



Original article

Tafenoquine for malaria prophylaxis in adults: An integrated safety analysis



Anne Novitt-Moreno^a, Janet Ransom^a, Geoffrey Dow^{b,*}, Bryan Smith^b,
Lisa Thomas Read^c, Stephen Toovey^d

^a Fast-Track Drugs & Biologics, North Potomac, MD 20878, USA

^b 60° Pharmaceuticals LLC, Washington DC 20036, USA

^c United States Army Medical Materiel Development Activity (USAMMDA), Ft Detrick, MD 21702, USA

^d Pegasus Research, 4103 Bottmingen, Switzerland

ARTICLE INFO

Article history:

Received 26 April 2017

Received in revised form

5 May 2017

Accepted 6 May 2017

Available online 8 May 2017

Keywords:

Tafenoquine

Malaria

Safety

Tolerability

8-aminoquinoline

Adverse events

ABSTRACT

Background: Tafenoquine is a new prophylactic antimalarial drug. The current analysis presents an integrated safety assessment of the Tafenoquine Anticipated Clinical Regimen (Tafenoquine ACR) from 5 clinical trials, including 1 conducted in deployed military personnel and 4 in non-deployed residents, which also incorporated placebo and mefloquine comparator groups.

Methods: Adverse events (AEs) were coded according to the Medical Dictionary for Regulatory Activities (MedDRA[®], Version 15.0) and summarized. Among all subjects who had received the Tafenoquine ACR, safety findings were compared for subjects who were deployed military personnel from the Australian Defence Force (Deployed ADF) versus non-deployed residents (Resident Non-ADF).

Results: The incidence of at least one AE was 80.6%, 64.1%, 67.6% and 94.9% in the mefloquine, placebo, tafenoquine Resident Non-ADF and tafenoquine Deployed ADF groups, respectively. The latter group had a higher incidence of AEs related to military deployment. AEs that occurred at $\geq 1\%$ incidence in both tafenoquine sub-groups and at a higher frequency than placebo included diarrhea, nausea, vomiting, gastroenteritis, nasopharyngeal tract infections, and back/neck pain.

Conclusions: Weekly administration of tafenoquine for up to six months increased the incidence of gastrointestinal AEs, certain infections, and back/neck pain, but not the overall incidence of AEs versus placebo.

Clinical Trial Registration Numbers/ClinicalTrials.gov Identifiers: NCT02491606; NCT02488980; NCT02488902.

© 2017 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

Malaria, a protozoan infection that targets human erythrocytes, is a potentially fatal illness that is transmitted by Plasmodium-infected mosquitoes. In the US, the overall trend of malaria cases has been increasing, with 84% of patients requiring hospitalization [1]. In spite of the considerable risks associated with malaria, over 90% of US patients who developed malaria in 2013 had not adhered to a medically-advised chemoprophylaxis drug regimen [1].

Historically, mefloquine was once a favored prophylactic

antimalarial, due to its efficacy and convenient weekly dosing schedule [2]. However, mefloquine's association with adverse neuropsychiatric effects has prompted safety concerns [3] and has curtailed mefloquine's use by the US military [4]. As alternatives to mefloquine, doxycycline, atovaquone/proguanil, and primaquine all require daily dosing, which can decrease compliance, and all are associated with bothersome gastrointestinal side effects, among other safety problems [5–8]. Hence, due to the dosing inconvenience and safety drawbacks of existing prophylactic antimalarials, a safe and effective alternative drug has been sought.

Tafenoquine is a primaquine analog being developed for malaria prophylaxis in adults. Like primaquine, tafenoquine is an 8-aminoquinoline; however, its half-life of ~2 weeks is considerably longer, allowing for weekly dosing [8]. Tafenoquine is active against Plasmodium parasites *in vitro* and has been tested successfully

* Corresponding author. 60° Pharmaceuticals LLC, 1025 Connecticut Ave NW, Suite 1000, Washington DC 20036, USA.

E-mail address: Geoffdow@60degreespharma.com (G. Dow).

against malaria in animal models [9]. In man, the anticipated clinical regimen (ACR) of tafenoquine for malaria prophylaxis is 200 mg orally (PO) daily for 3 consecutive days (the loading dose), followed by 200 mg PO once weekly. This regimen has proven effective for malaria prophylaxis in both non-immune [10] and semi-immune subjects [2].

For the Tafenoquine ACR, safety data comes from 5 clinical trials (Table 1), all previously published. These include: Study 033, a randomized, double-blind, active-controlled trial of tafenoquine vs. mefloquine in non-immune Australian Defence Force (ADF) soldiers deployed to East Timor (now Timor Leste) [11]; Studies 030, 043, and 45, all randomized, double-blind, placebo-controlled trials of tafenoquine in residents of malaria endemic regions of Africa [2,12,13]; and Study 057, a randomized, double-blind, placebo-controlled safety study of tafenoquine in healthy adult residents of the United States (US) or the United Kingdom (UK) [14]. Because tafenoquine like primaquine [15] can cause hemolysis in individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency, these clinical trials have excluded G6PD-deficient subjects, as well as pregnant women. Of the 5 trials, only Study 033 lacked a placebo control group for ethical and operational reasons [10].

A goal of the present analysis was to present an integrated safety and tolerability assessment of the Tafenoquine ACR across the 5 studies in which it was utilized (Table 1). To assure a uniform approach to adverse event (AE) coding, this analysis employed a unified, updated, and consistent coding system for AEs. In addition, targeted analyses were performed to allow for safety comparisons between subgroups that were potentially impacted by disparate extrinsic factors, especially military deployment under warlike conditions.

2. Methods

2.1. Ethical approval and subject consent

Descriptions of the ethical approval process and subject consent

procedures for each study are provided in the individual study publications. Briefly, study protocol and consent forms were reviewed and approved by one or more of the following scientific and ethical review boards: the Scientific Steering and Ethical Review Committee of the Kenya Medical Research Institute (Studies 030 and 043); the Ghanaian Ministry of Health (Study 045); the Australian Defence Medical Ethics Committee (Study 033); and the institutional review boards of the Walter Reed Army Institute for Research (Study 043) and the US Army (all studies). In trials conducted in Africa, local approval of the study was granted by traditional chiefs and community leaders. Tribal language consent forms were read by or to every prospective subject, and informed affirmation or informed consent was obtained from those residents wishing to participate. In studies 033 and 057, subjects provided informed consent based on study information provided in English.

2.2. Conduct of the studies

Detailed descriptions of the screening, randomization, drug administration, and clinical assessments employed in the 5 studies have been provided previously [2,11–14]. All 5 studies included healthy adults who were not G6PD deficient as determined by pre-study testing. All females were non-pregnant and non-lactating. Good health was verified by medical history, physical examination, and clinical laboratory testing [complete blood count (CBC), serum biochemistry, dipstick urinalysis]. For African studies where antimalarial pre-treatments were administered (Studies 030, 043, and 045), Giemsa-stained thick and thin blood smears were performed to confirm parasite clearance prior to initiating study medications. All study drugs were administered with a meal. Safety assessments included reports of AEs; abnormalities in CBC, methemoglobin levels, and serum biochemistry; and urinalysis. Also, based on sporadic reports of mild elevations of serum creatinine in Study 033, changes in glomerular filtration rate (GFR) by iothalamate clearance were assessed in all subjects in Study 057 [14]. In addition, targeted ophthalmologic assessments were

Table 1
Overview of Study design: Clinical Trials that Assessed the Safety and Tolerability of the Prophylactic Anticipated Clinical Regimen (ACR) of Tafenoquine.

	Study 030	Study 043 ^a	Study 045 ^a	Study 033	Study 057
Year(s) Conducted	2000	1997	1998	1999–2000	2003–2006
Study Design ^b	R, DB, PC, AC	R, DB, PC	R, DB, PC, AC	R, DB, AC	R, DB, PC
Parameters Assessed	Safety and Efficacy	Safety and Efficacy	Safety and Efficacy	Safety and Efficacy	Safety
Population Characteristics	Healthy adult residents of malaria-endemic area	Healthy adult residents of malaria-endemic area	Healthy adult residents of malaria-endemic area	Healthy non-immune Australian military population (ADF) deployed to malaria-endemic area	Healthy adult residents of US and UK
Study Location	Nyanza Province, Kenya	Nyanza Province, Kenya	Kassena Nankana District, Ghana	Bobonaro District and capitol (Dili) of East Timor (now Timor Leste)	Maryland, USA and Berkshire, UK
Pre-Treatments Administered ^c	Halofantrine 250 mg × 3 days	Halofantrine 250 mg × 3 days	Quinine 10 mg/kg tid x 4 days, then doxycycline 100 mg bid x 7 days and Primaquine 30 mg × 14 days	None	None
No. Subjects:					
TQ-ACR ^d	104	55	93	492	81
MQ ^e	101	0	46	162	0
Placebo	101	61	94	0	39
Duration of Study	24 weeks	10–15 weeks	13 weeks	26 ± 4 weeks	24 weeks
Drug Dosing					
Safety Follow-up after Study Drug Dosing	4 weeks	4 weeks	4 weeks	24 weeks	24 weeks

^a Tafenoquine doses other than the Anticipated Clinical Regimen (ACR) were also administered in this study. Only information for the ACR group is reported here.

^b R = Randomized, DB = Double-Blind, AC = Active Comparator (Mefloquine), PC=Placebo-Controlled.

^c Pre-treatments were given to eradicate any pre-existing parasitemia in the African studies. Study drug administration commenced 4–5 days after pre-treatments ended.

^d TQ-ACR = Tafenoquine Anticipated Clinical Regimen of 200 mg × 3 days, then 200 mg weekly.

^e MQ = Mefloquine 250 mg × 3 days, then 250 mg weekly.

Download English Version:

<https://daneshyari.com/en/article/5670654>

Download Persian Version:

<https://daneshyari.com/article/5670654>

[Daneshyari.com](https://daneshyari.com)