Review Article

Comprehensive analysis and critical review of randomized clinical trials on safety profiling of Hydroxychloroquine and Belimumab

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ABSTRACT

Systemic Lupus Erythematosus (SLE), an autoimmune disorder is characterized by multiorgan damage, flares, and heterogeneity in its clinical symptoms. The treatment strategy for this notorious disease focuses on long-term antiSLE treatment to improve the quality of life, prevent flares, and suppress the immune system. Thus, the chronic use of SLE medicines makes it inevitable to study the safety and tolerability of drugs in large populations. In this comprehensive analytical study, Hydroxychloroquine (HCQ), which is known for its safe use in SLE, and Belimumab, which is comparatively a novel monoclonal antibody were critically analyzed for their adverse events. We performed the absolute risk, relative risk ratio, and odds ratio analysis after critically scru tinizing the clinical trials for significant adverse effects. HCQ showed major effects on the eye and heart. However, based on the results, HCQ was found to be safer than Belimumab, as a few serious complications were found associated with Belimumab. Our results were found to be as per the previous metaanalysis. This comprehensive review is aimed at analyzing the safety profiles of two widely used drugs for SLE Ie HCQ and Belimumab. We have conducted this review, critical analysis was done to critically a nalyze the clinical trials, and to gather the information of interest from these trials. Both anti-SLE drugs; HCQ and Belimumab were found to be safe for use against SLE. But comparatively, HCQ showed a safer profile than Belimumab which can be attributed to HCQ's longterm history of use since 1955. The observation emphasized the researchers for further clinical trials with a more standardized approach, specifically for Belimumab to determine its safety and tolerability in the post-marketing stage.

Key words: Systemic lupus erythematosus, belimumab, hydroxychloroquine, safety, risk analysis

Systemic Lupus Erythematosus is a systemic disease, involving a multiorgan system and is chronic. It results in severe damage to the organ system and its dysfunction. SLE is the result of a multistep cascade of immune system abnormalities starting with the inability of the cells to clear apoptotic bodies, which results in the activation of both arms of the immune system (adaptive and innate immunity), formation of immune complexes, and tissues' inflammation that results in an autoimmune process [1]. Apoptosis has a crucial role in the development of lupus. Increased non-cleared apoptotic debris is linked to inflammation and the generation of autoantibodies [2]. Autoantigens are released by apoptotic cells [3].

These can produce noticeable levels of type 1 interferon by activating TLR7 and TLR9 in dendritic cells [4, 5]. The aetiology of SLE includes aberrant clearance of immunological complexes (ICs) and apoptotic cells and low thresholds of B and T lymphocyte activation that result in loss of self-tolerance and autoantibody synthesis. Interaction of genetic predisposition, immunological, and hormonal variables, and environmental triggers is necessary for the clinical commencement of SLE. SLE shows itself in a range of clinical manifestations. The symptoms can range from hair loss (that can be thought of as mineral deficiency) and light sensitivity to lethal conditions like inflammation of the myocardium, brain, and nephrons. Thus, symptoms of SLE are heterogeneous and may differ in different individuals or among the same individual for different periods [1]. The complex nature of SLE makes it more difficult to treat because of its unpredictable symptoms [6].

SLE can affect both genders, but it affects women more than men. The ratio of SLE in males to females is 1 man against 13 women making it a feminine disease [7]. The disease is common in African lineage and African Americans inhabiting European countries and the United States. Interestingly and controversially, the disease is rare in Africa itself [8]. According to the Centre for Disease Control and Prevention, there are around 322,000 probable or confirmed cases of SLE, with the prevalence being higher in African Americans, American Indians, and Alaska Natives [9, 10]. For SLE

"Standard of care" therapy consists of immunomodulators, antimalarials, corticosteroids, immunosuppressive, and cytotoxic agents. The purpose of this treatment includes 1) minimizing the activity level of the immune activation by using immunosuppressants and by avoiding the triggers 2) protecting the organs from damage 3) minimizing the risk of comorbid conditions associated with lupus 4) reduction of pain and lethargy. The treatment is necessary for the early stages of SLE to avoid known triggers and to maximize the effects of immunomodulators. This critical review aims to analyse the safety profiles of the two drugs used for the treatment of SLE I-e HCQ and belimumab.

SLE is a challenging disease with current therapy aimed to restore the imbalance of the dysregulated immune system. B cells are important in the development of SLE's pathophysiology. Therefore, attempts to interfere with disease activity by targeting B lymphocytes for selective depletion using monoclonal antibodies is a promising strategy to increase therapeutic effectiveness. Thus, recent therapies focus on the development of monoclonal antibodies. Belimumab is an immunoglobulin monoclonal antibody that was approved by Food and Drug Administration in 2011 for treating adults with SLE [11]. It is a fully human antibody that inhibits soluble B lymphocyte stimulator (BLyS), which in turn inhibits the production of a crucial cytokine that is essential for B cell survival, proliferation, and differentiation [12 – 14].

Therapy with belimumab is a helpful treatment option for patients with active SLE despite conventional therapy due to the adaptability of the route of administration and the ease of the once-weekly regimen. The belimumab is metabolized by proteolytic enzymes and the proteolytic enzymes are not only restricted to hepatic tissue. Moreover, the level of hepatic enzymes e.g., Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) had no discernible effect on the pharmacokinetics of belimumab in trials. Thus, no dose adjustment of Belimumab is necessary for patients with hepatic impairment. The previous studies reported Belimumab to cause bronchitis, diarrhoea, viral upper respiratory tract infections (URTI), multifocal leukoencephalopathy, fatal hypersensitivity, and infusion reactions [15, 16]. HCQ is an alkalinizing substance. It is a lysosomotropic medication having high cell permeability that is accumulated in lysosomes where it raises the pH [17].

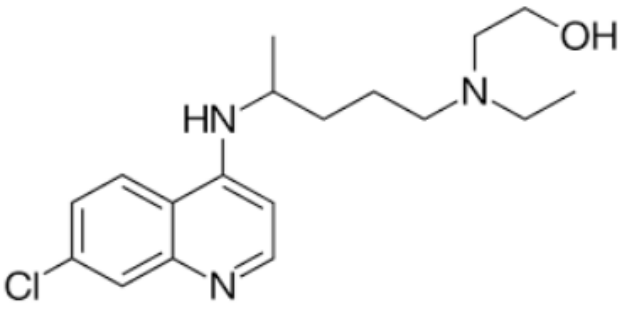

Figure 1 – Chemical structure of HCQ

HCQ was originally used as an antimalarial drug, but also found beneficial for treating autoimmune conditions like rheumatoid arthritis and SLE. It has been demonstrated to slow the onset of disease, maintain remission, lessen the likelihood of complications, and decrease the frequency of disease flare-ups [18,19]. HCQ has a broad spectrum of activity and safety profiles; thus, it can be given to the majority of SLE patients and can be continued throughout pregnancy. HCQ-associated toxicity is uncommon, minor, and typically reversible and it can reduce lupus activity in pregnant women without endangering the unborn child [20]. The Adverse Drug Reactions (ADR) requiring clinical aid include ocular ADRs and effects on the heart [21].

The present review is aimed at analyzing the safety profiles of HCQ and Belimumab by the critical review as HCQ was recently used in the global pandemic of covid-19 and recent data is available on HCQ safety profiling. The review will focus on statistically analyzing the adverse drug effects of the two drugs: HCQ and Belimumab and theoretically choosing the best drug choice for SLE. This can be done by signal detection from scientific databases; clinicaltrial.gov, PubMed, and other research articles.

METHODOLOGY

This critical review is aimed at analyzing the pharmacovigilance studies and comparing the adverse effects of the two drugs used for treating SLE.

Database selection: We searched authentic electronic databases PubMed, Google Scholar, NCBI (National Center for Biotechnology Information), and ScienceDirect to collect data. These scientific databases help find citations for sources, which can broaden the scope of the articles retrieved. For unpublished data extraction and collection of data directly from clinical trials, the website clinicaltrials.gov was used. For the clinical trials search, the keywords HCQ, Belimumab, and SLE were employed. All clinical trials that focussed on the safety and efficacy of HCQ and Belimumab were considered acceptable for the study. Because the number of clinical trials was small, thus, the area of research was broadened to the published articles as well. The trials were then scrutinized for inclusion and exclusion criteria.

Inclusion and exclusion criteria: A PICO (patient, intervention, comparison, and outcomes) approach was applied to include the studies in this comprehensive review. All the participants in the clinical trials were included in this study. Patients of both sexes (males and females) of age more than 18 were enrolled. The outcomes considered for this critical analysis were serious adverse effects, all-cause mortality, serious adverse events, and non-serious adverse events. The adverse effects of the drugs after treating the patients with HCQ and Belimumab were compared with the adverse effects observed in the Placebo

group. The data relating to adverse events were considered for extraction. The data was extracted in the form of the number of persons having adverse events.

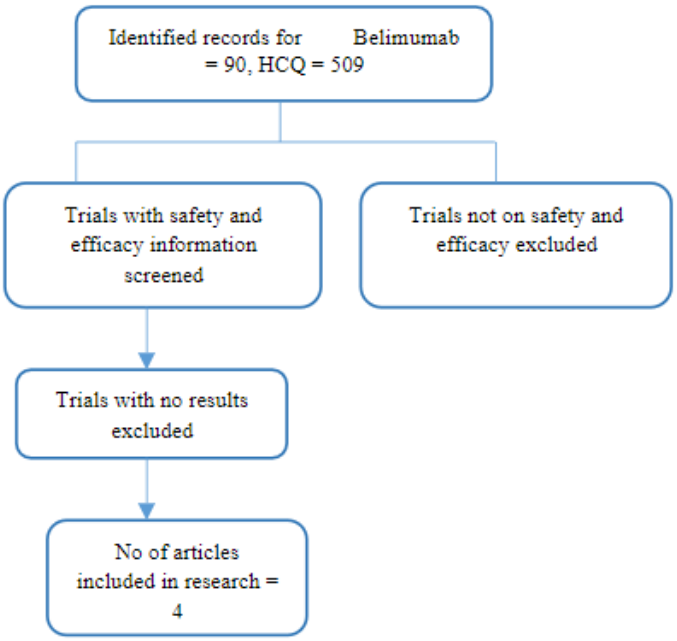

Figure 2 – Flow diagram of search strategy

Statistical Analysis: All the statistical analyses were performed using Microsoft Excel software. We extracted the number of persons from trials and then the percentage of persons having Adverse Events was determined.

Percentage of participants having AE = $\frac{\text{No. of participants reporting AE} \times 100}{\text{Total Participants}}$	--1
AR % = $\frac{\text{Number of participants having AE} \times 100}{\text{Total number of participants}}$	--2
Risk difference = Absolute risk of an adverse event in (Belimumab group - HCQ group)	--3
OR = $\frac{\text{Odd ratio in the treatment group}}{\text{Odd ratio in the control group}}$ OR = $\frac{a/c}{b/d}$ Where a = Number of participants in the treatment group with AE c = Number of participants in the treatment group without AE b = Number of participants in control group with AE d = Number of participants in control group without AE	--4
RR = $\frac{\text{Absolute Risk of AE in Belimumab treated group}}{\text{Absolute Risk of AE in Hydroxychloroquine treated group}}$	--5

The formula employed for the percentage determination is given in equation 1. The absolute risk, relative risk, risk difference, and odds ratio were calculated. The absolute risk was calculated by dividing the number of participants having Adverse Effects (AE) by the total number of participants for both drugs (HCQ and Belimumab) separately. The formula for absolute risk is given in equation 2. The risk difference was calculated by equation 3. The odds ratio shows the likelihood that an outcome will occur given a specific exposure in comparison to the chances of the event occurring without that exposure [22]. The odds ratio ranges from 0 to 1 and is always positive. If the OR is 1, it means that there is no difference in the outcome of interest between the treatment and the control. When the OR is greater than 1, the treatment is more likely than the control to cause the desired outcome [23]. The odd ratio was calculated using the following formula mentioned in equation 4. Relative risk compares the likelihood of a health event (in the present study, the adverse event) among two groups. Relative Risk was determined using equation 5.

RESULTS

We identified 90 records for Belimumab and 509 studies on HCQ. The clinical trials not focussing on safety and efficacy were excluded. The articles on safety and efficacy were then screened for inclusion in studies. Among the selected trials, the trials having no results posted were also excluded and finally, four articles were included in this critical analysis. To compare the data on adverse effects between Belimumab and HCQ, the risk difference and relative risk between the two were calculated. Table 1 shows the risk difference and relative risk between the two drugs.

Table 1 – Risk difference and Relative Risk calculation

	AR BEL	AR HCQ	RD	p1/p2 (RR)
Gastrointestinal disorders	31.88	15.66	16.22	2.04
General disorders	10.43	6.56	3.87	1.59
Nervous system disorder	20.80	3.27	17.53	6.36
Psychiatric disorders	9.61	2.18	7.43	4.41
Skin disorders	3.60	4.61	-1.01	0.78
Cardiac Disorders	1.27	4.36	-3.09	0.29
Eye Disorders	0.33	0.49	-0.16	0.67
Immune Disorders	0.35	0.37	-0.02	0.95

*AR – Absolute Risk, RD – Risk Difference, RR – Relative risk, HCQ – Hydroxychloroquine, BEL – Belimumab

The results showed the major effects of Belimumab on the gastrointestinal tract, nervous system, and heart. In some of the participants, Belimumab was found associated with depression, suicidal thoughts, and changes in sleep patterns (insomnia). The positive value of risk difference in Table 1 indicates that

Belimumab has an increased risk of causing gastrointestinal disorders, general disorders, nervous systems, and Psychiatric disorders compared to HCQ in patients. While the negative value of risk difference for Belimumab indicates the increased risk of skin disorder, eye disorders, immune disorders, and cardiac disorders by HCQ.

The results show the relative ratio of Belimumab /HCQ of 2 for GIT problems which indicates that the persons taking Belimumab are twice as likely to suffer from gastrointestinal issues as the people taking HCQ. Similarly, the relative risk ratio for the general disorder is 2 (2X risk to suffer from general problems if the person is taking Belimumab), for Nervous disorders, the RR ratio came out to be 6.4, and for Psychiatric disorders, it is 4.41. Skin disorders show a relative risk ratio of 0.78 indicating that Belimumab is less likely to cause skin problems as compared to HCQ, in other words, HCQ is 1.3 times more likely to cause skin problems than Belimumab.

Likewise, the RR ratio for the cardiac disorder is 0.29 showing 3.5 times increased risk of having cardiac abnormality for people taking HCQ with dyspnoea and chest pain as major effects. for eye disorder RR ratio is 0.66 showing a 1.5X risk for patients taking HCQ, and the ratio for immune disorders is surprisingly 0.92 which somewhat shows the equal risk of getting an immune disorder with the use of HCQ and Belimumab. Moreover, 2 cases of mortality were observed in patients taking Belimumab, while no allcause mortality was observed when the patients were administered a placebo or HCQ. Then we compared the adverse effects of the drugs Belimumab and HCQ with respect to the placebo and calculated the odds ratio. Table 2 shows the odds-ratio calculation for Belimumab.

Table 2 - Odd Ratio calculation for Belimumab

	BEL	PL	OR
Gastrointestinal disorders	31.88	33.00	0.95
General disorders	10.43	10.45	1.00
Nervous system disorder	20.80	23.84	0.84
Psychiatric disorders	9.61	9.68	0.99
Skin disorders	3.59	3.62	0.99
Cardiac Disorders	1.27	1.91	0.66
Eye Disorders	0.33	0.00	0.33
Immune Disorders	0.34	0.17	2.00

*****BEL – Belimumab, PL – Placebo, OR – Odds Ratio

The odds ratio for Belimumab showed the value of 1 for a gastrointestinal disorder, general disorder, Psychiatric disorders, and Skin problems. This predicts an equal probability of Belimumab and Placebo showing these disorders. In the case of Immune disorders, the odds ratio is 2, indicating two times increased risk of Belimumab to induce immune abnormality compared to placebo. 0.33 Odds-ratio for Eye disorder, and 0.66 for Cardiac disorder show rather a protective role of Belimumab for these organs compared to Placebo. For HCQ, in one of the trials we selected, the adverse effects of HCQ have been compared with Ascorbic acid so, for this trial, the odds ratio was compared with Ascorbic acid. The results of this are illustrated in Table 3.

In the present trial, Ascorbic acid acted as a placebo equivalent. While the second trial of HCQ as Chemoprevention for COVID-19 for High-Risk Healthcare Workers had no placebo as the trial was during an ongoing pandemic situation. The participants enrolled in the study were on-duty high-risk healthcare workers receiving HCQ and the placebo group might increase the chance of covid19. In the trial, HCQ did not show any risk to the Nervous system and Psychiatric related disorders. However, Oddsratio for eye disorder was found to be 98.96, indicating 99 times increased risk of having an eye disorder for a person taking HCQ as compared to Ascorbic acid. The odds ratios are 2.5, 277.5, and 3 for gastrointestinal disorders, skin disorders, and immune disorders respectively showing a multifold increase in the risk of these disorders if a patient is taking HCQ compared to Ascorbic acid.

Table 3 – Odd Ratio calculation for HCQ

	HCQ	AA	OR
Gastrointestinal disorders	9.58	4.03	2.52
General disorders	4.42	7.58	0.56
Nervous system disorder	0.01	0.01	1.00
Psychiatric disorders	0.01	0.01	1.00
Skin disorders	2.7	0.01	277.46
Cardiac Disorders	0.01	0.01	1.00
Eye Disorders	0.98	0.00	98.96
Immune Disorders	0.74	0.24	3.10

*HCQ – Hydroxychloroquine, AA – Ascorbic acid, OR-Odds ratio

DISCUSSION

The recent advancements in the molecular mechanism of SLE and SLE's association with the immune arm led to the development of novel monoclonal antibodies against SLE. SLE is an autoimmune disorder thus main clinical strategy behind antibody design is to target immune cells to inhibit the overactivation of the immune system and the overproduction of cytokines [24]. This critical analysis was focused on comparing the two SLE drugs Belimumab and HCQ. There is no doubt that B cells are crucial to the development of SLE and Belimumab has a recognized function in SLE treatment [25].

Additionally, clinical trials have demonstrated the effectiveness of belimumab by demonstrating a beneficial improvement in disease activity. Based on its efficacy, Food and drug administration approved it in 2011 [26]. Whereas, HCQ has a long history of use in SLE since it was approved in 1955 for SLE treatment [27]. Given its broad spectrum of activity,

Recently, HCQ was frequently used as a protective treatment for Covid-19. The use of this drug globally provided a golden chance for clinicians and researchers to look widely at the adverse events associated with HCQ. Thus, we performed a critical review of the recent clinical trials conducted on diverse populations for HCQ during the Covid-19 pandemic.

We compared the adverse events of HCQ with a relatively novel monoclonal antibody Belimumab by critically analyzing the clinical trials, and utilizing that data to calculate absolute risk, relative risk, and odds ratio for drugs. The trials of Belimumab reported a range of adverse events from gastrointestinal discomforts to serious Psychiatric disorders. However, the results of the trials observed under the scope of the study were not in harmonization. The results observed in one of the trials reported a 41.7% risk of gastrointestinal, and 28.61% risk of Nervous system disorders. These results observed were almost double the AEs observed in the other trial of the same drug. Similarly, the risk for general disorders was almost 16 times greater than in another trial for Belimumab. However, the trials presented an equal percentage risk for Cardiac and eye disorders. The significant heterogeneity in results reported by the trials can be presented as the difference in the number of the study group and the ethnicity of the population selected for the trial as one trial employed Americans and the other trial was conducted on Americans, Europeans, and Asians.

Trials for HCQ showed a safe profile in comparison to Belimumab. However, we also observed discrepancies in the results of the HCQ trials. The absolute risk for gastrointestinal, general, and skin disorders was found to be 21.74%, 8.7%, and 6.52% for one trial against the minute values of 9.58%, 4.42%, and 2.7% for another. Interestingly, the trial also failed to provide any adverse effect on Cardiac disorders, the more pronounced effects for which HCQ is famous. Again, this can be attributed to uneven sample size, differences in entry requirements, and the environment in which the trials are being conducted. Belimumab caused 2 mortalities while HCQ showed no mortality. The odds ratio calculated for HCQ and Belimumab trials presented an abrupt trend with a range of values from 0.3 to 277. The odds ratio for Belimumab/Placebo showed a value of 0.3 while 98.96 for HCQ/Placebo for eye disorders. 0.3 indicates three times more effect of Placebo on eyes and rather a protective role of Belimumab for eyes. On the other hand, 98.96 for HCQ/Placebo showed 99 times increased tendency of HCQ to cause eye ailments.

The most common cardiac effects reported in our study by HCQ include chest pain, dyspnoea, QT prolongation, and QT syndrome. These results for HCQ are in concordance with previous studies as the previous studies conducted for HCQ showed the increased probability of the drug for cardiomyopathy, eye disorders, and skin hyperpigmentation [28]. In addition to corneal deposits, dysfunction in the ciliary body, posterior subcapsular lens opacity, uneven macular pigmentation, and hydroxychloroquine can result in side effects including a ring of macular pigment dropout. Additionally, the HCQ manufacturers claim that HCQ is contraindicated in already existing maculopathy conditions [29]. In some studies, for example, HCQ-induced retinopathy was found to be more common in those who used the drug for longer than five years, with a prevalence of 7.5%, and between 20 and 50% in people who used it for longer than twenty years [28].

The results of our clinical trials' analysis revealed that Belimumab has the highest drug-related adverse effects that range from gastrointestinal disorders, and general disorders, to more serious events in nervous systems, and Psychiatric disorders. Belimumab treatment presented one case of a successful suicidal attempt and 2 cases of mortality. The results of our study resonate with the Belimumab Assessment of safety study (BASE) trial and Medicines and Healthcare Products Regulatory Agency UK drug update who suggested the increase in Psychiatric disorders and mortality rate. After the critical analysis of the results, we concluded that except for the effects of HCQ on heart and retinopathy, HCQ was found to be safer than Belimumab. Previous studies also confirm the safety of HCQ [17].

The safe safety profile of HCQ can be due to the tolerability of the drug attributed to the well-established and long-term use of HCQ in the general population while Belimumab in turn is a novel agent. However, a critical point here is that the trials conducted for Belimumab also showed adverse effects with Placebo. Thus, the odds-ratio calculated for Belimumab showed neglected adverse effects with Belimumab except for the immune system disorder that is again the known AE of Belimumab. However, contrary to HCQ, Belimumab was found associated with suicidal attempts and depression cases which makes HCQ a safer drug than Belimumab.

CONCLUSION

The critical analysis of the adverse effects of the drugs, Belimumab and HCQ showed the safe profile of both drugs. Like the previous studies, HCQ showed major adverse effects on the heart and eyes, while Belimumab was found associated with immune system disorders. Though both drugs were found to be safe for anti-SLE treatment because of their long-term use, HCQ was found to be safer, having less serious adverse effects than Belimumab. Thus, based on the results and observed heterogeneity in the results, it can be concluded that for result homogeneity and to further evaluate the safety and efficacy of Belimumab, high-quality randomized controlled clinical trials on larger population sizes are needed.

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