2] Yuan J, Wu Y, Li H, et al. Professor Guowei Xuan's experience in treating chronic urticaria from the angle of system theory. *J New Chin Med* 2014;46:25–7.
- [3] Su B, Xiong Z, Zhao B, et al. Analysis of the relationship between serum vitamin D and dehydroepiandrosterone sulfate levels with Th1/Th2 cytokines and immunoglobulins in patients with chronic spontaneous urticaria. *Int J Lab Med* 2020;41:435–9.
- [4] Chen Q, Zhong H, Chen WC, et al. Different expression patterns of plasma Th1-, Th2-, Th17- and Th22-related cytokines correlate with serum autoreactivity and allergen sensitivity in chronic spontaneous urticaria. *J Eur Acad Dermatol Venereol* 2018;32:441–8.
- [5] Gao R, Bi M, Zhang Y. Detection and significance of serum total IgE, complements and correlation of Th1/Th2 cytokines in spontaneous urticaria patients. *Chin J Dermatol Venerol Integ Trad W Med* 2015;14:298–300.
- [6] Xiao S, Jin H, Korn T, et al. Retinoic acid increases Foxp3+ regulatory T cells and inhibits development of Th17 cells by enhancing TGF-beta-driven Smad3 signaling and inhibiting IL-6 and IL-23 receptor expression. *J Immunol* 2008;181:2277–84.
- [7] Zhang L. Research on imbalances of peripheral blood Th17 cells and Treg cells in Anaphylactoid purpura children. *Chin J Immun* 2015;31:1404–6.
- [8] Jiang Y, Diao Q, Shi B, et al. Detection of Th17 and Treg related cytokines in serum of patients with atopic dermatitis. *J Clin Dermatol* 2016;45:411–3.
- [9] Jia H, Cheng G. Expressions and significance of Th17 Treg cell and related cytokines in peripheral blood in patients with SLE. *Hebei Med* 2018;24:1277–81.
- [10] Chen Y, Hu F, Huang H, et al. The effect of Treg and Th17 cells in Hashimoto's thyroiditis patients with normal thyroid function. *Med J West China* 2018;30:1438–42.
- [11] Kayama Y, Raaz U, Jagger A, et al. Diabetic cardiovascular disease induced by oxidative stress. *Int J Mol Sci* 2015;16:25234–63.
- [12] Ciprandi G, De Amici M, Berardi L, et al. Serum neopterin levels in spontaneous urticaria and atopic dermatitis. *Clin Exp Dermatol* 2011;36:85–7.
- [13] Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1–9.
- [14] Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010;25:603–5.
- [15] Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses; 2009. Available at: [http://www.ohri.ca/programs/clinical\\_epidemiology/oxford.asp](http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). Accessed: July 22, 2020.
- [16] Lo CK-L, Mertz D, Loeb M. Newcastle-Ottawa Scale: comparing reviewers' to authors' assessments. *BMC Med Res Methodol* 2014;14:1–5.
- [17] Zhu H, Yang J, Li R, et al. Safety assessment in randomized controlled clinical trials. *Chin J Dermatol* 2014;47:53–4.
- [18] Luo H, Yang J, Sun H, et al. The clinical significance of changes in levels of peripheral blood helper T cell 17 (Th17), regulatory T cells (Treg) and related cytokines in patients with chronic spontaneous urticaria (CSU). *Zhejiang Clin Med J* 2019;21:393–5.
- [19] Yang J. Role of Th17/Treg cell imbalance in the Pathogenesis of Chronic Spontaneous Urticaria. Guangdong, China: Guangdong Medical University; 2013.
- [20] Kong Q. Effect of Angelica yinzi on the Immune Imbalance of Serum Th17/Treg in Patients With Chronic Spontaneous Urticaria Based on the Theory of "flat modulate yin and yang". Sichuan, China: Chengdu University of Traditional Chinese Medicine; 2019.