REVIEW ARTICLE

Use of Tafenoquine and Other Therapies in the Antimalarial Treatment- A Systematic Review

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Abstract

Despite the intensification of control measures, the malaria parasite *Plasmodium vivax* poses a major challenge in the elimination of the disease. This type of malaria parasite causes a persistent stage in the liver where it suffers the action of the hypnozoites, a form of *P. vivax* that is very relevant at this stage of the infection and causes relapse of the disease and continued transmission.

This systematic review discusses an innovative treatment for malaria with tafenoquine (TQ), an 8-aminoquinoline synthetic primaquine analog that is used in one dose for malaria relapse prevention and prophylaxis due to its longer half-life and its effects on the human body.

Along with the use of tafenoquine, it is also necessary to discuss Glucose-6-phosphate dehydrogenase (G6PD) deficiency, and the interaction of this enzyme with 8-aminoquinolines, since both drugs may induce hemolytic anemia in patients with G6PD deficiency. Therefore, a test for this deficiency is necessary before patients undergo treatment with these drugs.

The use of other drugs combined with tafenoquine is also reported. The drugs Primaquine, chloroquine, and other analogs, such as artemisinin and hybrids, are discussed in this article, along with their combined use and their greater or lesser help in the treatment.

Keywords: Malaria, Tafenoquine, Treatment.

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Introduction

Malaria is a common parasitosis in tropical areas around the world and is considered a major public health problem.[1] It is estimated that 300 million individuals contract this parasite annually and about 1.5 to 2 million people die. Moreover, the disease is one of the main causes of infant child mortality in the African continent; it is estimated that about 3,000 children die daily from parasites. Brazil, India, China, Afghanistan, and the entire African continent have the highest rates of malaria contamination in the world.[2]

Recently, several studies have shown the latency of these parasites, which is a recurrence in the individual's liver by forms that aren't treatable by the same drugs as the acute attack. The most common forms of parasites that affect humans are *Plasmodium vivax, Plasmodium ovale,* and *Plasmodium malariae. A*mong these parasites, the *P. vivax* form is predominant in South America and Asia, causing anemia, infant mortality, and comorbidities in general.[3] From the bite of the *Anopheles* mosquito, the infecting form – sporozoites- reaches the individual's blood, goes to the liver, and begins its maturation from 10 to 15 days. After that, the parasite acquires the mature form – merozoite- and invades the red blood cells, where the parasite has asexual erythrocytic reproduction every 48 hours (it is at this stage that casual prophylactic drugs act). However, the *P. vivax* infection has a hepatic form called hypnozoite which remains latent, to then develop into pre-erythrocytic schizogonia.[4]

Nevertheless, 8-aminoloquine therapy results in an agonist to the reproduction of the parasite, especially the hypnozoite form in hepatocytes. Furthermore, "Radical healing" is a treatment agonist for latency in the liver, in which 8-aminoloquines and schizocidal agents are combined. This is justified because of esquizontocidal agents fight the acute phase and hypnozoitocidal treatment prolongs latency.[5] Tafenoquine (TQ; SB-252263 or WR238605) is an antimalarial drug of the class of 8-aminoquinoline that has recently been approved as a single-dose therapy (300 mg) combined with a standard adult dose of chloroquine (1500 mg of base free in staggered dosage over 3 days).[6] The advantage of tafenoquine over the other 8-aminoquinolines, such as primaquine, is its slow elimination (half-life of 12 to 17 days), thereby there is greater uptake on the part of individuals.[4]

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Methodology

This article is a systematic review that followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses. For its implementation, the following databases were consulted: Virtual Health Library (acronym in Portuguese BVS) and

PubMed. In those databases, the following keywords were used: "malaria," "tafenoquine," and "treatment."

The studies that had the following inclusion criteria were chosen: publication date from 2014 to 2021 and having a direct link to the theme. Articles with a publication date before the limit year, articles that include animals (mice and monkeys) and those that didn't have a direct link to the theme were excluded.

From the total of 274 articles found through the research search strategy, 100 were found on BVS and 174 on PubMed. 114 articles were excluded due to their date, resulting in 60 articles. Then, 7 articles were excluded because they were duplicates. After the selection, 53 articles remained, chosen from their title with the abstracts to be fully read. Subsequently, 12 were excluded because they weren't related to the theme or they included animals. After that, 41 articles remained, then 10 were excluded because they weren't related to the theme. Finally, 31 articles were chosen for full reading of the text and then used to write this systematic review. Two articles were selected by manual selection, which resulted in 33 articles as final references (Figure 1).

Results and Discussion

Tafenoquine

The World Health Organization (WHO) recommends the treatment of *P. vivax* with a chloroquine (CQ) or artemisinin therapy followed by 8-aminoquinoline therapy. Before tafenoquine, the 8-aminoquinoline therapy used primaquine (PQ), which had to be administered for fourteen days, but there was a high rate of treatment withdrawal.[7] It is known that in locations with a low rate of malaria transmission, mainly in the northern hemisphere, mass antimalarial drug administrations (MDA) could be the answer to finally eradicate the disease in these areas.[8]

Tafenoquine was already considered important for antimalarial treatment four decades ago, but it was initially considered only as a prophylactic medication. Studies about tafenoquine started in 1979, but only 70 years later, in 2018, was it approved for use as a chemoprophylactic by the US FDA.[5] Primarily, tafenoquine was approved as a prodrug for the treatment of malaria, it is converted to its active form by the gene CYP2D6 and takes the parasite to death.[9] After its approval, it started to be considered important as a radical cure, with a single oral dose of 300 mg, in patients older than 16 years old.[10]

In this regard, two different formulations were developed, with the same active ingredient, from two different manufacturers, namely Arakoda® and Krintafel®,[11] manufactured in the USA, and Kodatef® and Kozenis,® manufactured in Australia. Although, according to the study, Arakoda® and Kodatef® formulations are indicated for causal prophylaxis, which acts on the prevention of all human malaria, except relapses of *P. vivax* or *P. ovale*. For the radical cure, that is, prevention of relapses caused by latent hypnozoites in the liver, Krintafel® and Kozenis® formulations are applicable, and can be administered at the blood-stage of the disease, or when the treatment is complete. Finally, Presumptive Anti-Recurrence Therapy (PART), also known as post-exposure prophylaxis or terminal prophylaxis, uses Arakoda® and Kodatef,® replacing Primaquine, in asymptomatic individuals recently exposed to malaria. However, none of these formulations are licensed for PART. Thus, for chemoprophylaxis, when administering a schizonticide, a dose of 300 mg of any formulation of tafenoquine can be used instead of Primaquine. It is worth mentioning that a single dose is effective for radical cure, in addition to being sufficient for causal prophylaxis during travel, only a 200 mg attack dose for 3 days and a maintenance dose of 200 mg weekly, and a single dose of 200 mg 7 days after the last maintenance dose. Therefore, tafenoquine is a good alternative for causal prophylaxis and PART, with a high potential to change the approach for radical cure.[4] Krintafel® is a means to the collective end of latent malaria, in a way that interrupts the disease cycle, eliminating the "human reservoir" of hypnozoites in the liver.[12]

Tafenoquine (2,6-dimethoxy-4-methyl-5-[{3trifluoromethyl}-phenoxy]–8-[{4-amino-1-methylbutyl}amino] quinoline), or etaquine (Figure 2), can act in the liver stage, as well as in the blood stage, against *P. vivax*. It was developed in the 1980s, under the identifier WR238605, as a primaquine analog with the advantage of being long-acting on the body.[10] This second-generation 8-aminoquinoline

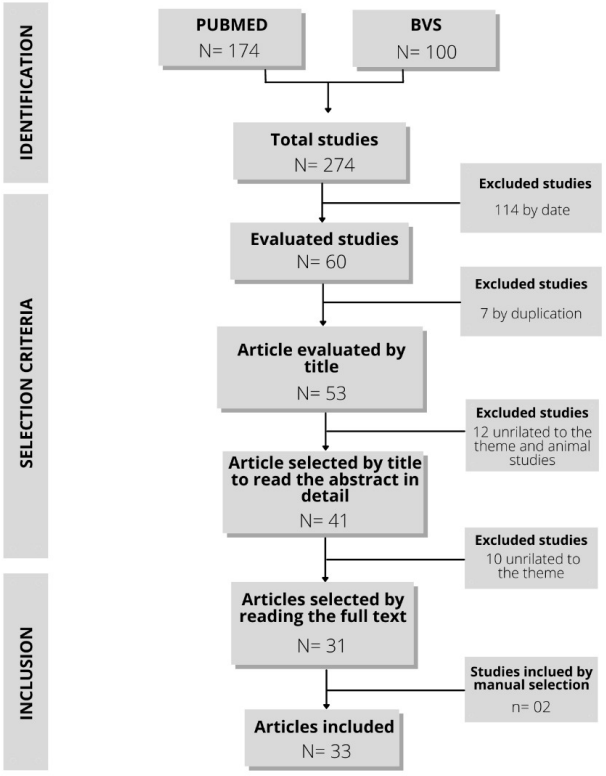

Figure 1: Systematization of the studies chosen in this review.

has a 5- substituted phenol ether, an inert functional group that protects 5-position of the quinoline and gives to the compound a stability from the oxidation protection.[13] This means that it was developed from the primaquine to be more stable.[3]

Tafenoquine has a pharmacokinetic profile, which, after being evaluated by several studies, shows maximum plasma concentrations reaching between 12 and 16 hours after administration. In addition, it has an approximate volume of distribution of 1.6 L, and long elimination half-life, around 13 to 19 days. Also, it is possible to increase the adsorption and minimize the side effects of the gastrointestinal tract through the administration of tafenoquine with food. In different studies, a population-based approach was made and showed that body weight, sex, age, ethnicity and co-administration of antimalarial drugs did not have major impacts on the tafenoquine pharmacokinects.[10] As well as this, it is confirmed that large genetic effects do not interfere with the body response to tafenoquine.[14] It is not explicit how exactly tafenoquine acts on the body, killing the parasite,[15] but it is known that it involves the generation of reactive oxidative intermediates.[3]

Tafenoquine therapy can be used in three separate ways: radical cure regimen, primary prophylaxis, and terminal prophylaxis. For the first, it would be necessary to administer it to a patient who has tested positive for malaria, this would be important for the care of the patient after diagnosis. For prophylaxis, whether primary or terminal, the drug can be administered without the patient having been tested for malaria, however, the patient must have suspected exposure to the parasite, which implies being in the coverage of a wide group of people. Thus, for primary prophylaxis, the dose that presents better results than the placebo is above 50 mg per week, and when doses of 200 mg per week are administered, there may be protection for 6 months after exposure. As for terminal prophylaxis, the ideal dose would be 1200 mg in 3 days, so that it is better than primaquine, at doses of 22.5 mg per day for 14 days, in this case the prevention of relapses of *P. vivax* is included for 1-year after tafenoquine is administered, however, compared to primaquine, tafenoquine may have more serious adverse effects than primaquine. On the other hand, when there is the administration of another drug in primary prophylaxis (excluding tafenoquine and primaquine), so as to enable terminal prophylaxis, tafenoquine proves more effective than primaquine, although in high doses tafenoquine presents more adverse effects.[16]

After the comparison analysis between the treatment with tafenoquine and primaquine, it was observed that in a prophylactic treatment, these drugs have the same efficacy. However, it was seen that in cases of treatment with tafenoquine there was a higher rate of adverse events, such as anemia, which still leaves doubts about the applicability of its clinical use.[7] In this context, it was assumed that tafenoquine is 100% effective, while primaquine offers only 70% effectiveness. Furthermore, it is suspected that tafenoquine may offer prophylaxis for 60 days in both the blood and liver stages (Figure 3).[17] If the relapse is still happening, even with the slow elimination of tafenoquine, the blood stage will be reduced, because the parasite will find suppressive concentrations of tafenoquine in the liver. It is important to highlight that the tafenoquine dose, the number of hypnozoites in the liver, the intensity of previous malaria exposure, and the degree of immunity are decisive in the probability of relapse.[3]

Contraindications for the use of tafenoquine include: patients with a history of psychosis, hemolytic anemia,

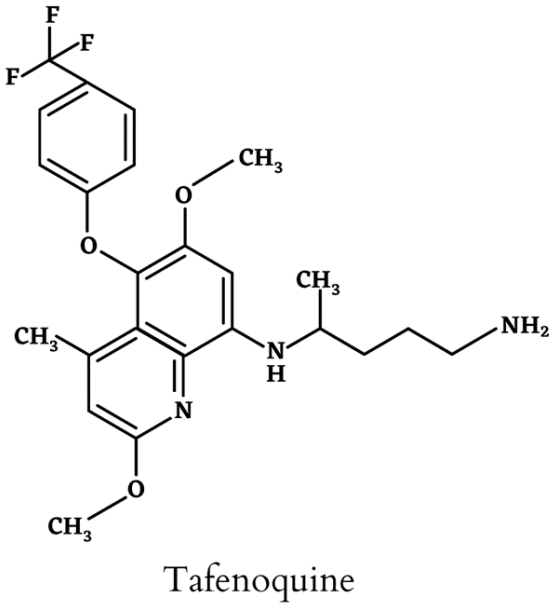

Figure 2: Tafenoquine formula.

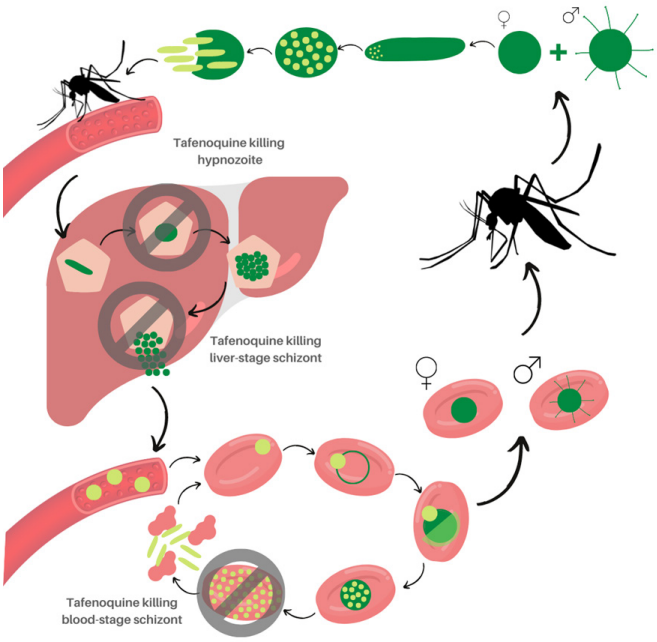

Figure 3: Malaria biological cycle, with liver and blood-stages of *Plasmodium sp*. being killed by tafenoquine.

methaemoglobinemia, some hypersensitive reactions, pregnant women, and those with G6PD deficiency. The big dilemma is that for the applicability of tafenoquine to become possible, it would be necessary to introduce mandatory G6PD tests, which would make treatment expensive and hinder the population's access.[18]

G6PD Deficiency

Enzymatic deficiency of glucose-6-phosphate dehydrogenase (G6PD) is caused due to mutations in the G6PD gene, which is located in the X chromosome, which shows a sex-related abnormality. Patients with G6PD deficiency are at risk of developing hemolysis after the use of 8-aminoquinolines, which is a family to which tafenoquine belongs, so testing for deficiency is mandatory before prescribing this drug to malaria patients. The availability of G6PD activity tests to protect against hemolytic events involving G6PDd will serve as the first major gateway to the introduction of tafenoquine in the treatment against malaria.[4] It is worth mentioning that TQ can provide substantial operational advantages, but it will not eliminate the need for primaquine. More work needs to be done to establish the safety or otherwise of alternative primaquine regimens in areas of severe and moderately severe variants of G6PDd.[19]

The erythrocytes of patients with G6PD deficiency are at risk of developing hemolysis when subjected to oxidative stress, such as the use of medications which cause hemolytic anemia. Because of this reaction, the World Health Organization (WHO) recommends that before using drugs from the 8-aminoquinolyl family, patients should be tested to rule out the deficiency.[14] There are two types of tests on the market that show the activity of the G6PD gene in humans: qualitative tests show results in which the activity of G6PD is less than or equal to 30%, and quantitative tests that present more efficiency by showing patients with gene activity greater than or equal to 30%.[19] In qualitative tests, such as fluorescence spots, intermediates are considered normal. Quantitative tests are more efficient in the intermediate identification of the deficiency.[20]

Many studies show that men, because they are homozygous genotypes for G6PD, have a higher percentage of severe disabilities; however, many women of heterozygous genotype also have disabilities, but it is said to be an intermediate and it is only serious cases that present a risk for hemolysis.[21] The article by CHU (2019) demonstrates the importance of increasing tests of glucose-6-phosphate dehydrogenase deficiency, since qualitative tests diagnose certain women with intermediate deficiency and such patients can be treated wrongly.

Systemic Effects of Tafenoquine Use

The study showed that the treatment with tafenoquine triggers erythrocytes apoptosis due to the reduction in its cellular size, alteration of its membrane, and phosphatidylserine translocation to the erythrocyte surface. This is due to the fact that the necessary drug concentration to trigger the apoptosis is found in the plasma of patients that are treated with tafenoquine. The apoptosis is potentiated by the drug when there are favorable conditions, such as iron deficiency, dehydration, sepsis, Wilson's disease, and G6PD deficiency. The effect of tafenoquine on cell membrane changes occurs when calcium enters from extracellular space to the cytosol since the phosphatidylserine translocation occurs with the removal of extracellular Ca^{2+}. As a result, the decrease in erythrocyte count by apoptosis can lead to anemia, providing that apoptosis exceeds erythropoiesis.[22]

In addition, some contaminations by *P. vivax* form hepatic stages by hypnozoites, which cause recurrent infections from weeks to months after the first infection. Frequency in relapses, especially in children, can lead to chronic diseases, severe anemia, malnutrition, growth retardation, and low school attendance. Phase III clinical trials showed that the use of tafenoquine could clean the liver of *P. vivax* hypnozoites with the use of a single dose of 300 mg. However, it is also essential to note that tafenoquine can lead to severe hemolysis cases, and it also has a long half-life, longer than other antimalarial drugs, causing the patients a greater exposure to the drug.[23]

Ophthalmological Effects of Tafenoquine Use

Some studies have analyzed the ophthalmological effect of the tafenoquine single dose (300 mg) in healthy subjects who were followed for 90 days. The methods used in the study in question had the necessary sensitivity to perceive changes that occurred early in the retina, possibly a consequence of treatment with tafenoquine. The study showed reports of self-limited mydriasis and photophobia, which are adverse events due to antimalarial drug use, without the need for treatment. However, the study does not rule out the possibility of the effect of TQ on the retina in subjects with previous retinal injury. Thus, there was no evidence of clinically relevant risk of ocular impairment in the short-term using 300 mg tafenoquine as a single dose. These findings are essential because tafenoquine will be used in underdeveloped regions with poor access to eye care.[24]

In addition, a randomized, double-blind study with participants between 20–60 years of age infected with *P. vivax* evaluated the effectiveness and ophthalmic safety of TQ, providing grounds for safety for concentrations exceeding the therapeutic concentration. The study showed that short-term TQ (three days) could lead to mild keratopathy, which was evaluated, but the results were inconclusive. It is important to note that tafenoquine has cationic amphiphilic characteristics and, therefore, sequelae in the corneas are expected. Phospholipidosis (intracellular accumulation of lipids forming myeloid bodies that are not metabolized by lysosomal phospholipases) is correlated with amphiphilic drugs. It is essential to note that these accumulations occur with the use of chloroquine; however, there was no evidence of clinically significant ocular toxicity in the study. This fact means that the use of tafenoquine over chloroquine as an antimalarial drug is more favorable.[25]

Nervous System Effects of Tafenoquine Use

The effects of antimalarial drugs on the nervous system can also be analyzed with a review of a recent clinical and non-clinical literature review that investigated the effect of tafenoquine on neuroanatomical structures in humans. It was found that a dose two times higher than the prophylactic used by tafenoquine did not demonstrate specific neurological signs. However, the use of tafenoquine can lead to hematological toxicity, such as erythrocyte apoptosis already mentioned in this article, considering that the dose of the drug limits this toxicity.[26]

Other Effects and Symptoms of Tafenoquine Use

In addition to the systemic effects already mentioned, tafenoquine use can also cause gastrointestinal disorders, such as nausea and vomiting, but these gastric effects can be reduced if the drug is administered with meals. In general, the study also points out the use of tafenoquine associated with severe hemolysis due to higher daily or weekly doses (> 200 mg). The extensive use of tafenoquine can cause photophobia, increased serum creatinine, and serum alanine aminotransferase, as well as corneal deposits or epithelial keratopathy.

It is also vital to investigate the G6PD deficiency before using TQ due to the high risk of hemolytic anemia. Finally, tafenoquine should be prescribed with caution to individuals with psychiatric disorders, as serious psychiatric events have been reported in patients with a previous medical history of psychiatric disorders. Anxiety, abnormal sleep, changes in mood, and difficulty sleeping were observed; such sequelae occurred due to the longer half-life of tafenoquine.[27]

Other Medicines Important for Malaria Cure

Drug treatment remains the front line for malaria treatment as there is no effective vaccine yet. The most commonly used antimalarials are: 4-aminoquinolines, arylaminoalcohols, 8-aminoquinolines, artemisinins, and antifolates, in addition to respiratory chain inhibitors and some antibiotics. In this sense, drawbacks of these drugs, such as short half-life, low oral bioavailability, high dosages, and toxicities, interfere significantly in a possible eradication of malaria since they cause low adherence with the patient and corroborate the resistance of parasites to the above mentioned drugs.[28] It is clear that if the mechanisms of aminoquinolines were better known, the development of antimalarial drugs would be accelerated, as they allow for a broader therapeutic action, in addition to presenting less associated effects such as toxicity associated with G6PD deficiency.[29]

Chloroquine

Chloroquine is still the main medicine to treat malaria in endemic areas of the world, but the existence of resistant strains of *P. vivax* has made it impractical for this drug alone. Because of this, remedies such as artemisinin and tafenoquine are included in this propaedeutic, but there are still very few studies that seek to answer these questions related to parasites.[30]

It is important to highlight the benefit of the single dose of chloroquine and tafenoquine in preventing relapses of *P. vivax*, since this dosage presents a low risk of neurological or psychiatric adverse events (NPAE) and the same is true for chloroquine alone or a combination of primaquine and chloroquine.[6] The studies of chloroquine together with tafenoquine were compared and found that the prevalence of nervous system disorders occurred before 30 days of study and at a percentage of 12% and 10%, respectively. In addition, psychiatric adverse events were observed in 4% and 23% of patients, respectively, and these were reduced to insomnia and low prevalence anxiety. When analyzing individual adverse effects, headache and dizziness were present in 5% of the patients, with higher incidence of dizziness and lower incidence of headache in the tafenoquine/chloroquine ratio. This study suggests a favorable profile of NPAEs for tafenoquine/chloroquine, similar to chloroquine alone, in that a low prevalence of mild to moderate severity events was reported, that is, these medicines have low effects on the Central Nervous System when administered in a single dose. Finally, tafenoquine/chloroquine reduced malaria recurrence in an average of 70% of patients in 6 months, when compared to chloroquine alone.[6]

Primaquine

Primaquine is an 8-aminoquinoline and is the only hypnozoiticide available today. The administration of this compound is very positive because the transport of hypnozoites is asymptomatic in the body and, therefore, the only means of treatment is the mass medication route (MDA). When thinking of a radical cure for *P. vivax*, with the elimination of the hypnotic form, a propaedeutic is necessary that combines primaquine and a schizonicide30. According to the clinical trials of this study, with the use of primaquine, a rate of 60% of lower risk of malaria recurrence was obtained when compared to a placebo, even without evidencing the benefit of the administration made only by the patient.[30]

Among the contraindications of this compound, the consequence of causing hemolysis, i.e., rupture of red blood cells in patients with G6PD deficiency, in the body is relevant. This makes it unsuitable for pregnant women because the possible deficiency of the fetus is unknown. To mitigate this consequence, primaquine is being administered at an interval of 14 days, which is causing low adherence and consequently low efficacy. It is important to emphasize that the effectiveness of primaquine varies according to the strains of parasites and this interferes with dosages in order to prevent relapses and the risks from radical cure.[30] It is worth mentioning that even with the supra-therapeutic dose of tafenoquine, the Npaes occurred less frequently than when compared to primaquine and chloroquine. However, there was a greater trend in the occurrence of vertigo and headache when higher doses of tafenoquine were administered.

Another study also reported comparative data of tafenoquine in relation to primaquine, with the aim of achieving radical cure for the *P. vivax* form. Thus, it is notable

that both medications have the ability to cause a slight decrease in hemoglobin level among patients with normal G6PD enzyme activity, with small differences between the groups in incidence and severity.[31] In addition, in the Global Assessment of Tafenoquine Hemolytic Risk (GATHER), the first outcome in hemoglobin level occurred in 4 out of 166 patients medicated with tafenoquine and in 1 out of 85 patients in the primaquine group. These tests were performed on male patients genotypically and phenotypically normal to G6PD enzyme and no clinical intervention was necessary. In addition, changes in red blood cells and hematocrit were similar in the treatment groups, even with a small decrease, and recovery was observed on day 60.[32]

Another topic to be considered is the integrated safety analysis of the use of tafenoquine/primaquine. Thus, it was not imperative that any of the patients needed medical interference to reduce the level of hemoglobin, since in all groups, the level of red blood cells spontaneously returned to the baseline value. During the 6-month test, there was an adverse effect of mild to moderate severity in 97% of the tafenoquine group and 94% of the primaquine group. On the other hand, the percentage with severe adverse events was very similar in both compounds and all these effects were resolved spontaneously. In terms of efficacy, recurrences of malaria for 6 months in the analyzed groups were not reported, and there was a rate of 74% in the tafenoquine group and 76% in the primaquine group.[32]

Tafenoquine is believed to have a longer-lasting action and to be more effective than primaquine when analyzed in vitro and with animal studies. In preclinical studies tafenoquine shows better activity against the hepatic and erythrocytic forms of malaria when compared to primaquine. In conclusion, there is little or no difference between TQ and PQ in the prevention of recurrences, adverse effects, normal G6PD status and recurrence prevention.[7]

Artemisinin

The administration of artemisinin is with fixed dose and, in most cases, it is very effective in the asexual form of *P. vivax* in the blood, in which the stages cause clinical symptomatology. Asexual parasites proved to be 2,000 times more susceptible to most antimalarials, especially Acts. The combined therapy of artemisinin has become the main therapy against falciparum malaria and among these interactions there is tafenoquine-artemisinin.[32]

In strains of *P. falciparum*, tafenoquine, when combined with artemisinin, showed synergistic interactions with *P. vivax* in the asexual stage. This synergism may be due to the fact that these two drugs have different mechanisms, and this prevents a competitive inhibition of the same drug targets, causing the two to operate at the same time. This interactivity is very positive because it can directly impact the results of agile healing at a lower presence. There were no reports of adverse pharmacokinetic interactions between the above-mentioned compounds.[32]

Futures Perspectives

After the complete analysis of the benefits and harms of antimalarial treatment with tafenoquine, it is noted that with the possibility of successful radical cure and prophylaxis, there will be the prevention of future relapses, which will interrupt the biological cycle of transmission between man and mosquito, resulting in mass reduction of cases. Consequently, individuals who fit the contraindication conditions for treatment with tafenoquine will also benefit from this interruption in the transmission of malaria, impacting the public health of several regions.[33] Therefore, more clinical trials are needed to prove the risk benefit of using tafenoquine in mass instead of other drugs, so that the goal of a radical cure is achieved.[3]

Conclusion

The present systematic review points out some considerations regarding tafenoquine. The use of the recently approved prodrug tafenoquine in the treatment of malaria, applied in a single dose, has had promising results against hypnozoites and a 60-days prophylaxis against infections in the blood stage or in the liver during the disease. However, it is not clear how tafenoquine kills the parasite. Although tafenoquine has had good results, it is not indicated as a transmission blocking drug against *P. falciparum*, nor is it indicated for patients with G6PD, due to the high risk of developing hemolytic anemia, and it is always necessary to perform a blood test. On the human organism, tafenoquine can cause anemia in adults, and severe anemia and growth retardation in children, in addition to adverse ophthalmological effects, which did not require treatment. On a positive note, tafenoquine did not show ocular toxicity–as with the use of chloroquine and specific neurological signs. Tafenoquine can, however, cause gastrointestinal disturbances and adverse psychiatric effects. As well as Tafenoquine, other medicines in the same class as Tafenoquine, and their effect on *P. vivax,* were also briefly discussed and the results showed that chloroquine used in a unique dose has a beneficial effect on parasite relapses, the compound primaquine actually has been used successfully against hypnozoticide and artemisinin has a promising effect on the asexual form of *P. vivax* in the blood. Besides all these promising results, these medicines require further studies to prove their effectiveness against malaria so that the treatments can be more assertive and comprehensive.

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