IS AVAILABILITY OF ARTESUNATE ASSOCIATED WITH THE PROGNOSIS OF IMPORTED MALARIA IN SPAIN?

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Dear Editor,

Although there is a lot of aspects we stil need to understand about treatment with artemisinins[1], there is no doubt about their efficacy in treating malaria. Artesunate (AS) has demonstrated its superiority against quinine for treatment of severe malaria in terms of reduction of mortality in different randomized clinical trials performed in endemic countries and subsequent meta-analysis[2-4]. Despite having been established as the first line treatment by WHO and several national guidelines[5,6], its full implementation in non-endemic countries has not been completed.

We performed a cross-sectional study to assess the impact of accessibility of AS for treating imported malaria in Spain. Data about malaria cases admitted in different hospitals of Spain was obtained from the public National Health System database (CMBD) from 2007 to 2017, aggregated by different autonomous communities (a first-level political and administrative division). Information about availability of AS was obtained through two rounds of calls to pharmacies of the non-monographic public hospitals in Spain. The primary outcome for the analysis was defined using aggregated mortality rates and a secondary outcome was defined using a composite outcome defined as death during admission or prolonged hospitalization (> 7 days)).

Data about availability of AS was obtained from 183 (55.1%) of the 332 public hospitals inquired. The answer was similar regardless the hospitals size: 59.2% (74/125) of hospitals with ≥500 beds, 55.6% (55/99) of hospitals with 200-499 beds and 50.0% (54/108) of hospitals with <200 beds (p=0.369). AS was available in 45.9% (84/183)

hospitals, being the first treatment option for severe malaria in 84.0% (68/81) of them (3 hospitals missing data). A decreasing trend in availability of AS was observed depending on the hospital size (73.0% for ≥500 beds hospitals vs 47.3% for 200-500 beds hospitals vs 7.4% for <200 beds hospitals, p-for-trends < 0.001).

Between 2007 and 2017, 7731 malaria cases were reported, with an overall mortality of 1%. A significant reduction in mortality was found when the first and the second study period were compared (1.3% in 2007-2011 vs 0.8% in 2012-2017, p=0.027). Median length of hospitalization did not differ between death and survival cases (5 days (IQR 2-14); 4 days (IQR 3-6), p=0.105). Age > 65 years (OR 6.8, 95%CI 3.6-12.6) and foreign origin (OR 4.3, 95%CI 1.5-12.1) were found to be associated with higher mortality in an adjusted regression model (Table). A decrease in the incidence of the secondary outcome was observed in those autonomous communities in which AS was introduced in at least 25% of hospitals before 2015 (Median 30.8% [IQR: 24.0-33.9%] vs 20.7% [IQR: 18.7-24.8%], p=0.049).

In conclusion, availability of AS seems to be associated with a better outcome in patients with imported malaria attending Spanish hospitals. The lack of AS is especially worrying in smaller hospitals. Although these hospitals are less likely to admit severe malaria cases, usually transferred to tertiary specialized units, availability of AS in any health-care facility regardless its size is essential to ensure patients to receive an adequate treatment as soon as possible. Accessibility to health-care facilities may have an impact on mortality and prolonged hospitalization, as it could be the case of vulnearable populations such as patients of foreign origin. Our results reinforce the importance of ensuring a proper distribution and availability of AS in hospitals in non-endemic countries, as well as the need of promoting policies to optimize the access to

health care systems for all citizens, in order to improve the outcome of imported malaria.

REFERENCES

[1] Marco-Hernández J, Camprubí D, Aylagas C, Gupta H, Castro P.Failure of intravenous artesunate treatment for Plasmodium falciparum malaria in a splenectomized traveller: A diagnostic challenge. *Travel Med Infect Dis*. 2019;30:142-143.

[2] Dondorp A, Nosten F, Stepniewska K, Day N, White N. Artesunate versus quinine for treatment of severe falciparum malaria: a randomized trial. *Lancet* 2005;366:717-25.

[3] Dondorp AM, Fanello CI, Hendriksen IC, Gomes E, Seni A, Chhaganlal KD, Bojang K, Olaosebikan R, Anunobi N, Maitland K, Kivaya E, Agbenyega T, Nguah SB, Evans J, Gesase S, Kahabuka C, Mtove G, Nadjm B, Deen J, Mwanga-Amumpaire J, Nansumba M, Karema C, Umulisa N, Uwimana A, Mokuolu OA, Adedoyin OT, Johnson WB, Tshefu AK, Onyamboko MA, Sakulthaew T, Ngum WP, Silamut K, Stepniewska K, Woodrow CJ, Bethell D, Wills B, Oneko M, Peto TE, von Seidlein L, Day NP, White NJ; AQUAMAT group. Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): an open-label, randomised trial. *Lancet* 2010;376:1647-57.

[4] Sinclair D, Donegan S, Isba R, Lalloo DG: Artesunate versus quinine for treating severe malaria. *Cochrane Database Syst Rev* 2012:Cd005967.

[5] World Health Organization (WHO). Guidelines for the treatment of malaria, second edition. 2010 [Geneva, Switzerland].

[6] Muñoz J, Rojo-Marcos G, Ramírez-Olivencia G, Salas-Coronas J, Treviño B, Perez Arellano JL, Torrús D, Muñoz Vilches MJ, Ramos JM, Alegría I, López-Vélez R, Aldasoro E, Perez-Molina JA, Rubio JM, Bassat Q. Diagnosis and treatment of

imported malaria in Spain: Recommendations from the Malaria Working Group of the Spanish Society of Tropical Medicine and International Health (SEMTSI). *Enferm Infecc Microbiol Clin* 2015; 33(6):e1-e13.

Table – Factors associated with mortality and long hospitalization in malaria patients admitted to hospital in Spain (2007-2017).

	Descriptive analysis	Bivariate analysis		Adjusted analysis	
	n/N (%)	OR (95% CI)	p- value	OR (95% CI)	p- value
Mortality					
Sex					
Male	53/5117 (1.04%)				
Female	24/2609 (0.92%)	1.12 (0.69-1.83)	0.628	1.34 (0.79-2.26)	0.275
Age					
>65 years	15/279 (5.38%)	6.77 (3.80-12.06)	<0.001*	**6.78 (3.65-12.61)**	<0.001*
≤65 years	62/7452 (0.83%)				
Nationality					
Foreigner/migrant	4/118 (3.39%)	3.82 (1.37-10.67)	0.010*	**4.30 (1.53 – 12.10)**	0.006*
Spanish	66/7261 (0.91%)				
Secondary Outcome (mortality or >7 days of hospitalization)					
Sex					
Male	839/4196 (20.00%)				
Female	514/2186 (23.51%)	0.81 (0.72-0.92)	0.001*	**0.83 (0.73-0.94)**	0.004*
Age					
>65 years	122/234 (52.14%)	4.36 (3.34-5.67)	<0.001*	**4.39 (3.36-5.74)**	<0.001*
≤65 years	1231/6153 (20.01%)				
Nationality					
Foreigner/migrant	35/120 (29.17%)	1.59 (1.06-2.37)	0.022*	**1.72 (1.15-2.56)**	0.008*
Spanish	1261/6134 (20.56%)				

Table – Descriptive, bivariate and multivariate analysis of factors associated with mortality and long hospitalization in malaria patients admitted to Spanish hospitals between 2007 and 2017. Primary outcome defined as mortality during hospitalization. Secondary outcome defined as death during admission or prolonged hospitalization (> 7 days).

* Statistically significant p- values.