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*Original Article*

# The effect of hydroxychloroquine on Treg, Th1, and Th2 cells in rheumatoid arthritis treatment

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**Abstract:** Objective: The purpose of this study was to investigate the therapeutic effect of hydroxychloroquine on rheumatoid arthritis (RA) and to analyze the treatment's effect on patients' Treg, Th1, and Th2 cells. Methods: A total of 160 RA patients admitted to our hospital were divided into a study group (SG, n = 80) or a control group (CG, n = 80) according to the treatment each patient received. The CG was treated with methotrexate, and the SG was treated with methotrexate and hydroxychloroquine. The treatment efficiency, the biochemical index levels, the CD4+ T lymphocyte expressions, the differences in their joint symptoms before and after the treatment, and the differences in the patients' pain levels before and after the treatment were compared between the two groups. The incidence of adverse reactions was also compared. Results: The effective rate of treatment in the SG was 97.50%, which was higher than the rate of 82.50% in the CG ($P < 0.05$). After 6 months of treatment, the incidence of adverse reactions in the SG was significantly higher than it was in the CG. CRP, ESR, and RF in the SG were all lower than they were in the CG ($P < 0.05$). The IFN-γ, IL-10, and IL-35 expression levels in the SG were significantly lower than they were in the CG after the treatment ($P < 0.05$). The tender joint counts (TJC) and swollen joint counts (SJC) showed no significant differences between the two groups before the treatment ($P > 0.05$) and were lower in the SG than they were in the CG ($P < 0.05$). There were no significant differences in the VAS, PGA, or PhGA between the two groups before the treatment, and the above indicators in the SG were all lower than they were in the CG after the treatment ($P > 0.05$). Conclusion: Hydroxychloroquine therapy has a good clinical effect on RA patients, for it can significantly improve the expression abnormalities of CD4+ T lymphocytes, improve patients' laboratory parameters and clinical symptoms, and achieve high treatment safety.

**Keywords:** Hydroxychloroquine, rheumatoid arthritis, Treg cells, Th1 cells, Th2 cells, impact

## Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disease with joint destruction as its main clinical symptom and chronic inflammatory changes of the synovial joints as its pathological feature [1]. Clinical practice has shown that patients with RA often have destruction of the articular cartilage, bones, and the joint capsules in addition to pathological changes in the synovium, and the final clinical outcomes are mostly joint deformity or loss of joint function [2]. Epidemiological data show that RA has a global distribution, with a prevalence rate of 0.32%-0.36% in China, and this figure has been increasing yearly. As the disease can eventually seriously impact an individual's ability to work, the early diagnosis and treatment of RA are recommended to improve the prognosis [3, 4].

Current research shows that the causative factors of RA are complex, and most studies point out that RA is a consequence of a combination of factors, such as environmental factors, genetic susceptibility, and immune dysfunction [5]. Among them, immune dysfunction is currently recognized by most scholars, and studies have revealed that autoimmune responses and multiple immune cells play an important role in the pathogenesis and development of RA. For example, it has been shown that IL-17 secreted by Th17 cells of the CD4+ T cell line is associated with the occurrence of many autoimmune diseases and may play an important role in RA; Th1 and Th2 cells of the CD4+ T cell line also secrete a variety of cytokines that lead to immune dysfunction, resulting in immunopathological damage and accelerating the development of autoimmune diseases. These findings

provide a more solid theoretical basis for this study [6, 7]. Hydroxychloroquine, a 4-aminoquinoline derivative antimalarial drug, has anti-inflammatory, immunomodulatory and anti-infective effects in addition to its antimalarial effect, and in recent years, this drug has been shown to have a better therapeutic effect on RA as well, but there is little clinical evidence on its mechanism [8]. This study aimed to investigate the effects of hydroxychloroquine in the treatment of RA on CD4+ T-cell subsets by setting up a controlled analysis, so as to provide a clinical basis for determining the mechanism of hydroxychloroquine in its treatment of RA.

## Materials and methods

### *General information*

A total of 160 RA patients admitted to our hospital from January 2019 to December 2019 were enrolled and divided into a study group (SG, n = 80) or a control group (CG, n = 80) according to the treatment option each patient received.

Inclusion criteria: patients (1) who met the diagnostic criteria for RA proposed by the American College of Rheumatology (ACR) in 1987 and who had significant clinical symptoms [9], (2) patients who were clearly conscious and able to cooperate with the research, (3) patients who had certain self-care abilities, (4) patients who had disease duration of 6 weeks, and (5) patients who had complete medical records. This study was approved by the ethics committee of the hospital. The patients or their families signed a written informed consent.

Exclusion criteria: patients (1) who also suffered from mental illness, (2) patients who were hypersensitive to the drugs used in the study, (3) patients who had taken hormonal drugs in the three months prior to the study, (4) patients with a drug or alcohol dependence, (5) patients who were pregnant or lactating, (6) patients who also had other autoimmune diseases such as systemic lupus erythematosus, (7) patients who had serious infections in the two months prior to the study or who had active hepatitis or HIV infection in the last six months, and (8) patients who also had malignant tumors.

Elimination criteria: patients (1) who died during the study, (2) patients who asked to withdraw during the study, and (3) patients who participated in clinical studies of other drugs during the study period.

### *Intervention methods*

All the enrolled patients were treated with the drugs in addition to the conventional RA treatment (such as diet adjustment, moderate exercise, etc.). The patients in the CG were treated with a combination of non-steroidal anti-inflammatory drugs (NSAIDs) as the main regimen, including meloxicam (Boehringer Ingelheim Shanghai Pharmaceutical Co., Ltd., H2-0020217) and methotrexate tablets (Shanghai S.Y. Shinyi Pharmacy Co. Ltd. H31020644, 2.5 mg/time, 4 times/week). The SG was additionally treated with hydroxychloroquine sulfate tablets (Shanghai S.Y.C.P. Pharmaceutical Co. Q.D. 0.2 g/time). The treatment duration was 6 months in both groups.

### *Observation indicators and evaluation criteria*

*Treatment efficiency:* The clinical treatment effect of the two groups of patients was evaluated at 6 months of treatment, and the treatment effect was divided into the three categories of markedly effective, effective, and ineffective with reference to the US ACR20/ACR50 criteria [10], where markedly effective means that the laboratory and clinical indicators are improved by 70%, effective means that the improvement reached 50%, and ineffective means that the improvement of the laboratory and clinical indicators was less than 20%. Effective rate = (number of markedly effective + number of effective)/total cases × 100%.

*Changes in CRP, ESR, and RF before and the after treatment:* Before the treatment and at 6 months after the treatment, 10 ml of morning fasting blood was collected from the two groups of patients, centrifuged, and stored at -80°C. The quantification of the laboratory indices were uniformly carried out, in which the CRP was measured using the rate scattering turbidimetric method with a normal reference value of w 10 mg/L, the ESR was measured using the Weiss method with a normal reference value of ≤ 15 mm/h in males and ≤ 20 mm/h in females, and the RF was measured using the latex agglutination method with a normal reference value of 0-20 IU/ml.

*The CD4+ T lymphocyte expressions before and after the treatment:* After reviewing the

**Table 1.** Comparison of baseline data between the two groups ($\bar{x} \pm s$)/[n (%)]

| General information | | Study group (n = 80) | Control group (n = 80) | $t/X^2$ | *P* |
|---|---|---|---|---|---|
| Gender | Male | 46 | 44 | 0.051 | 0.822 |
| | Female | 34 | 36 | | |
| Age (years) | | 47.98±2.31 | 48.02±2.41 | 0.057 | 0.955 |
| Average duration of illness (months) | | 28.38±2.31 | 28.18±2.71 | 0.355 | 0.724 |
| Average weight (kg) | | 63.19±2.31 | 63.23±2.41 | 0.076 | 0.94 |
| Education level | Illiterate | 8 | 6 | 0.341 | 0.672 |
| | Primary school | 18 | 20 | | |
| | Junior high school | 24 | 22 | | |
| | High school and above | 30 | 32 | | |
| Marital status | Married | 64 | 66 | 0.082 | 0.775 |
| | Single | 16 | 14 | | |
| Monthly income (Yuan) | < 1000 | 16 | 20 | 0.334 | 0.625 |
| | 1000-3000 | 28 | 26 | | |
| | > 3000 | 36 | 34 | | |

related literature, blood samples were collected from the two groups of patients with IFN-γ as the representative of the Th1 cells, IL-10 as the representative of the Th2 cells, and IL-35 as the representative of the Treg cells. Before the treatment and at 6 months after the treatment, the IFN-γ, IL-10, and IL-35 levels were determined using enzyme-linked immunosorbent assays (ELISA).

*Clinical symptoms before and after treatment:* The TJC and SJC were determined before the treatment and at 6 months after the treatment, and inter- and intra-group comparisons were performed.

*Changes in the patient pain levels before and after treatment:* The visual analogue scale (VAS) was used to assess the pain levels in the two groups of patients before and at 6 months after the treatment, with 0 indicating no pain and 10 indicating severe pain. The PGA scale was mainly used to assess the patients themselves, covering 0-10 points, with higher scores representing a worse disease condition. The MDGA scale was used to assess the patients' status by doctors on a 01-10 scale, with 0 representing healthy and 10 representing the worst possible condition [11].

*Incidence of adverse effects:* The incidence rate of various adverse events such as leukocytosis, oral ulcers, gastrointestinal reactions, hepatic and renal dysfunction, etc., in the two groups of patients was recorded by the medical staff, and the differences between the groups were compared.

*Statistical analysis*

The collected data were processed using SPSS20.0 software to carry out the statistical analysis. The measurement data were expressed as ($\bar{x} \pm s$) and compared using Student's t tests. The count data were expressed as [n (%)] and examined using chi-square tests. For continuous variables, Student's t tests were used to compare the differences before and after the treatment. $P < 0.05$ indicates that a difference is statistically significant [12].

## Results

*Comparison of the baseline data*

There were no significant differences in the clinical information such as gender, age, or disease duration between the two groups ($P > 0.05$), which were comparable (**Table 1**).

*Comparison of the differences in the treatment effectiveness*

There were 60 cases of markedly effective, 18 cases of effective, and 2 cases of ineffective, for a total effective rate of 97.50% in the SG. In the CG, there were 50 cases of markedly effective, 16 cases of effective, and 14 cases of ineffective, for a total effective rate of 82.50%, and the difference between the two groups was significant ($P < 0.05$) (**Table 2**).

**Table 2.** Difference in the treatment effectiveness between the two groups [n (%)]

| Grouping | Number of cases | Markedly effective | Effective | Ineffective | Effective rate |
|---|---|---|---|---|---|
| Study group | 80 | 60 (75.00) | 18 (22.50) | 2 (2.50) | 78 (97.50) |
| Control group | 80 | 50 (62.50) | 16 (20.00) | 14 (17.50) | 66 (82.50) |
| $X^2$ | - | - | - | - | 5.000 |
| *P* | - | - | - | - | 0.025 |

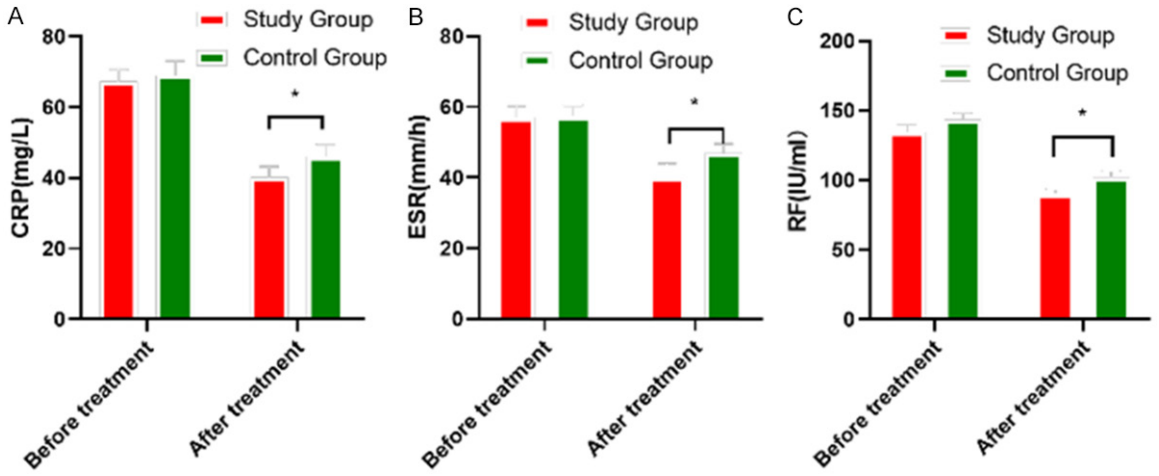


**Figure 1.** Comparison of the differences in the laboratory indices. No significant differences were observed in the CRP, ESR, or RF levels between the two groups before the treatment ($P > 0.05$), and the CRP (A), ESR (B), and RF (C) levels of the patients in the study group after the treatment were significantly lower than they were in the control group ($P < 0.05$); *$P < 0.05$.

*Changes in the CRP, ESR and RF levels*

The patients' CRP, ESR, and RF levels in the SG were significantly lower than they were in the CG ($P < 0.05$), and the comparisons between the groups before and after the treatment showed that the CRP, ESR, and RF levels of the patients in both groups were significantly reduced after the treatment ($P < 0.05$) (**Figure 1**).

*The CD4+ T lymphocyte expressions before and after the treatment*

At 6 months after the treatment, the CD4+ T lymphocyte expressions in the SG were significantly lower than they were in the CG ($P < 0.05$), and the expressions were significantly lower than they were before the treatment ($P < 0.05$) (**Figure 2**).

*Comparison of the clinical symptoms*

The TJC and SJC were not significantly different between the two groups before the treatment ($P > 0.05$), but at 6 months after the treatment, the TJC and SJC in the SG were significantly lower than they were in the CG ($P < 0.05$) (**Figure 3**).

*Comparison of the differences in the pain levels*

After the treatment, the two groups' pain scores were significantly lower than they were before treatment ($P < 0.05$), and the VAS, PGA, and PhGA scores of the SG were significantly lower than they were in the CG ($P < 0.05$) (**Figure 4**).

*Comparison of the incidence of adverse events*

The difference in adverse events between the two groups was not statistically significant ($P > 0.05$) (**Table 3**).

## Discussion

Rheumatoid arthritis (RA) is a relatively common clinical disease of the systemic autoimmune system [13]. The main clinical manifestations include symmetric arthritis, joint destruction, etc. Pathological experiments show that

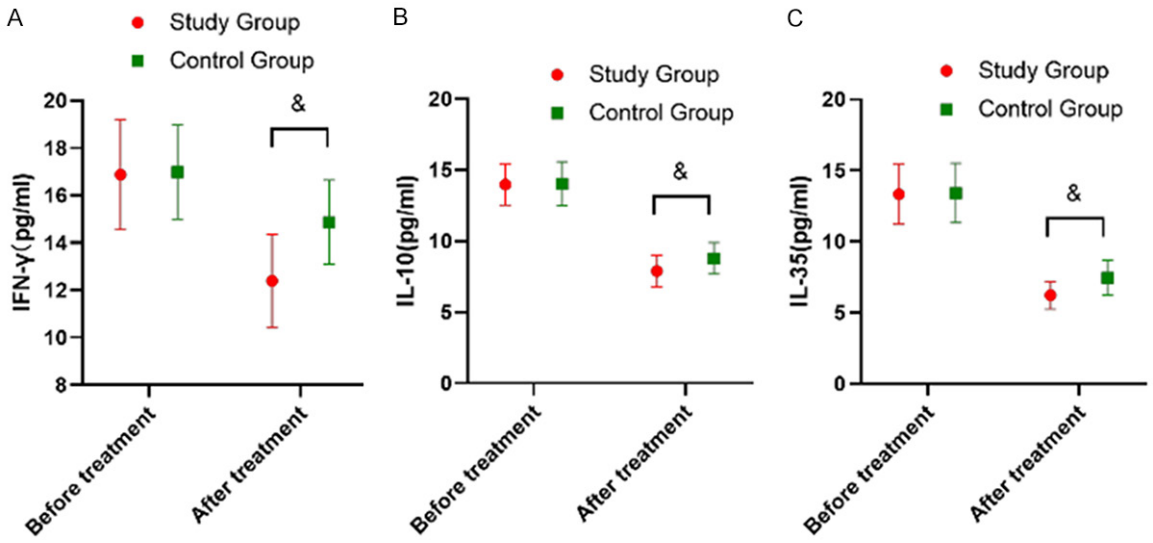


**Figure 2.** CD4+ T lymphocytes expressions. The IFN-γ (A), IL-10 (B) and IL-35 (C) levels of the patients in the study group were significantly lower than they were in the control group ($P < 0.05$); &$P < 0.05$.

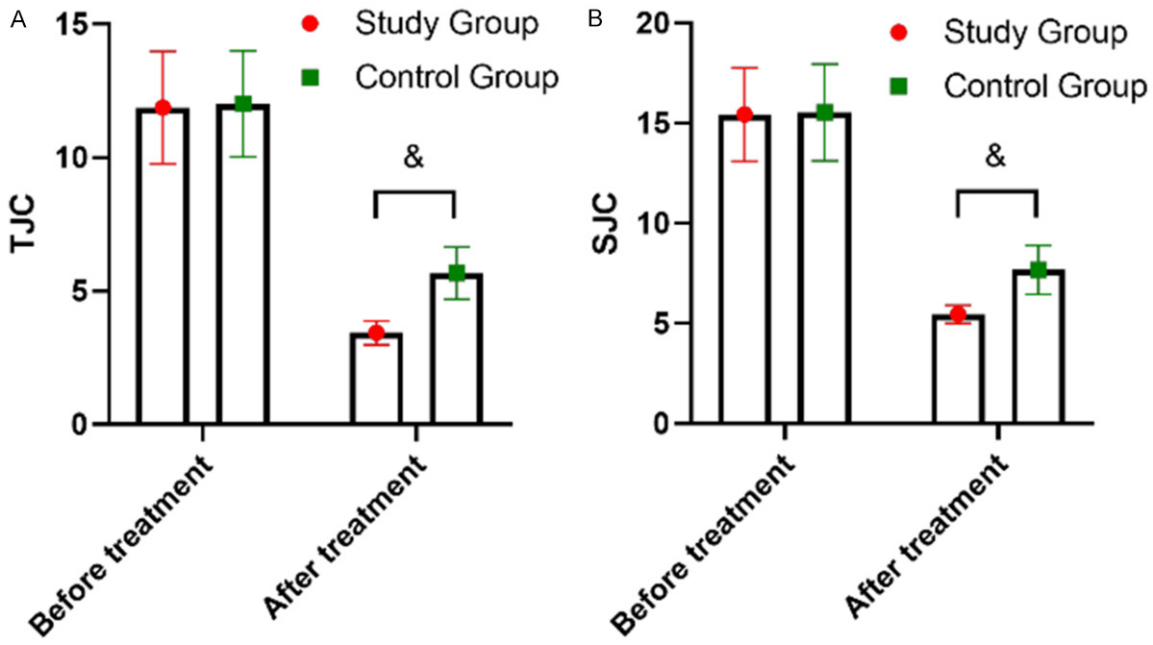


**Figure 3.** Comparison of the clinical symptoms. The TJC (A) and SJC (B) of the patients in the study group were significantly lower than they were in the control group ($P < 0.05$); &$P < 0.05$.

the main pathological changes in patients with RA are the formation of pannus, which promotes bone erosion, cartilage erosion, and eventually leads to joint ankylosis, the loss of joint function, and even deformity [13]. Data show that patients with advanced RA develop significant joint function deficits, have a high disability rate , and their quality of life is greatly affected [14].

The pathogenesis of RA is still unclear, but more and more studies have shown that RA is a multifactorial disease in which environmental factors, genetic factors, and immune dysfunction all play a role [15]. Several in vitro and animal experiments have shown that T-cell immune dysregulation is closely associated with the onset and development of RA, and auxiliary T cells are clinically classified into four

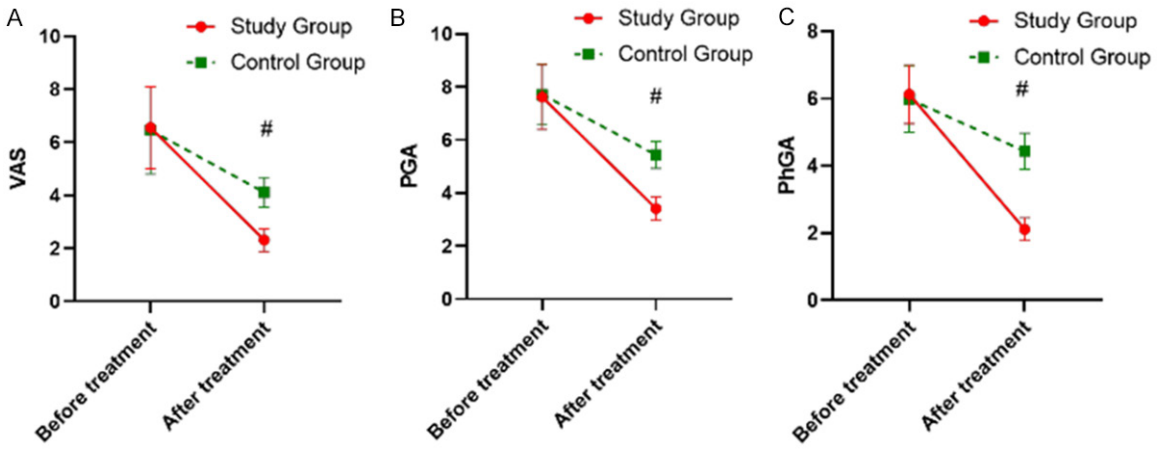


**Figure 4.** Changes in the patient pain levels. The VAS (A), PGA (B), and PhGA (C) scores of the patients in the study group were significantly lower than they were in the patients in the control group ($P < 0.05$); #$P < 0.05$.

**Table 3.** Comparison of the incidence of adverse events [n (%)]

| Grouping | Number of cases | Decreased white blood cells | Mouth ulcers | Gastrointestinal reactions | Liver and kidney function abnormalities | Total incidence rate |
|---|---|---|---|---|---|---|
| Study group | 80 | 2 (2.50) | 6 (7.50) | 2 (2.50) | 0 (0.00) | 10 (12.50) |
| Control group | 80 | 4 (5.00) | 4 (5.00) | 2 (2.50) | 2 (2.50) | 12 (15.00) |
| $X^2$ | - | - | - | - | - | 0.105 |
| $P$ | - | - | - | - | - | 0.745 |

subpopulations, Th1, Th2, Treg, and Th17 [16]. It has been found that there is a dynamic balance between Th1 and Th2 cells, and when this balance is broken, the immune function of the body will be disturbed, resulting in immunopathological damage and ultimately promoting the occurrence and development of autoimmune diseases [17]. Hydroxychloroquine is a commonly used anti-malarial drug with a similar mechanism of action to that of chloroquine, but its toxicity is generally lower than that of chloroquine. Previous studies on hydroxychloroquine have focused on the treatment of malaria, but in recent years there have been reports showing that hydroxychloroquine also has a clinical efficacy in the treatment of immune diseases [18]. A comparative study of adjuvant arthritis (AA) rats found that hydroxychloroquine significantly improved the synovial tissue lesions of AA rats, with significantly reduced inflammatory lesions and significantly improved mobility [19]. It has also been noted that hydroxychloroquine is effective at improving the self-care ability and joint function in RA patients, and it has a positive effect on improving the prognosis of RA patients [20].

In this study, we analyzed the efficacy of hydroxychloroquine in the treatment of RA and its effect on Treg, Th1, and Th2 cells in patients by setting up different subgroups, and the results showed that the treatment efficiency of the patients in the SG reached 97.50%, which was much better than of the treatment efficiency in the CG (82.50%). The results of a prospective controlled study on RA patients indicated that compared with the intervention of methotrexate alone, the addition of hydroxychloroquine to the methotrexate could significantly improve the clinical efficacy of the treatment in patients, from 55.8% to 77.9%, with a more significant improvement of the clinical symptoms in patients, which is similar to the results in this study [21]. We acknowledge that the traditional treatment option of RA mostly relies on NSAIDs. Although such drugs can relieve the clinical symptoms, they cannot shorten the course of the disease, and the long-term application of glucocorticoids is likely to induce osteoporosis or other adverse outcomes. Hydroxychloroquine can inhibit cholinesterase and monoamine oxidase activity, significantly inhibits the proliferation of fibroblasts and lymphocytes, and

relieves swelling and pain, so patients' clinical symptoms are improved significantly after treatment with this drug [22, 23]. A clinical retrospective analysis of 140 RA patients showed that after hydroxychloroquine intervention, the inflammatory cytokine levels, such as IL-17 and IL-23, in RA patients were significantly reduced, with significant differences before and after treatment, which is similar to the results of this study [24]. In this study, we found that the abnormal immune regulation of T cells is closely related to the onset and development of RA. Clinically, helper T cells are divided into four subgroups, namely Th1, Th2, Treg, and Th17, according to the different cytokine types. Th1 cells are involved in mediating cellular immunity and mediating the cellular immune response, and IL-2, TNF-γ, and TNF-β are representatives of the Th1 cytokines. Th2 can assist in the activation of B cells and play the role of humoral immunity, and IL-4 and IL-10 are representatives of Th2 cytokines. Treg is a type of T cell subgroup that can control the autoimmune reactivity in the body, and TGF-β and IL-35 are representatives of Treg cytokines [25]. Hydroxychloroquine has a significant anti-inflammatory effect and is effective in reducing local inflammatory effusion and relieving joint pain, so the patients in the SG had a significant reduction in their CRP, ESR, and RF levels after the treatment. In addition, hydroxychloroquine can inhibit the activity of T-lymphocytes and hinder the production of antigenic macrophages, thus reducing the level of IgG synthesized by B cells and exerting an anti-rheumatic effect by regulating the secretion and synthesis of cytokines. In fact, the patients in the SG were better than the CG patients in terms of the number of compression arthralgia, swollen joints, and the pain levels, which may explain the mechanism of action of hydroxychloroquine against rheumatism [26]. There was little difference in the incidence of adverse events between the two groups, indicating that hydroxychloroquine did not affect the treatment safety.

In summary, hydroxychloroquine therapy has a good clinical effect on RA patients, and it can significantly improve the CD4+ T lymphocyte expression as well as the laboratory parameters and clinical symptoms of patients with a high therapeutic safety. The novelty of this study lies in exploring the mechanism of hydroxychloroquine in the treatment of RA through a comparative analysis, which was carried out from a cellular perspective to provide a theoretical basis for the application of hydroxychloroquine in RA. The shortcomings of this study include the lack of representativeness of the results due to the small sample size and the lack of long-term patient follow-up.

## Disclosure of conflict of interest

None.

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