Efficacy and safety of chloroquine plus prednisone for the treatment of autoimmune hepatitis in a randomized trial

Lydia T de Moraes Falcão, Debora R B Terrabuio, Marcio A Diniz, Andrea da Silva Evangelista, Fabricio G Souza and Eduardo L R Cancado*

*Division of Gastroenterology and Hepatology, Hospital das Clinicas, University of São Paulo School of Medicine, Laboratory of Medical Investigation of Immunopathology of Schistosomiasis (LIM 06), Institute of Tropical Medicine of University of São Paulo, São Paulo, Brazil and ‡Biostatistics and Bioinformatics Research Center, Samuel Oschin Comprehensive Cancer Institute, Cedars Sinai Medical Center, Los Angeles, California, USA

Key words
antimalarial drug, autoimmune hepatitis, chloroquine, remission.

Accepted for publication 27 August 2019.

Correspondence
Lydia T de Moraes Falcao, Division of Clinical Gastroenterology and Hepatology, Hospital das Clinicas, University of Sao Paulo School of Medicine, Avenida Doutor Eneas de Carvalho Aguiar, 255, Sao Paulo/SP 05403-000, Brazil.
Email: lydiatmf@yahoo.com.br

Declaration of conflict of interest: The authors have no conflict of interest. Eduardo Cançado received a grant from the Federico Foundation.

Abstract

Background and Aim: Standard treatment for autoimmune hepatitis (AIH) consists of prednisolone and azathioprine. However, alternative therapy is required for non- or partial responders and in cases of side effects. The aim of this study was to evaluate the treatment outcomes associated with chloroquine plus prednisone in AIH patients.

Methods: Fifty-seven patients were recruited to receive either azathioprine or chloroquine, both with prednisone, in a randomized trial. The primary end-point was complete remission, based on normalization of aminotransferase levels in the first 6 months of treatment plus maintenance for at least 18 months, with minimal or no inflammatory activity in the liver biopsy. Secondary end-points were partial and non-response, severe side effects, and treatment withdrawal.

Results: There were no differences between groups regarding clinical, serological, histological, and treatment characteristics at baseline. There were no significant differences in the biochemical response rate (67.7 vs 53.8%, P = 0.41) or the complete remission rate (32.26 vs 15.38%, P = 0.217). However, despite the long study period, the sample size was smaller than that required for a noninferiority study. The mean prednisone dose was similar in both groups. There was a nonsignificantly higher rate of adverse effects and a tendency toward improvement in glycemic and cholesterol profiles in the chloroquine group (P = 0.09 and P = 0.07, respectively).

Conclusions: The combination of chloroquine and prednisone exhibited potentially beneficial effects in AIH patients (ClinicalTrials.gov: NCT02463331).

Introduction

Autoimmune hepatitis (AIH) is a chronic inflammatory disease that progresses to cirrhosis in the absence of treatment.1,2 The standard therapy, consisting of prednisolone and azathioprine, induces biochemical remission in most patients. Nonetheless, a complete response, including clinical, biochemical, and histological remission, is the most desirable treatment end-point as it leads to a greater chance of maintaining remission after treatment withdrawal.3,4

Nonrandomized trials and case reports evaluating alternative therapies for AIH, comprising budesonide, mycophenolate, and calcineurin inhibitors, have reported clinical–laboratory improvement with all treatments.5–7 Of these treatments, only budesonide and mycophenolate were compared to standard therapy. More recently, coadministration of allopurinol along with azathioprine has been used to redirect the metabolism of thiopurine to 6-thioguanine, and salvage therapies, such as mechanistic target of rapamycin (mTOR) inhibitors and biologicals (rituximab and infliximab), have been used to a very limited degree for poor responders to the standard autoimmune hepatitis (AIH) treatment, with high rates of side effects.8

Chloroquine is an antimalarial drug that is a well-established treatment for autoimmune rheumatic diseases, mainly as an adjuvant to modulate inflammation. There are reports of improved survival rates in lupus patients after chloroquine treatment.9–11 The mechanism of action of chloroquine involves several steps of the immune response. Chloroquine interferes with lysosomal phagocytic function, reduces antigenic presentation by antigen-presenting cells, and triggers the initiation and perpetuation of an immune response. Concomitantly, it inhibits the production of cytokines (such as interferon alpha and tumor necrosis factor alpha), and they inhibit the Th17 response.10,12

A Brazilian pilot study demonstrated that chloroquine was effective for the maintenance of AIH remission after standard treatment discontinuation.13 Based on this study, our group conducted a double-blind randomized trial comparing chloroquine...
and placebo after treatment discontinuation in patients with complete remission, which demonstrated a significant reduction in HAI recurrence in the chloroquine group.\textsuperscript{14} The drug was safe even in cirrhotic patients.

Considering the benefits of chloroquine in extrahepatic autoimmune diseases, its safety in cirrhotic patients, and its effectiveness in maintaining AIH remission, the aim of this study was to evaluate whether chloroquine could induce AIH remission in a randomized trial.

Methods

Patients. The period of inclusion was from 2003 to 2012. The inclusion criteria were as follows: age >18 years; definite AIH diagnosis according to the 1999 criteria of the International Autoimmune Hepatitis Group (IAIHG)\textsuperscript{15}; and treatment indication: increase of aminotransferase level >10-fold or >5-fold the upper normal value along with gammaglobulin level >2-fold the upper normal value or inflammatory activity in a liver biopsy (active chronic hepatitis, plasma cells/rosettes, or confluent necrosis). Not all patients were initially biopsied for specific reasons, such as thrombocytopenia, or because they had a definitive diagnosis of AIH, with clinical signs of cirrhosis.

Treatment-naive and previously treated patients who relapsed after treatment withdrawal were included. Relapse was defined according to the IAIHG criteria\textsuperscript{15} as the increase of aminotransferase levels >twofold the upper limit in at least two measures, with continuous increases in their values. The exclusion criteria were as follows: clinical signs of decompensated cirrhosis such as ascites, encephalopathy, or gastrointestinal bleeding; pregnancy; and overlapping syndromes.

Study design. This was an interventional, single-center, open-label, randomized controlled trial undertaken in Brazil. The authors designed the protocol, acquired and maintained the data, and conducted the statistical analysis. The protocol was approved by the local ethics committee (ID: 0571/04) and registered in the ClinicalTrials.gov database (NCT02463331). All subjects signed a written informed consent form before enrolment, and the study was conducted according to good clinical practices and the Declaration of Helsinki.

Interventions and safety. For the standard treatment group, azathioprine was administered at an initial daily dose of 50 mg and adjusted by up to 2 mg/kg/day according to tolerance and the results of the laboratory tests. In addition, prednisone was given at an initial dose of 30 mg/day and gradually tapered to 5–15 mg/day. The chloroquine plus prednisone group received 250 mg/day chloroquine diphosphate and the same prednisone regimen as the standard treatment group. All patients attended monthly consultations during the first 6 months of the protocol in order to assess treatment tolerance and undergo laboratory tests. After month 6, medical appointments were made every 2 months. Adverse effects were recorded and characterized as drug-related or not. All chloroquine users underwent initial and annual ophthalmologic evaluation. The drug was withdrawn according to the guidance of the ophthalmologists.

Primary outcome. The primary outcome was complete remission (including biochemical response and histological remission). Complete remission is characterized by normalization of aminotransferase levels in the first 6 months of therapy (biochemical response) and maintenance within the normal range for at least 18 months. At 18 months, liver biopsies were performed to assess histological remission, which was defined as minimal or no periportal activity evaluated by experienced liver pathologists. However, if there was an exacerbation, the 18-month biochemical response period was restarted.

Secondary outcomes. Secondary outcomes included treatment failure, partial response, and adverse effects that led to drug withdrawal. Treatment failure was defined as a decrease of 50% in serum aminotransferase levels by month 6 of treatment despite adequate adherence to therapy. Partial response was defined as a decrease of more than 50% in serum aminotransferase levels but without normalization. Although chloroquine and azathioprine are not formally contraindicated during pregnancy, treatment was discontinued if a patient became pregnant.

Autoantibody testing. Antinuclear (ANA), antismooth muscle (ASMA), antiliver/kidney microsomal type 1 (anti-LKM1), and antiliver cytosol (anti-LC1) antibodies were tested using an indirect immunofluorescence method on rat substrates. Antisalubrin liver antigen/liver pancreas (anti-SLA/LP) antibodies were detected using a Quanta Lite SLA enzyme-linked immunosorbent assay (ELISA) kit (INOVA Diagnostic Inc.; San Diego, CA, USA).

Sample size and randomization. The estimated required sample size was 122 participants per group considering a noninferiority margin of 15% for the proposed therapy. Generally, noninferiority studies require a large sample, which is a challenge in studies of unusual diseases such as AIH. Thus, the sample size was arbitrarily defined as the sample size achieved after 9 years of study, with an expectation that approximately 70 participants (approximately 35 per group) would be recruited (at an average rate of eight patients per year).

Eligible patients were randomized to receive either azathioprine or chloroquine, both with prednisone. Over the 9 years, only 57 patients fulfilled the eligibility criteria and agreed to participate in the trial. The number of participants in each group was different because enrollment was conducted in the form of a lottery; 35 azathioprine treatment spaces and 35 chloroquine treatment spaces were sequentially numbered from 1 to 70, and the patients were assigned a random number (from 1 to 70) and then allocated to the corresponding group. The head of the outpatient clinic, one of the trial investigators, registered and assigned participants to the proposed interventions.

Statistical analysis. Quantitative variables are expressed as mean ± SD, while qualitative variables are expressed as percentages. The 95% confidence intervals were calculated for the mean dose of prednisone for patients who achieved a biochemical response and for those who achieved complete remission. Data were analyzed using the Mann–Whitney U test, Anderson–Darling test, and Fisher’s exact test when applicable. All calculations were performed using the statistical package R (R Core...
Team, Vienna, Austria, 2014). A two-sided \( P \) value <0.05 was considered statistically significant.

## Results

**Baseline characteristics of patients.** Fifty-seven patients were included from 2003 to 2012. The follow-up period was variable because, if an exacerbation occurred during treatment, the 18-month period of assessment of serum aminotransferase levels would be restarted before the liver biopsy was taken. There were no differences in clinical, biochemical, or histological characteristics at baseline (Table 1).

Regarding the type of AIH, anti-SLA/LP reactivity is reported separately as it has been related to a different disease behavior in comparison to AIH type 1 (characterized by the presence of ANA and/or ASMA) and AIH type 2 (characterized by the presence of anti-LKM1 and/or anti-LC1 autoantibodies). However, some patients tested positive for ANA and/or ASMA and anti-SLA/LP simultaneously, and so, they were classified as AIH type 1 patients and as anti-SLA/LP carriers (Table 1).

In this study, 33 participants (57.9%) were undergoing treatment for the first time, and 24 (42.1%) were undergoing retreatment. Follow-up data on the participants are shown in Figure 1.

**Table 1 Clinical, laboratory, and histological characteristics of patients at baseline**

|                        | AZA/PD group (n = 31) | CQ/PD group (n = 26) | \( P \)  |
|------------------------|-----------------------|----------------------|---------|
| Female gender          | 24 (77.4%)            | 21 (88.5%)           | 0.32    |
| Age                    | 37.23 ± 17.63         | 37.54 ± 15.99        | 0.89    |
| AST (U/L), UNL: <319/ <37\( \Delta \) | 352.47 ± 68.85    | 306.31 ± 67.14      | 0.85    |
| ALT (U/L), UNL: <319/ <41\( \Delta \) | 323.03 ± 53.31    | 302.23 ± 65.43      | 0.48    |
| ALP (U/L), UNL: <1049/ <120\( \Delta \) | 187.1 ± 29.75       | 135.52 ± 14.3       | 0.43    |
| GGT (U/L), UNL: <369/ <61\( \Delta \) | 195.59 ± 37.55     | 185.76 ± 35.98      | 0.80    |
| Albumin (g/dL) (normal range 3.4–4.8) | 3.83 ± 0.12        | 3.68 ± 0.12         | 0.38    |
| Total bilirubin (mg/dL) (normal range: 0.2–1.0) | 3.53 ± 1.07     | 2.64 ± 0.68         | 0.48    |
| Gamma globulin (g/dL) (normal range: 0.7–1.5) | 2.63 ± 0.26      | 2.78 ± 0.29         | 0.81    |
| IgG (mg/dL) (normal range: 952–1538) | 2516 ± 388.06     | 3571.33 ± 711.62    | 0.29    |
| INR (normal range: 0.95–1.2) | 1.24 ± 0.2         | 1.23 ± 0.25         | 0.66    |
| Cirrhosis at onset\( ^{1} \) | 11 (44%)             | 14 (66.7%)           | 0.15    |
| Liver histology at AIH diagnosis | 27 (87.0%)        | 21 (80.7%)           | 0.71    |
| AIH type 1             | 24 (77.4%)            | 21 (80.7%)           | 1       |
| ANA (>1:80)            | 4 (16.6%)             | 2 (9.5%)             | 0.67    |
| SMA (>1:80)            | 11 (45.8%)            | 9 (42.8%)            | 1       |
| ANA + SMA              | 9 (37.5%)             | 10 (47.6%)           | 0.55    |
| AIH type 2             |                       |                      |         |
| Anti-LKM1 (>1:80)      | 3 (9.7%)              | 2 (7.7%)             | 1       |
| Anti-SLA/LP            | 9 (29.0%)             | 8 (30.8%)            | 1       |
| Pretreatment IAIHG diagnostic score |                       |                      |         |
| Definite AIH (16–22)\( ^{2} \) | 30/31 (96.8%)   | 26/26 (100%)         | 1       |
| Initial therapy        | 18 (58.1%)            | 14 (53.8%)           | 0.79    |

\( ^{1} \)The diagnosis of cirrhosis was based on histological alterations and clinical and laboratory features.

\( ^{2} \)One patient in the azathioprine group had pretreatment probable AIH but demonstrated a definite diagnosis after relapsing when prednisone was withdrawn.

AIH, autoimmune hepatitis; ALP, alkaline phosphatase; ALT, alanine aminotransferase; ANA, antinuclear antibodies; Anti-SLA/LP, antisoluble liver antigen/liver pancreas antibodies; ASMA, antismooth muscle antibodies; AST, aspartate aminotransferase; AZA, azathioprine; CQ, chloroquine; GGT, gamma glutamyltranspeptidase; IAIHG, International Autoimmune Hepatitis Group; IgG, immunoglobulin G; INR, international normalized ratio; LKM, liver/kidney microsomal; PD, prednisone; UNL, upper normal limit.

**Primary outcome.** The biochemical response rate up to month 6 of treatment is shown in Table 2. For the azathioprine group, the mean azathioprine dose was 89.29 ± 5.34 mg/day, and for the chloroquine group, the chloroquine dose was fixed at 250 mg/day. The mean prednisone doses are described in Table 2, with no significant difference between the groups (\( P = 0.18 \)). The 95% confidence intervals were calculated for the mean dose of prednisone.

After 18 months of maintenance of biochemical remission, liver biopsy was performed to evaluate complete remission. Eleven patients did not undergo liver biopsy due to loss to follow-up, pregnancy, or clinical deterioration (Fig. 1). In the azathioprine group, 21 patients maintained a biochemical response, and 16 of them underwent liver biopsies. In the chloroquine group, 14 patients maintained a biochemical response, and 8 of them underwent liver biopsies. There was no significant difference in the complete remission rate between the study groups (Table 2). The mean dose of azathioprine at the time of histological remission was 82.5 ± 6.51 mg/day. The mean prednisone doses are described in Table 2.

Biochemical response rates and complete remission rates were also compared between treatment-naive and relapsed patients, with no significant differences between groups (Fig. 2).

**Secondary outcomes.** Patients were withdrawn from the protocol due to serious adverse effects, clinical deterioration, pregnancy, partial response, or treatment failure (Fig. 1).
Among patients who did not achieve complete remission and were followed up, there were cases of histological remission after treatment with another therapeutic regimen. Among them, four patients received triple therapy with low-dose azathioprine, chloroquine, and prednisone due to specific reasons (arthralgia, diabetes, dyslipidemia, or intolerance to higher doses of azathioprine). Of these patients, two had previous disease remission using azathioprine and relapsed after treatment discontinuation. One of these two patients had previous complete remission with 125 mg/day azathioprine and 12.5 mg/day prednisone, and after triple therapy, remission was achieved at doses of 75 and 10 mg/day, respectively. The other patient had complete remission with 125 mg/day azathioprine and 12.5 mg/day prednisone, and after triple therapy, remission was achieved at doses of 50 and 12.5 mg/day, respectively.

**Safety issues.** The regimens studied were well tolerated. The adverse effects related to each drug were classified in relation to severity according to the Common Terminology Criteria for Adverse Events (CTCAE)\(^\text{16}\) (Table 3). Comorbidities such as diabetes, arterial hypertension, dyslipidemia, and obesity were diagnosed in both study groups, and prednisone may have played a role in their development. Although prednisone doses were similar in both groups, there was a tendency toward improvement in glycemic and cholesterol profiles in the chloroquine group (\(P = 0.09\) and \(P = 0.07\), respectively) (Fig. 3). There was a case of sepsis in the chloroquine group at the beginning of treatment when the dose of prednisone was still high, and chloroquine was not yet fully effective. Two patients in the chloroquine group had clinical deterioration, with decompensated cirrhosis, even after achieving a biochemical response. Both reported poor treatment compliance prior to decompensation.

---

**Figure 1** Flow chart of patients followed up.

**Table 2** Evaluation of biochemical response and complete remission rates in the study groups

| Treatment evaluation | AZA/PD group (\(n = 31\)) | CQ/PD group (\(n = 26\)) | \(P\) |
|----------------------|----------------------------|---------------------------|------|
| Biochemical response | 21 (67.7%)                 | 14 (53.8%)                | 0.41 |
| Prednisone dose (mg/day) | 13.9 (CI: 6.7–7.8) | 10.25 (CI: 9.3–11) | 0.18 |
| Mean time to obtain biochemical response (days) | 351.33 ± 287.71 | 227.5 ± 217.83 | 0.16 |
| Complete remission\(^1\) | 10 (32.26%) | 4 (15.38%) | 0.21 |
| Prednisone dose (mg/day) | 10.6 (CI: 9.6–11.7) | 11.6 (CI:9.8–13.1) | 0.25 |
| Mean time to obtain complete remission (days) | 1181.58 ± 461.48 | 1092.57 ± 622.46 | 0.61 |
| Histological remission (considering only patients with liver biopsy) | 10/16 (62.5%) | 4/8 (50.0%) | 1 |

\(^1\)After 18 months of maintained biochemical response with histological remission.
AZA, azathioprine; CI, confidence interval 95%; CQ, chloroquine; PD, prednisone.
Adverse effects in the azathioprine and chloroquine group are described in Table 3. There were no cases of severe cytopenia, but treatment was discontinued in one patient due to gastric intolerance in the azathioprine group. Maculopathy was observed in two patients in the chloroquine group, but there were no cases of ophthalmological complaints. Chloroquine was discontinued in four patients: in two cases due to dermatological effects and in two patients due to chloroquine deposition in the retinal macula. None of the patients who had adverse effects due to chloroquine had previously used the drug they took in this study. The follow-up of these patients ranged from 151 to 696 days.

Discussion

In this study, the response to standard therapy was different from the rates reported in literature as most studies report biochemical improvement with azathioprine and prednisone in approximately 90% of cases and complete remission in 40–70% of cases.\textsuperscript{1,2} Despite the recommendation of European and American Guidelines to reduce the corticosteroid dose weekly, the dose was reduced monthly, and even then, the complete remission rate in the standard therapy group was considerably lower than those reported in European and American studies.\textsuperscript{1,2}

Czaja \textit{et al.} compared North American and Brazilian patients with type 1 AIH and observed that the Brazilian patients had an earlier disease onset, higher serum levels of aminotransferases and gammaglobulin at onset, and more ASMA positivity,\textsuperscript{17} which may partly explain the divergent data in this study and the previous studies regarding the immunosuppressive therapy response. Additional reasons for the severity of AIH in our study are the high frequency of anti-SLA/LP reactivity, which is related to severe clinical conditions, with a worse prognosis and a greater chance of relapse,\textsuperscript{18,19} and the genetic background of Brazilian patients, involving a higher frequency of human leukocyte antigen (HLA DR13), which has been connected to a more severe disease status.\textsuperscript{20}

Regarding the rates of biochemical response and complete remission, the rates were lower in the chloroquine group but with no significant differences. According to the histological remission rates among the patients who underwent liver biopsies, the rates were similar in both groups. Nevertheless, no definitive conclusion about noninferiority can be made due to the sample size.

Response to therapy was compared between treatment-naive and relapsed patients, with no differences in biochemical response rate or complete remission rate between groups. In the literature, relapsers are more likely to become cirrhotic, but the

Table 3

| Adverse event                        | AZA/PD group (n = 31), n (%) | CQ/PD group (n = 26), n (%) |
|--------------------------------------|-----------------------------|-----------------------------|
| Grade 3                              |                             |                             |
| Ophthalmological                     | 0                           | 2 (7.7)                     |
| Psychosis                            | 1 (3.2)                     | 0                           |
| Grade 2                              |                             |                             |
| Dermatological                       | 0                           | 2 (7.7)                     |
| Neuropathy                           | 0                           | 1 (3.8)                     |
| Ophthalmological                     | 0                           | 2 (7.7)                     |
| Headache                             | 0                           | 1 (3.8)                     |
| Diabetes of difficult control        | 1 (3.2)                     | 0                           |
| Hypertension of difficult control    | 1 (3.2)                     | 0                           |
| Gastric intolerance                  | 1 (3.2)                     | 0                           |
| Grade 1                              |                             |                             |
| Dermatological                       | 1 (3.2)                     | 0                           |
| Ophthalmological                     | 0                           | 2 (7.7)                     |

AZA, azathioprine; CQ, chloroquine; PD, prednisone.

Figure 2

Comparison of biochemical response and complete remission rates between treatment-naive patients and relapers. The percentages of each response in the azathioprine and chloroquine groups are given in the columns. ( ), Treatment-naive (n = 32/57); ( ), relapers (n = 25/57).

Figure 3

Patients’ metabolic comorbidities during the follow-up.

Groups: ( ), AZA+PD; ( ), CQ+PD. AZA, azathioprine; CQ, chloroquine; PD, prednisone.
chance of complete remission is no different from that of treatment-naive patients.\textsuperscript{21}

There was a higher rate of treatment failure in the chloroquine group compared to the standard therapy group, although the partial response rate in the chloroquine group is not different from the rate reported in the literature.\textsuperscript{19–22} The prednisone dose was also similar in both groups, ruling out the possibility of bias due to the prednisone dose being greater in the chloroquine group. Adherence to therapy and possible adverse effects were assessed at each visit, and the higher treatment failure in the chloroquine group could not be explained by lack of adherence to therapy.

In this trial, there was a high occurrence of prednisone-induced comorbidities such as obesity, dyslipidemia, diabetes, and hypertension in both groups. However, there was a tendency toward lower frequencies of these comorbidities (especially diabetes and dyslipidemia) in the chloroquine group, despite the similar corticosteroid doses in both groups. Authors have described favorable metabolic effects of antimalarial drugs as lipid and glucose profiles improve in patients with rheumatological diseases who are treated with chloroquine or hydroxychloroquine.\textsuperscript{23–25} Decreased hepatic cholesterol synthesis, increased cholesterol receptor levels, and changes in insulin metabolism and intracellular signaling may explain these beneficial metabolic effects that are additional advantages of using antimalarial drugs for treating autoimmune diseases as corticosteroids are almost mandatory for the treatment of these diseases.

The main adverse effects in the chloroquine group were dermatological, which are expected in $<$10\% of chloroquine users, and ophthalmological, which are even rarer.\textsuperscript{26} Trials involving rheumatologic patients suggest a risk of chloroquine deposition in the retinal macula of 1\%, leading to the recommendation of annual ophthalmologic evaluation after 5 years of continuous chloroquine use.\textsuperscript{27} On the other hand, there were many diabetic and hypertensive patients in our study, and retinopathy related to these comorbidities could be a confounding factor in the examination of the eye fundus.

Regardless of the reason for nonresponse, all nonresponders to the AIH treatment received another treatment. In the chloroquine group, four patients achieved complete remission with prednisone, azathioprine, and chloroquine. This finding points to the possibility of future studies using chloroquine, an antimalarial drug, as an adjunct to the standard therapy, which could minimize the side effects of the azathioprine plus prednisone(s) regimen.

The main limitations of the study were the fact that the number of patients enrolled was lower than the number required to demonstrate noninferiority of chloroquine and the use of ophthalmologic examination instead of fundus autofluorescence or spectral-domain optical coherence tomography to define chloroquine deposition in the retinal macula.\textsuperscript{27} However, the results of the study provide a stimulus for conducting larger multicenter randomized clinical trials. In addition, failure to perform more specific ophthalmologic examinations to diagnose maculopathy was not a major issue as the treatment time was less than the period usually required for maculopathy development (5 years).\textsuperscript{27}

As AIH is an uncommon disease, a multicenter study is required to recruit enough participants. On the other hand, this was the first randomized trial evaluating the effects of chloroquine in the treatment of AIH compared to standard therapy. Despite the limitations of the study, the results are very encouraging and suggest that chloroquine could be used as an adjuvant in therapeutic regimens, considering the scarce options for the treatment of AIH, as chloroquine does not have immunosuppressive effects.

Acknowledgment

The authors thank Prof. Dr Flair Jose Carrilho for facilitating the development of this study at Hospital das Clinicas of University of São Paulo School of Medicine.

References

1. Mans MP, Czaja AJ, Gorham JD et al. Diagnosis and management of autoimmune hepatitis. Hepatology. 2010; 51: 2193–213.
2. European Association for the Study of the Liver. EASL clinical practice guidelines: autoimmune hepatitis. J. Hepatol. 2015; 63: 971–1004.
3. Johnson PJ, McFarlane IG, Williams R. Azathioprine for long-term maintenance of remission in autoimmune hepatitis. N. Engl. J. Med. 1995; 333: 958–63.
4. Czaja AJ. Review article: permanent drug withdrawal is desirable and achievable for autoimmune hepatitis. Aliment. Pharmacol. Ther. 2014; 39: 1043–58.
5. Mans MP, Woynarowski M, Kreisel W et al. Budesonide induces remission more effectively than prednisone in a controlled trial of patients with autoimmune hepatitis. Gastroenterology. 2010; 139: 1198–206.
6. Zachou K, Gatselis NK, Arvaniti P et al. A real-world study focused on the long-term efficacy of mycophenolate mofetil as first-line treatment of autoimmune hepatitis. Aliment. Pharmacol. Ther. 2016; 43: 1035–47.
7. Rubin JN, Te HS. Refractory autoimmune hepatitis: beyond standard therapy. Dig. Dis. Sci. 2016; 61: 1–6.
8. Beretta-Piccoli BT, Mieli-Vergani G, Vergani D. Autoimmune hepatitis: standard treatment and systematic review of alternative treatments. World J. Gastroenterol. 2017; 23: 6030–48.
9. Solomon VR, Lee H. Chloroquine and its analogs: a new promise of efficacy of mycophenolate mofetil as first-line treatment of autoimmune hepatitis. Aliment. Pharmacol. Ther. 2016; 43: 1035–47.
10. Rubín JN, Te HS. Refractory autoimmune hepatitis: beyond standard therapy. Dig. Dis. Sci. 2016; 61: 1–6.
11. Beretta-Piccoli BT, Mieli-Vergani G, Vergani D. Autoimmune hepatitis: standard treatment and systematic review of alternative treatments. World J. Gastroenterol. 2017; 23: 6030–48.
12. Solomon VR, Lee H. Chloroquine and its analogs; a new promise of an old drug for effective and safe cancer therapies. Eur. J. Pharmacol. 2009; 625: 220–33.
13. Wallace DJ, Gudsookar VS, Weisman MH, Venuturupalli SR. New insights into mechanisms of therapeutic effects of antimalarial agents in SLE. Nat. Rev. Rheumatol. 2012; 8: 522–33.
14. Van Vollenhoven RF, Mosca M, Bertsias G et al. Treat-to-target in systemic lupus erythematosus; recommendations from an international task force. Ann. Rheum. Dis. 2014; 73: 958–67.
15. Da Silva JC, Mariz HA, Da Rocha LF et al. Hydroxychloroquine decreases Th17-related cytokines in systemic lupus erythematosus and rheumatoid arthritis patients. Clinics (Sao Paulo). 2013; 68: 766–71.
16. Mucenic M, De Mello ES, Cançado EIR. Chloroquine for the maintenance of remission of autoimmune hepatitis: results of a pilot study. Arq. Gastroenterol. 2005; 42: 249–55.
17. Terrabuo DRB, Diniz MA, Falcão LTM et al. Chloroquine is effective for maintenance of remission in autoimmune hepatitis: controlled, double-blind, randomized trial. Hepatol. Commun. 2018; 3: 116–28.
18. Alvarez F, Berg PA, Bianchi FB et al. International Autoimmune Hepatitis Group Report: review of criteria for diagnosis of autoimmune hepatitis. J. Hepatol. 1999; 31: 920–38.
19. Trotti A, Colevas AD, Seter A et al. CTCAT V3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. Semin. Radiat. Oncol. 2003; 13: 176–81.
17 Czaja AJ, Souto EO, Bittencourt PL et al. Clinical distinctions and pathogenic implications of type 1 autoimmune hepatitis in Brazil and the United States. J. Hepatol. 2002; 37: 302–8.

18 Chen Z-X, Shao J-G, Shen Y et al. Prognostic implications of antibodies to soluble liver antigen in autoimmune hepatitis. Medicine (Baltimore). 2015; 94: e953.

19 Kirstein MM, Metzler F, Geiger E et al. Prediction of short- and long-term outcome in patients with autoimmune hepatitis. Hepatology. 2015; 62: 1524–35.

20 Czaja AJ, Carpenter HA, Moore SB. Clinical and HLA phenotypes of type 1 autoimmune hepatitis in North American patients outside DR3 and DR4. Liver Int. 2006; 26: 552–8.

21 Lamers MMH, van Oijen MGH, Pronk M, Drenth JPH. Treatment options for autoimmune hepatitis: a systematic review of randomized controlled trials. J. Hepatol. 2010; 53: 191–8.

22 Czaja AJ. Current and prospective pharmacotherapy for autoimmune hepatitis. Expert Opin. Pharmacother. 2014; 15: 1715–36.

23 Hage MP, Al-Badri MR, Azar ST. A favorable effect of hydroxychloroquine on glucose and lipid metabolism beyond its anti-inflammatory role. Ther. Adv. Endocrinol. Metab. 2014; 5: 77–85.

24 Borba EF, Bonfá E. Long-term beneficial effect of chloroquine diphosphate on lipoprotein profile in lupus patients with and without steroid therapy. J. Rheumatol. 2001; 28: 780–5.

25 Kavanaugh A, Adams-Huet B, Jain R, Denke M, McFarlin J. Hydroxychloroquine effects on lipoprotein profiles (the HELP trial): a double-blind, randomized, placebo-controlled, pilot study in patients with systemic lupus erythematosus. J. Clin. Rheumatol. 1997; 3: 3–8.

26 Ruiz-Irastorza G, Ramos-Casals M, Brito-Zeron P, Khamashta MA. Clinical efficacy and side effects of antimalarials in systemic lupus erythematosus: a systematic review. Ann. Rheum. Dis. 2010; 69: 20–8.

27 Marmor MF, Kellner U, Lai TYY, Melles RB, Mieler WF. Recommendations on screening for chloroquine and hydroxychloroquine retinopathy (2016 revision). Ophthalmology. 2016; 123: 1386–94.