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Review

Antimalarial compounds: from bench to bedside

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Summary

The emergence and spread of drug-resistant malaria parasites is the major threat to effective malaria control. So far, malaria control has relied heavily on a restricted number of chemically related drugs belonging to either the quinoline or the antifolate groups. Only recently have the artemisinin-type compounds been used widely, predominantly in Southeast Asia. Experience has shown that resistance eventually curtails the life span of antimalarial drugs. If measures are not applied to contain resistance, the investment put into the development of new drugs will be squandered.

Current efforts focus, on the one hand, on research into novel compounds with mechanisms of action that are different to the traditionally used drugs, and, on the other hand, on measures to prevent or delay resistance when drugs are introduced. Drug discovery and development are long, risky and expensive ventures. Whilst very few new antimalarial drugs were developed in the last quarter of the 20th century (only four of the nearly 1400 drugs registered worldwide during 1975–1999), various private and public institutions are at work to discover and develop new compounds. Today, the antimalarial pipeline is relatively healthy. Projects are underway at different stages of drug development, from pre-development to registration. However, there is relatively little novelty, as current development projects still rely upon the traditional quinoline, antifolate and, in particular, artemisinin compounds. New structures are expected from the more upstream discovery efforts but it will take time before they become drugs.

Therefore, whilst waiting for the drugs of tomorrow, there is a pressing need for immediately available, effective and affordable drugs that will have long life spans. Drug combinations that have independent modes of action are seen as a way of enhancing efficacy while ensuring mutual protection against resistance.

Most research work has focussed on the use of artesunate combined with currently used standard drugs, namely mefloquine, amodiaquine, sulfadoxine/pyrimethamine and chloroquine. There is clear evidence that combinations improve efficacy without increasing toxicity. However, the absolute cure rates that are achieved by combinations vary widely and are dependent on the level of resistance of the standard drug. From these studies, further work is underway to produce fixed dose combinations that will be packaged in blister packs. Malaria control programmes need efficacious drugs that can be used with ease by the populations of endemic countries.

This review will summarise current antimalarial drug developments and outline recent clinical research that aims to bring artemisinin-based combinations to those that need them most.

Key words: artemisinin, drug development, malaria.

Current challenges in malaria chemotherapy

Malaria is a global disease but most of the burden is in sub-Saharan Africa where falciparum malaria affects particularly young children and pregnant women. The number of currently available antimalarial drugs is few. Those that are easily affordable by many malaria-endemic countries are restricted to chloroquine (CQ), sulfadoxine/pyrimethamine (S/P), quinine and amodiaquine (AQ). In Southeast Asia, mefloquine (MQ) alone or in combination with artesunate (AS) tends to be used. Artemisinin derivatives are increasingly used throughout the tropical world, although the World Health Organization (WHO) recommends their use only in combination with another antimalarial drug (World Health Organization, 2001). Today, we have several loose (non-fixed)-dose and one fixed-dose artemisinin-based combination, artemether–lumefantrine.

From a public health perspective, drug resistance is a critical factor that undermines malaria control. *Plasmodium falciparum* resistance to CQ and S/P is widespread. There are also foci of MQ, halofantrine and AQ resistance

(Wongsrichanalai et al., 2002). The clinical consequences of such resistance are well described in terms of increased morbidity and mortality, especially amongst young African children (Greenwood et al., 1987; Murphy et al., 2001). In certain areas, notably Indonesia and parts of Oceania, CQ-resistant *Plasmodium vivax* is an emerging problem (Baird et al., 1995).

One factor in the emergence of drug-resistant *P. falciparum* has been the over-reliance on the two principal classes of antimalarial drugs; namely, the quinoline (e.g. CQ) and antifolate (S/P) drugs for treating falciparum malaria. Experience has shown that S/P is very vulnerable to resistance (Watkins and Mosobo, 1993; Plowe, 2003). In Thailand, S/P had an effective life span of just five years (White, 1992). S/P resistance is also a worrying development in East Africa (Oguto et al., 2000; Legros et al., 2002). Because CQ and S/P are inexpensive, they have been used and recommended even in the face of poor efficacy. Another important consideration is access to good diagnosis and treatment. Poverty and the inability to travel to a local clinic often result in the purchase of sub-therapeutic doses of CQ in many parts of rural Africa and treatment in the home (Marsh et al., 1999). Drug use that leads to low drug concentrations lingering in the blood is a powerful selective pressure for the development of resistant parasites (White, 1992). Overcoming or reducing resistance requires the adoption of several strategies; central to these is the use of effective chemotherapy for those who need it.

In order for this objective to be reached, we will indeed need new molecules with novel structures and targets to circumvent resistance (Rosenthal, 2003). But we also need to develop and implement strategies to protect drugs against resistance. Resistance to single-drug therapies will inevitably occur. Drug combinations, which have been standard practice for viral and bacterial diseases, are now being adopted for malaria as well.

The artemisinin derivatives in combination with standard antimalarials are now being promoted as the best therapeutic option for treating drug-resistant malaria and retarding the development of resistance (White et al., 1999; White, 1999; World Health Organization, 2001). The artemisinin derivatives are currently the most rapidly acting and potent antimalarial drugs (White, 1997). These pharmacodynamic effects are due to their rapid absorption and activity against many stages of the malaria life cycle, from young asexual forms (rings) to early sexual forms (gametocytes; Kumar and Zheng, 1990). Their half-lives are short (<1 h for AS), which protects them from resistance. They reduce gametocyte carriage and infectivity and have been the main reason why transmission has been reduced on the Thai–Myanmar border (Targett et al., 2001; Price et al., 1996; Nosten et al., 2000). Tolerability of these drugs is excellent (White, 1998). Data on their safety during pregnancy are limited but encouraging (McGready et al., 2001). They are not generally recommended for use during the first trimester unless better alternatives are unavailable or unsuitable.

The global antimalarial pipeline

Historically, antimalarial drugs have come onto the market slowly, but prospects are becoming brighter. Prior to the Second World War, quinine, pamaquine, CQ and mepacrine were developed. These were followed by proguanil and AQ (in the 1940s), primaquine and pyrimethamine (1950s), S/P (1960s), artemisinin (1970s, in China) and then a spurt of drugs in the 1980s: MQ, halofantrine and various Chinese compounds – pyronaridine (PRN), piperaquine (PPQ) and the artemisinin derivatives artemether and AS. More recently, there has been dihydroartemisinin (DHA). However, the use of these Chinese compounds has been confined almost exclusively to China itself and a few other Asian countries; only recently have the artemisinin derivatives been adopted more widely. In the past ten years, three new antimalarial drugs have been registered in Western countries and made available on the open market: atovaquone–proguanil (for treatment of uncomplicated malaria and prophylaxis in travellers), injectable artemether (also referred to as artemotil, for the treatment of severe malaria) and artemether–lumefantrine (co-artemether, for the treatment of uncomplicated malaria).

Two considerations emerge. First, there are few affordable treatments for malaria today, especially to treat uncomplicated paediatric malaria in Africa. In practice, the vast majority of cases in the world today (which occur in Africa) are treated with drugs that are cheap but by and large ineffective (CQ or S/P). Second, the current R&D model, which (with few exceptions) is largely based on public sector basic research and discovery of products to be then developed by the private sector, has been ineffective in providing innovative antimalarial drugs. Only four of the nearly 1400 drugs registered worldwide during 1975–1999 (Trouiller et al., 2002) were antimalarials. The truly innovative products, artemisinin and its derivatives, were discovered in China but their distribution is still limited because their developments do not meet international criteria. It is worth noting here that the rules and criteria regulating drug development have changed significantly in the recent past. Stricter criteria are being applied today than in the past, particularly with the adoption of the guidelines of the International Conference for Harmonisation [ICH; refer to the official web site (http://www.ich.org/) for details]. As a consequence, developing a new drug is now more expensive and takes longer. This, along with the low solvability of the markets that these drugs are intended for, explains in part the low output of new antimalarial drugs by the Western, research-based pharmaceutical industry. The world's drug market is highly skewed; more than 80% of the US$ 337 billion market in 1999 was in the USA, Europe and Japan, which account for less than 20% of the world's population.

Other factors concur. Traditionally, Western countries have promoted antimalarial drug research during the colonial era, and in case of war in endemic countries (e.g. MQ during the Vietnam war). Today, neither condition exist, and the traveller market alone does not suffice. However, the future is looking brighter.

A number of drugs and drug combinations are in various stages of development (Table 1). The majority of these drugs will be used for treating uncomplicated falciparum malaria. Funding for these projects is from a variety of sources from the private and public sectors. A brief description of each drug is presented below, limited to drugs intended for the treatment of uncomplicated falciparum malaria. The majority are combinations of existing antimalarial drugs with an artemisinin derivative. Here, we will detail developments in this area.

Chlorproguanil–dapsone (LapDap), a non-artemisinin-containing fixed-dose antifolate combination similar to S/P developed jointly by GlaxoSmithKline (GSK) and WHO/TDR (Tropical Disease Research), is undergoing regulatory scrutiny in the UK (Lang and Greenwood, 2003). The two separate entities have been in use for several years. They were combined in order to obtain an antifolate combination with shorter residence time in the body than S/P and hence a lower probability of selecting resistant parasites. The drug compares well with S/P (Sulo et al., 2002) in controlled studies in East Africa and was effective in patients who failed on S/P (Mutabingwa et al., 2001). However, there is some debate regarding its optimal role in treating falciparum malaria in Africa because it shares similar genetic mechanisms of resistance as S/P and its life span may be short if used widely. This might compromise the eventual use of LapDap itself and when combined with AS [chlorproguanil–dapsone–artesunate (CDA)]. CDA is at an early phase of development, with funding by Medicines for Malaria Venture (MMV), GSK and WHO/TDR, having completed pre-clinical toxicological studies. Phase I clinical trials have yet to start.

Coartemether (Riamet®, Coartem®) is a fixed-dose combination of artemether (a rapidly acting, short-lived antimalarial) and lumefantrine (a long-resident drug also referred to as benflumetol). The registered indications and branding for this drug cover treatment, including standby treatment, of uncomplicated malarial episodes caused by pure or mixed *Plasmodium falciparum* infections. The combination is expected to confer mutual protection against resistance and prevent recrudescence after artemether therapy. The components of this combination were originally studied and developed in China by the Academy of Military Medical Sciences (AMMS), Beijing and Kunming Pharmaceutical Factory (KPF), Kunming. The combination product has been registered in China since 1992 but underwent further development when Novartis signed a collaborative agreement in 1994 with AMMS, KPF and CITITEC, the technology arm of the China International Trust and Investment Corporation (CITIC). Studies for international registration started in 1995. The drug was registered in Switzerland in 1999 and has since received marketing authorisation in several endemic and non-endemic countries. Coartemether is marketed under a dual-branding, dual-pricing strategy. Riamet® (six doses over either 3 days or 5 days) is available in developed, non-endemic countries as a standby treatment for travellers at a price comparable with the latest antimalarial introductions. Coartem® is registered and marketed in malaria-endemic countries as either a four- or six-dose treatment of uncomplicated falciparum malaria at prices comparable with locally available products. Recently, an agreement was reached between Novartis and WHO for the drug to be made available to the public sector of developing countries at a preferential price. Many clinical trials have been conducted both with the original Chinese combination product and the subsequent product for international registration, mostly with the four-dose regimen. Recently, a Cochrane review (Omari et al., 2003) identified eight randomized, controlled trials comparing coartemether with standard treatment for uncomplicated falciparum malaria (2117 participants). The meta-analysis concluded that the four-dose coartemether regimen was superior to CQ and equivalent to S/P in areas of CQ resistance but inferior to MQ and MQ–AS in areas of multidrug resistance. The six-dose regimen was equivalent to MQ–AS but was reported to be better tolerated (Vugt et al., 1999; van Vugt et al., 2000). Work between Novartis and WHO has led to a more user-friendly packaging of the six-dose treatment for improved adherence, which is now being field tested. Paediatric formulation is also being developed.

Table 1. *Summary of the global drug development pipeline for antimalarial drugs for the treatment of uncomplicated* P. falciparum

Project and phase of development
Late phase
Chlorproguanil–dapsone
Mid phase
Artesunate–amodiaquine
Artesunate–sulfadoxine/pyrimethamine
Paediatric co-artemether
Dihydroartemisinin–piperaquine
Early phase
Chlorproguanil–dapsone–artesunate
Artesunate–pyronaridine
Fosmidomycin
Short-chain chloroquine
Artemisone
Isoquine

The combination of DHA and PPQ was developed in China (Artekin™) and is registered in China and Cambodia. It has been evaluated extensively in clinical trials in Thailand, Vietnam, Cambodia and China (Denis et al., 2002). Efficacy has been high and tolerability uniformly excellent in all trials in these multidrug-resistant areas including Hai Nan, China, where PPQ-resistance was common after extensive use of mass prophylaxis. Initially, the coformulation also included PPQ and trimethoprim (CV8). This product is still part of national policy in Vietnam. PPQ is an orally active bisquinoline discovered by Rhône-Poulenc in the early 1960s and developed for clinical use in China in 1973. PPQ is approximately equivalent to CQ against sensitive parasites and is significantly more effective than CQ against resistant *P. falciparum.* PPQ replaced CQ as the recommended treatment for falciparum malaria in China in 1978. Overall, 194,140 kg of PPQ phosphate, equivalent to

140 000 000 adult doses, were used for mass prophylaxis and treatment. Surveillance at the time found no adverse events other than rare cases of a rash. DHA is the active metabolite of AS and artemether. It has equivalent clinical efficacy to the more widely used AS. A development programme has been developed between Holleykin and Guangzhou University (China), The University of Oxford, MMV and WHO/TDR to support the international registration of the drug.

AS–AQ and AS–S/P have completed clinical trials in Africa (see below). AS–MQ has been widely used in Thailand and other parts of Southeast Asia as a non-fixed combination, where it proved highly effective in areas of MQ resistance. AS–AQ and AS–MQ will be further developed as fixed-dose combinations and will undergo all the pertinent pre-clinical and clinical studies before registration. A blister pack of AS–S/P has been developed using age-based dosing and is being used in clinical trials in Africa. The two new fixed-dose combinations (AS–AQ and AS–MQ) are currently being developed by a number of partners in Brazil, Malaysia, Thailand and France. MSF and WHO/TDR are the coordinating bodies, and funding has been obtained from the European Commission. This development will cover the full spectrum from formulation pharmaceutics to Phase 3 clinical trials. This work is being conducted to meet the necessary standards for drug registration.

Several other drugs and drug combinations are in an early phase of development. AS–PRN builds on the rationale of using an artemisinin derivative with a longer-acting partner drug. PRN is a Mannich base antimalarial compound that has been synthesized and developed in China, where it obtained marketing authorization for the treatment of malaria in the 1980s. It has proven efficacy against drug-resistant falciparum malaria in Africa (Ringwald et al., 1996). The efficacy in Thailand of polybioavailable formulation against multidrug-resistant malaria was less than 90% (Looareesuwan et al., 1996). In the same setting, a better formulation was >95% effective (S. Looareesuwan, V. Navaratnam and P. L. Olliaro, unpublished).

Work is being planned for drugs that are chemical alterations of well-established antimalarial drugs. Artemisone is a metabolically stable semi-synthetic derivative of artemisinin that is being developed by Bayer & MMV. Several trioxanes obtained by total synthesis are now available and are being assessed for further development by MMV. Isoquine is an isomeric derivative of AQ that should not generate the toxic quinone-imine metabolites that are thought to have a role in the hepatic and neutrophil toxicities. The development of this drug is also being coordinated by MMV. Short-chain CQ analogues with better efficacy on CQ-resistant isolates are being researched at Tulane University.

A novel compound, fosmidomycin, has recently been tested in small numbers of patients. Fosmidomycin inhibits 1-deoxy-D-xylulose 5-phosphate reductoisomerase, an enzyme of the nonmevalonate pathway of isoprenoid biosynthesis, which is absent in humans but present in many pathogens and plants. Fosmidomycin was well tolerated and produced modest cure rates (Lell et al., 2003; Missinou et al., 2002). However, it is a drug worthy of more trials and could be used in combination with other antimalarials.

Clinical trials of AS-based combinations in Africa

In 1998, WHO/TDR, USAID and the Wellcome Trust agreed to commence a series of clinical trials to assess the efficacy and tolerability of AS combined with three standard antimalarial drugs (CQ, AQ and S/P) in Africa and Latin America. WHO/TDR was to be the coordinating and managerial body.

The criterion for using a particular drug at a given site was that its efficacy was not less than 75%. CQ was used in West Africa, and the other two drugs in several countries across Africa. Two trials were conducted in Latin America, using AQ in Colombia (trial ongoing) and S/P in Peru. This report focuses on the African studies. The institutions involved are listed in Table 2. These were randomised, double-blind, placebo controlled trials that were conducted under Good Clinical Practices (GCP). Common clinical protocols and an analytical plan were used; the latter was designed so that an individual patient data (IPD) meta-analysis could be done. Collectively, they represent the largest series of antimalarial drug trials ever conducted. There were 11 sites in eight African countries (Table 2).

All the S/P studies had three arms: S/P alone and two dosing regimens of AS. The CQ and AQ studies used three days of AS (Table 3). The dose of AS was 4 mg kg^{-1} day^{-1} for three days or one day (S/P studies only). The results of one day of AS are not reported here. AS/placebo was provided by Sanofi-Synthélabo/Guilin, AQ by Warner-Lambert/Parke-Davis (now Pfizer) and S/P by the International Dispensary Association.

The primary efficacy end points were the parasitological cure rates at days 14 and 28. Secondary efficacy parameters were the rates of parasite and fever clearances and gametocyte carriage rates. Molecular genotyping was used to distinguish between recrudescent and fresh infections; these results were used to correct the day 28 cure rates (missing PCR data were excluded). PCR and drug analyses were conducted for the genetic mutations of drug resistance and population pharmacokinetics, respectively. These results will be reported elsewhere.

Results

A preliminary analysis is presented here. A full account with IPD meta-analysis will be published elsewhere. Individual studies are also being published. These results form the basis of the new WHO recommendations on the use of combination therapies for malaria (World Health Organization, 2001).

Primary outcomes

AQ studies

The addition of AS to AQ resulted in an increased cure rate in Gabon and Kenya but not in Senegal on days 14 and 28 (Table 3; Adjuik et al., 2002).

Table 2. *Countries and centres participating in the randomised controlled trials of artesunate combinations in Africa*

Country	Executing institution	Drug	Number enrolled
Gabon	Tübingen University – A. Schweizer Hospital, Lambaréné, Gabon	AQ	220
Senegal	Rouen University – Hôpital Charles Nicolle	AQ	321
Kenya	African Medical Research Foundation (AMREF)	AQ	400
Subtotal			941
The Gambia	Medical Research Council (MRC)	S/P	600
Kenya	Kenyan Medical Research Institute (KEMRI)	S/P	600
Uganda	Epicentre – Mbarara University	S/P	425
Malawi	Queen Elizabeth Hospital, Blantyre	S/P	450
Subtotal			2075
São Tomé	Lisbon University – Prince Leopold Institute, Antwerp – São Tomé Ministry of Health	CQ	400
Burkina-Faso	Centre National de Lutte Contre le Paludisme (CNLP)	CQ	300
Côte d'Ivoire	Institute P. Richet, Bouaké	CQ	300
Subtotal			1000
Total			4016

AQ, amodiaquine; CQ, chloroquine; S/P, sulfadoxine/pyrimethamine.

Table 3. *Cure rates of the 3-day AS combinations and the standard drugs – CQ, AQ or S/P – in African children with acute, uncomplicated falciparum malaria*

		Day 14*			Day 28*		
Drug	Study	AS 3 days	Standard drug	*P*	AS 3 days	Standard drug	*P*
AQ	Gabon	92/94 (97.9)	86/96 (89.6)	0.035	85/94 (90.4)	77/98 (78.6)	0.024
	Kenya (AMREF)	175/192 (91.1)	140/188 (74.5)	0.000	144/179 (80.4)	98/182 (53.8)	0.000
	Senegal	148/160 (92.5)	147/157 (93.6)	0.693	133/149 (89.3)	125/141 (88.7)	0.693
S/P	The Gambia	185/189 (97.9)	185/195 (94.9)	0.191	182/187 (97.3)	174/191 (91.1)	0.0098
	Kenya (KEMRI)	175/192 (91.1)	143/192 (74.5)	0.000	142/179 (79.3)	104/181 (57.5)	0.000
	Malawi	132/139 (95.0)	69/130 (53.1)	0.000	102/120 (85.0)	36/113 (31.9)	0.000
	Uganda	100/117 (85.5)	84/146 (57.5)	0.000	86/110 (78.2)	60/131 (45.8)	0.000
CQ	Burkina-Faso	120/147 (81.6)	53/143 (37.1)	0.000	96/130 (73.8)	34/131 (26.0)	0.000
	Côte d'Ivoire	29/128 (22.7)	20/138 (14.5)	0.087	14/117 (12.0)	11/130 (8.5)	0.087
	São Tomé	156/188 (83.0)	37/177 (20.9)	0.000	108/172 (62.8)	24/173 (13.9)	0.000

AQ, amodiaquine; CQ, chloroquine; S/P, sulfadoxine/pyrimethamine.
*Numerator/denominator (%)

S/P studies

In The Gambia, cure rates were similar on day 14 but were higher by day 28 (von Seidlen et al., 2000). In Uganda, Malawi and Kenya, the background failure rates of S/P alone were high. Cure rates were increased significantly by the addition of AS.

CQ studies

CQ cure rates were low in all three countries. AS improved significantly the cure rates in Burkina-Faso and São Tomé but not in Côte d'Ivoire.

Secondary outcomes

Parasite clearance rates were significantly faster in all trials except Côte d'Ivoire with both three days and, in the S/P studies, one day of AS compared with the standard drug alone (Fig. 1). Fever clearance rates were consistently faster in the S/P studies but not always in the CQ and AQ studies. Gametocyte carriage was reduced significantly in the S/P (Fig. 2) and CQ studies by the AS regimens, but the effect of AS in the AQ studies was inconsistent.

Tolerability of the combinations and the standard drugs was good in all studies (full details to be published elsewhere). Generally, there was no increase in the proportion of patients reporting adverse events in the AS arms compared with the single agents. Remarkable side effects in the AQ and AQ–AS arms were mild itching in nine patients (1%) and drug-induced vomiting in 11 patients (1.2%). In the S/P study in Kenya, 16 (2.7%) children developed mild, papular rashes. Serious adverse events (SAE) were few and mostly due to signs of severe malaria, e.g. convulsions, anaemia and coma. One child with AQ-induced vomiting was admitted to hospital. There were five deaths, all unrelated to study drugs. Haematology

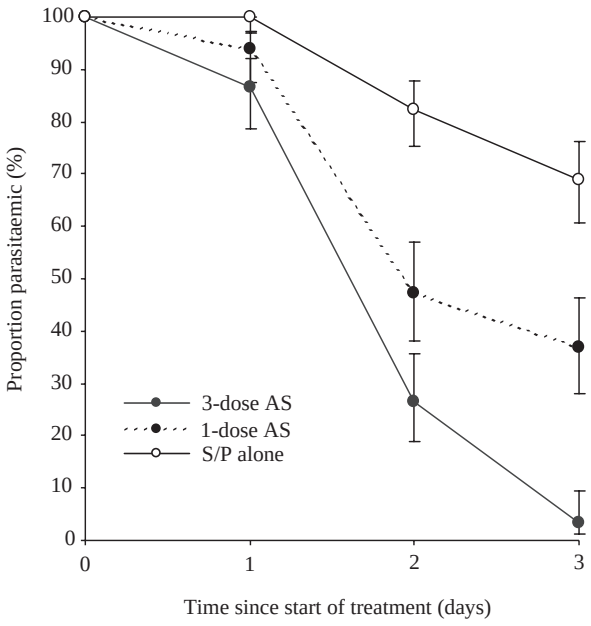

Fig. 1. Parasite clearance of artesunate with sulfadoxine/pyrimethamine (AS–S/P) *versus* S/P alone. Although these data are from Uganda, they are representative of all the artesunate studies. The addition of artesunate increases the rate of parasite clearance.

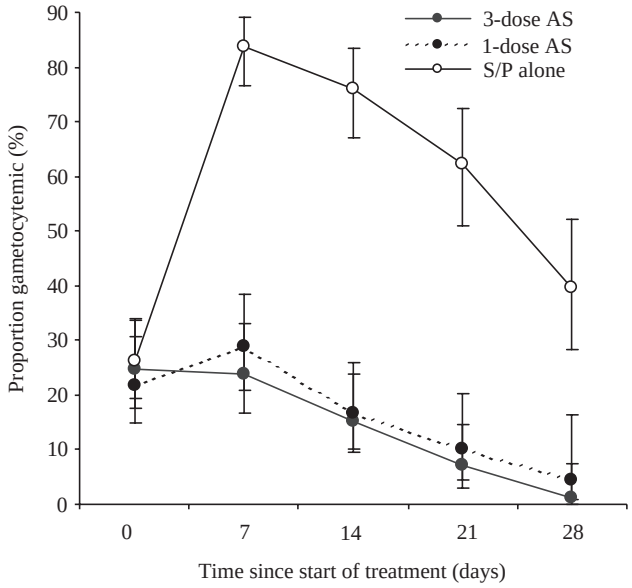

Fig. 2. Gametocyte carriage of sulfadoxine/pyrimethamine (S/P) alone and combined with one or three days of artesunate (AS). Data from Uganda.

results showed that the mean haemoglobin increased by day 28 and was generally similar between the combination and standard drug arms. In the AQ study, there was a decline in the mean neutrophil counts, reaching a nadir on day 21 and rising thereafter. Nine (6%) of 153 children developed neutropenia (neutrophil count <1000), one of whom was parasitaemic. The clinical significance of this neutropenia is unclear. All children were afebrile and asymptomatic. Biochemistry results were unremarkable. Mean creatinine and liver enzyme values were stable. Raised liver enzymes present on day 0 resolved during follow-up.

Towards the development of optimal age-based dosing of fixed-dose combinations

Optimal drug use by communities relies upon easily understood and easy to use drug regimens. Blister packs of 'AS and S/P' and 'AS and AQ' have been developed as an interim measure whilst waiting for more fixed-dose combinations (see above). This strategy should improve adherence to treatment. The blister packs have been designed for four age categories: (1) <1 year, (2) 1–6-year olds, (3) 7–13-year olds and (4) 14 years and above. Compared with weight-based dosing, age-based dosing will result in less precise dosing on a mg kg^{-1} basis. Nevertheless, using a database of some 140 000 patients from endemic countries, the proportion of patients who will receive an acceptable dose in mg kg^{-1} has been maximised and is at least 88% for AQ and 95% for S/P (W. R. J. Taylor, F. ter Kuile and P. L. Olliaro, unpublished).

Conclusions

There has been a dearth of new, effective therapies for malaria. This dire situation is now changing and prospects are becoming brighter. Today, there are more compounds in development than ever, mostly artemisinin-based combinations. The availability of artemisinin and the adoption of combinations has been the most notable and significant development of the past few years. Otherwise, there is little novelty in the compounds currently under development. Newer molecules are expected to come from more upstream research efforts.

Artemisinin-based combinations hold the promise of overcoming drug-resistant malaria: AS–MQ, Artekin™ and the six-dose coartemether are effective in areas of multidrug resistance. There are prospects, at least for the latter two, to be used in Africa as well. The clinical trials conducted in African children, a key target group, showed that combining AS with a standard drug resulted in a significant improvement of cure rates over those of the standard drugs. However, the absolute day 28 cure rates for falciparum malaria in some studies was still relatively low because of the high degree of resistance to the standard drug. Tolerability was similar for both the combination arms and the standard drugs. Gametocyte carriage was reduced, most notably in the S/P arms. On a large scale, this might reduce malaria transmission over the long term.

Fixed-dose combinations are generally agreed to be better than unfixed doses for patient adherence. Blister packs of fixed-dose AS-based combinations have been designed for clinical trials in Africa. Information from these trials will be of value to malaria control programmes. Further research is required to assess more fully the efficacy, safety and long-term public health impact of artemisinin-based combinations.

Compliance with international standards of production and research is paramount if these products are to be registered and adapted widely. Cost of treatment has been brought up, time and again, as a limitation to the adoption of these combinations in resource-constrained settings. Their costs today are in the range of US$1–2.4 for an adult treatment. So, they are significantly more expensive than CQ or SP. However, both emerging data and modelling studies show that the adoption of combinations as first-line therapies will lead to overall net savings for both individuals and health systems. Moreover, cost-of-goods is decreasing with increasing demand of active principles.

Note added in press

Chlorproguanil–dapsone was registered in the UK in August 2003.

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