Infection (2019) 47:655–659
https://doi.org/10.1007/s15010-019-01286-6

CASE REPORT

Five cases of *Plasmodium vivax* malaria treated with artemisinin derivatives: the advantages of a unified approach to treatment

Angela Corpolongo[1] · Raffaella Pisapia[1] · Alessandra Oliva[1] · Maria Letizia Giancola[1] · Paola Mencarini[1] · Nazario Bevilacqua[1] · Piero Ghirga[1] · Andrea Mariano[1] · Antonella Vulcano[1] · Maria Grazia Paglia[1] · Emanuele Nicastri[1]

Received: 11 October 2018 / Accepted: 19 February 2019 / Published online: 26 February 2019

Abstract

Objectives In endemic countries with a high level of chloroquine resistance, *Plasmodium vivax* malaria is associated with high morbidity and mortality. In these areas, the dihydroartemisinin–piperaquine combination resulted in clinical response, a more rapid clearance of parasitaemia, compared to chloroquine therapies, and reduction of recrudescence or reinfection.

Methods We describe five cases of *Plasmodium vivax* malaria in returning travelers treated with dihydroartemisinin–piperaquine.

Results All patients showed the early parasite clearance and no side effects. Our preliminary results suggest that the dihydroartemisinin–piperaquine combination is effective and safe even in imported cases.

Conclusions A unified treatment policy using the artemisinin combination therapy should be adopted even in non-endemic countries and larger studies are underway to support this strategy.

Keywords *Plasmodium vivax* · Imported malaria · Chloroquine resistance · Artemisinin combination therapy (ACT)

Abbreviations

P. vivax	*Plasmodium vivax*
INMI	National Institute for Infectious Diseases
ACT	Artemisinin combination therapy
PCR	Polymerase chain reaction
DP	Dihydroartemisinin–piperaquine
AL	Artemether–lumefantrine
CQ	Cloroquine

Background

Plasmodium vivax (*P. vivax*) is the most widely distributed species of *Plasmodium* outside of Africa. In 2017, malaria caused an estimated 216 million cases globally and *P. vivax* accounted for more than half of all malaria cases in Asia and Latin America [1]. Autochthonous cases of *P. Vivax* malaria have been reported also in Europe [2]. In endemic countries, *P. vivax* can be associated with severe disease and death, especially in areas with high grade of chloroquine resistance where partially effective therapy and recurrent

Angela Corpolongo and Raffaella Pisapia have contributed equally to the paper.

✉ Raffaella Pisapia
raffaella.pisapia@inmi.it

Angela Corpolongo
angela.corpolongo@inmi.it

Alessandra Oliva
alessandra.oliva@inmi.it

Maria Letizia Giancola
mletizia.giancola@inmi.it

Paola Mencarini
paola.mencarini@inmi.it

Nazario Bevilacqua
nazario.bevilacqua@inmi.it

Andrea Mariano
andrea.mariano@inmi.it

Antonella Vulcano
antonella.vulcano@inmi.it

Maria Grazia Paglia
mariagrazia.paglia@inmi.it

Emanuele Nicastri
emanuele.nicastri@inmi.it

[1] National Institute for Infectious Diseases Lazzaro Spallanzani-IRCCS, Via Portuense, 292, 00149 Rome, Italy

infections lead to severe anaemia and fatal malaria mostly in young children [3–8].

In some countries as the New Guinea Islands, Indonesia, Myanmar, India, Ethiopia, and South America, chloroquine (CQ) resistance against *P. vivax* is an emerging problem also due to the absence of reliable and sensitive methods for the detection and monitoring of antimalarial drug's efficacy [9]. In these areas, several comparison trials have been conducted to compare the efficacy of chloroquine and artemisinin combination therapy (ACT) [10–12].

Artemisinin combination therapy demonstrated a faster clinical response and clearance of *P. vivax* parasitaemia than chloroquine with a reduction and delay in recurrence due to recrudescence or reinfection [13, 14]. In particular, the association dihydroartemisinin–piperaquine (DP) showed greater efficacy than other associations, leading to a rapid reduction of parasite biomass and to a post-treatment prophylactic effect decreasing the rate of reinfection and relapse due to the long half-life of piperaquine [15–17]. Furthermore, in endemic areas for *P. falciparum* also, misdiagnosis by routine microscopy of coinfection is frequent leading to severe consequence due to already widespread of chloroquine resistant *P. falciparum* [18]. For these reasons, in endemic countries, the treatment and elimination strategies had been reviewed and a unified ACT-based treatment policy has been adopted.

In Europe, the current strategy for *P. vivax* malaria treatment still includes the use of chloroquine for patients coming from chloroquine sensitive areas, for its wide availability and the low cost [19, 20].

In relation to the elimination program, we think that a unified treatment with ACT for all cases of imported malaria can support the goal of elimination, given effectiveness, and safety of the treatment.

To support the feasibility and efficacy of ACT use in *P. vivax* imported malaria, we describe five cases of imported *P. vivax* malaria treated with the association of dihydroartemisinin–piperaquine (Eurartesim®, Sigma-Tau, Italy) at "Lazzaro Spallanzani" National Institute for Infectious Diseases (INMI), Rome.

Case presentation

Five patients presented at the Infectious Diseases ward at INMI because of fever in returning travelers. Patients' age ranged from 23 to 53 years old: three were female, four were not Italian. Two patients had recently traveled for touristic purposes, while other two, living in Italy since many years, recently had visited friends and relatives in their country of origin; one patient was a migrant recently arrived in Italy. No patients had taken antimalarial prophylaxis during their travel. Demographic details are summarized in Table 1.

Presenting symptoms and main results from hematochemical tests are reported in Table 1. Malaria rapid antigen test (RDT-Carestart malaria HRP2/pLDH Combo test) resulted positive in all except in patient 3 probably due to a false-negative result. Blood smears resulted positive for *P. vivax* trophozoites in all cases; in one patient, schizonts were also identified. Diagnosis of *P. vivax* infection was subsequently confirmed by Polymerase Chain Reaction (PCR) assay in all the cases. The sensitivity to chloroquine was not performed.

These five patients have been enrolled in a multicentre study promoted by Sigma-Tau: "Eurartesim® in patients with imported uncomplicated *Plasmodium vivax* malaria". All the following inclusion criteria were satisfied: signature of informed consent, age > 18 years, uncomplicated malaria with microscopically confirmed monoinfection by *Plasmodium vivax* or mixed infection, ability to swallow oral medication, body weight between 24 and 100 kg for males and females, willingness to comply with the study protocol, and the study visit schedule.

All patients were shortly hospitalized for a careful clinical monitoring of possible and sudden complications, and for the surveillance of possible cardiological side effects of the treatment.

They started therapy with dihydroartemisinin–piperaquine 320/40 mg 3 cpr for 3 days, without clinical side effects and electrocardiogram alterations. In one case only, a mild increase of liver enzymes was evidenced at day 7 after the start of the therapy, with AST 66 U/L (normal range 15–40 U/L) and ALT 209 U/L (normal range 15–40 U/L), and then spontaneously regressed at follow-up. Parasite clearance time is summarized in Table 2.

All patients were discharged in good clinical conditions after 5–7 days of hospitalization. After excluding G6PD deficiency, all patients received oral primaquine for 14 days to prevent a relapse of *P. vivax* infection. Follow-up visits, performed in 3 patients until day 42 and in 1 patient at day 21, confirmed clinical cure and clearance of parasitaemia.

Conclusion and discussion

Our preliminary experience supports that DP treatment is safe and effective in the management of patients with *P. vivax* imported malaria. No side effects were reported in our patients and cure rate was maintained at day 42 of follow-up in three patients, though this follow-up time is not enough to define a complete cure due to possible relapse from hypnozoite stages up to 6 months [10].

Patients described in our brief report came from different geographical areas, as Indonesia and Ethiopia, where chloroquine resistance is described. Particularly, for the management of malaria in immigrants crossing several countries

Table 1 Demographic and clinical data

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Demographic data					
Age	23	33	53	31	43
Sex	M	F	F	M	F
Country of origin	Eritrea	Turkey	Italy	Eritrea	Pakistan
Country of malaria transmission	Ethiopia–Sudan–Lybia	Indonesia	Ethiopia	Eritrea	Pakistan
Reason for traveling	Migration	Tourism	Tourism	Visiting friends and relatives	Visiting friends and relatives
Clinical data					
Presenting symptoms	Fever, nausea, vomiting	Fever, headache, arthralgia	Fever, headache fatigue	Fever, headache fatigue	Fever, nausea, vomiting
Body temperature	40 °C	39 °C	38,5 °C	37 °C	37,5 °C
Physical examination	Splenomegaly	Hepato-splenomegaly	Hepato-splenomegaly	Normal	Hepato-splenomegaly
White blood cells (cells/µL)	12,200	6600	2300	5100	4500
Neutrophils (%)	62%	77%	82,9%	55,8%	70%
Red blood cells (cells/µL)	4,900,000	3,390,000	5,450,000	4,370,000	3,460,000
Haemoglobin (g/dL)	13.3	10.0	11.2	13.2	9.3
Platelets (cells/µL)	103,000	49,000	63,000	61,000	85,000
Total bilirubin (mg/dL)	2.2	0.57	0.6	0.7	–
AST (U/L)	18	34	42	17	21
ALT (U/L)	13	34	29	22	18
C-reactive protein (mg/dL)	6.9	0.3	0.3	–	7.1

before the final destination, different patterns of chloroquine sensitivity should be considered in relation to the different crossed countries. This uncertainty should support the use of a unified treatment approach.

Among different artemisinin-based combinations, the association of dihydroartemisinin–piperaquine has proved to be superior to artemether–lumefantrine (AL), with higher cure rates proved in different studies conducted in different regions. In a randomized-controlled study from Thailand comparing DP and CQ, fever and parasite clearance times were slower in the CQ group than in the DP group and, by day 28, recurrent infections were more frequent in patient treated with the CQ [15]. Comparable results have emerged from the meta-analysis by Naing et al., showing that DP is more efficacious than CQ and AL in treating uncomplicated *P. vivax* malaria with a better safety profile. The long half-life of piperaquine, in fact, adds to the efficacy of artemisinin derivative in rapidly reducing the parasite biomass, a prophylactic post-treatment effect decreasing the rate of reinfection and relapse [17].

Despite ACT is more expensive than chloroquine, its use may result more cost-effective, as suggested by the recent experience: indeed, the higher rate of cure and lower rate of recrudescence and reinfections contribute to make ACT a cost-saving approach [21].

Table 2 Diagnostic and follow-up data

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Malaria rapid test	Positive	Positive	Negative	Positive	Positive
PCR assay for *P. vivax*	Positive	Positive	Positive	Positive	Positive
Blood smear T 0	Numerous trophozoites	Some trophozoites	Numerous trophozoites	Numerous trophozoites	Some trophozoites
Blood smear T 24	Very rare trophozoites	Absence of trophozoites	Absence of trophozoites	Rare trophozoites	Very rare trophozoites
Blood smear T 48	Absence of trophozoites	Absence of trophozoites	Absence of trophozoites	Very rare trophozoites	Absence of trophozoites
Baseline parasitemia				10,750 tr/μL	
Fever clearance time	24 h	24 h	48 h	48 h	24 h
Parasite clearance time	48 h	24 h	24 h	72 h	48 h
Adverse events	No	No	No	No	No
Cure rate at day 7	NA	Complete	Complete	Complete	Complete
Cure rate at day 21	NA	Complete	Complete	Complete	Complete
Cure rate at day 42	NA	NA	Complete	Complete	Complete

All patients took the dose of DP 320 mg/40 mg 3 tablets daily as the manufacturer's prescriptions. This dosage, according to WHO, is under-dosed in overweighed patients and in less-than 5-year-old children, resulting in a lower cure rate, and higher rate of recrudescence [1]. None of our five patients was at risk of under-dosing.

The issue of drug under-dosing, especially in children younger than 5 years, has been recently discussed in a systematic review by Commons et al. about the effect of chloroquine dose on *P. vivax* recurrences. The authors point out that, given that parasites rate of *P. vivax* peak at 2–6 years of age, the chloroquine under-dosing should carefully be considered in view of the implementation of efficacious treatment [22].

Another point to discuss is the possible emergence in the future of resistant plasmodium due to the wider use of ACT as mutations have been already described in *P. vivax* malaria in Cambodia, though the clinical equivalence of these mutation is still unclear [23]. The clinical impact of ACT resistance is already evident for *P. falciparum* malaria: recently, a case of DP treatment failure in an uncomplicated case imported from Ethiopia has been described showing recrudescence after the initial recovery [24].

Despite all the criticisms discussed, we believe that, to sustain the efforts for malaria elimination, a more extended unified malaria treatment would have practical and malariometric advantages such as the rapid reduction in parasite and gametocyte biomass, [5, 7, 8], the reduction in recrudescence also in chloroquine-sensible areas [22], the high cure rate, the limitation of further spread of chloroquine resistance, and a better management of misdiagnosed *P. falciparum* coinfection.

In light of these evidences, we believe that this therapeutic strategy should be adopted for patients with imported non-falciparum malaria also, because a treatment standardization is essential in view of global malaria eradication [25]. Moreover, this approach is important also for the comparison of data between endemic and imported malaria cases, and for the sharing of clinical experiences. For the purpose of treatment standardization, some clinical trials are already in progress to validate this strategy, and our data may represent a support for clinicians of western countries to timely adopt this approach.

The future challenges in treatment of *P. vivax* malaria are likely to include the emergence of resistance to ACT, stimulating an ongoing research effort in new pharmaceuticals and control strategies.

Author contributions AC and RP drafted the manuscript, substantial contributed to design the study, participated in the acquisition and analysis of data, and gave the final approval of the version to be published; AO, MLG, PM, NB, P.G, A.M, A.V, MGP, and EN substantial contributed to design the study, participated in the acquisition and interpretation of data, and gave the final approval of the version to be published; EN substantial contributed to design the study and gave the final approval of the version to be published. All authors read and approved the final manuscript.

Funding This work was supported by the Ministero della Salute, Italia-Ricerca Corrente, Istituti di Ricovero e Cura a Carattere Scientifico, and Sigma-tau.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Consent Written informed consent was obtained from the patients for publication of this study and any accompanying material. All patients' personal data have been anonymised.

Availability of data and material Data sharing is not applicable to this article as no data sets were generated or analysed during the current study.

References

1. World Health Organization. World malaria report. Geneva: World Health Organization; 2017. http://www.who.int/malaria/publications/world-malaria-report-2017/report/en/.
2. Barrado L, Ezpeleta C, Rubio JM, Martín C, Azcona JM, Arteaga M, Beristain X, Navascués A, Ongay E, Castilla J. Source identification of autochthonous-introduced *Plasmodium vivax* malaria. Spain Infect. 2017;45:111–4. https://doi.org/10.1007/s15010-016-0941-8 **(epub 2016 Aug 26)**.
3. Douglas NM, Lampah DA, Kenangalem E, Simpson JA, Poespoprodjo JR, Sugiarto P, Anstey NM, Price R. Major burden of severe anemia from non-falciparum malaria species in Southern Papua: a hospital-based surveillance study. PLoS Med. 2013;10:e1001575.
4. Tjitra E, Anstey NM, Sugiarto P, Warikar N, Kenangalem E, Karyana M, Lampah DA, Price RN. Multidrug-resistant *Plasmodium vivax* associated with severe and fatal malaria: a prospective study in Papua, Indonesia. PLoS Med. 2008;5:e128.
5. Naing C, Whittaker MA, Nyunt Wai V, Mak JW. Is *Plasmodium vivax* malaria a severe malaria?: a systematic review and meta-analysis. PLoS Negl Trop Dis. 2014;8:e3071.
6. Mueller I, Galinski MR, Baird JK, Carlton JM, Kochar DK, Alonso PL, del Portillo HA. Key gaps in the knowledge of *Plasmodium vivax*, a neglected human malaria parasite. Lancet Infect Dis. 2009;9:555–66.
7. Beg MA, Khan R, Baig SM, Gulzar Z, Hussain R, Smego RA Jr. Cerebral involvement in benign tertian malaria. Am J Trop Med Hyg. 2002;67:230–32.
8. Carlini ME, White AC Jr, Atmar RL. Vivax malaria complicated by adult respiratory distress syndrome. Clin Infect Dis. 1999;28:1182–3.
9. Price RN, von Seidlein L, Valecha N, Nosten F, Baird JK, White NJ. Global extent of chloroquine-resistant *Plasmodium vivax*: a systematic review and meta-analysis. Lancet Infect Dis. 2014;14:982–91.
10. Ratcliff A, Siswantoro H, Kenangalem E, Maristela R, Wuwung RM, Laihad F, Ebsworth EP, Anstey NM, Tjitra E, Price RN. Two fixed-dose artemisinin combinations for drug-resistant falciparum and vivax malaria in Papua, Indonesia: an open-label randomised comparison. Lancet. 2007;369:757–65.
11. Douglas NM, Anstey NM, Angus BJ, Nosten F, Price RN. Artemisinin combination therapy for vivax malaria. Lancet Infect Dis. 2010;10:405–16.
12. Gogtay N, Kannan S, Thatte UM, Olliaro PL, Sinclair D. Artemisinin-based combination therapy for treating uncomplicated *Plasmodium vivax* malaria. Cochrane Database Syst Rev. 2013;10:CD008492.
13. Visser BJ, Wieten RW, Kroon D, Nagel IM, Bélard S, van Vugt M, Grobusch MP. Efficacy and safety of artemisinin combination therapy (ACT) for non-falciparum malaria: a systematic review. Malar J. 2014;13:463. https://doi.org/10.1186/1475-2875-13-463 **(review)**.
14. Tavul L, Hetzel MW, Teliki A, Walsh D, Kiniboro B, Rare L, Pulford J, Siba PM, Karl S, Makita L, Robinson L, Kattenberg JH, Laman M, Oswyn G, Mueller I. Efficacy of artemether-lumefantrine and dihydroartemisinin-piperaquine for the treatment of uncomplicated malaria in Papua New Guinea. Malar J. 2018;17:350. https://doi.org/10.1186/s12936-018-2494-z.
15. Phyo AP, Lwin KM, Price RN, Ashley EA, Russell B, Sriprawat K, Lindegardh N, Singhasivanon P, White NJ, Nosten F. Dihydroartemisinin-piperaquine versus chloroquine in the treatment of *Plasmodium vivax* malaria in Thailand: a randomized controlled trial. Clin Infect Dis. 2011;53:977–84.
16. Leang R, Barrette A, Bouth DM, Menard D, Abdur R, Duong S, Ringwald P. Efficacy of dihydroartemisinin-piperaquine for treatment of uncomplicated *Plasmodium falciparum* and *Plasmodium vivax* in Cambodia, 2008 to 2010. Antimicrob Agents Chemother. 2013;57:818–26.
17. Naing C, Racloz V, Whittaker MA, Aung K, Reid SA, Mak JW, Tanner M. Efficacy and safety of dihydroartemisinin-piperaquine for treatment of *Plasmodium vivax* malaria in endemic countries: meta-analysis of randomized controlled studies. PLoS One. 2013;8:e78819. https://doi.org/10.1371/journal.pone.0078819.
18. Barber BE, William T, Grigg MJ, Yeo TW, Anstey NM. Limitations of microscopy to differentiate *Plasmodium* species in a region co-endemic for *Plasmodium falciparum, Plasmodium vivax* and *Plasmodium knowlesi*. Malar J. 2013;12:8.
19. Askling HH, Bruneel F, Gerd B, Castelli F, Chiodini PL, Grobusch MP, Lopez-Vélez R, Paul M, Petersen E, Popescu C, Ramharter M, Schlagenhauf P. Management of imported malaria in Europe. Malar J. 2012;11:328. https://doi.org/10.1186/1475-2875-11-328 **(published online 2012 Sep 17)**.
20. Lalloo DG, Shingadia D, Bell DJ, Beeching NJ, Whitty CJM, Chiodini PL, PHE Advisory Committee on Malaria Prevention in UK Travellers. UK malaria treatment guidelines 2016. J Infect. 2016;72:635–49. https://doi.org/10.1016/j.jinf.2016.02.001 **(epub 2016 Feb 12)**.
21. Devine A, Kenangalem E, Burdam FH, Anstey NM, Poespoprodjo JR, Price RN, Yeung S. Treatment-seeking behavior after the implementation of a unified policy of dihydroartemisinin-piperaquine for the treatment of uncomplicated malaria in Papua, Indonesia. Am J Trop Med Hyg. 2018;98:543–50. https://doi.org/10.4269/ajtmh.17-0680 **(epub 2017 Dec 21)**.
22. Commons RJ, Simpson JA, Thriemer K, Humphreys GS, Abreha T, Alemu SG, Añez A, Anstey NM, Awab GR, Baird JK, Barber BE, Borghini-Fuhrer I, Chu CS, D'Alessandro U, Dahal P, Daher A, de Vries PJ, Erhart A, Gomes MSM, Gonzalez-Ceron L, Grigg MJ, Heidari A, Hwang J, Kager PA, Ketema T, Khan WA, Lacerda MVG, Leslie T, Ley B, Lidia K, Monteiro WM, Nosten F, Pereira DB, Phan GT, Phyo AP, Rowland M, Saravu K, Sibley CH, Siqueira AM, Stepniewska K, Sutanto I, Taylor WRJ, Thwaites G, Tran BQ, Tran HT, Valecha N, Vieira JLF, Wangchuk S, William T, Woodrow CJ, Zuluaga-Idarraga L, Guerin PJ, White NJ, Price RN. The effect of chloroquine dose and primaquine on *Plasmodium vivax* recurrence: a WorldWide Antimalarial Resistance Network systematic review and individual patient pooled meta-analysis. Lancet Infect Dis. 2018;18:1025–34. https://doi.org/10.1016/S1473-3099(18)30348-7 **(epub 2018 Jul 20)**.
23. Popovici J, Kao S, Eal L, Bin S, Kim S, Ménard D. Reduced polymorphism in the Kelch propeller domain in *Plasmodium vivax* isolates from Cambodia. Antimicrob Agents Chemother. 2015;59:730–3. https://doi.org/10.1128/AAC.03908-14 **(epub 2014 Nov 10)**.
24. Russo G, L'Episcopia M, Menegon M, Souza SS, Dongho BGD, Vullo V, Lucchi NW, Severini C. Dihydroartemisinin-piperaquine treatment failure in uncomplicated *Plasmodium falciparum* malaria case imported from Ethiopia. Infection. 2018;46:867–70. https://doi.org/10.1007/s15010-018-1174-9 **(epub 2018 Jul 6)**.
25. WHO. Eliminating malaria. 2016. http://www.who.int/malaria/publications/atoz/eliminating-malaria/en/.