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REVIEW ARTICLE

Recent advances in the treatment of malaria and future aspects

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ABSTRACT

This digest covers some of the most important developments in the widely published discovery of malaria drugs between 2010 and 2012. The need to develop new antimalarial drugs is urgent. In order to reduce the symptoms, such medications may target the blood stage of the disease, the liver stage to prevent relapses, and the transmission stage to protect other humans. The blood stage pipeline is becoming stable, but this should not be a source of complacency, as a high standard is set by the current therapies. Drug development very liver-oriented activities and transmission phases are in their infancy, but the attention is earned as targeting these phases may be instrumental in eradicating malaria.

INTRODUCTION

Malaria is a major infectious disease in tropical and subtropical areas, with over 40% of the world's population being exposed to varying rates of malaria risk across 100 countries considered to be a significant worldwide health concern [1]. The most dangerous and often fatal type of malaria is Plasmodium falciparum. Other human malaria cases, including P. vivax, P. ovale, P. malariae, and sometimes P. knowlesi may have serious acute diseases but death rates are low [2-3]. It is estimated that about 500 million persons are infected with malaria every day, causing some 1-2 million deaths. Early and realistic therapies for global malaria control are becoming increasingly important as successful diagnosis decreases both malaria complications and mortality. Medical conditions may be hard to distinguish from other tropical diseases on the basis of patients' signs and symptoms [4-7]. Consequently, diagnosis using laboratory technology is obviously required and the current malaria diagnostic approaches and their effects in resource-rich and resource-poor environments [8].

Pathogenesis

Productively induced with Plasmodium falciparum due to its ability to trigger inflammation of the red blood cells (RBC) cytoadherence to vascular endothelium and consequential end-organ dysfunction. Certain plasmodium species can cause severe disease and AKI, although they are debated about their capacity to cause coma [9-11].

➢ Microvasular Obstruction

Adult autopsy and retinopathy-positive children who die from cerebral malaria display prominent brain microvasculature sequestration compared to adults with fatal noncerebral malaria and retinopathy-negative children. Postmortem studies confirm parasitized RBC sequestration in adults and children's renal glomerular and peritubular capillaries [12].

➢ Endothelial Activation

Microvascular tissue hypoxia caused by obstruction is exacerbated by microvascular dysfunction and increased demand for oxygen. In adults with cerebral malaria, there is an

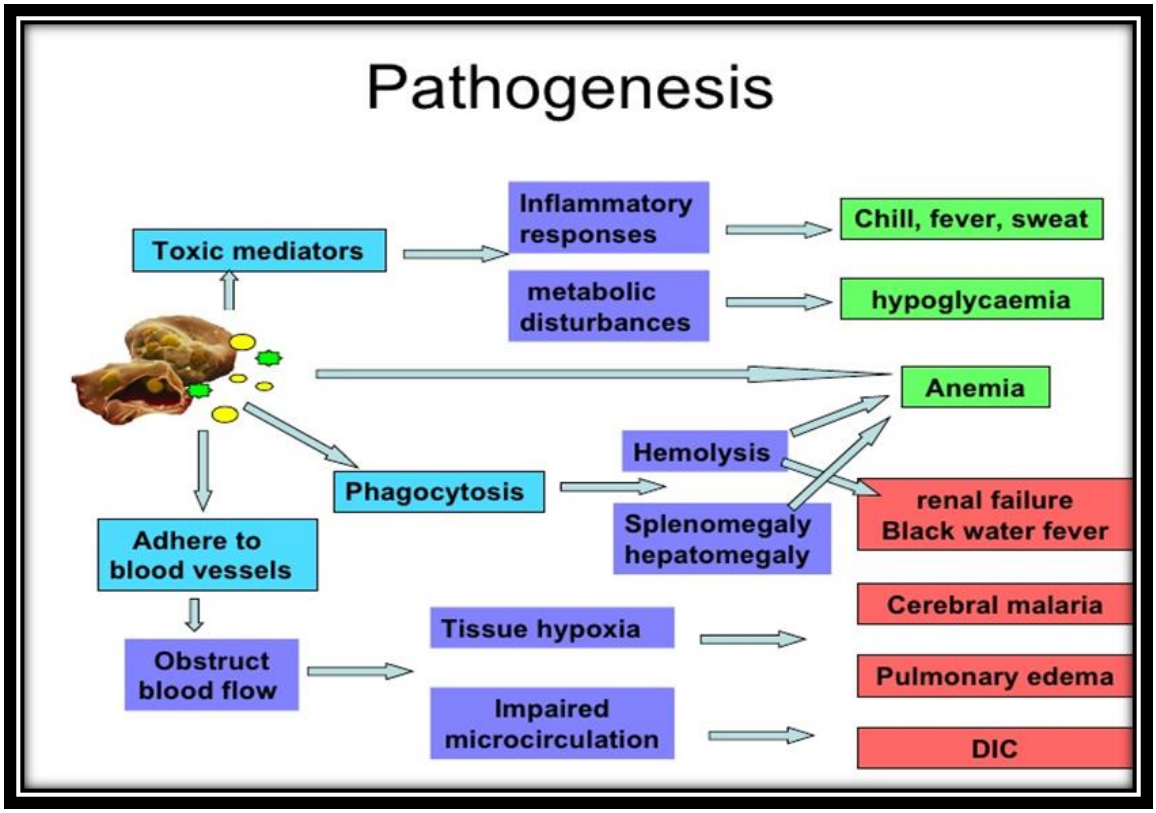

Figure 1: Pathogenesis of Malaria

endothelial and astroglic activation of the brain, with varying inflammatory particular case and a minor improvement in the brain-blood barrier. In children with strictly defined retinopathy-positive cerebral malaria, endothelial barrier breakdown is observed especially in sequestration areas [13].

- **Cytokinins**

There has been a recent analysis of the role of cytokines and chemokines in cerebral malaria. Many of these experiments, however, are in the murine experimental model of cerebral malaria, whose validity has been questioned. Human studies have shown conflicting evidence regarding the association between cerebral malaria and numerous cytokine levels, such as tumor necrosis factor α (TNFα) [14].

Diagnosis of Malaria

Malaria is a possible medical emergency and should be treated as appropriate. Delays in diagnosis and treatment in many countries are leading causes of death.

1. Clinical Diagnosis of Malaria

Clinical diagnosis is based on the signs and symptoms of the patients and on the results of the examination. The first symptoms of malaria include fatigue, migraine, exhaustion, myalgia, chills, dizziness, abdominal pain, diarrhea, nausea, vomiting, anorexia, and pruritus. A clinical diagnosis of malaria is still challenging due to the non-specific nature of the signs and symptoms that significantly overlap with other common and life-threatening diseases, such as common viral or bacterial infections [15-16].

2. Laboratory Diagnosis of Malaria

In laboratories malaria is diagnosed with various techniques such as traditional diagnosis by the staining of small, thick peripheral blood streams, other concentration techniques, such as quantitative buffalo (QBC) methods, fast diagnostic testing like OptiMAL, ICT, ParaScreen, SD bioline and Paracheck and molecular diagnostic methods. Malaria is diagnosed using different techniques [17].

3. Molecular Diagnosis of Malaria

Latest advances in molecular biology, e.g. PCR, LAMP, MS, Mass Spectrometry (MS) and Cytometric Flow (FCM) testing technologies have allowed for a comprehensive characterization of the malaria parasite and generate new strategies for malaria diagnosis [18].

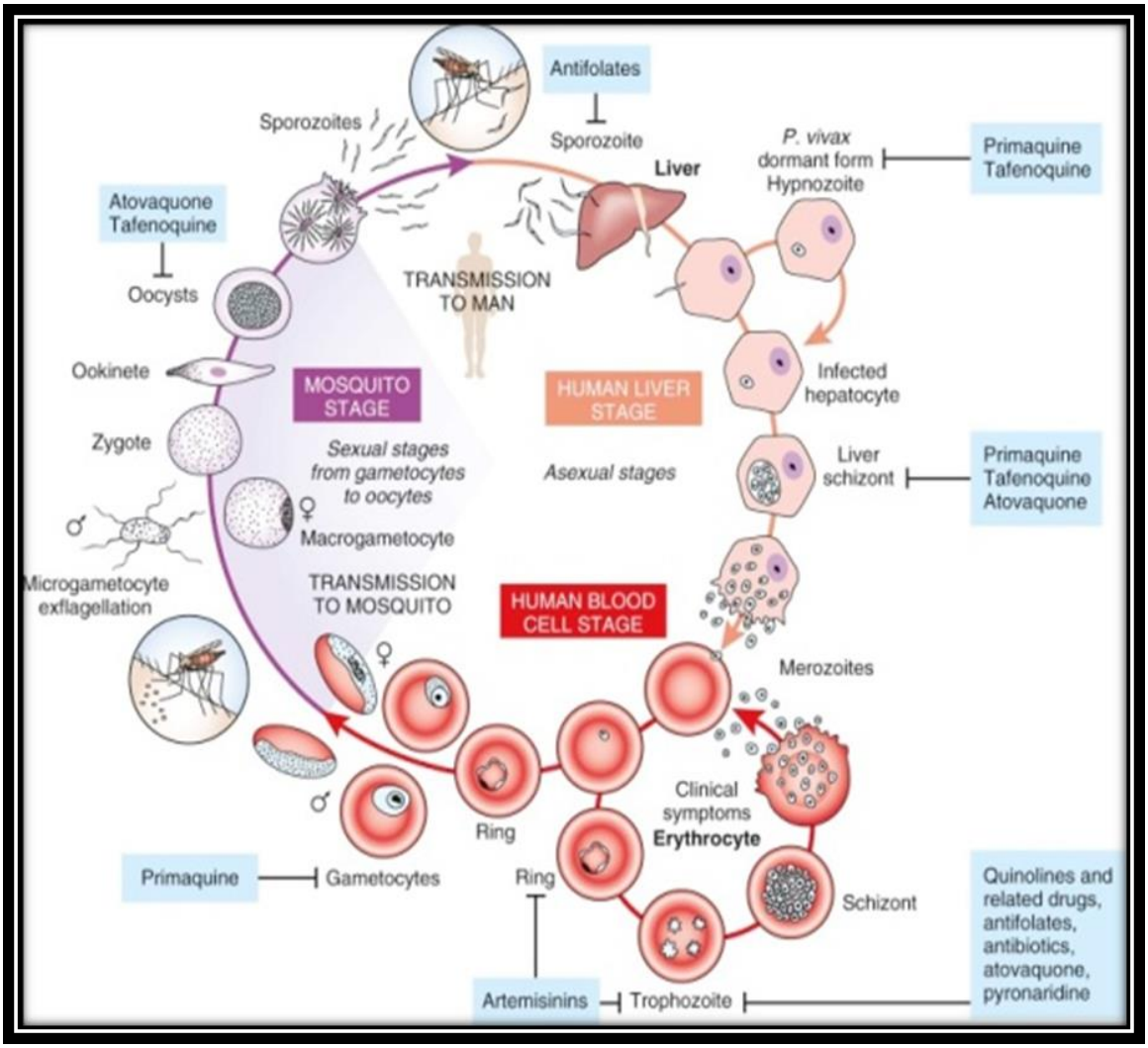

Figure 2: Antimalarial Drugs Acting on Stages of Malaria

Classification Antimalarial Drugs:

1. **4-Aminoquinolines:** Chloroquines, amodiaquine, piperaquine.
2. **Cinchona Alkaloids:** Quinine, qunidine and proguanil.
3. **8-Aminoquinoline:** Pyrimethamine and primaquine.
4. **Biguanides:** Proguanil and cholrproguanil.
5. **Sulfonamide and Sulfone:** Sulfadoxine, dapsone and sulfamethopyrazine
6. **Quinoline-Methanol:** Mefloquine.
7. **Antibiotics:** Tetracycline, doxycycline and clindamycin
8. **Sesquiterpenes Lactones:** Artesunnate and artemether
9. **Amino Alcohols:** Halofantrine, lumefantrine
10. **Napthoquinone:** Atovaquone [19]

Recent Advances:

➢ **Current Line of Therapy**

The global acceptance of artemisinin-based combinations (ACTs) as first-line therapies has resulted in widespread resistance to most groups of antimalarial drugs. ACT is a mixture of two medicines which have been approved for the treatment of serious malaria. The most popular combinations currently in use are artemether + lumefantrine, artesunate + amodiaquine, artesunate + SP (sulfadoxine + pyrimrethamine) and dihydroartemisinin + piperaquine [20-21].

According to WHO recommendations, the latest protocol is a 3-day course of artemisinin that aims to flush out most of the parasite with the remaining parasites that the partner medication (lumefantrine/ amodiaquine /piperaquine) destroys (WHO, 2015b). Artemisinin and its derivatives have a fast onset of action, but the bloodstream is rapidly cleared, so it is important

to combine it with a slow clearance rate drug. Primaquine has the interesting distinction between acting on the malarial parasite both in the liver and blood level. As prophylactics, Primaquine, Atovoquone and Proguanil are used [22-23].

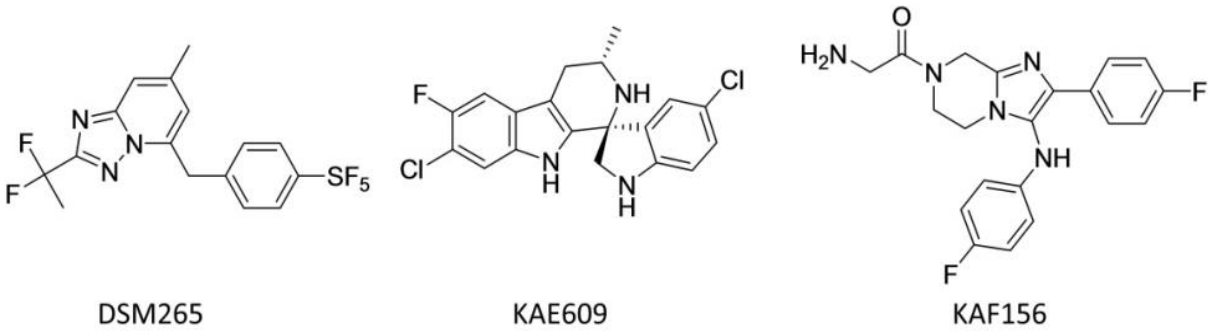

Figure 3: Drug Candidates Currently in Phase 2 Clinical Trials.

- **Move Towards Eradication**

The discovery of antimalarial drugs has always concentrated on targeting the erythrocytic (blood) stages of the life cycle of parasites. In the blood stage, the parasite can be easily studied, whereas the pre-erythrocytic (liver) stage can only be studied by isolating parasites directly from the mosquito and infecting liver cells to establish an assay. Owing to the lack of proper culture techniques and cumbersome animal models, the quest for drugs operating on the pre-erythrocytic (liver) stage was stagnant in the past. A crucial advance in the discovery of new and newer leads was the development of a phenotypic screening method (Meister et al., 2011) by the Novartis-GNF collaboration that targets the parasite lifecycle at the liver level. Currently, research has concentrated on developing compounds that are active against both the liver and blood stages of the malarial parasite; in poorer countries, such an antimalarial would be highly effective in eradicating the burden of disease. KAE609 is the first antimalarial drug candidate to obtain effective clinical proof-of-concept in over 20 years with a novel mechanism of action [24]. The phenotypic screening of a Novartis library of 12,000 natural products and synthetic compounds against P. falciparum has revealed a spirotetrahydro-β-carboline hit. To improve potency and oral bioavailability, the spirotetrahydro-βcarboline hit was optimized for the clinical candidate KAE609. *In vitro*, KAE609 has potent activity against both the pre-erythrocytic (liver) and erythrocytic (blood) stages of the malaria parasite. A parasite plasma membrane Na-ATPase that controls sodium and osmotic homeostasis, spirotetrahydro-β-carbolines inhibit + PfATP4. In a P. berghei rodent model of blood-stage malaria, a single oral dosage of KAE609 produced a cure. In collaboration with the Genomics Institute of the Novartis Research Foundation (GNF), the Biomedical Primate Research Centre and the Swiss Tropical Institute, the entire study was carried out at the Novartis Institute for Tropical Diseases in Singapore. This compound has currently completed Phase 2a studies and is undergoing studies of malaria challenge in healthy volunteers (controlled operation of human induced blood stage) (MMV, 2016). The imidazolopiperazine scaffold was described by a Novartis-GNF partnership as an enticing hit based on a screening program using a cell-based proliferation assay. GNF19 and GNF156 (Fig. 3) led to further optimization of these imidazolopiperazine scaffolds, of which GNF156 was found to be more promising. In addition to targeting the asexual but also sexual stages of the malarial parasite life cycle, KAF156 (GNF156) strikes. The compound is currently undergoing clinical trials in phase 2a (MMV, 2016). DSM265 is a triazolopyrimidine-based dihydroorotate dehydrogenase (DHODH) enzyme inhibitor (Phillips et al., 2015). It is the first inhibitor of DHODH to achieve clinical growth for the treatment of malaria [25]. Plasmodium's ability to synthesize the nucleotide precursors needed for the synthesis of DNA and RNA was found to attack the compound. DSM265, which destroys P. falciparum in the blood and liver, is a long-acting inhibitor for the treatment and prevention of malaria. DSM265 is a possible drug combination partner for the treatment of either a single dose of malaria or a weekly dose of continuous disease prevention. The compound is currently undergoing phase 2 clinical trials in patients with P. falciparum or P. vivax and is currently

undergoing phase 1b studies in which its effectiveness in combination with OZ439 against blood-stage parasites is being evaluated [26]. A new class of antimalarials - quinolone-3-diarylethers - has been developed by researchers from the University of South Florida, Drexel University, Monash University, the Portland Veteran Affairs Medical Center, and the Oregon Health and Science University along with Medicines for Malaria Venture (MMV) (Broadwith, 2013). Driven by endochin, ELQ300 was the first antimalarial pyridone-based drug developed by GSK. To improve its metabolic stability, the diaryl ether group, part of the pyridone-based compound, has been found. As a preclinical candidate, ELQ300 was chosen as it targets the liver and blood stages of falciparum malaria, as well as the gametocytes, zygotes, and ookinetes, which are critical for the transmission of the disease. The mitochondrial cytochrome bc complex, responsible for ATP and pyrimidine synthesis, is inhibited by ELQ300. It is suspected that, compared to current drugs targeting the same pathway, it will be hard for the parasite to develop resistance. In the clinical production of this drug, however, low aqueous solubility and elevated crystallinity proved to be an obstacle. However, it was found that the compound's bioreversible Olinked carbonate ester prodrug, called ELQ 337, delivers the active drug at concentrations adequate for a single dose cure. In partnership with MMV, Dundee University developed DDD498, a new drug candidate that shows the potential to address a number of clinical needs, including single-dose therapy, blocking transmission and chemoprotection. DDD498 was developed against bloodstage malaria parasites from a screening program. This drug targets translation elongation factor 2 (eEF2), which is responsible for the translocation of the ribosome based on GTP along the messenger RNA, and is necessary for protein synthesis. To improve this possible antimalarial treatment, Merck Serono and MMV joined hands to (MMV, 2015). DDD498 showed EC < 50 1 nM against the P. berghei and P. yoelii liver schizontal forms. DDD498 strongly inhibited the development of both male and female gametes at similar concentrations. After 7 days with an EC of 1.8 nM 50, DDD498 blocked subsequent oocyst development in the mosquito. This compound is currently undergoing toxicology preclinical GLP trials. Together with MMV, P218 was developed by BIOTEC (National Center for Genetic Engineering and Biotechnology, Thailand) as a dihydrofolate reductase inhibitor. PfDHFR mutations lead to changes in its geometry, thus limiting pyrimethamine activity. The team developed P218 using SBDD in such a way that it illustrates permanent inhibition. P218 demonstrates excellent selectivity against PfDHFR, thereby providing human beings with protection. This candidate's clinical condition is not known at this time. From the AZ (AstraZeneca) array, small molecules numbering 500,000 were screened and TAPs (triaminopyrimidines) were recognized as promising lead sequence for further assessment. The compounds have a novel +-action mechanism involving V-type H ATPase inhibition. The optimization of TAPs in medicinal chemistry resulted in the selection of MMV253 as a candidate drug with ideal properties such as novel chemical class, novel mechanism of action, fast kill *in vitro* and *in vivo*, long half-life expected in humans and strong safety margins in rats and guinea pigs.

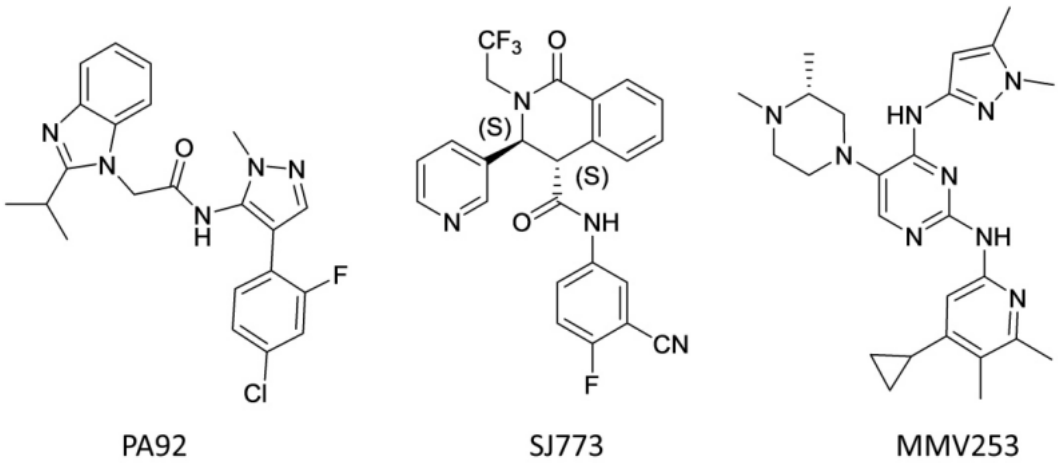

Figure 4: Compounds Currently in Preclinical Stages

As the recorded half-life in humans is 36 hours, TAPs give the potential for a single dose cure in combination with appropriate partner drugs. It is involved in clinical development against several strains of P. falciparum, including those resistant to existing antimalarials as well as novel antimalarials. The TAPs rapidly destroy plasmodium parasites, and the emergence of spontaneous resistance to this chemical class under *in vitro* conditions is unusual. It is expected that the compound will soon complete preclinical studies. The proteasome is a multi-component protease complex that regulates main processes such as the cell cycle and the presentation of antigens. Compounds that target the proteasome are potentially useful tools for the treatment of pathogens that rely on proteasome function for survival and replication. Proteasome inhibitors are known to suppress all stages of the malarial parasite life cycle. The key challenge, however, was the lack of selectivity of the parasite over the host cells, rendering them harmful to humans. A small molecule which can destroy the parasite in mice with few side effects has recently been documented by researchers. The molecule acts in the parasites, but to a much lesser degree in the host, by inhibiting the proteasome, the protein-degrading machine of the cell. It is suspected that selective proteasome inhibitors complement existing antimalarial drugs. Recent results also indicate proteasome inhibitors suppress strains immune to artemisinin. In order to recognize sequences preferred for degradation by parasite proteasomes but not human ones, Matthew Bogyo and his team at Stanford University School of Medicine first screened a library of peptides. To design selective inhibitors, they used the knowledge (Goldman, 2016). Together with the MRC Molecular Biology Laboratory team, they used cryoelectron microscopy to obtain a parasite proteasome structure bound to a planned inhibitor. This malarial proteasome structure at the inhibitor-binding site helped to further optimize the inhibitors. To destroy artemisinin-sensitive and resistant malaria parasites, a parasite-selective inhibitor, a peptide like molecule called WLL-vs, was created. Without any apparent adverse effects, a single dose of WLL-vs significantly decreased parasite levels in mice. To reduce the spread of 224, WLL-vs may be combined with artemisinin if it can pass efficacy and toxicity studies. The Harvard and Broad Institute group of Stuart Schreiber (Kato et al., 2016) described bicyclic azetidine BRD7929 as novel agents that reach all three stages of the malaria lifecycle. They screened a synthetic library of 100,000 members developed using Diversity Focused Synthesis that allowed them to access chemical space that was previously unknown. This molecule was able to block transmission and had activity in many *in vivo* models against both the liver and blood phases (P. falciparum and P. berghei). BRD 7929 inhibits the parasite's cytosolic phenylalanyl tRNA synthetase and thus affects protein synthesis. Before it can reach the clinic, BRD 7929 requires more optimization; however, identifying Phenylalanyl tRNA synthetase as the target should enable researchers around the world to develop new drugs that work through this mechanism [27].

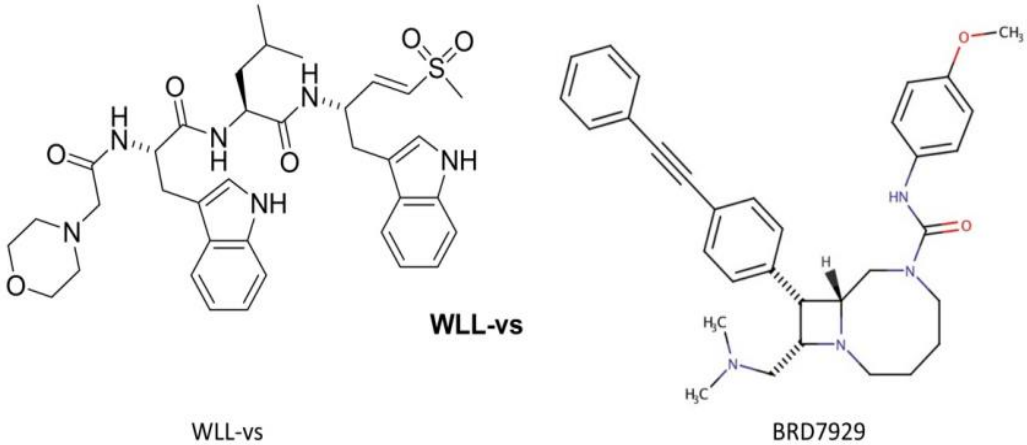

Figure 5: Structures of Proteasome Inhibitor WLL-vs and Bicyclic Azetidine BRD7929.

Future Aspects/Considerations

PfATP4 seems to be the hot target for researchers in clinical trials with as many as 3 drug candidates. In addition to blood-stage activity, all three medications have transmission blocking activity. The most promising of the lot with operation against more than one step of the parasite life cycle seem to be KAE609 and DDD498. The current pipeline looks solid and exciting, with quite a few of them having a new mechanism of action that demonstrates that eEF2, V form + H-ATPase have been explored as new targets. Further investigation is warranted both in terms of the novel chemical matter and the biological pathways inhibited by the screening cascade and the hits found by the Stuart Schreiber group.

In the development of the vaccine, finding the protein structure used by mosquitoes to infect humans could help. The early signs shown by CRISPR and inhibitors of proteasome are promising and it is quite hopeful that in the future they will be part of the treatment agenda. MMV has played a major role in the buildup of this pipeline of drugs. MMV's R&D portfolio also contains several drug formulations which are there in the later stages of clinical trials. Although the drugs in the pipeline indicate that they are a one-man army, it would be more logical for these drugs to be given in conjunction with artemisinin derivatives (if approved for human use). R&D investments and cooperation with numerous other research organizations have proven to be a winning strategy in accelerating the drug development process in the sense of malaria. Owing to the lack of adequate resources or the unavailability of suitable techniques/technologies, one will never know how many compounds synthesized worldwide have seen their way into the bin. It is not shocking to see how much developing countries contribute to R&D activities. It is imperative, therefore, that the respective governments take these problems seriously. A molecule that can target the blood stage of the disease to relieve the symptoms, the liver stage to avoid relapses, and the transmission stage to protect other human beings will be a full ideal kit. The doors of genomics have been opened by late researchers to pursue a response to this question. Therefore, a malaria vaccine is a very important possibility in the immediate future. The production of newer drugs with wide-ranging efficacy against all forms of the disease needs continued progress in the battle against malaria. Increased R&D funding, more collective activities, and disciplined oversight of WHO protocols will play a major role in eradicating malaria. The balanced use of mosquito control, anti-Plasmodium treatments, and a general improvement of sanitation and awareness, methods used by developing countries to eliminate malaria, are preferably antimalarial strategies for prevention. In order to build and extend the spectrum of combination therapies against the blood stage and other parasite stages, expanding the current extensive pipeline will go a long way in helping to achieve the long-awaited aim of eliminating malaria [28-29].

CONCLUSION

The infectious disease caused by protozoan parasites belonging to the genus Plasmodium is malaria. The disease, especially in populations in African and South East Asian countries, has been a major cause of mortality and morbidity. Over the years, a well-developed treatment regimen using artemisinins as an effective antimalarial and other safety prevention measures has played a significant role in reducing the global malaria burden. Latest findings of drug resistance to artemisinins, however, should be a wake-up call, as artemisinins have been the backbone of disease care in the recent past. New antimalarials that can be involved in more than one step of the parasite life cycle are needed. These can be complementary to artemisinins and can also assist in tracking the danger of drug resistance. The current analysis focuses on clinical drug candidates that are involved in more than one step of the life cycle of malarial parasites.

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