8-Aminoquinolines & Babesiosis – A Clinical Research and Safety Perspective

April 19, 2024

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Survey

Chronic Babesiosis: A Medical Mystery

BARRY MARSHALL
Proved *H. pylori* was an important human pathogen

1984 – Drank a batch of *H. pylori* to fulfil Koch's postulates*

1998 – "Everyone was against me, but I knew I was right"

2005 – Nobel Prize in Physiology

HENRY LINDNER

2022 - Proposed that *B. odocoilei* is an important cause of chronic fatigue symptoms in humans in the U.S.**

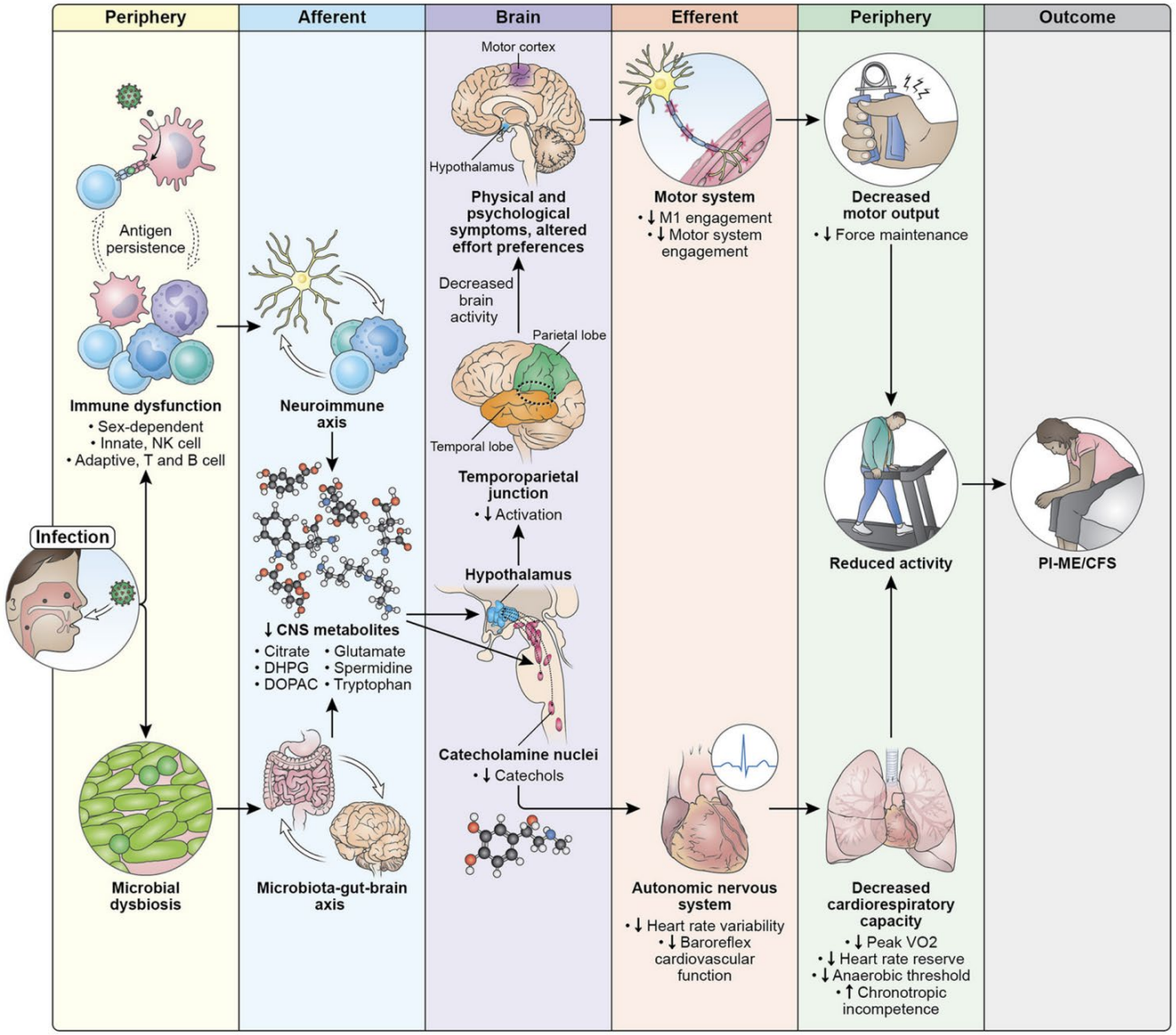
Currently unproven medical hypothesis…..

But anecdotally we encounter patients with chronic fatigue-like symptoms, a clinical diagnosis of babesiosis, and a prescription for tafenoquine

Marshall et al. MJA (1985) 142:436-439, ** Scientific presentation at ILADS 2022

Post-Infection “Long” Syndromes* – Babesia & 8AQs

- Are *Babesia* spp triggering pathogens?



- Can 8-AQs impact disease burden by killing organisms?
- Can this be done at safe and well-tolerated doses?

Walitt et al. Nature Communications (2024) 15:907

Disclaimer, Off-Label Use Statement & CME Goals

I am an Officer, Director & Shareholder in 60 Degrees Pharmaceuticals INC. 60 Degrees Pharmaceuticals has a commercial interest in tafenoquine for babesiosis.

Opinions expressed are speaker's own and do not necessarily reflect those of 60 Degrees Pharmaceuticals, INC or any of its stakeholders.

Tafenoquine is FDA-approved for malaria prevention (ARAKODA) and single dose treatment of *P. vivax* malaria in combination with chloroquine (KRINTAFEL). Tafenoquine is not approved for any indication in Europe. Primaquine (generic) is approved by FDA & EMEA for presumptive anti-relapse treatment of vivax malaria. I will be making reference to primaquine and tafenoquine by their generic names.

Presentation of safety data for tafenoquine for the prophylaxis indication included herein is not complete and physicians should refer to PI (www.arakoda.com)

Neither tafenoquine or primaquine has been proven to be effective for treatment or prevention of babesiosis and neither molecule is approved by the FDA or EMEA for such indications.

This presentation will address the data from the scientific literature relating to 8-aminoquinolines supporting the scientific hypothesis that tafenoquine might provide benefit for babesiosis, and a research program directed towards that goal.

<u>CME goals are:</u>

- Development history, pharmacology, and mode of action of 8-aminoquinolines
- Case study review of tafenoquine and primaquine use in babesiosis patients
- Highlights of safety profile of the FDA-approved prophylactic dosing regimen of tafenoquine
- Research gaps and future clinical trials

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The forward-looking statements contained in this communication are based on knowledge of the environment in which the Company currently operates and are subject to changed based on various important factors that may affect the Company's operations, growth strategies, financial results and cash flows, and as well as other factors beyond the Company's control as of the date of this presentation.

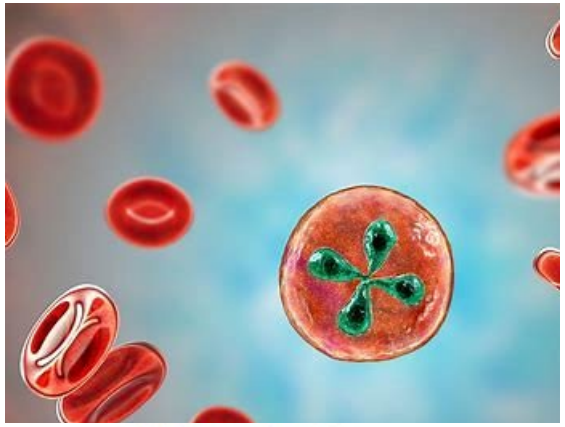
Important factors that could cause our actual results and financial conditions to differ materially from those indicated in the forward-looking statements include, among others, the following: there is substantial doubt as to our ability to continue on a going-concern basis; we might not be eligible for Australian government research and development tax rebates; if we are not able to successfully develop, obtain FDA approval for, and provide for the commercialization of non-malaria prevention indications for Tafenoquine (Arakoda or other regimen) or Celgosivir in a timely manner, we may not be able to expand our business operations; we cannot guarantee our ability to conducted successful clinical trials; and we have no manufacturing capacity which pits at risk of lengthy and costly delays of bringing our products to market. More detailed information about the Company and the risk factors that may affect the realization of forward-looking statements is set forth in the Company's filings with the Securities and Exchange Commission (SEC), including our Annual Report on Form 10-k and our subsequent Quarterly Reports on Form 10-Q. Investors and security holders are urged to read these documents free of charge on the SEC's website at www.sec.gov. As a result of these matters, changes in fact, assumptions not being realized or other circumstances, the Company's actual results may differ materially from the expected results discussed in the forward-looking statements contained in this presentation.

In light of these risks, uncertainties and assumptions, you should not place undue reliance on these forward-looking statements, which speak only as of the date of this presentation. Although we believe our expectations are based on reasonable assumptions, we can give no assurance that our expectations will materialize. Unless required by law, we undertake no obligation to update or revise any forward-looking statements, whether as a result of new information, future events, or otherwise.

Babesiosis & 8-Aminoquinolines
Why Do We Care?

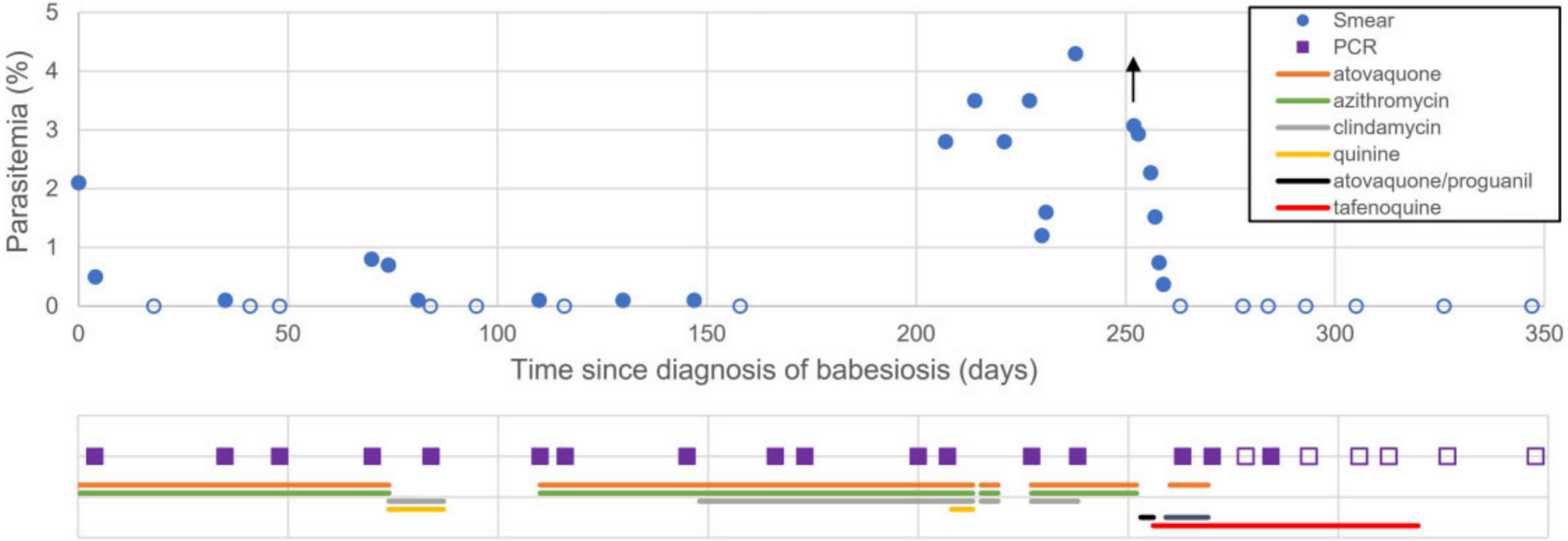
About Babesiosis*

- Tick-borne disease caused by protozoan parasites of the genus *Babesia*
- Invades red blood cells causing:
  - Non-specific flu-like symptoms, anemia
  - Potential severe complications
  - Death (1.6% mortality rate in hospitalized patients/10% in those with cardiac complications)
  - May be refractory to treatment in immunosuppressed patient
- Common in Mid-West and North-Eastern U.S, parts of Europe
  - Geographic range expanding and incidence increasing
- Common coinfection with Lyme disease (10% of cases in U.S.)
- One of the common co-infections managed during treatment of post-treatment Lyme disease



More information at: CDC - Babesiosis

Case Study #1*



- 80 yo RI resident
- History of Type II diabetes, cold agglutinin disease and monoclonal B-cell lymphocytosis requiring rituximab and bendamustine
- Presented with febrile illness and babesiosis was confirmed by microscopy (2.1% parasitemia) and *B. microti* PCR
- Cure achieved after tafenoquine administration (600 mg load then 300 mg/week for 9 weeks)

*Rogers et al 2023. CID 76:741-744. doi: 10.1093/cid/ciac473

Babesiosis Patient Volume and Standard of Care (Second Cut)

- **At risk populations are potentially large but poorly defined in medical literature**
- **Standard of care treatment regimens for babesiosis are long, complicated, or don't exist**

Potential Indications	Potential Patient/Prescription Volume (U.S.)	Existing Standard of Care
Treatment	~ 38,000*	First Line: Azithromycin + atovaquone for 10 days or > 6 weeks if immunosuppressed**
Prevention Post Exposure (tick bites) Pre-Exposure	 Up to 400,000*** Up to 1.2 million #	Insect repellents, protective clothing
Chronic Disease Low End (new/cumulative based on Lyme coinfection) High End (if prominent causative agent of CFS)	 Up to 9,500&/190,000& Millions	No specific FDA-approved treatments

* Total babesiosis patients in U.S. may be approximately 47,000 per year based on the observation that there are 476,000 lyme infections each year, 10% of which are also babesiosis coinfections (Krause et al JAMA 1996;275:1657-16602, Krugeler et al *Emerg Infect Dis* 2021;27:616-61). Approximately 80% of adult babesiosis infections are symptomatic, yielding a treatable patient pool of about 38,000. There are up to 1,400 hospitalized cases per year in the U.S (Bloch et al 2022 Nov 8;9(11):ofac597. doi: 10.1093/ofid/ofac597. eCollection 2022 Nov.), an unknown (i.e. < 1,400) number of of which represent immunosuppressed patients. ** According to IDSA guidelines.*** Based on the observation that 50,000 tick bites are treated in US emergency rooms each year, representing about 12% of the total number (Marx et. al., MMWR 2021;70:612-616) # Determined on a pro rata basis using company estimates of malaria market as being 550,000 three-week prescription per year amongst an at-risk travel population of ~ 10 million, versus a seasonally adjusted at-risk population for *B. microti* infection in the U.S. of ~ 22.5 million. &Approximately 10% (based on coinfection rate) of the number of new/cumulative case incidence in U.S. in 2020 (estimated cumulative PTLDS cases from Delong et al. 2019 Apr 24;19(1):352. doi: 10.1186/s12889-019-6681-9, new cases of PTLDS calculated by multiplying the number of new Lyme cases (476,000) per year * 20% treatment failure for acute cases)

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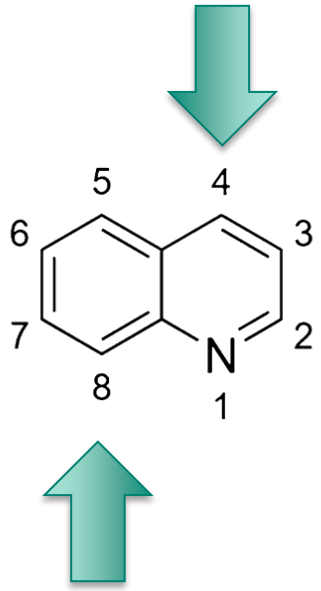
8-Aminoquinolines & Development Rationale for Malaria

What is an 8-aminoquinoline?

4-Amino and 4-Aminoalcohol antimalarials contain an N-containing side chain at the 4-position of the quinoline ring



8-Aminoquinoline antimalarials contain an N-containing side chain at the 8-position of the quinoline ring

Examples of 8-aminoquinolines used in clinical practice prior to availability of tafenoquine

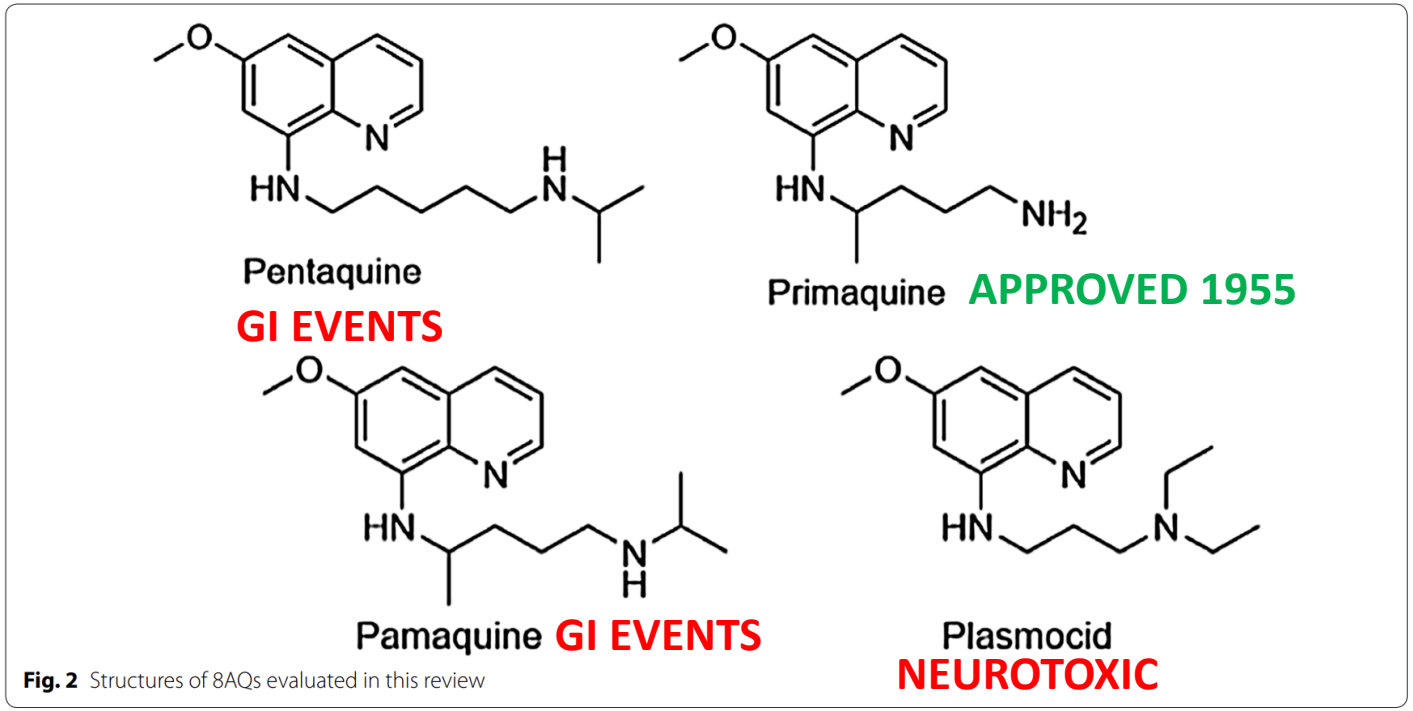
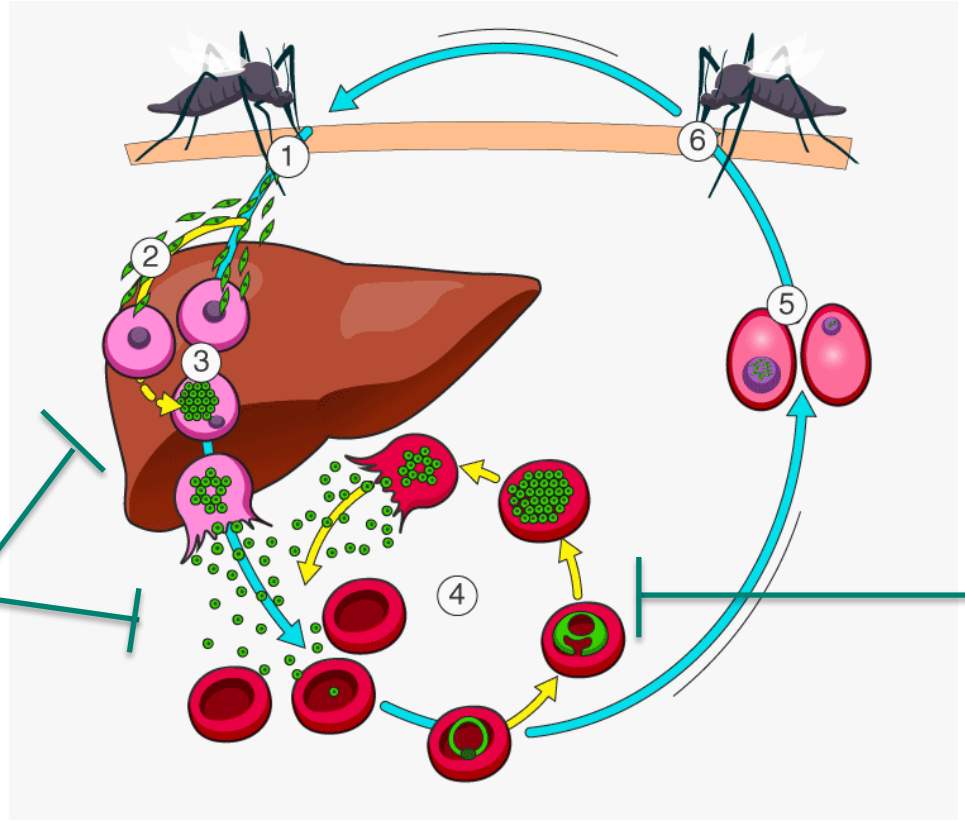


Fig. 2 Structures of 8AQs evaluated in this review

Malaria Life Cycle Targets of 4 and 8-Aminoquinolines

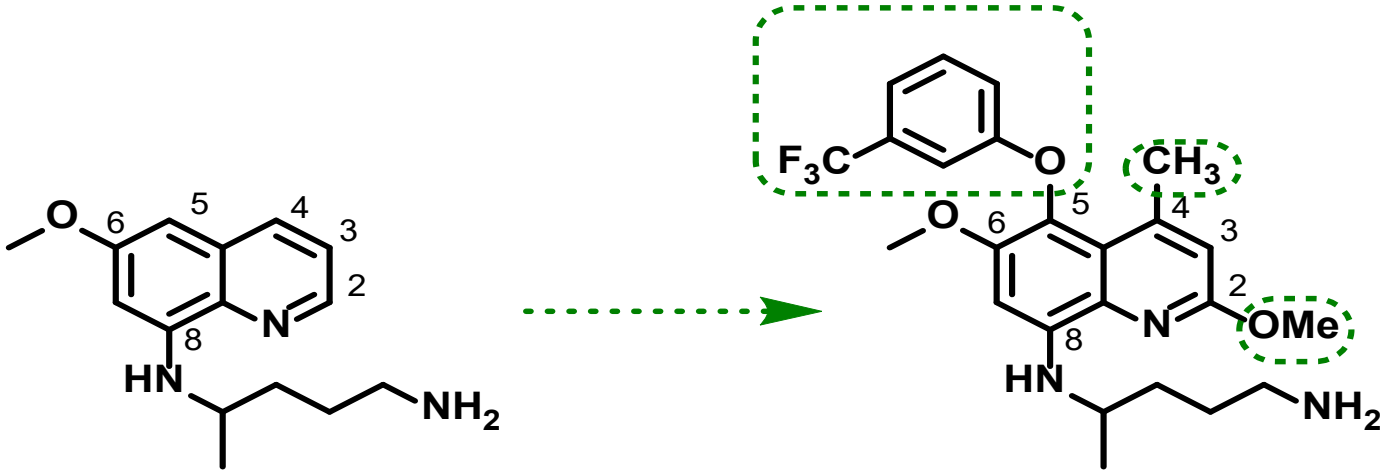


8AQs*

4AQs

- * Degree of inhibition of blood stage inhibition differs by type of 8-aminoquinoline and malaria species
- Prevention of malaria requires killing of all liver stages and/or all blood stages

Rationale for Tafenoquine as Chemoprophylactic Antimalarial



PRIMAQUINE

- Half-Life: 6h
- Kills hepatic stages
- Weak activity against blood stages

TAFENOQUINE

- Half-Life: 14 days
- Kills hepatic stages
- Kills blood stages in vivo

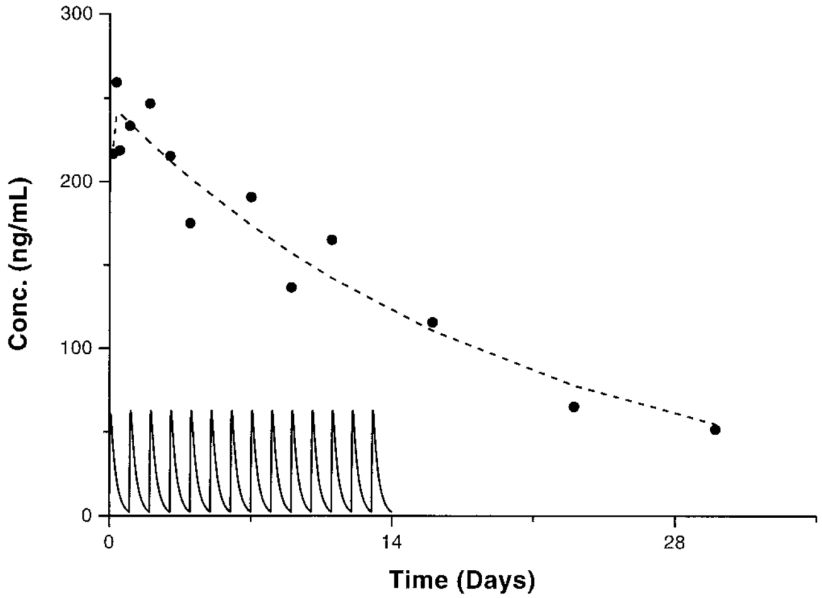


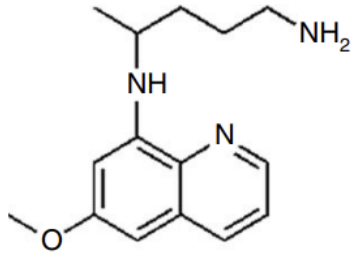
FIGURE 3. Observed (●) and fitted (– – –) plasma concentrations resulting from a single 600-mg oral dose of WR 238605 versus modeled concentrations from 14 daily 15-mg doses of primaquine (–).

8-Aminoquinoline Mode of Action (Babesiosis & Malaria & Host)

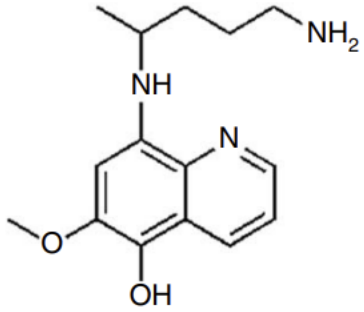
Primaquine MOA for Malaria*

- Site specific induction of oxidative stress

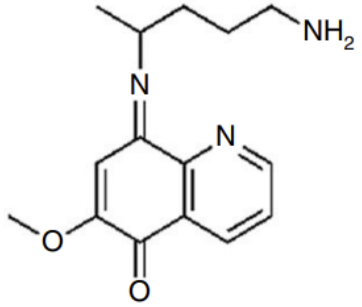
PQ

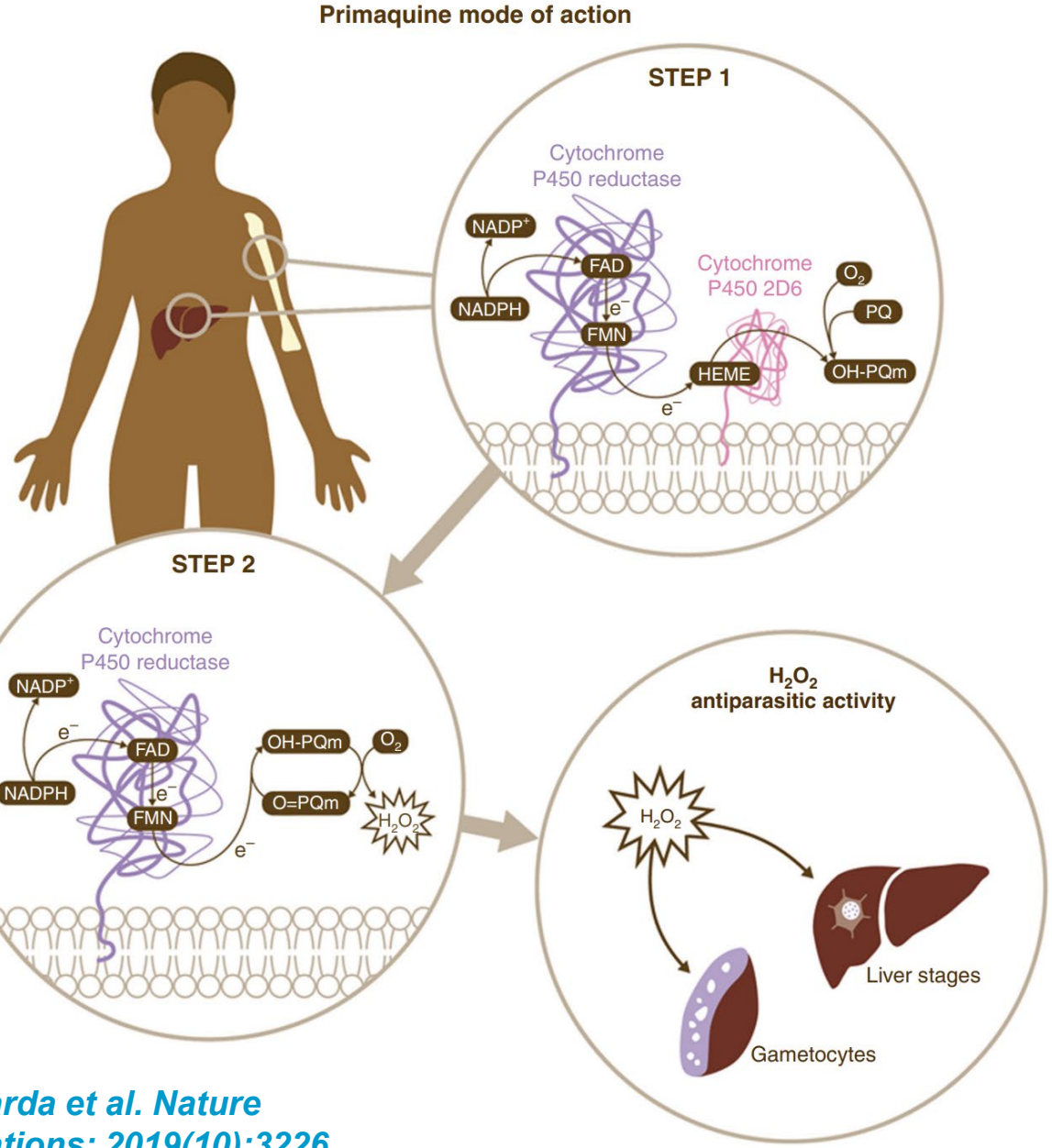


OH-PQm



O=PQm

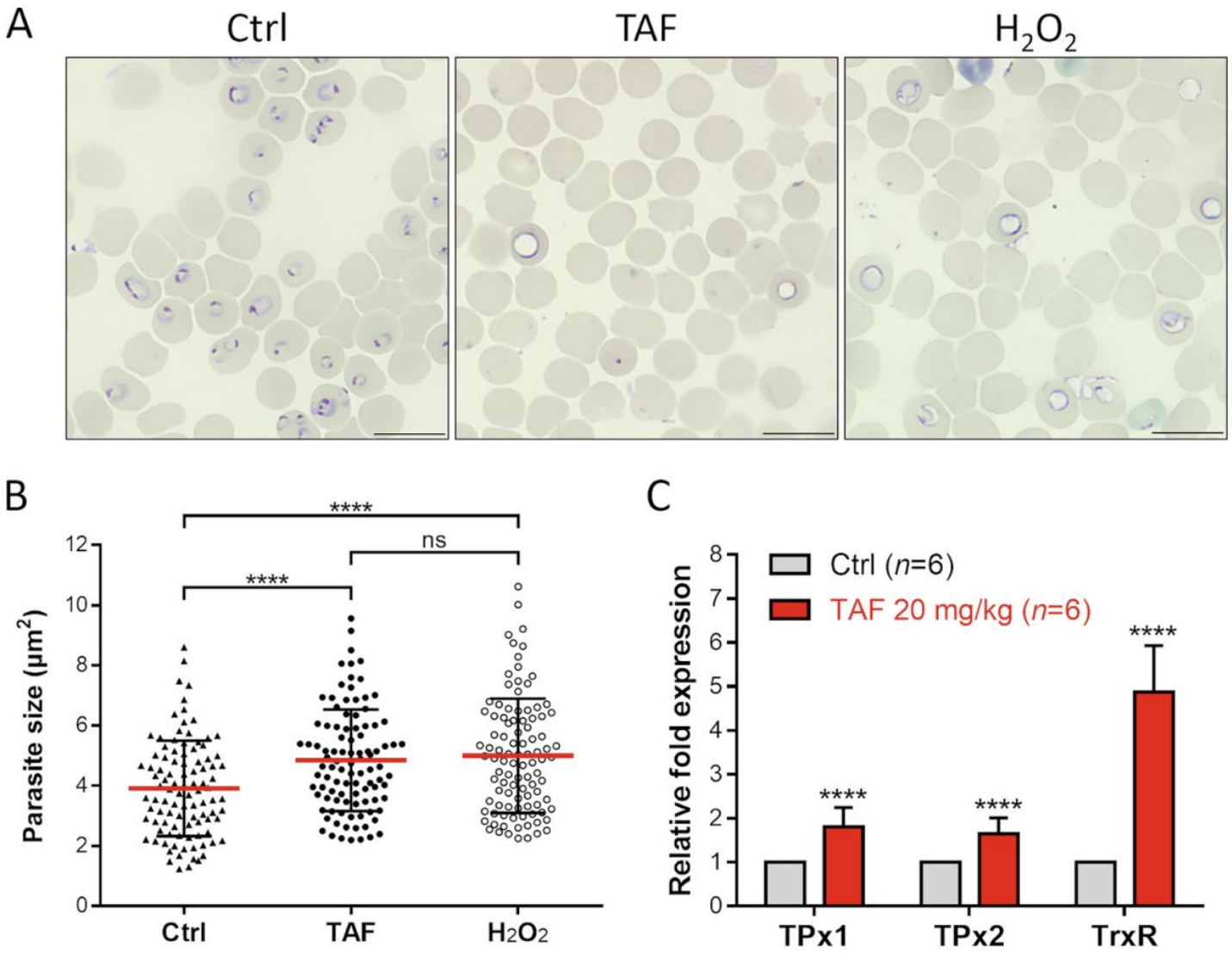




Cammarda et al. Nature Communications: 2019(10):3226

Tafenoquine MOA for Babesiosis*

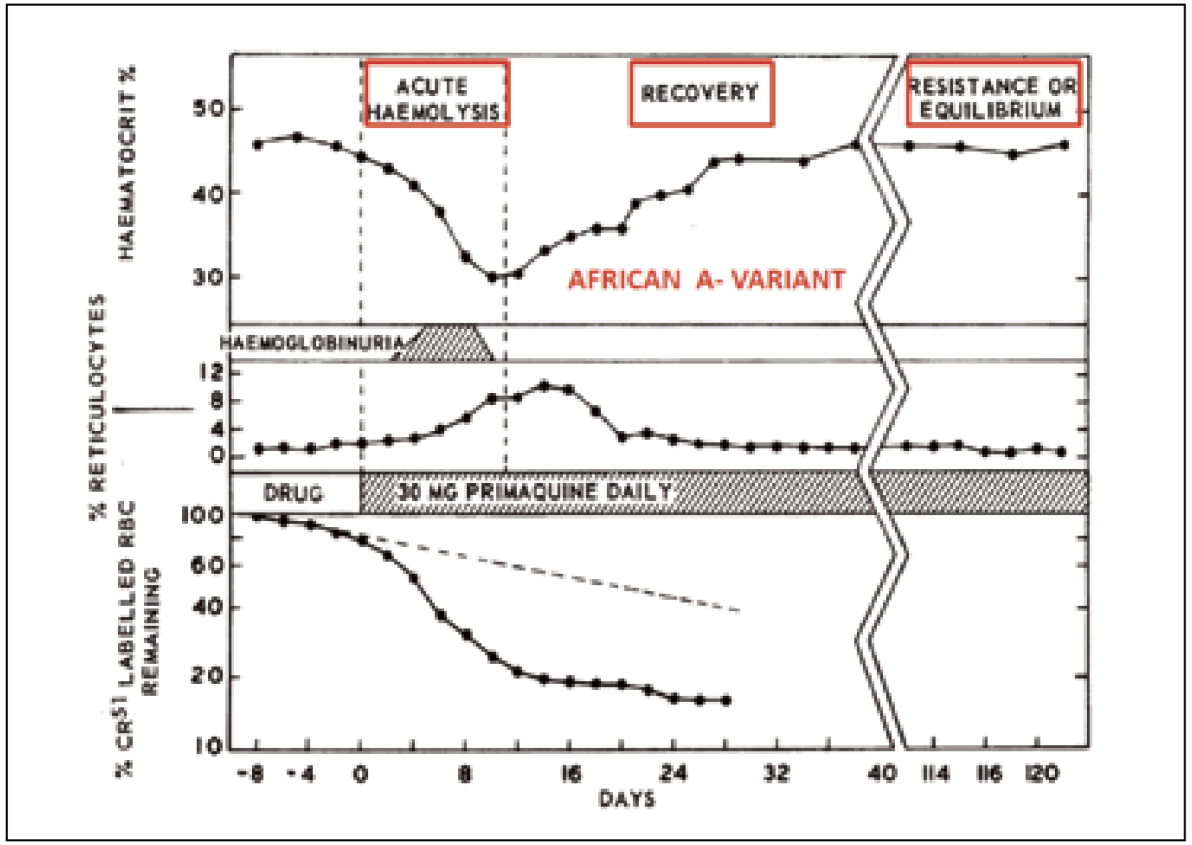
- Tafenoquine induces oxidative stress in *Babesia* parasites *in vivo*

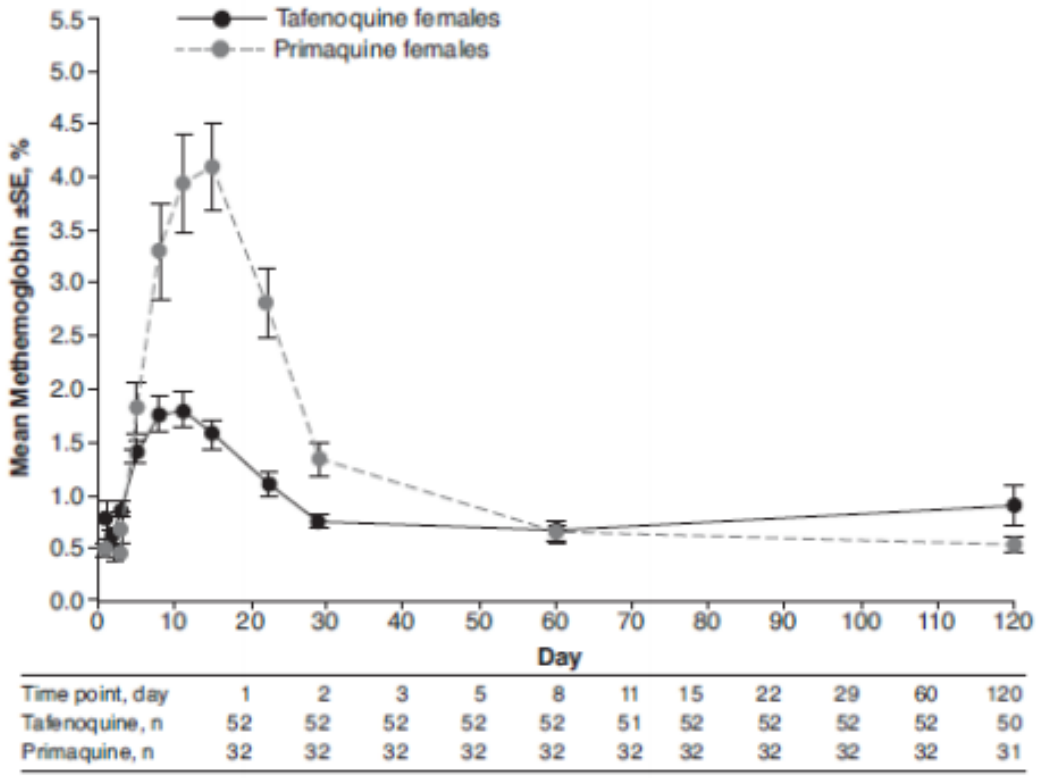


*Liu et al AAC 2021:65(Issue 7);e00204-21

Oxidative Toxicity to Host*

- Host response to oxidative stress is adaptive at tolerated doses





Time point, day	1	2	3	5	8	11	15	22	29	60	120
Tafenoquine, n	52	52	52	52	52	51	52	52	52	52	50
Primaquine, n	32	32	32	32	32	32	32	32	32	32	31

- Hemolytic toxicity in G6PD deficiency
- Continuous dosing with 30 mg primaquine
- Transient methemoglobinemia
- 15 mg PQ for 14 days/300 mg TQ once

Adapted from Recht et al. Safety of 8-aminoquinoline antimalarials. WHO 2014 and published data from GSK's P. vivax program

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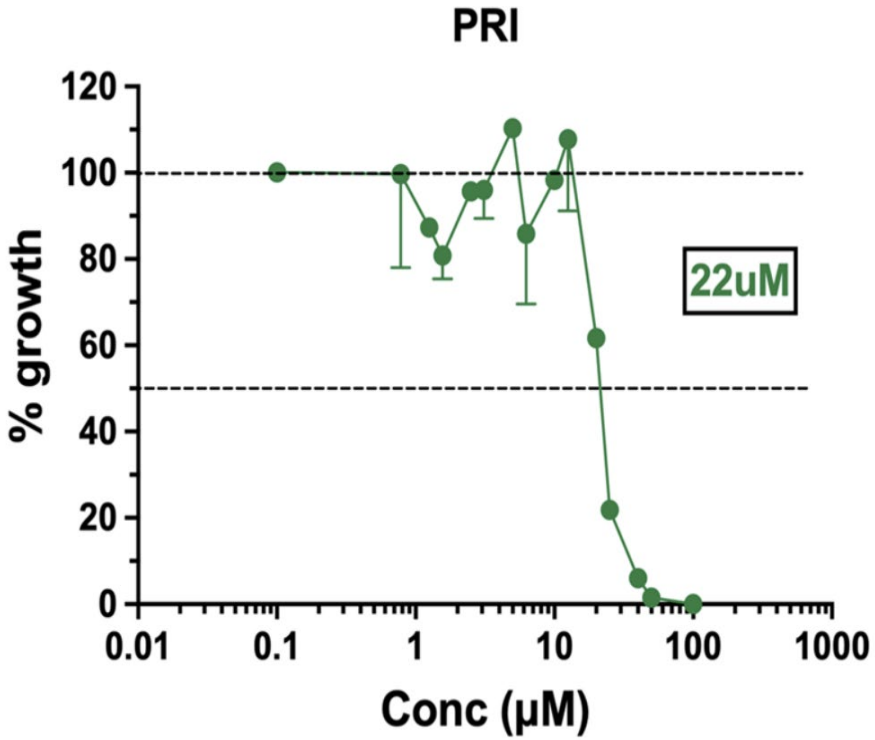
Non-Clinical Efficacy of 8-Aminoquinolines (Malaria and Babesiosis)

Primaquine is Active *In Vitro* (*B. bovis*) and *In Vivo* (*B. microti*-BALBc)*

Table 3. *In vivo* inhibitory rate of azithromycin, atovaquone, primaquine, and robenidine to *B. microti* from days 9 and 11 post-inoculation and the detection status of protozoan in blood thereafter

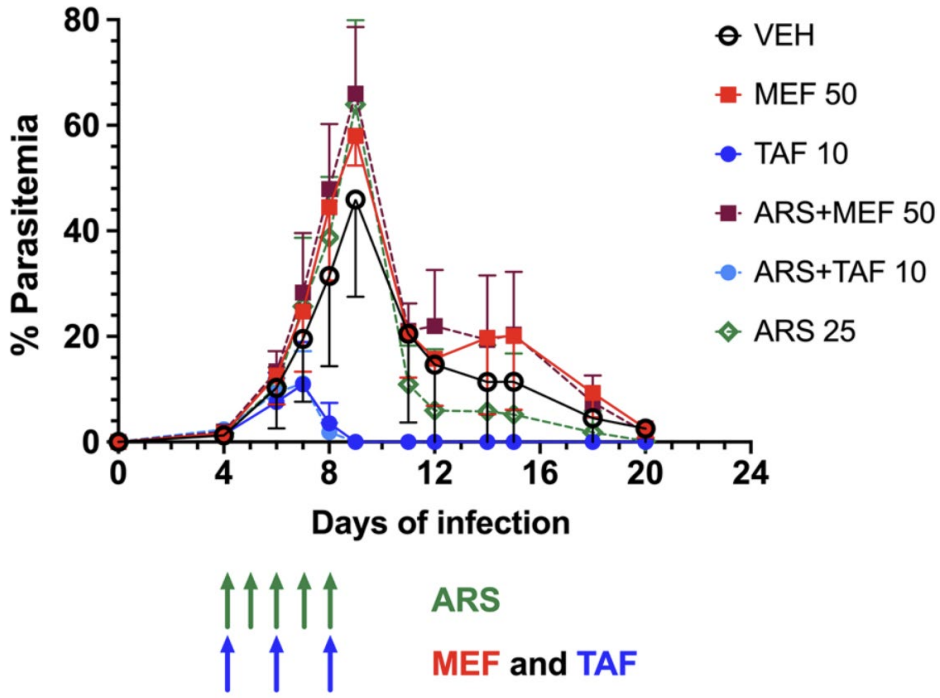
Drug	Dosage (mg/kg•day×day)	Mean inhibitory rate on the days PI[a] (%)		Detection status of *Babesia* on the days PI[b]						
		9	11	14	16	18	21	23	25	28
Azithromycin	25×4	74.82	81.90	D	D	N	N	N	N	N
	50×4	95.71	97.50	D	D	N	N	N	N	N
	100×4	94.72	99.00	D	D	N	N	N	N	N
Atovaquone	25×4	76.89	73.70	D	D	N	N	N	N	N
	50×4	86.80	76.90	D	D	N	N	N	N	N
	100×4	93.40	90.60	D	D	N	N	N	N	N
Primaquine	25×4	78.33	74.00	D	D	N	N	N	N	N
	50×4	89.56	97.20	D	D	N	N	N	N	N
	100×4	100.00	100.00	N	N	N	D	D	D	D
Robenidine	25×4	100.00	100.00	N	N	N	D	D	D	D
	50×4	100.00	100.00	N	N	N	N	N	D	D
	100×4	100.00	100.00	N	N	N	N	N	N	N

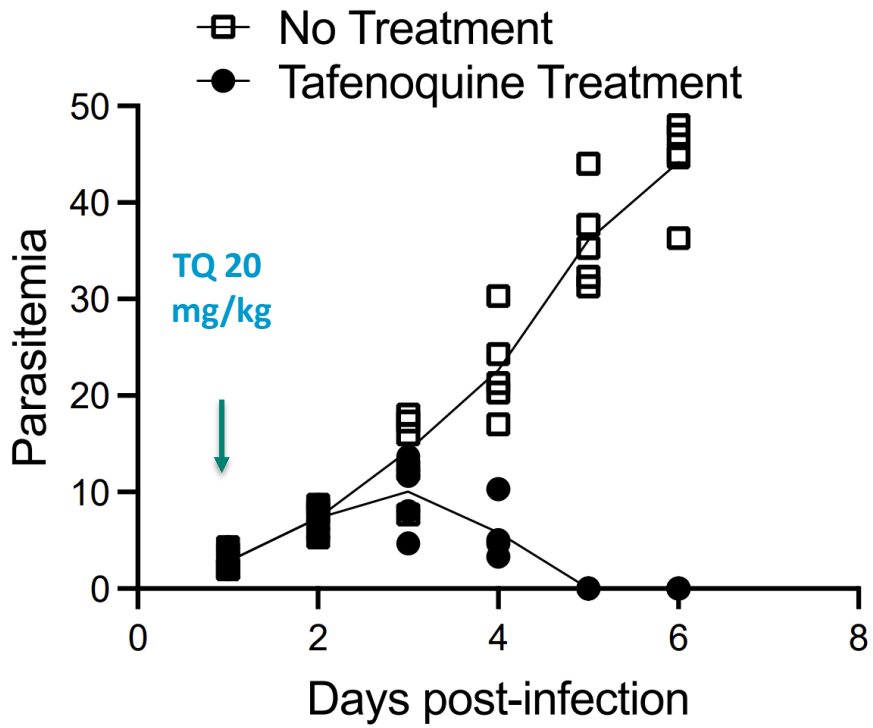
[a] Results are expressed as percent inhibition of EIR in treated animals compared to untreated controls on day 9 and day 11 post infection; [b] Results are expressed as detection status of *B. babesia* in treated animals from day 14 to day 28; PI: post infection; N: protozoans were not detected; D: protozoans were detected



**Yao et al J Infect Dev Ctries 2015; 9(9):1004-1010.doi:10.3855/jidc.5500; Carvalho et al. Parasites Vectors (2020) 13:362*

Tafenoquine – Efficacy Against *B. microti* in BALBc Mice*



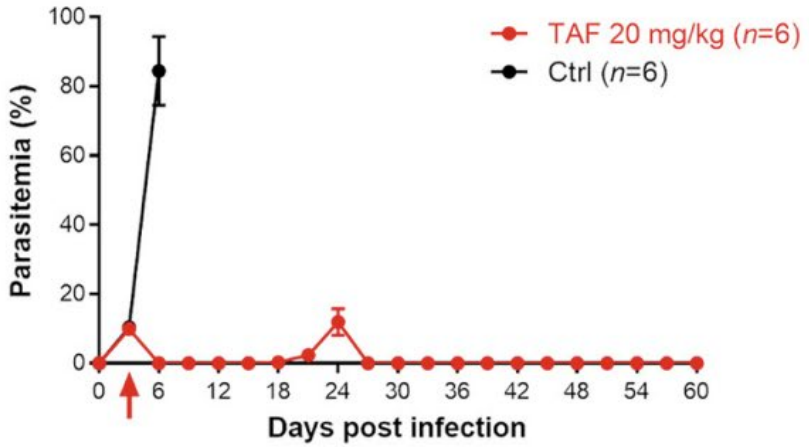


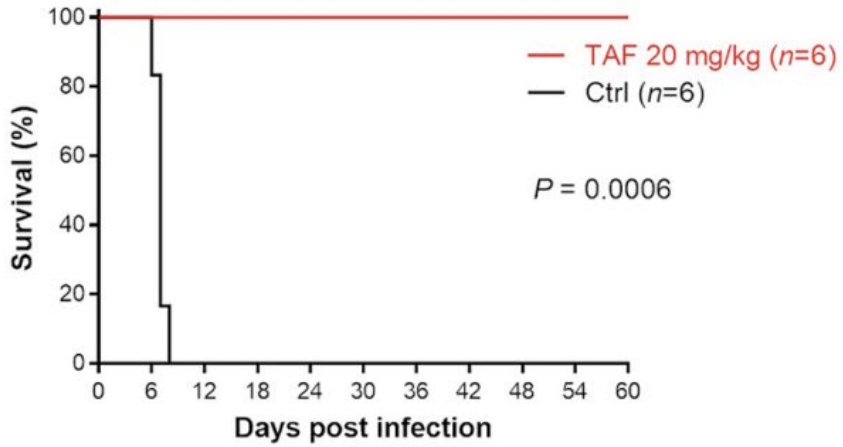
- Tafenoquine (20-30 mg/kg) rapidly clears parasitemia in BALBc mice

**Carvalho et al. Parasites Vectors (2020) 13:362*
and Mordue et al. 2023 Pathogens 12(9):1113. doi: 10.3390

Tafenoquine – Efficacy Against *B. microti* in Mice*

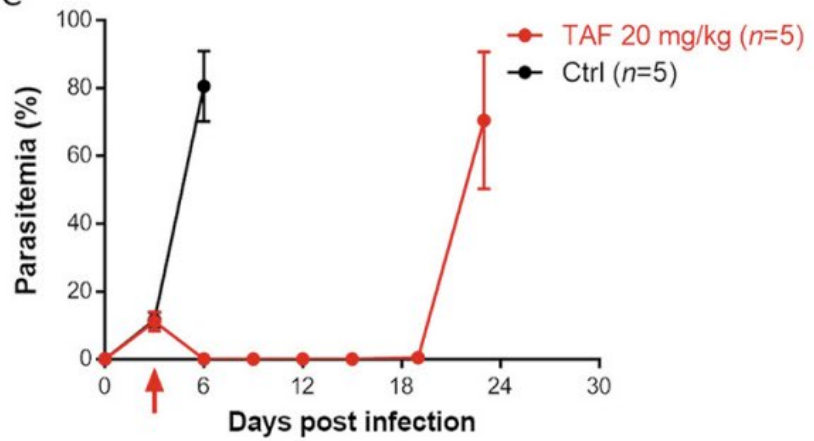
BALB-C - IMMUNOCOMPETENT





SCID - IMMUNOCOMPOMISED

C



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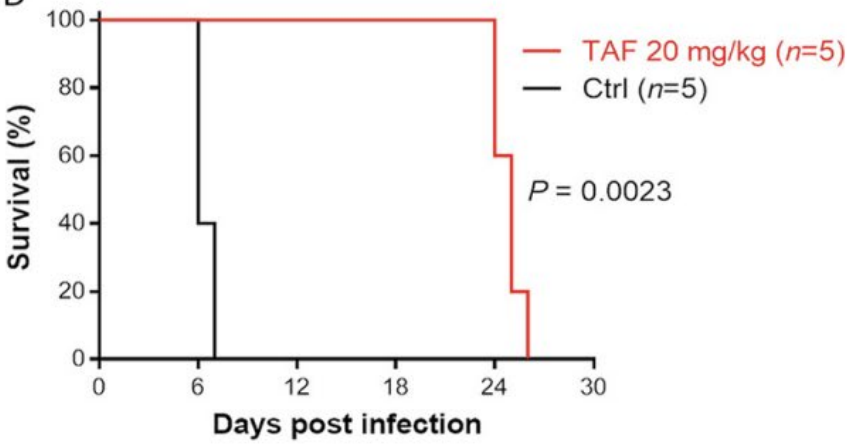
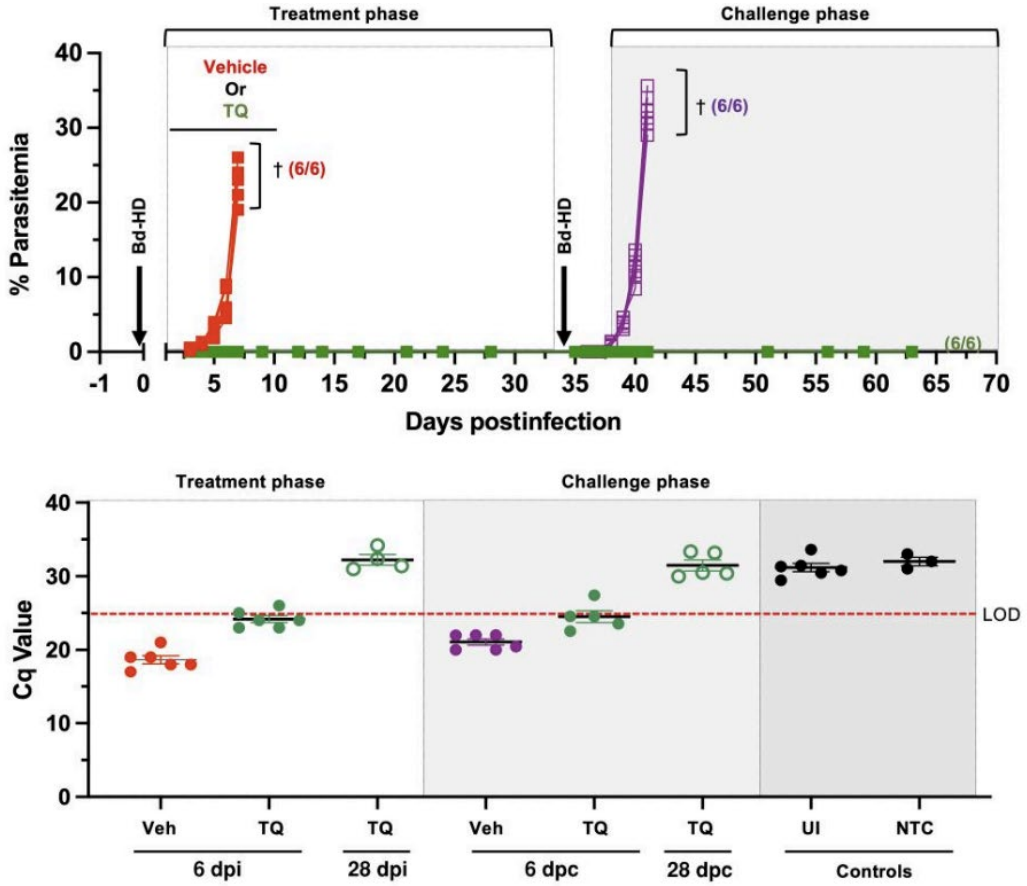
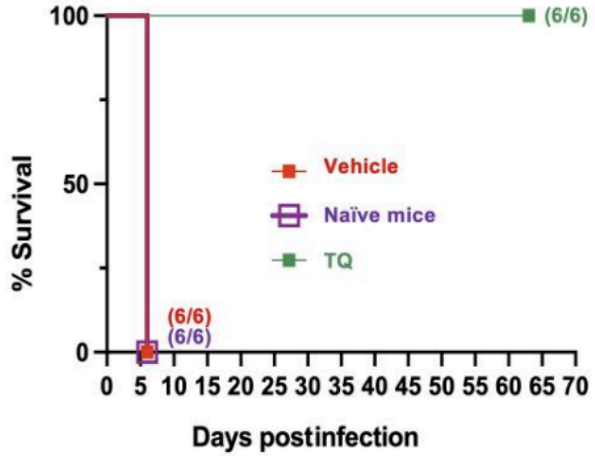


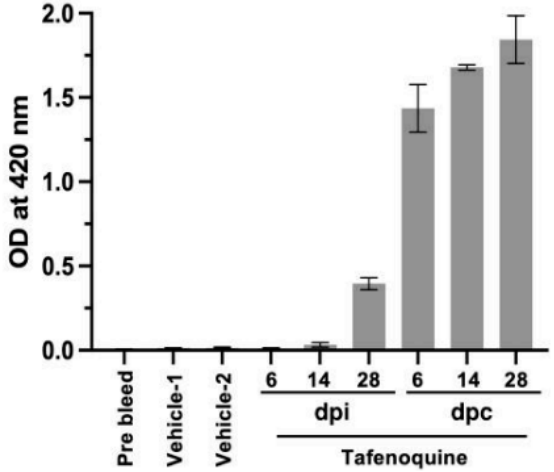
- Tafenoquine (20 mg/kg) rapidly clears parasitemia, induces self-limiting infection in immunocompetent mice
- Single dose tafenoquine rapidly clears parasitemia, but is insufficient to cure immunocompromised mice

Liu et al AAC 2021:65(Issue 7);e00204-21

Tafenoquine – Longer Regimens Confer Sterile Protection*







- Longer regimens of tafenoquine (10 mg/kg x 10) prevents establishment of, and clears, initial and repeat challenge with a lethal inoculum of *B. duncani*, allowing generation of protective IGG antibodies

Vydyam et al 2024. JID 229:161-172

Tafenoquine Against Murine Malaria*

CAUSAL PROPHYLAXIS (LIVER STAGES)

Table 1 The causal prophylactic activities of tafenoquine (TQ) and primaquine (PQ) by using real time *in vivo* image system (IVIS) following single dose (−1 or 0 day after inoculation) or daily oral administrations for 3 days multiple doses (−1, 0, and 1 day after infection) against challenge with 50,000 sporozoites of the ANKA strain of *P. berghei* intravenously in male C57BL/6 albino mice with positive and negative controls (n = 5–20 each)

Test agents	Dose (mg/kg)	Oral dose	Date of dosing	Suppression rate (%) IVIS*			Blood Infection by FCM*	Number of C57BL/albino mice			Delay in patency (days after onset in controls)	Effects
				24 h	48 h	72 h		Challenged	Protected completely	Causal prophylaxis		
Tafenoquine	10	3 days	−1, 0, 1	100	100	100	0/5	5	5	5/5	-	Full CP
	5	3 days	−1, 0, 1	90.4	100	100	0/13	13	13	13/13	-	Full CP
	2.5	3 days	−1, 0, 1	100	100	100	2/5	5	3	3/5	-	Partial CP
	1.25	3 days	−1, 0, 1	84.7	92.3	98.9	4/5	5	1	1/5	2,4,4,7	Suppression
	5	Single	−1	68.7	98.6	100	0/10	10	10	10/10	-	Full CP
	5	Single	0	66.0	91.1	98.5	4/5	5	1	1/5	4,2,4,9	Partial CP

- Tafenoquine 15-30 mg/kg is causally prophylactic

BLOOD SCHIZONTICIDAL

Table 3 Tafenoquine (TQ) wild-type (WT) dose-ranging studies using C57BL/6 mice

Day dose administered[a]	PQ dose (mg/kg)	No hepatic IVIS signal[b]	No asexual erythrocytic infection (parasitemia)[c]	No sexual erythrocytic infection (gametocytemia)[c]
Erythrocytic treatment model				
D4	5	NA	0/5	0/5
	10	NA	0/5	0/5
	20	NA	4/5	4/5

- Tafenoquine 20 mg/kg cured 80% of blood stage infections

Li et al 2014. Malar J 13:141. doi: 10.1186/1475-2875-13-141 and Milner et al 2016. Malaria J 15(1):588. doi: 10.1186/s12936-016-1632-8

600 mg Tafenoquine is Causally Prophylactic in Humans

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, May 1998, p. 1293–1294 Vol. 42, No. 5
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Prophylaxis of *Plasmodium falciparum* Infection in a Human Challenge Model with WR 238605, a New 8-Aminoquinoline Antimalarial

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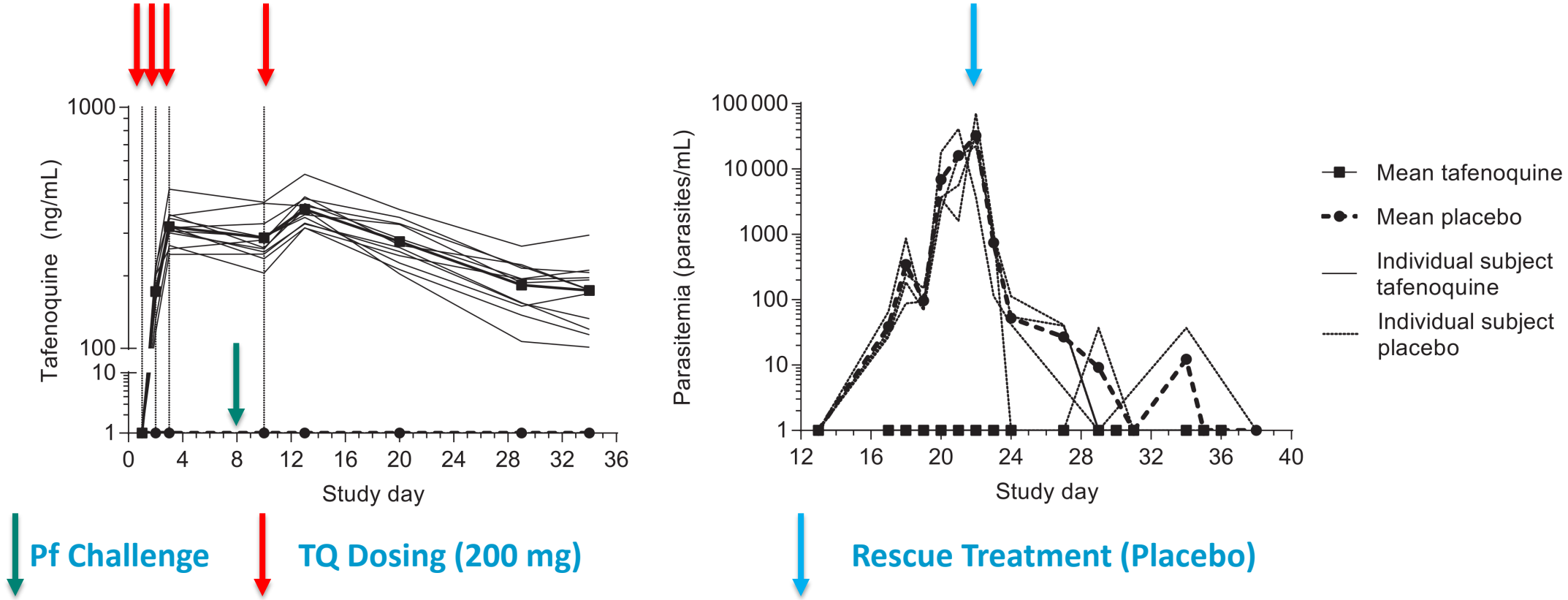
The prophylactic efficacy of WR 238605, a primaquine analog, was studied with a human *Plasmodium falciparum* challenge model. A single oral dose of 600 mg, administered 1 day prior to challenge, successfully protected three of four subjects. The fourth subject developed mild, oligosymptomatic malaria on day 31, with drug concentrations one-half of those in the protected individuals. WR 238605 appears to be a promising prophylactic drug for *P. falciparum* malaria.

800 mg Tafenoquine Prevents Establishment of Malaria Following Blood Stage Challenge*



- In this prophylaxis study parasitemia in the tafenoquine arm never increased above the detection limit by PCR

**McCarthy et al 2019 CID 69: 480-486*

1200 mg Tafenoquine Completely Clears Established *P. vivax* Infection*

- Adult *P. vivax* patients were randomized to receive 1200 mg tafenoquine or chloroquine/primaquine

- Tafenoquine cured all patients but parasite and gametocyte clearance times were slower than the chloroquine arm

Group	Daily dose	Day 1	Day 2	Day 3	Days 4–18
Tafenoquine	Tafenoquine 400 mg	▮▮	▮▮	▮▮	
	Chloroquine placebo	▯▯▯▯	▯▯▯▯	▯▯	
	Primaquine placebo				▯
Chloroquine/ primaquine	Tafenoquine placebo	▯▯	▯▯	▯▯	
	Chloroquine 1000 mg	▮▮▮▮	▮▮▮▮		
	Chloroquine 500 mg			▮▮	
	Primaquine 15 mg				▮

▮ Active treatment, number of capsules.

▯ Placebo, number of capsules.

Treatment	Parasite clearance time, h			Gametocyte clearance time, h			Fever clearance time, h		
	N	Mean (SD)	Median (range)	N	Mean (SD)	Median (range)	N	Mean (SD)	Median (range)
Tafenoquine	41	82.5 (32.3)	84.0 (12–156)	34	49.1 (33.0)	48.0 (0–156)	31	41.1 (31.4)	36.0 (0–108)
Primaquine/ chloroquine	24	40.0 (15.7)	36.0 (24–84)	19	22.7 (16.4)	24.0 (0–60)	18	24.7 (17.7)	24.0 (0–60)

**Fukuda et al 2017 PLoS One 12(11):e0187376*

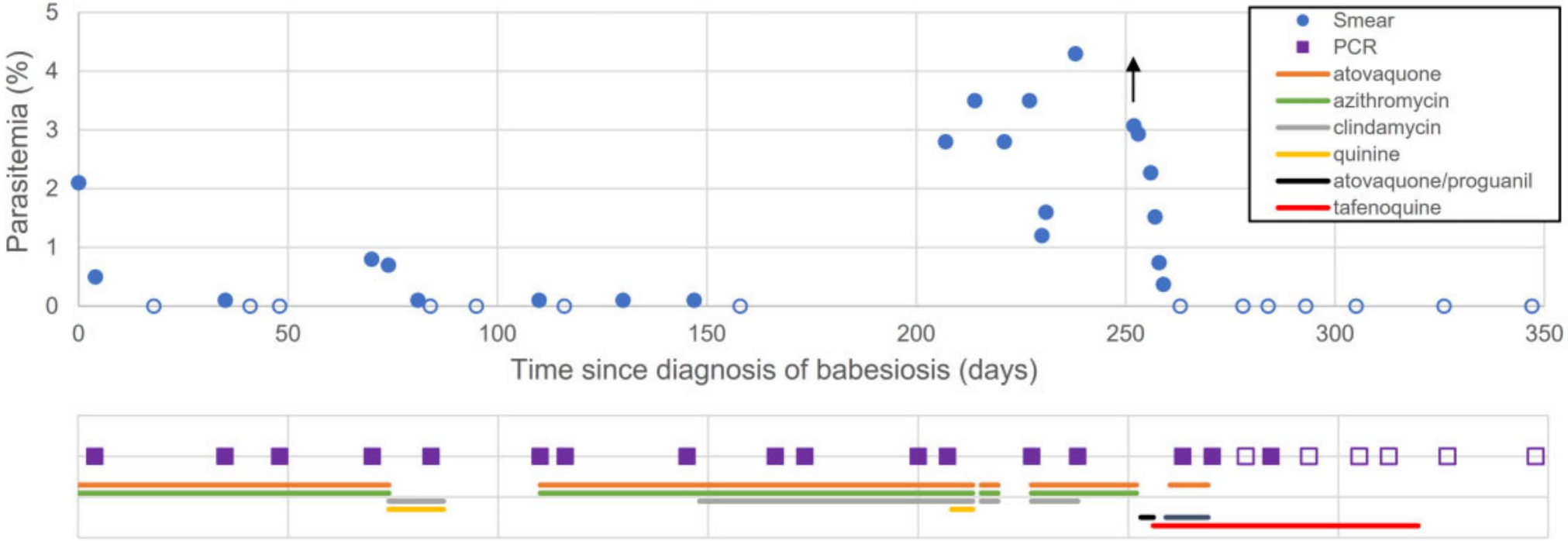
Use of 8-Aminoquinolines for Babesiosis (Practice of Medicine)

Primaquine

- Searched PUBMED using following terms: “Primaquine + babesiosis”
  - Single case study where a *B. microti* infection misdiagnosed as malaria was unsuccessfully treated with a combination of primaquine and dihydroartemisinin
  - Asuaga et al Emerg Infect Dis. 2018 Aug;24(8):1588-1589. doi: 10.3201/eid2408.180180

- Polled several investigators regarding use of primaquine for acute *B. microti* infection
  - Primaquine not actively used

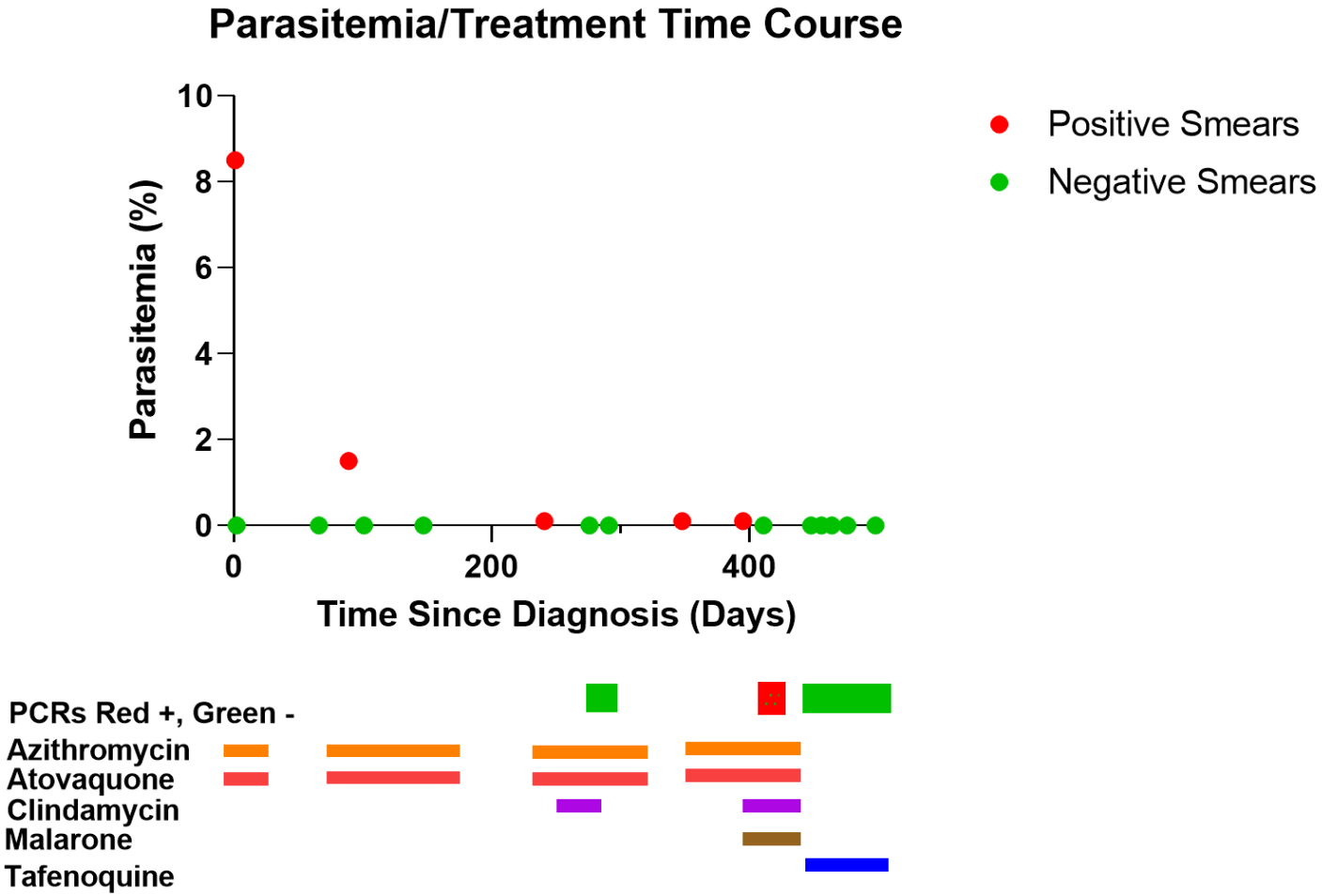
Tafenoquine Case Study #1*



- 80 yo RI resident
- History of Type II diabetes, cold agglutinin disease and monoclonal B-cell lymphocytosis requiring rituximab and bendamustine
- Presented with febrile illness and babesiosis was confirmed by microscopy (2.1% parasitemia) and *B. microti* PCR
- Cure achieved after tafenoquine administration (600 mg load then 300 mg/week for 9 weeks)

*Rogers et al 2023. CID 76:741-744. doi: 10.1093/cid/ciac473

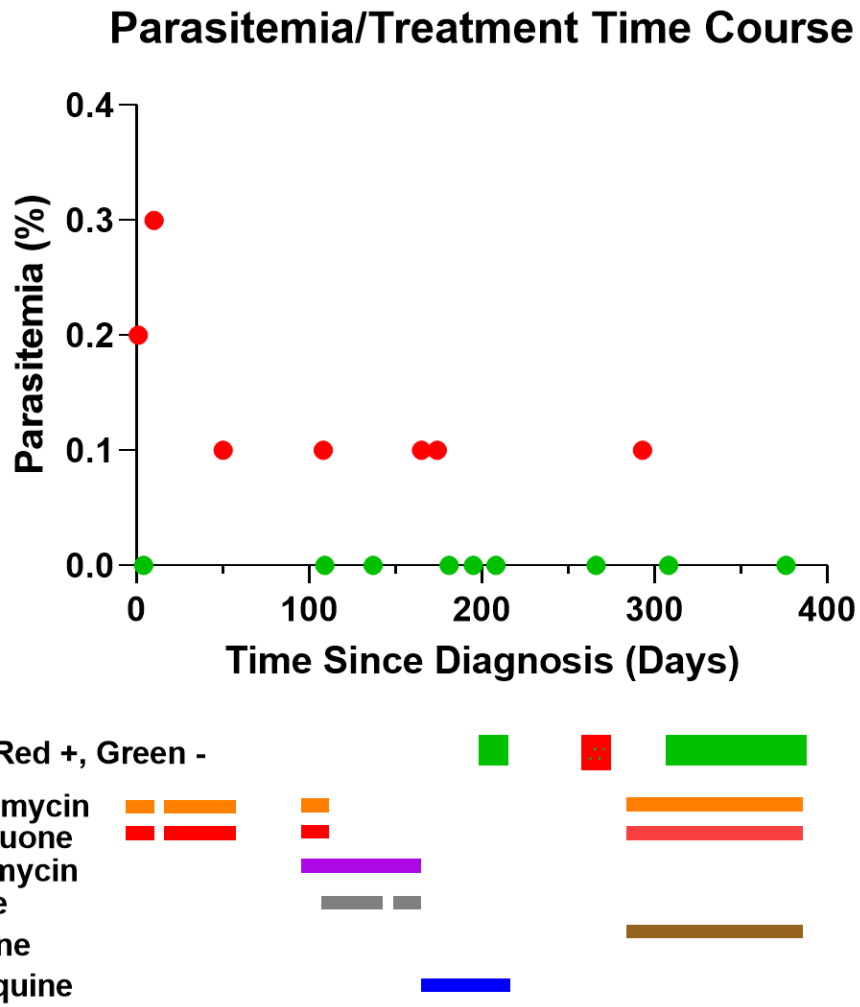
Tafenoquine Case #2*



- 36 yo male
- History of granulomatosis with polyangiitis. Treated two years prior with rifixumab
- Presented with febrile illness and babesiosis was confirmed by microscopy (8.5%)
- Patient was on 7.5 -20 mg prednisone at the time of first hospitalization – not considered to be immunosuppressed by investigators
- Cure achieved after tafenoquine administration (600 mg load then 200 mg weekly)
- Investigators stated that patient was not immunocompromised and seroconverted just prior to TQ administration

**Marcos et al 2022. IDCases 27:e01460. doi: 10.1016/j.idcr.2022.e01460.*

Tafenoquine Case #3*



**Prasad and Wormsner 2022. Pathogens 15:1051. doi: 10.3390/pathogens11091051*

- 74 yo female
- History of B-Cell lymphoma treated with 6 cycles of R-CHOP ending three years prior.
- History of polymyalgia rheumatica treated with 5 mg prednisone and toxclizumab ending 9 months prior.
- Hospitalized for cold autoimmune anemia treated with 60 mg prednisone tapered to 5 mg. Babesiosis was diagnosed by blood smear (0.2%).
- Rounds of azithromycin/atovaquone then clindamycin/quinine failed
- Tafenoquine (600 mg load, 200 mg for five weeks) cleared parasitemia (three negative PCRs) but was discontinued due to neutropenia:
  - Nadir 325/µl 5 days after discontinuation
  - Recovered to 1300/µl 12 days after discontinuation
- Cure of subsequent relapse was achieved with continuous azithromycin/atovaquone/malarone

Comments on Cases #1

- Clinical outcomes (as stated by investigators)
  - Case 1 – Cure
  - Case 2 – Unclear due to improving immune status and administration of other drugs
  - Case 3 – Relapse

- Comments on clinical outcomes
  - At least one negative PCR achieved in all cases
  - Decline in parasitemia consistent with animal studies and clinical experience with malaria

- Comments on neutropenia in Case 3
  - Lots of tafenoquine on board as neutrophil count increased from 325 to 1300/µl between day 5 and Day 12 following last dose of tafenoquine
    - Tafenoquine half-life is 17 days according to prescribing information
  - Neutropenia observed in 1 of 301 patients in long term safety study

Comments on Cases #2

- Research Gaps
  - What cure rate can be achieved using the malaria prophylactic dosing regimen.
  - No systematic evaluation has been conducted.

Safety of Primaquine (30 mg) and Tafenoquine (200 mg)

Recommended/Approved Dosing for Malaria Prophylaxis

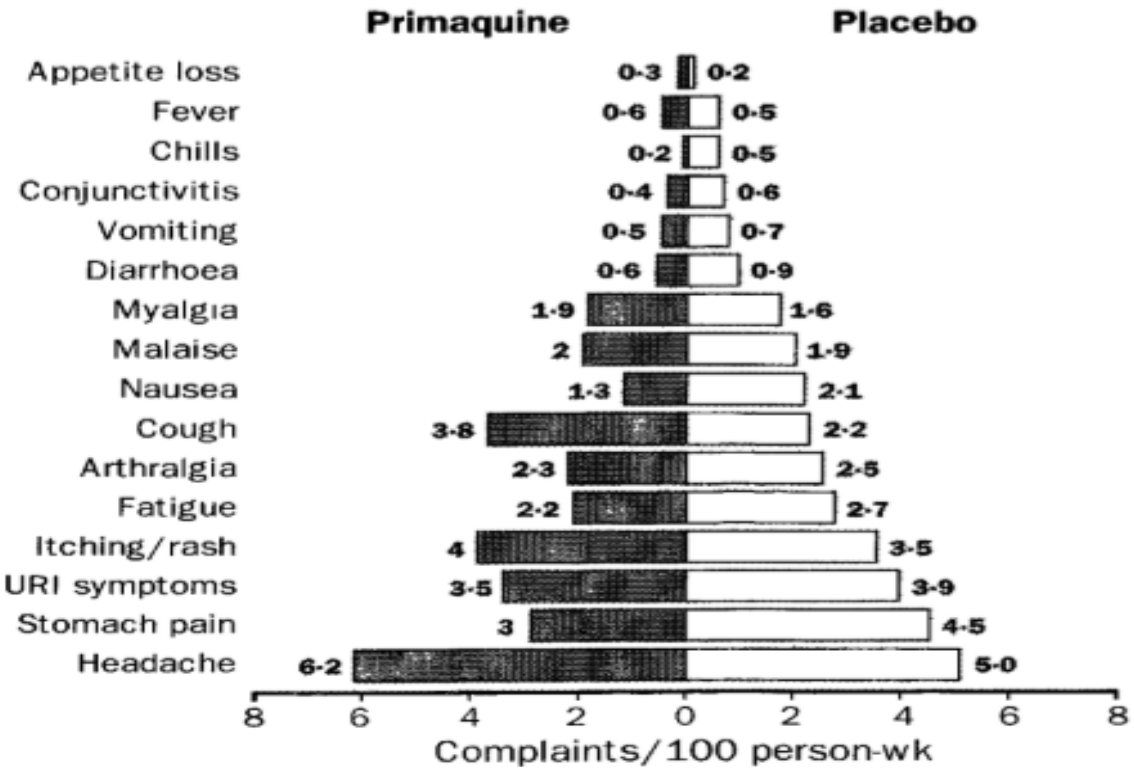
- **Primaquine:**
  - 30 mg/day
  - (CDC Guidance: CDC - Malaria - Travelers - Choosing a Drug to Prevent Malaria)

- **Tafenoquine:**
  - 200 mg/day for three days then 200 mg weekly
  - Prescribing information for ARAKODA (www.arakoda.com)
  - Long term (12 month) safety study: Novitt-Moreno et al 2022

Tolerability of Primaquine for Malaria Prophylaxis

Adverse event	Primaquine No. of events	Primaquine Incidence density	Placebo No. of events	Placebo Incidence density	RR	95% CI	P
Headache	34	1.01	74	1.63	0.62	0.41–0.93	.02
Abdominal pain	34	1.01	33	0.73	1.39	0.86–2.23	.18
Cough	31	0.92	84	1.85	0.50	0.33–0.74	<.001
Nausea	20	0.59	34	0.75	0.79	0.46–1.38	.41
Dizziness	19	0.56	19	0.42	1.35	0.72–2.53	.36
Neck/back pain	18	0.53	19	0.42	1.28	0.67–2.42	.46
Cold/flu	18	0.53	30	0.66	0.81	0.45–1.45	.47
Pruritis	15	0.45	30	0.66	0.67	0.36–1.25	.21
Myalgia	15	0.45	22	0.49	0.92	0.47–1.78	.80
Fever	14	0.42	29	0.64	0.65	0.35–1.23	.18
Malaise	12	0.33	14	0.31	1.15	0.54–2.48	.72
Arthralgia	12	0.36	21	0.46	0.77	0.38–1.56	.47
Diarrhea	9	0.27	13	0.29	0.93	0.39–2.20	.87
Vomiting	9	0.27	8	0.18	1.51	0.59–3.89	.39
Chills	7	0.21	5	0.11	1.88	0.61–5.82	.27
Chest pain	6	0.18	6	0.13	1.35	0.44–4.14	.61
Sore throat	6	0.18	24	0.53	0.34	0.14–0.79	.01
Respiratory difficulty	5	0.15	15	0.33	0.45	0.17–1.20	.11
Anorexia	4	0.12	2	0.04	2.69	0.53–13.7	.23
Insomnia	5	0.15	3	0.07	2.24	0.56–9.0	.26

6 MO
Baird et al 1992
Am J Trop Med Hyg. 52:479-84.



12 MO
Fryauff et al 1995
Lancet 46(8984):1190-3

- **Primaquine and placebo equally well tolerated following daily administration for up to 12MO**

Overall Safety & Tolerability of Tafenoquine @ Prophylactic Dose*

Comparative safety findings for the tafenoquine weekly prophylactic regimen, dosing for ≤6 Months versus dosing for 52 Weeks.

	Dosing for ≤6 months				Dosing for 52 Weeks	
	Tafenoquine 200 mg Weekly Regimen[a]			Placebo in Resident Population (n = 295)	Tafenoquine 200 mg Weekly Regimen (n = 301)	Placebo (n = 298)
	Overall (n = 825)	Deployed Australian Defence Force (n = 492)	Resident Populations (n = 333)			
Studies Included	030, 033, 043, 045, 057[b]	033	030, 043, 045, 057	030, 043, 045, 057	60PH04	60PH04
Total No AEs	3496	2204	1292	1045	1353	1273
AEs of This Intensity, n(%)						
Mild	3026 (86.6%)	1864 (84.6%)	1162 (89.9%)	919 (87.9%)	948 (70.1%)	811 (63.7%)
Moderate	423 (12.1%)	317 (14.4%)	106 (8.2%)	111 (10.6%)	372 (27.5%)	431 (33.9%)
Severe	35 (1.0%)	22 (1.0%)	13 (1.0%)	8 (0.8%)	29 (2.1%)	29 (2.3%)
Life-Threatening	N/A[c]	N/A	N/A	N/A	2 (0.1%)[d]	1 (0.1%)
Missing/Unknown	12 (0.3%)	1 (0.04%)	11(0.9%)	7(0.7%)	2 (0.1%)	1 (0.1%)
Subjects with at Least One AE, n (%)	692 (83.9%)	467 (94.9%)	225 (67.6%)	189 (64.1%)	274 (91.0%)	268 (89.9%)
Subjects with an SAE, n (%)	47 (5.7%)	26 (5.3%)	21 (6.3%)	10 (3.4%)	19 (6.3%)	15 (5.0%)

Novitt-Moreno et al 2022. TMAID 45:102211

Tafenoquine - Common Adverse Events*

Number and percentage of subjects with "Very common" adverse events occurring in ≥10% of subjects of either study group - safety population.

MedDRA SOC/Preferred Term	Tafenoquine (N = 301)	Placebo (N = 298)	p-value[a]
Eye Disorders			
Cornea Verticillata	164 (54.5%)	11 (3.7%)	<.001
Gastrointestinal Disorders			
Diarrhea	32 (10.6%)	24 (8.1%)	0.326
Nausea	39 (13.0%)	23 (7.7%)	0.044
Infections And Infestations			
Upper Respiratory Tract Infection	88 (29.2%)	107 (35.9%)	0.097
Nervous System Disorders			
Dizziness	20 (6.6%)	32 (10.7%)	0.083
Headache	78 (25.9%)	81 (27.2%)	0.781

- Tafenoquine should be administered with food
- Cornea verticillate is reversible upon cessation of drug and does not impact vision

**Novitt-Moreno et al 2022. TMAID 45:102211*

Tafenoquine - Comments on Adverse Events of Special Interest #1*

- **Methemoglobinemia:**
  - Label has warning about methemoglobinemia
  - Methemoglobinemia increased on average by 2.4% before returning to baseline
  - No instances of symptomatic methemoglobinemia or methemoglobin value > 10% observed

- **Hemolytic anemia:**
  - Contraindicated in individuals with G6PD deficiency due to the risk of hemolytic anemia (1 of 3184 patients in the pre-marketing safety database required a transfusion due to failure to administer a G6PD test due to an administrative error)
  - Transient (< 0.5 g/DL) asymptomatic decline in hemoglobin observed in G6PD normal individuals
  - 2/301 individuals reported anemia

- **Opthalmologic Safety:**
  - Tafenoquine predictably causes cornea verticillata – Reversible and no impact on vision
  - No elevated risk of serious ophthalmologic safety events (e.g. retinopathy)

Novitt-Moreno et al 2022. TMAID 45:102211

Tafenoquine - Comments on Adverse Events of Special Interest #2*

- **Psychiatric Safety:**
  - Contraindicated in individuals with uncontrolled serious psychiatric disorders
    - Unclear if this reflects a real risk or due to design errors in early Phase I/II trials
  - No increased risk of psychiatric events in those with prior mental health history v those without when prescribed according to the regulatory labeling

- **Renal Safety:**
  - Mean creatinine increased 7.8 umol/L, returning to baseline 12 weeks after cessation of dosing

- **Drug-Drug Interactions:**
  - TQ is an OCT-2 and MATE substrate *in vitro*
  - FDA advises against coadministration with substrates of these inhibitors (e.g. metformin or dofetilide)

Novitt-Moreno et al 2022. TMAID 45:102211,
ARAKODA Prescribing Information

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Tolerability of Higher Doses

Tafenoquine - Experience with Higher Dosing

- Clinical Trials:
  - Edstein et al 2001 – 400 mg x 3 then 400 mg monthly (N=104)
  - Shanks et al 2003 – 400 mg x 3, 400 mg x 3, then 400 mg weekly (N=119)
  - Elmes et al 2009 – 400 mg x 3 OD and BID (N=567)
  - Fukuda et al 2021 – 400 mg x 3 (N=41)
- Tolerability and general adverse event information available
- No systematic placebo-controlled safety studies comparable to Novitt-Moreno et al 2021
- No regulatory labeling around 400 mg dose

Mild-Moderate GI Events Relative to Comparator (200 and 400 mg)

Metric	Green	Moreno	Moreno	Shanks	Shanks	Shanks	Elmes***		
Dose (mg)	600	200 mg x 3, 200 mg weekly for 10-24 w	200 mg x 3, 200 mg weekly for 48 w	200 mg x 3, 200 mg weekly for 13 w	400 mg x 3	400 mg x 3, 400 mg weekly for 13 w	200 x 3	400 [200 BID] x 3	400 x 3
Weight [kg]	82*	65	No data	61.5	60	61.5	79.5	78.5	81.4
Daily Dose [mg/kg]	7.3	3.1	3.1	3.25	6.67	6.5	2.5	5.1	4.8
Loading Dose [mg/kg]	7.3	9.3	9.3	6.75	20.1	19.5	7.5	15.3	14.4
Monthly Dose in First Month [mg/kg]	7.3	21.7	21.7	22.75	20.1	45.5	7.5	15.3	14.4
Average Monthly Dose [mg/kg]	NA	14-16	14	16	NA	32	NA	NA	NA
Population	U.S. HVTs	U.S. U.K., Kenyan, Ghanian HVTs	U.S., Aust. HVTs	Kenyan HVTs	Kenyan HVTs	Kenyan HVTs	Aust. soldiers	Aust. soldiers	Aust. soldiers
N	52	333	301	60	60	59	204	161	406
GI AEs Above Background (%)	< 8*	-1.6**	7	1	5	18	0.8	24.2	29.7

**Weight not stated in clinical study so used average for U.S. population for stated demographic. Incidence of specific adverse adverse events not stated so used difference in all adverse events between placebo and TQ.*
*** Difference in GI adverse events between TQ and placebo groups in pooled clinical trials*
****Incidence of GI events is relative to primaquine 7.5 mg TID + doxycycline 100 mg/day. Open label study*

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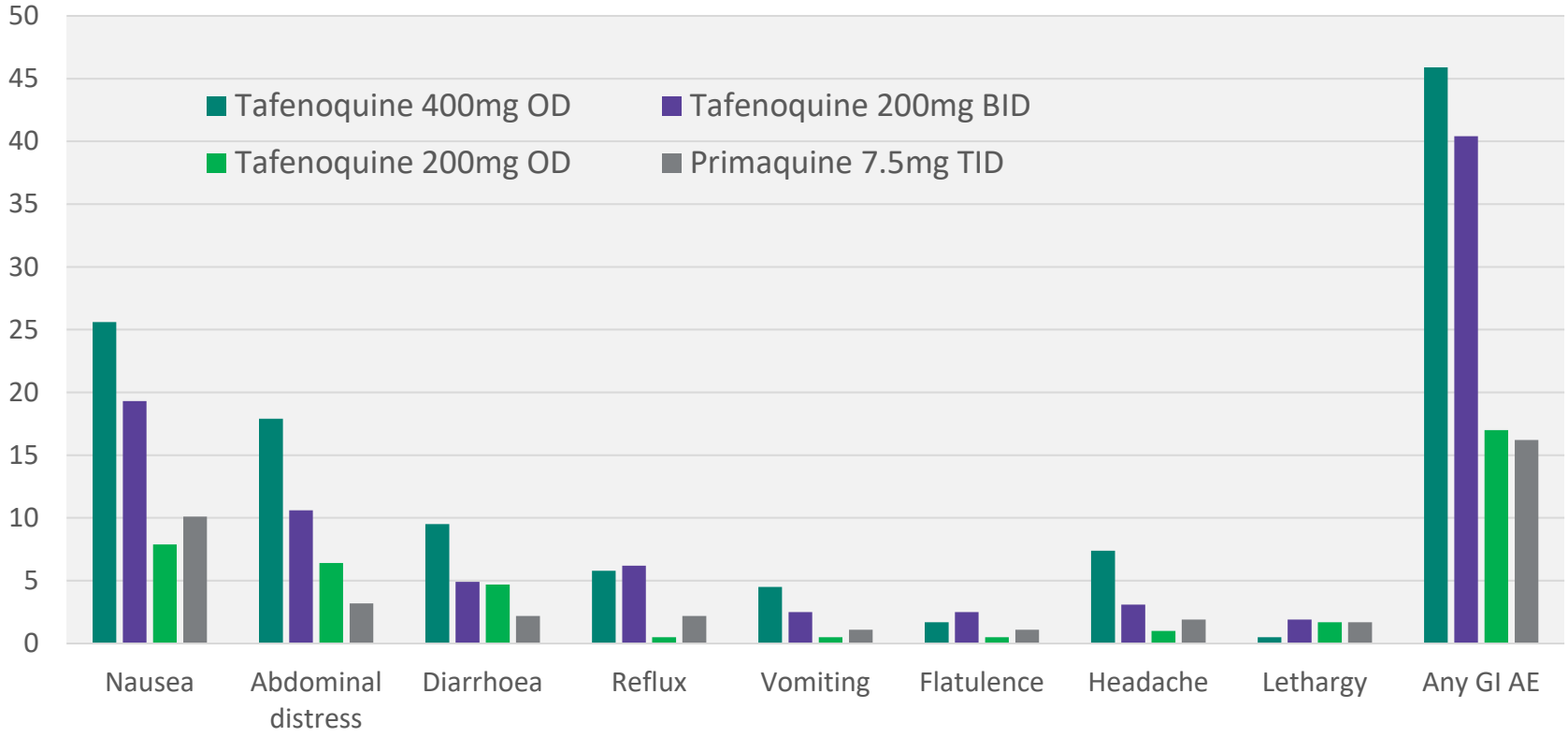
1200 mg v 600 mg load (open label)

Comparison of the rates of AE (%) between healthy subjects administered **3d courses of ARAKODA** and a **14d course of primaquine plus doxycycline** for post-exposure *P. vivax* malaria prophylaxis



Future Research & Clinical Trials

A Future Research Agenda

- Clinical Research Goals
  - **Demonstrate clearance of parasitemia in immunocompetent individuals (600-1200 mg)**
  - Evaluate cure rate of tafenoquine in relapsing babesiosis (loading dose then repeat weekly dosing as needed)
  - **Evaluate ability of tafenoquine to provide clinical benefit in patients with chronic infection**
- Market Research Goals:
  - Treatment of acute babesiosis
  - Pre and post-exposure prophylaxis of babesiosis
  - Chronic babesiosis
- PCR survey of *Babesia* spp present in patients with chronic fatigue symptoms

Tafenoquine in Patients Hospitalized for Acute Babesiosis

[See NCT06207370: Study Details | Oral Tafenoquine Plus Standard of Care Versus Placebo Plus Standard of Care for Babesiosis | ClinicalTrials.gov]

A Phase II/III, Double-Blind, Randomized study to Evaluate Oral Tafenoquine Plus Standard of Care Versus Placebo Plus Standard of Care for Babesiosis

Patients: Hospitalized patients with laboratory confirmed *Babesia* infection
Sample Size/Analysis: Will enroll N=33, before conducting an interim analysis/sample size reanalysis (if needed)

Tafenoquine Dose: 200 mg/day on Days 1,2,3 and 4, with dosing initiated within 48 h of hospitalization
Standard of Care: IDSA recommended course of atovaquone-azithromycin

Primary Endpoint: Time to (patient reported) sustained clinical resolution of the following symptoms of babesiosis over 90 days (± one week): sweats, joint aches, cough, loss of appetite, muscle aches, headache, chills or shivering, feeling hot or feverish, nausea, fatigue (low energy or tiredness), vomiting

Key Secondary Endpoint: Time to molecular cure (TTMC) as assessed using longitudinal NAT testing through Day 90 days (± one week). NAT test is an FDA-approved RNA-based test used by U.S. blood banks to reduce risk of transmission through blood donation. Detects *B. microti* with 95% confidence at 3 copies/ml

Planned Open Label Study of Tafenoquine - Chronic Babesiosis*

An Open Label Compassionate Use (Expanded Access) Study of Tafenoquine in Chronic Babesiosis Patents
(Company is planning, has not submitted to an IRB or FDA)

Key Inclusion Criteria:

- Diagnosis of chronic babesiosis & self-reported post-exertional malaise or cognitive problems preceding 90 days
- Medical history confirming infection or willing to confirm infection with laboratory tests
- Willing to conduct online survey (babesiosis symptoms, SF-36, multidimensional fatigue inventory (MFI))

Tafenoquine: 200 mg/day on Days 1,2,3 and 4, then 200 mg weekly through Day 89
SOC: No concomitant med exclusions except quinine or per tafenoquine PI

Primary Endpoint: Change from base-line through Day 90 in patient-reported MFI – Physical Activity Score
PP Analysis Population:

- All patients taking 8 x 100 mg tablets with a primary endpoint outcome
- All patients with confirmed past or present babesiosis (lab test or documented herxing following prior ATV treatment)
- All patients with MFI > 13 (or >10 on reduced activity scale) + deficits on specific SF36 subscales

Secondary Endpoint:

- Serious adverse events in all subjects through (including those not in primary analysis population)
- MFI and SF-36 subscale scores at different time points
- Incidence of herxing at different time points

**Subject to change based on KOL, regulator and/or IRB feedback*

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Thank you for your attention!

Link to survey below: