Review Article

The Role of Hydroxychloroquine as a Steroid-sparing Agent in the Treatment of Immune Thrombocytopenia: A Review of the Literature

Fatemeh Mohammadpour[1], Mona Kargar[1], Molouk Hadjibabaie[1]

[1]Research Center for Rational Use of Drugs, Tehran University of Medical Sciences, Tehran, Iran

ABSTRACT

Immune Thrombocytopenia (ITP) is an autoimmune disease in which platelet destruction causes thrombocytopenia. Due to the known steroid toxicities, alternative agents have been evaluated for the treatment of these patients. We aimed to review the literature and find evidences regarding the potential benefits of hydroxychloroquine (HCQ) as a steroid-sparing agent in the treatment of ITP. We searched English language articles within Web of Science, PubMed, and Scopus. Cohorts, clinical trials, case reports, conference papers, and letters were included. We excluded papers which either focused on administration of HCQ for non-ITP conditions or studies on other treatment modalities for ITP. In total, 54 ITP cases with either primary or systemic lupus erythematosus (SLE)-associated ITP were included in four studies (SLE-associated ITP; $n = 23$). All patients have received corticosteroids previously and >90% received other agents with HCQ concomitantly. Overall response was achieved in more than 60% of patients. Sustained response in 18 (33.3%) patients was associated with no treatment or HCQ alone. One of the studies reported a significantly better response in patients with definite SLE compared to those with positive antinuclear antibody and no definite SLE. Similarly, another study found a nonsignificant trend toward better long-term response in patients with definite SLE compared to incomplete SLE. The included articles reported the efficacy of the HCQ with acceptable safety. Available data regarding the use of HCQ for this indication are spare and more studies are needed in ITP with different severity. It seems that HCQ can be considered as an option in the treatment of SLE-associated ITP, and although promising, currently, the place of HCQ in the treatment of ITP continues to evolve.

KEYWORDS: *Hydroxychloroquine, idiopathic thrombocytopenic purpura, immune thrombocytopenia, immune thrombocytopenic purpura, systemic lupus erythematosus*

Received: August 2017.
Accepted: December 2017.

INTRODUCTION

Immune Thrombocytopenia (ITP) is an autoimmune disease, associated with platelet destruction and temporary or persistent thrombocytopenia, caused by platelet autoantibodies[1-3] detected in both adults and children.[4] In Europe, the annual incidence of ITP has been estimated at 2.8–3.9/100,000 adult population.[5] This autoimmune disease was first described as "idiopathic thrombocytopenic purpura." In 2009, the International Working Group proposed replacing the term "idiopathic thrombocytopenia" with the term "immune thrombocytopenia" while keeping the abbreviation.[6]

ITP can be categorized as primary or secondary. The diagnosis of primary ITP is established once other

Access this article online

Quick Response Code:

Website: www.jrpp.net

DOI: 10.4103/jrpp.JRPP_17_60

Address for correspondence:
Dr. Mona Kargar, E-mail: mkargar@razi.tums.ac.ir

How to cite this article: Mohammad pour F, Kargar M, Hadjibabaie M. The role of hydroxychloroquine as a steroid-sparing agent in the treatment of immune thrombocytopenia: A review of the literature. J Res Pharm Pract 2018;7:4-12.

causes associated with ThrombocytoPenia are ruled out and ITP is developed in isolation.[7] Secondary ITP can result from chronic infections, lymphoproliferative or myeloproliferative disorders, pregnancy, and autoimmune disorders[8] such as systemic lupus erythematosus (SLE).[4] In other words, thrombocytopenia does not develop in isolation and is normally associated with other conditions or drug exposure.[9]

Among the secondary causes of ITP, SLE is one of the autoimmune conditions in which thrombocytopenia is a well-known hematologic presentation.[10] The prevalence of thrombocytopenia has been estimated at 15%–20% in these patients.[11] In addition, in up to 16% of these patients, ITP may precede SLE, even after long periods (up to 10 years).[12] While distinguishing between primary and secondary ITP is clinically relevant,[7] diagnosis of secondary ITP and distinction between these conditions is sometimes challenging.[9] In patients with primary ITP, positive antinuclear antibody (ANA), antiphospholipid (APL) antibody, antithyroid antibody, and positive direct red cell antiglobulin tests are often present.[9]

In general, measurement of ANA titer is the first standard laboratory screening test for autoimmune diseases.[13] In addition, it is recognized as the best laboratory tool for screening patients with SLE.[11,14] Despite the association between ANA titer and SLE, most patients with ITP and positive ANA titer do not show any clinical signs or symptoms of generalized autoimmune diseases.[14] This can be due to the fact that ANA is neither completely sensitive nor specific and may be even transiently found in 16% of the general population.[11] In addition, the presence of ANA or APL antibody without the clinical signs and symptoms indicative of SLE or APL syndrome is not suggestive for secondary ITP.[7]

The clinical course of ITP greatly varies in adult patients and ranges from asymptomatic cases to fatal bleeding. However, patients generally complain of mucocutaneous or subcutaneous bleeding when looking for treatment.[15] Therefore, the necessity of treatment for patients with ITP depends on the severity of thrombocytopenia and clinical evidence of bleeding.[16] In addition, treatment should be tailored individually[9] considering disease-related and patient-related factors[16] such as age, lifestyle, risk of bleeding, and patient's preferences.[6] Moreover, treatments for primary and secondary ITP are basically different.[7]

Based on the international consensus report and evidence-based practice guideline by the American Society of Hematology, the standard treatment for primary ITP includes corticosteroids as the first-line agent.[7,17] Other first-line treatments include intravenous immunoglobulin and intravenous anti-D administration.[6,17] For the treatment of patients with secondary ITP, targeting the underlying disease is often the main approach.[7] In patients with secondary ITP due to SLE, corticosteroids are the first-line agents for cases with more severe involvement.[18] However, selection of the standard treatment for patients with significant thrombocytopenia and disease symptoms is quite difficult due to the lack of standard guidelines.[19] Currently, several agents are used in the treatment of patients with ITP, although the safety and efficacy of these agents are not satisfactory.[20] Recently, drugs such as high-dose dexamethasone, rituximab, and thrombopoietin receptor agonists (TPO-RA) have been used for intensifying the treatment effects and increasing remission.[21] Despite the availability of several pharmacological options, treatment is sometimes challenging. In fact, long-term treatment with corticosteroids is associated with toxicities, which led to the idea of "minimizing steroid exposure" as a preferred approach when response to treatment is observed.[9] In addition, high cost of treatment with TPO-RA,[22] variability of response, and low rate of long-term remission with rituximab[22] are considerable issues. Moreover, there are concerns regarding the safety of immunosuppressive agents such as azathioprine, cyclophosphamide, mycophenolate mofetil, and cyclosporine.[9]

When investigating the use of second-line agents for ITP, problems such as diversity in the assessment of efficacy, outcomes, and definitions, besides the unavailability of comparative clinical trials, should be taken into consideration.[23] Among other medications, hydroxychloroquine (HCQ) is an immunomodulator agent, which has been used for a long time in the treatment of SLE, rheumatoid arthritis, and other autoimmune disorders.[24,25] The potential use of HCQ as a steroid-sparing agent is an interesting subject. The current study was designed in the light of limitations in the available pharmacotherapy options and the potential benefits of HCQ in the treatment of ITP. In this study, we aimed to review the literature to find published articles regarding the efficacy and safety of HCQ in patients with ITP.

Methods

In order to review the English language literature on the efficacy of HCQ in the treatment of ITP, we searched major electronic databases, including Web of Science, PubMed, and Scopus. In addition, to obtain further relevant articles, we manually searched the references of related papers and evaluated the

articles in this process; no time limits were set for the publication date. The literature search was finished in October 2016.

We evaluated the retrieved articles in terms of the inclusion and exclusion criteria. All cohort studies, clinical trials, case reports, conference papers, and letters were included in our search. We read the full text of the articles to avoid missing any data regarding the administration of HCQ in ITP patients.

Based on the objectives of the current study, we excluded irrelevant papers, which either focused on the administration of HCQ in the treatment of diseases other than ITP (such as rheumatoid arthritis) or studies about treatment modalities other than HCQ for ITP. Only one relevant conference paper was excluded, as its data were published in an original article, which was among our included papers [Figure 1].

The data of the included articles were presented in two tables. We tabulated the study characteristics, patients' demographics, and data related to HCQ treatment and response [Table 1]. Moreover, the features of the case reports are presented in another table [Table 2]. In a study by Arnal *et al*.,[26] which had a wide heterogeneity in drugs and treatment modalities, the number of included patients was limited to those who received HCQ.

Results

Based on our search, only four studies were retrieved.[19,26-28] These studies are summarized in Table 1.

Inclusion and exclusion criteria

Based on our literature review, only Khellaf *et al*. had clearly defined the inclusion and exclusion criteria. The included patients had ITP and marked thrombocytopenia, defined as platelet count <50 × 10^9/L on at least two consecutive laboratory tests. In addition, patients with thrombocytopenia were included if ANA titer was ≥1/160 and at least 1 previous treatment for ITP did not result in a sustained response (SR).[19] Moreover, patients with other conditions, which could be associated with ITP (such as HIV, hepatitis C, lymphoproliferative disorders, thyroid disease, and drug-induced ITP), were excluded; nonetheless, patients with SLE remained in the study.[19]

Using a similar definition proposed by Khellaf *et al*.,[19] Arnal *et al*.[26] included patients with "frank autoimmune thrombocytopenia." They included only patients with definite or incomplete SLE.[19,26] In both studies, patients with SLE were eligible only if thrombocytopenia was the predominant manifestation of SLE.[19,26] In addition,

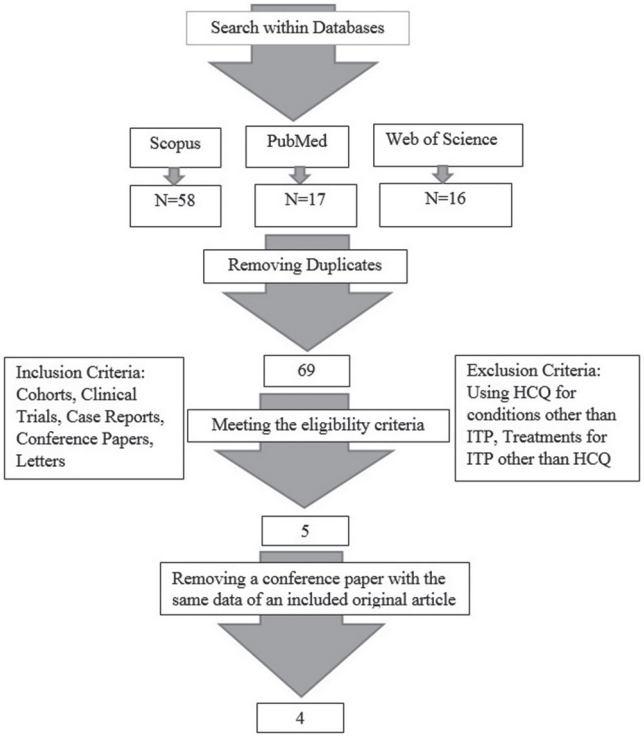

Figure 1: The flowchart of the searched databases and the number of articles

Arnal *et al*. emphasized on the lack or presence of mild extra hematological SLE flares at the time of thrombocytopenia diagnosis.[26] The exclusion of patients with diseases other than SLE, which could be the underlying cause of ITP or drug-induced thrombocytopenia, was almost similar in both studies.[19,26] Moreover, patients were excluded if thrombotic thrombocytopenic purpura was the cause of low platelet count at disease onset.[26]

Definitions for ITP

Expectedly, the case reports did not present any definitions for ITP.[27,28] However, Khellaf *et al*.[19] used the definition of ITP, proposed by the European Hematology Association Scientific Working Group on thrombocytopenia in 2009.[7] On the other hand, Arnal *et al*. used the definition presented by George *et al*., which indicates the presence of thrombocytopenia in patients with a normal bone marrow containing normal or high megakaryocyte count.[26]

Diagnostic criteria for systemic lupus erythematosus

Arnal *et al*.[26] used the 1982 definition by the American Rheumatism Association (ARA). According to ARA, definite SLE is diagnosed in patients with ≥4 criteria, while incomplete SLE is confirmed in the presence of 3 diagnostic criteria. However, use of the revised criteria of ARA classification may result in more diagnoses of

Table 1: Characteristics of the included studies

First author	Year	Country	Study	Number of patients with SLE	Number of ANA + (without SLE)	Number of study patients	Follow-up	Previous treatments	Concomitant treatment along with the initiation of HCQ	OR	Treatment with SR	Platelet count (platelet/L) before HCQ	Duration of HCQ	HCQ dose	Platelet count (platelet/L) after HCQ	Safety of HCQ
Khellaf *et al.*[19]	2014	France	Retrospective cohort	12	28	40	Median 64 months (6-146)	Median 2 (range 1-5) treatments: Corticosteroids (n=40), IVIG (n=15), dapsone (n=2), danazol (n=5), AZT (n=1), SPLN (n=2)	36 (90%) Prednisone - mean initial dose: 50 mg/days (range 30-65 mg/day) (n=36), dapsone (n=8), danazol (n=5)	24/40 (60%) Initial OR (first 8 weeks): 11/40 (27%) all CR and R were SR except for 1 at the end of follow up	No treatment (n=5), HCQ alone (n=12), HCQ + dapsone (n=2), HCQ + prednisone >10 mg/days (n=4), HCQ + prednisone <10 mg/days (n=1)	Mean 14±13×10^9	Median 5 years (range 0.4-12 years)	200 mg/days (n=3), 200 mg BD (n=33), 600 mg/days (n=4)	After 8 weeks: 35×10^9 (range 13-40×10^9)	No retinal deposit or toxic effects in eyes
Blasco[28]	2013	Spain	Case report	1	1 (moderate titer)	1	7 years<	Cyclic pulses of high-dose IVIG + corticosteroids without sustained remission	1 (100%) prednisone 5 mg/days	100%	HCQ alone	15×10^9	>7 years: 1 month HCQ + prednisolone, 2 months without treatment, 5 years HCQ alone	400 mg/days (1 month) then 300 mg/days	In 15 days, platelet >100×10^9	NA
Bockow *et al.*[27]	2013	USA	Case report	2 SLE + Sjögren's syndrome	2	2	18 months and 1 week	IVIG + high-dose prednisone (60 mg/days)	1 (100%) prednisone 15 mg/days + Vitamin D 50,000 IU/week	100%	HCQ 200 mg BD + Vitamin D 50,000 IU/weeks	43×10^9	14 months and 1 week	400 mg/days	Variable 215,000	No side effects
							4.5 years	Prednisone	1 (100%) prednisone 40 mg/days + Vitamin D 50,000 IU/week		HCQ 200 mg/days + prednisone 2 mg/days + Vitamin D 50,000 IU/months	8×10^9	4.5 years	400 mg/days then 200 mg/days	Variable 169,000	

Contd...

Table 1: Contd...

First author	Year	Country	Study	Number of patients with SLE	Number of ANA + of study (without SLE)	Number patients	Follow-up	Previous treatments	Concomitant treatment along with the initiation of HCQ	OR	Treatment with SR	Platelet count (platelet/L) before HCQ	Duration of HCQ	HCQ dose	Platelet count (platelet/L) after HCQ	Safety of HCQ
Arnal *et al*.[26]	2002	France	Cohort retrospective	8 definite	NA	11	31±16 months for patient with SR	Prednisone (*n*=4), prednisolone + IVIG (*n*=3), prednisolone + HDMP (*n*=2), prednisolone + IVIG + VBL (*n*=1) prednisolone + SPLN + VCR + IVIG + CPM + danazol (*n*=1)	10 (90.9%) Prednisone (range 0.3-1 mg/kg) (*n*=10)	7 (64%) CR (*n*=4; 36%); PR (*n*=3; 27%)	HCQ + prednisolone <0.2 mg/kg/days (*n*=7)	52±43×10^9 (range 6-125)	3-91 months (31±17 months for responders)	400 mg/days for 10 patients, 600 mg/days for 1 case	>150×10^9 (*n*=4); between 50×10^9 and 150×10^9 (*n*=3); <50×10^9 (*n*=4)	NA

AZT=Azathioprine, CPM=Cyclophosphamide, HDMP=High-dose methylprednisolone, IVIG=Intravenous immunoglobulin, NA=Not available, OR=Overall response, PR=Partial response, SPLN=Splenectomy, SR=Sustained response, VBL=Vinblastine; VCR=Vineristine, SLE=Systemic lupus erythematosus, ANA=Antinuclear antibody, CR=Complete response, HCQ=Hydroxychloroquine, BD=Twice a day, R=Response

definite SLE, compared with the 1982 version of this classification. Accordingly, 15 patients were diagnosed with incomplete SLE based on the 1982 criteria, while the revised criteria indicated 4 cases with definite SLE among them.

Although Khellaf *et al*. used a similar definition for definite SLE, they classified patients with <4 criteria in the non-SLE group.[19] Based on this classification, 12 (30%) patients were diagnosed with SLE (4, 5, and 6 criteria in 8, 2, and 2 patients, respectively), while the remaining 28 patients were without SLE (2 and 3 criteria in 13 and 15 patients, respectively). In the case reports, the authors only mentioned that the patients were diagnosed with SLE.[27,28] Moreover, in terms of SLE activity, Khellaf *et al*. and Arnal *et al*. used the SLE disease activity index (SLEDAI).[16,26]

Positive antinuclear antibody titer

ANA positive antibody with a titer of ≥1/160 was one of the inclusion criteria in the study by Khellaf *et al*. They also pointed that the immunofluorescence technique applied on HEp-2 cell substrate was the selected laboratory method for the measurement of ANA.[19] Moreover, Bockow *et al*.[27] noted that the patients had high titers of ANA. In one of their patients, the titer of ANA was 1:640. Blasco[28] also indicated moderate ANA titers in his patient; nonetheless, the ANA titer was not mentioned. In the study by Arnal *et al*.,[26] the ANA titer of 15 patients with incomplete SLE was reported. These patients (out of 56 patients) received different treatments in the survey. However, the number of patients with positive ANA titer, who were treated with HCQ, was not presented.

Other symptoms

Several symptoms were reported in patients in the case reports. In the study by Blasco,[28] the reported patient presented with asthenia, Raynaud's phenomenon, oral aphthae, urticaria, malar rash, photosensitivity, chronic polyarthritis, leukopenia, mild hypocomplementemia, and a history of autoimmune thyroid disease. In addition, Bockow *et al*.[27] reported two cases diagnosed with SLE and/or Sjögren's syndrome. These patients were cytopenic and showed sicca symptoms; both patients had positive anti-SSA/Ro autoantibodies. One of the patients also suffered from joint pain, while the other had elevated total complement activity.

Definition and timing of response to treatment

Definition of response to treatment was presented in two studies. Khellaf *et al*.[19] categorized response to treatment as follows: "complete response" (CR) when the platelet count is ≥100 × 10^9/L; "response" when the platelet count is 30–100 × 10^9/L (at least twice the

Table 2: Characteristics of case reports

Author	Platelet count before HCQ (platelet/L)	Duration	Treatment	Platelet count after treatment with HCQ (platelet/L)
Blasco[28]	15×10^9	30 day	HCQ 400 mg/days + prednisone 5 mg/days	100×10^9
		2 years	HCQ 300 mg/days	130×10^9
		2 months	HCQ withdrawal	70×10^9
		5 years	HCQ	160×10^9
Bockow *et al*.[27]	43×10^9	2 weeks	HCQ 200 mg BD + prednisone 15 mg/days + Vitamin D 50,000 IU/week	55×10^9
		6 weeks	HCQ 400 mg/days + prednisone 10 mg/days + Vitamin D 150,000 IU/week	114×10^9
		6 months	HCQ 400 mg/days + prednisone 5 mg/days + Vitamin D 50,000 IU twice a week	140×10^9
		1 month	HCQ 400 mg/days + prednisone 5 mg/days; Vitamin D discontinued	18×10^9
		3 weeks	HCQ 400 mg/days + prednisone 30 mg/days + Vitamin D 50,000 IU twice a week	91×10^9
		1 month later	Prior treatment	137×10^9
		4 months	HCQ 400 mg/days + prednisone 5 mg/days + Vitamin D 50,000 IU twice a week	161×10^9
		6 weeks	HCQ 400 mg/days + Vitamin D 50,000 IU once a week; prednisone discontinued	215×10^9
	8×10^9	1 month	HCQ 200 mg BD + prednisone 40 mg/ days+Vitamin D 50,000 IU/week	72×10^9
		2 weeks	HCQ 200 mg BD + Vitamin D 50,000 IU/week + prednisone tapered to 15 mg	301×10^9
		6 weeks	HCQ 200 mg BD + Vitamin D 50,000 IU/week + prednisone tapered to 7.5 mg	89×10^9
		1 month	HCQ 400 mg/days + prednisone 7.5 mg/days + Vitamin D 50,000 IU was twice a week	244×10^9
		9 weeks	HCQ 400 mg/days + prednisone 5 mg/days + Vitamin D 50,000 IU twice a week	176×10^9
		1 month later	Prior treatment	212×10^9
		6 weeks	HCQ 400 mg/days + prednisone 4 mg/days + Vitamin D 50,000 IU twice a week	194×10^9
		16 weeks	HCQ 400 mg/days + prednisone 4 mg/days + Vitamin D 50,000 IU/week	182×10^9
		2.5 years after initial visit	HCQ 400 mg/days+prednisone 2 mg/days + Vitamin D 50,000 IU/week	169×10^9
		6 months (from 4 years after initial visit)	HCQ 200 mg/days + prednisone 2 mg/days + Vitamin D 50,000 IU once monthly	Stable

HCQ=Hydroxychloroquine, BD=Twice a day

initial count); and "treatment failure" when the platelet count is $<30\times10^9$/L or less than twice the initial count (or if the patient requires rescue treatment).

The assessment was based on the platelet count during the first 8 weeks of therapy. The mean time to CR and response following HCQ initiation was 5.6 (range, 2–10) and 3.07 (range, 2–6) months, respectively. In contrast, Arnal *et al*.[26] defined CR as platelet count $>150\times10^9$/L. The response was considered "partial" (PR) when the platelet count increased between 50 and 150×10^9/L (doubled); all other conditions were defined as failure. However, no definition was found in the case reports.[27,28]

Hydroxychloroquine initiation following diagnosis

Evaluation of the interval between the diagnosis of ITP and initiation of HCQ indicated a median of 4 months (range, 1 month to 10 years) and a mean of 14 months (range, 0.5–142 months) in studies by Khellaf *et al*.[19] and Arnal *et al*.,[26] respectively.

Treatment with hydroxychloroquine and other concomitant agents

The oral dose of HCQ ranged from 200 to 600 mg/d [Table 1]. HCQ was initiated with corticosteroids (prednisone) and several other agents in most patients. In fact, in a total of 54 patients in 4 studies, only 5 patients received HCQ alone. However, the outcomes of

these patients were not reported separately in studies. In the study by Khelaf *et al*.,[19] treatment with HCQ was initially in combination with another ITP treatment in 36 patients (90%); the most frequent agent was prednisone (36 cases). Moreover, in the study by Blasco,[28] the patient received prednisone concomitantly. In addition, both cases in the study by Bockow *et al*.[27] received prednisone plus Vitamin D. Finally, in the study by Arnal *et al*.,[26] 10 (90.9%) patients received prednisone, along with HCQ.

Sustained response with hydroxychloroquine

As shown in Table 1, SR was achieved in 34 out of 54 patients included in the articles (62.9%). Among these patients, SR in 18 (33.3%) patients was associated with no treatment or HCQ alone.

Factors associated with response to hydroxychloroquine

Khellaf *et al*.[19] showed that in univariate analysis, SLE-positive status was associated with a significantly higher SR to HCQ (10/12; 83%), compared to patients with positive ANA without definite SLE (14/28, 50%) ($P < 0.05$). In addition, Arnal *et al*.[26] found that long-term response (PR or CR) was more prevalent in patients with definite SLE (75%), compared to patients with incomplete SLE (33%). However, the difference was not significant ($P = 0.28$). None of the patients with incomplete SLE (3 out of 11 patients) showed long-term response to treatment (2 patients with failed response and 1 patient with PR).

Factors unrelated to treatment response

Khellaf *et al*.[19] found that age ($P = 0.66$), sex ($P = 0.872$), bleeding at diagnosis ($P = 0.24$), number of treatment agents before HCQ ($P = 0.46$), duration of ITP before HCQ ($P = 0.83$), SLEDAI score at HCQ onset ($P = 0.11$), ANA titer ≥ 1/320 ($P = 0.896$), positive anti-DNA antibodies ($P = 0.76$), positive antiplatelet antibodies ($P = 0.89$), and positive APL antibody ($P = 0.343$) were not significantly associated with SR to treatment with HCQ.

Other points

The association between Vitamin D deficiency and ITP was investigated in the study by Bockow *et al*.[27] Based on the reported cases, the authors suggested a synergistic effect between Vitamin D and HCQ in the treatment of thrombocytopenia. This conclusion was made as the combination regimen was more effective than monotherapy; however, the mechanism through which the effect is exerted is unknown.

Discussion

In this review article, we aimed to present evidence regarding the treatment of ITP with HCQ. Since this topic has not been explored extensively in the literature, we could not find homogenous data based on the available articles. The included papers only described the outcomes of 54 patients treated with HCQ. Nevertheless, we believe that several aspects of patients and their treatment should be evaluated more precisely in future studies.

As it was expected, all the patients had received corticosteroids before the initiation of HCQ. In addition, in >90% of patients, HCQ was not administered alone and concomitant treatment(s) – more frequently prednisone – was prescribed as well [Table 1]. Therefore, it seems that the observed response cannot be easily attributed to HCQ alone. However, it should be noted that patients who received this agent did not show satisfactory responses, while they had previously received corticosteroids. Moreover, delayed onset of HCQ effects, which was reported within 3 months for most patients,[19] precluded monotherapy with HCQ as the initial treatment.

In terms of efficacy, Khellaf *et al*. supported the concept of using HCQ as a "steroid-sparing agent."[19] Although the detailed results were not presented in their article, Khellaf *et al*. suggested that HCQ might not be as effective for patients with refractory SLE, who failed to respond to immunosuppressive agents or splenectomy.[19] Similarly, Arnal *et al*. showed that in combination therapy with prednisone and HCQ, 64% of patients could achieve long-term responses, which could lead to dose reduction or discontinuation of prednisone.[26] Since their patients only had moderate thrombocytopenia, the results cannot be extrapolated to all patients with different disease severity.[26]

In contrast, Blasco showed that corticosteroids can trigger the faster onset of response to treatment, while SR can be achieved with HCQ. Therefore, in the maintenance treatment of patients with refractory ITP, HCQ monotherapy may be a suitable option.[28] It was also proposed that the efficacy of HCQ is high enough as a first-line agent.[28] One of the important issues in the classification of patients with ITP is whether they have primary or secondary ITP. Khellaf *et al*. and Arnal *et al*. included patients with either primary or secondary (SLE-associated) ITP.[19,26] Moreover, patients in the case reports had SLE-associated ITP.[27,28] Therefore, none of these studies were performed solely on patients with primary ITP.

In terms of response to HCQ, a significantly better response was observed in patients with definite SLE as noted by Khellaf *et al*.,[19] and an insignificantly better response was reported in patients with definite SLE in the study by Arnal *et al*.[26] However, the limited number

of patients receiving HCQ in the latter study should be considered. Moreover, the threshold for platelet count in the definition of treatment response by Arnal *et al*. was higher than that reported by Khellaf *et al*. This might have influenced the categorization of patients with PR or response failure and can impede direct comparison of the results.

Another challenging issue regarding the diagnosis of ITP is the role of positive ANA status. Based on the international consensus, ANA is not a basic test for the diagnosis of ITP and is categorized among tests with potential application in the management of these patients.[17] In addition, Grimaldi-Bensouda *et al*. did not suggest routine ANA measurement due to the lack of association between ITP progression and ANA positivity.[5]

Data regarding the positive value of ANA titer also seem to be conflicting. In this regard, Al-Sayes *et al*. used the reference range of 1:40 for the positivity of ANA.[29] However, patients with low positive ANA titer can be diagnosed with primary chronic ITP, even though their response to corticosteroids seems to differ from those with negative ANA.[30] This finding was also pointed out by Abbasi *et al*.[14] They retrospectively studied patients with ITP, who received steroids as their initial treatment. ANA positivity was not significantly associated with the patients' demographics, family history, presence of autoimmune diseases, platelet count, hemoglobin level, or erythrocyte sedimentation rate (ESR), compared to patients with negative ANA. However, the authors found that the platelet count at 2 weeks after the initiation of therapy raised more significantly in patients with negative ANA, compared to patients with positive ANA (even after adjustments for sex, age, and ESR). In addition, they reported the significant negative effect of ANA positivity on reaching CR.[14] It was shown that unlike children, adult patients with positive ANA (titer >1/80) were not more susceptible to chronic ITP.[5]

Kellaf *et al*. justified the inclusion of patients with ANA titers above 1/160 due to the possibility of underlying connective tissue disorders at this threshold.[19] However, none of the included studies in this review focused on differences in HCQ treatment response between patients with positive and negative ANA. In the case reports and study by Khellaf *et al*., all the patients were ANA positive, which made such comparisons impossible.

The publication time of the retrieved studies is also an interesting point. Despite the long-term availability of HCQ in the market, use of this agent for the treatment of ITP is not longstanding. One of four studies included in this review was published in 2014.[19] Two studies were published in 2013[27,28] and one was published in 2002.[28] Moreover, another registered trial is currently recruiting participants.[31]

The most important limitation of this review article is the limited number of articles, addressing this issue. In addition, the heterogeneity in concomitant treatments and lack of well-designed clinical trials are other limitations of this study. In order to reduce heterogeneity among different studies, the European Medical Agency published a guideline on the clinical development of medicinal products in 2014, which are used for the treatment of chronic primary ITP;[32] overall, use of such guidelines can be very helpful.

Conclusion

It was previously proposed that thrombocytopenia can increase the risk of mortality in adult patients with ITP[6] and SLE.[12] In this regard HCQ as a steroid-sparing agent can be helpful for treatment purposes. In conclusion, it seems that HCQ can be an option in the treatment of patients with SLE-associated ITP. However, there is a scarcity of information in this area, and further studies are needed on ITP with different severities. Although promising, the status of HCQ in the treatment of ITP continues to evolve.

Authors' Contribution

Mohammadpour F. was responsible for performing the literature search, as well as preparing the manuscript draft. Kargar M. was responsible for extracting the articles, interpretation of the results and manuscript drafting. Hadjibabaei M. was responsible for the study concept and idea as well as editing the article.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Cooper N, Bussel J. The pathogenesis of immune thrombocytopaenic purpura. Br J Haematol 2006;133:364-74.
2. Boruchov DM, Gururangan S, Driscoll MC, Bussel JB. Multiagent induction and maintenance therapy for patients with refractory immune thrombocytopenic purpura (ITP). Blood 2007;110:3526-31.
3. Ruggeri M, Fortuna S, Rodeghiero F. Heterogeneity of terminology and clinical definitions in adult idiopathic thrombocytopenic purpura: A critical appraisal from a systematic review of the literature. Haematologica 2008;93:98-103.
4. Polverelli N, Palandri F, Iacobucci I, Catani L, Martinelli G, Vianelli N, *et al.* Absence of bi-directional cross-resistance of thrombopoietin receptor agonists in chronic refractory immune thrombocytopenia: Possible role of MPL polymorphisms. Br J Haematol 2013;161:142-4.
5. Grimaldi-Bensouda L, Nordon C, Michel M, Viallard JF, Adoue D, Magy-Bertrand N, *et al.* Immune thrombocytopenia

in adults: A prospective cohort study of clinical features and predictors of outcome. Haematologica 2016;101:1039-45.
6. Kistanguri G, McCrae KR. Immune thrombocytopenia. Hematol Oncol Clin North Am 2013;27:495-520.
7. Rodeghiero F, Stasi R, Gernsheimer T, Michel M, Provan D, Arnold DM, *et al.* Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: Report from an international working group. Blood 2009;113:2386-93.
8. Bussel JB. Therapeutic approaches to secondary immune thrombocytopenic purpura. Semin Hematol 2009;46:S44-58.
9. Cuker A, Cines DB. Immune thrombocytopenia. Hematology Am Soc Hematol Educ Program 2010;2010:377-84.
10. Patel N, Mody GM. Acute presentation of thrombocytopaenia in systemic lupus erythematosus is associated with a high mortality in South Africa. Lupus 2014;23:204-12.
11. Demir C, Esen R, Atmaca M, Efe S. Prevalence of autoantibodies related to some autoimmune disorders in patients with chronic idiopathic thrombocytopenic purpura. Clin Appl Thromb Hemost 2011;17:E114-8.
12. Bashal F. Hematological disorders in patients with systemic lupus erythematosus. Open Rheumatol J 2013;7:87-95.
13. Satoh M, Vázquez-Del Mercado M, Chan EK. Clinical interpretation of antinuclear antibody tests in systemic rheumatic diseases. Mod Rheumatol 2009;19:219-28.
14. Abbasi SY, Milhem M, Zaru L. A positive antinuclear antibody test predicts for a poor response to initial steroid therapy in adults with idiopathic thrombocytopenic purpura. Ann Hematol 2008;87:459-62.
15. Sultan S, Ahmed SJ, Murad S, Irfan SM. Primary versus secondary immune thrombocytopenia in adults; a comparative analysis of clinical and laboratory attributes in newly diagnosed patients in Southern Pakistan. Med J Malaysia 2016;71:269-74.
16. Stasi R, Provan D. Management of immune thrombocytopenic purpura in adults. Mayo Clin Proc 2004;79:504-22.
17. Provan D, Stasi R, Newland AC, Blanchette VS, Bolton-Maggs P, Bussel JB, *et al.* International consensus report on the investigation and management of primary immune thrombocytopenia. Blood 2010;115:168-86.
18. Hepburn AL, Narat S, Mason JC. The management of peripheral blood cytopenias in systemic lupus erythematosus. Rheumatology (Oxford) 2010;49:2243-54.
19. Khellaf M, Chabrol A, Mahevas M, Roudot-Thoraval F, Limal N, Languille L, *et al.* Hydroxychloroquine is a good second-line treatment for adults with immune thrombocytopenia and positive antinuclear antibodies. Am J Hematol 2014;89:194-8.
20. Salama A. Emerging drugs for immune thrombocytopenia (ITP). Expert Opin Emerg Drugs 2017;22:27-38.
21. Lambert MP, Gernsheimer TB. Clinical updates in adult immune thrombocytopenia. Blood 2017;129:2829-35.
22. Moukhadder HM, Chaya BF, Bazarbachi AH, Taher AT. Immune thrombocytopenia: A comprehensive review from pathophysiology to promising treatment modalities. Expert Opin Orphan Drugs 2016;4:1217-27.
23. Grace RF, Neunert C. Second-line therapies in immune thrombocytopenia. Hematology Am Soc Hematol Educ Program 2016;2016:698-706.
24. Rainsford KD, Parke AL, Clifford-Rashotte M, Kean WF. Therapy and pharmacological properties of hydroxychloroquine and chloroquine in treatment of systemic lupus erythematosus, rheumatoid arthritis and related diseases. Inflammopharmacology 2015;23:231-69.
25. Kaplan YC, Ozsarfati J, Nickel C, Koren G. Reproductive outcomes following hydroxychloroquine use for autoimmune diseases: A systematic review and meta-analysis. Br J Clin Pharmacol 2016;81:835-48.
26. Arnal C, Piette JC, Léone J, Taillan B, Hachulla E, Roudot-Thoraval F, *et al.* Treatment of severe immune thrombocytopenia associated with systemic lupus erythematosus: 59 cases. J Rheumatol 2002;29:75-83.
27. Bockow B, Kaplan TB. Refractory immune thrombocytopenia successfully treated with high-dose Vitamin D supplementation and hydroxychloroquine: Two case reports. J Med Case Rep 2013;7:91.
28. Blasco LM. Hydroxychloroquine alone for severe immune thrombocytopenic purpura associated with systemic lupus erythematosus. Lupus 2013;22:752-3.
29. Al-Sayes FM, Hindawi SI, Damanhouri GA, Attallah SM, Azaher FA, Akbar DH, *et al.* Autoimmune thrombocytopenia. Is it a different disease or different aspects of a single disease? Saudi Med J 2012;33:182-5.
30. Marmont AM. Antinuclear antibody (ANA)-positive thrombocytopenia: Primary, but with a difference. Blood 2009;114:2003-4.
31. Group CSTAR. Cyclophosphamide and Hydroxychloroquine for Thrombocytopenia in SLE (CHORUS). NLM Identifier: NCT02444728. Available from: https://www.clinicaltrials.gov/ct2/show/study/NCT02444728. [Last updated on 2017 Mar 09].
32. Guideline on the Clinical Development of Medicinal Products Intended for the Treatment of Chronic Primary Immune Thrombocytopenia. 2014 EMA/CHMP/153191/2013 Oncology Working Party; 2014.