Propensity Score Analysis of Artesunate Versus Quinine for Severe Imported Plasmodium falciparum Malaria in France

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Abstract

Background. Little is known on the use of artesunate compared to quinine for the treatment of imported malaria cases in non-endemic countries with high level of care. Therefore, we compared the two treatments in terms of mortality, hospital and intensive care unit discharge rates.

Methods. We analyzed the cohort of all severe imported malaria patients reported to the French National Reference Center from 2011 to 2017. After controlling for differences between quinine and artesunate treated individuals using the inverse probability of treatment weighting method, 28 day mortality rate was compared between the groups as well as hospital and ICU discharge rates using Kaplan Meier estimation and weighted Cox proportional hazard models.

Results. Overall, 1544 patients were enrolled. Fifty patients died, 18 in the quinine group (n=460) and 32 in the artesunate group (n=1084) corresponding to death rates of 3.9% 2.9% respectively. No difference was evidenced between quinine and artesunate neither in mortality nor in hospital discharge rate with HR= 1.03, CI 95% [0.47-2.25] and HR= 1.12, CI 95% [0.94-1.34] respectively. Artesunate was associated with a faster ICU discharge rate, HR = 1.18, CI 95% [1.02-1.36].

Conclusions. In a country with a high level of care, artesunate was associated with a shorter length of stay in the ICU and this supports the actual therapeutic transition, however no difference was found neither in terms of mortality nor in hospital discharge rates between artesunate and quinine patients.

Key points

In a country with high level of health care, no difference was demonstrated neither in mortality nor in hospital dicharge rate between quinine and artesunate in the treatment of severe malaria. However patients treated with artesunate had a shorter length of stay in the ICU.

The WHO recommended intravenous artesunate (AS) as a first-line treatment for all forms of severe malaria worldwide since 2010 [1]. This followed two large randomized trials conducted in Asia and Africa that compared AS and intravenous quinine (Q) in the treatment of severe malaria showing an absolute reduction in death rates among adults and children in favor of artesunate [2, 3]. In May 2011, The French national drug Agency (ANSM) has granted a temporary authorization for use of AS as it was not available in France before and had no marketing authorization [4]. In 2017, an update of the "2007 recommendations for the management of imported malaria", by the French society of Infectious Diseases (SPILF), endorsed and positioned artesunate as a first line treatment for severe malaria in France [5]. Studies performed in Western and endemic countries confirmed the efficacy of AS and showed an acceptable tolerance [6, 7]. Moreover, studies performed in Western countries highlighted the risk of an AS adverse event, which is post artesunate delayed hemolytic anemia (PADH) that appears during the 2nd or 3rd week after the end of treatment, showing the importance of follow-up [8].

Although AS tends to gradually replace quinine in the treatment of severe imported malaria in France, its use is still not mandatory and patients are still treated with Q, 70% in 2011 vs. 13% in 2015 according to the National reference French center of Malaria (NRC-M) 2017's annual report and there is no Good Manufacturing Practice-conform drug available yet. Moreover, little comparative data is available in high income countries like France comparing the use of AS instead of Q in managing severe imported malaria patients. Unfortunately, clinical randomized trials are no longer possible considering the previous published results confirming that AS saves more life than quinine and is better tolerated and considering the inadequate number of patients that can be included [2, 3, 9]. However, the effect of AS on reducing the death's rates was rigorously demonstrated only in endemic countries where there is no existing or poorly available ICU facilities. Questions remain on the generalization of those findings especially that the supportive care and ICU facilities as well as patient's characteristics may differ significantly in high income countries from endemic ones. A recently published study carried out between 2006 and 2010 on 155 severe malaria cases, treated with Q in intensive care unit (ICU) in France showed a mortality rate of 5% [10] whereas the surveillance of AS in France, showed a mortality rate of 3% [6]. However, these results are not comparable and the real impact of AS compared to quinine remains unknown.

Our study compared AS with Q in the treatment of severe imported malaria between 2011 and 2017 to determine the impact of using AS in terms of mortality, hospital and ICU discharge rates in high level of health-care.

METHODS

Study population

We analyzed a historical cohort of all *Plasmodium falciparum* severe imported malaria cases reported from 2011 to 2017 to the NRC-M, a network of 110 hospitals throughout France. All data were prospectively recorded. We used the case definition of the national French guidelines of the SPILF for management of imported malaria cases in 2007 [11]. A severe case of malaria was defined by a positive blood smear for the asexual form of *P. falciparum* and the presence of one or more severity criteria at admission (Supplementary Text S1). All patients that received AS or Q as first line treatment at the time of diagnosis of severe malaria were eligible.

Statistical analysis

The primary objective was to compare 28 day mortality rates between individuals receiving AS and Q. The secondary and third objectives were the hospital and ICU discharge rates following treatment administration. Analyses were on an intention-to-treat (ITT) basis, patients were analyzed depending on which arm they were assigned to initially. StataCorp (2013) Statistical Software: Release 13. College Station, TX: StataCorp LP was used for all analyses. Quantitative variables were expressed as median [Inter Quartile Range]. All reported p values are 2-tailed.

Missing data

All variables from the cohort were prospectively recorded, however some data were missing. Multiple imputation using Chained Equations approach (MICE) was used to fill in missing data [12]. Ten imputations (M=10) were chosen to obtain valid inference and reduce sampling variability resulting from the imputation process. Variables with a missing rate above 15% were excluded and the outcomes were included in the imputation model. All 10 datasets were analyzed and combined using Rubin rules [13].

Propensity score

Differences between AS and Q groups were analyzed using univariable logistic regressions. To avoid a statistically significant difference in outcome between the two groups of patients that may be observed in the absence of treatment effect but due to a difference in initial prognosis between the two groups compared we use a propensity score analysis approach (PS) [14]. The PS for each subject was defined as the conditional probability of receiving AS given the patient's individual baseline characteristics at admission. The index date for all the analyses was the day the patients start the treatment (day 0). PS was estimated from a logistic regression model that included factors predictive to the outcomes whether they were associated with the exposure or not as well as factors that might have influenced the treatment choice [15]. Factors associated with the outcomes were tested using univariable hazards models. All potential confounders that are known in the literature were also included [16, 17, 18, 19]. A different PS was calculated for each outcome as the number of selected subjects changed each time.

Variables included in the PS model are described in Supplementary Text S0.

Propensity scores were then used by inverse probability of treatment weighting method (IPTW) [15, 20]. The stabilized weights were calculated as p/PS for individuals who received AS, and as (1 – p)/(1 – PS) for individuals who received Q, where p is the overall marginal prevalence of treatment exposure [20]. The balance in characteristics between the 2 groups in the original and weighted samples was checked using standardized differences. Absolute standardized differences of less than 10% are sufficient to

demonstrate achieved balance [15, 20]. Propensity score analysis was performed in each imputed dataset. The treatment effect estimates from each imputed dataset were then combined to obtain an overall estimate [21].

Endpoints

In order to compare the mortality in the two groups, weighted Kaplan Meier estimates were calculated for each group, 28 days after the index date. Weighted Cox proportional hazards models were estimated, where the only variable included in the model was the treatment and patients in the Q group served as reference.

As for the second and the third objectives, a propensity score was calculated for subjects with observed data on length of stay in hospital and in ICU after performing analyses to make sure patients with missing and observed length of stay were comparable. In these analyses, the maximum observed length of stay in hospital and in ICU was assigned to patients who died corresponding to 66 days and 70 days respectively. Weighted Kaplan Meier estimates as well as Cox proportional hazards models were used to compare hospital and ICU discharge rates in the 2 treatment groups.

Ethical considerations

Ethical considerations are described in Supplementary Text S0.

RESULTS

The cohort comprised 1544 patients with severe *Plasmodium falciparum* malaria between 2011 and 2017 (Figure 1). The majority of cases contracted the disease in west and central Africa (92.5%). The most common severity criterion was hyperparasitemia (59%), followed by cerebral malaria (38%) and the median number of severity criteria was 2 [2-3]. The total number of patients having only a hyperparasitemia (>4%) as a severity criterion was 257/1544 (16.6%): 86 in quinine group (18.7%) and 171 in artesunate group (15.8%). The characteristics of the 2 groups are described in Table 1.

Missing data

In total 7 variables were imputed: the missing data percentage was 2.4% for region of malaria acquisition, 7.9% for parasitemia, 9.6% for platelet count, 10.7% for WBCs count, 9.5% for chemoprophylaxis, 10.1% for immunosuppression, 10.8% for patient's origin. The following variables had a high missing data rate, thus, they weren't included in the imputation model: length of travel 42%, presence of comorbidities >70% except immunosupression, reason of travel 25%.

Risk factor for death

A higher risk of death was observed in non-Africans patients, patients older than 60 years old and hyperparasitemic patients with a parasitemia level above 10% in univariable hazard models. Results also showed that the following severity criteria (cerebral malaria, circulatory collapse, respiratory distress, abnormal bleeding, acidosis, hyperlactatemia >5 mmol/L, hypoglycemia <2.2 mmol/L, creatininemia >265 micromol/L and clinical jaundice) were associated with death. Being treated in a center with an annual activity above 12 malaria cases per year was a protective factor (Supplementary Table S1).

Propensity score

Propensity score's distribution before using the IPTW method for each outcome is displayed in Supplementary Figure S1. Absolute standardized differences after weighting were below 10% for all characteristics showing that reasonable balance has been achieved (Supplementary Figure S2).

Mortality rate

Among the 1544 reported cases, 50 died: 32 patients (2.9%) in the AS group and 18 (3.9%) in the Q group. Two more patients in the Q group died at day 36 and day 40, both were censored at day 28 in the survival analysis. Among all deaths, 82% occured while receiving first line treatment while 18% have switched treatments. In the Q group, 140 patients had switched to artesunate, 6 of all the patients who died in the Q group were among those switchers wheareas 8 patients in the AS group had switched to Q with only one death occuring after switching.

The estimated weighted hazard ratio after multiple imputation and IPTW was HR= 1.03, 95%CI [0.47-2.25], p= 0.923, with no evidence for difference between the two groups with regard to the mortality rate. Figure 2A displays estimated weighted Kaplan Meier estimates.

Hospital discharge rate

In total 960 patients were analyzed, 255 in the Q group and 705 in the AS group (Supplementary Table S2). Older age, non-African origin, immunosuppressed patients, platelet count <10 G/L and severity criteria as neurological failure, respiratory distress, abnormal bleeding, acidosis, hyperlactatemia >5mmol/L, jaundice, renal failure and a hyperparasitemia level >10% were factors associated with a slower discharge rate when tested in univariable analyses. Admission in year 2016-2017 and male sex were associated with a faster discharge rate. The following variables, endemic region, presence of repeated convulsion and hemoglobin level < 7g/L were not associated with the outcome in univariable analysis, thus were not included in the PS model. Weighted proportionnal hazard ratio was 1.12, 95%CI [0.94 – 1.34], p=0.212, with no statistical evidence of difference in hospital discharge rates between the 2 treatment groups (Figure 2B). Median length of hospital stay was 6 [4-10] days in Q group and 5 [4-7] days in the AS group.

ICU discharge rate

This analysis was performed on 916 patients with 765 patients admitted in the ICU (Supplementary Table S3). The same factors associated with a slower hospital discharge rate were associated with a slower ICU discharge rate in univariable analyses except abnormal bleeding and immunosuppression. Year at admission was a variable that highly differentiated the groups and was weakly associated with the ICU discharge rate (p=0.048) so we excluded it from the propensity score model and we included it with the treatment variable in the final weighted Cox model. Patients on AS were discharged faster from the ICU compared to Q. A median of 2 [1-3] days was observed in AS group and of 3 [2-5] days in Q group. Weighted proportionnal hazard ratio was 1.18, 95%CI [1.02 – 1.36], p=0.03 (Figure 2C).

DISCUSSION

To the best of our knowledge, this observational study is the largest to compare Q and AS on mortality, hospital and ICU discharge rates in malaria non-endemic countries with high-level of care. No difference was evidenced neither in mortality nor in total length of stay in the hospital between the 2 treatment groups, while artesunate was associated with a shorter length of stay in the ICU compared to quinine.

Very little comparative data on the use of either treatment was available for severe malaria cases in non-endemic countries. Four non-randomized studies provided comparative information in the context of severe imported malaria [19, 23, 24, 25]. They all showed benefits of using artesunate over quinine. Kurth, *et al*. and Eder, *et al*. also showed a reduction in the time of parasitic clearance in favor of artesunate (75h vs. 96h) and (65h vs. 85 h) respectively. Rolling et *al*. showed a better tolerance with only post-delayed hemolytic anemia (PADH) reported as an adverse event for artesunate patients, while 71% of patients under quinine experienced hypoglycemia, cardiotoxicity or hearing disturbance. None of the previous studies in non endemic countries reported any difference in terms of mortality. The number of patients included was limited and statistical methods employed were simple.

Mortality rates reported in our study were very low in both the AS and the Q group (2.9% vs. 3.9% respectively) reflecting the importance of high level of care in the management of severe malaria cases. Estimated hazard ratio close to 1 and narrow confidence interval shows that a very large number of individuals would be needed to show a significant difference in mortality between the treatment groups. A study including 155 events which is 3 times more deceased patients might be needed to show a 1% difference in mortality between the groups with a power of 80% and clinical trials are no longer justified considering the previous published results and with regard to the number of patients that can be included in non-endemic countries. Moreover differences in mortality previously published between Q and AS patients were observed in endemic countries [2, 3], it is expected that the difference in mortality rates would be smaller in developed countries with high-level of care. Although AS did not reduce the total length of stay in the hospital, patients on AS were discharged faster from the ICU compared to Q. Shorter length of stay in the ICU is still beneficial in reducing the resources spent for patient's care per day. In France, the cost of a day spent in the ICU is of 2816 euros (www.aphp.fr). Besides, although the average cost of AS is currently higher than Q, the latest is administered 3 times daily while AS is administered once daily which is more convenient for patients as well as healthcare professionals taking care of them. This is supported by an economic evaluation of AS in south Asia that showed that the use of AS was cost-effective [26].

One of the main strengths of our study is the large sample size compared to others as participants were enrolled from 110 centers participating to the national surveillance network for malaria (NRC-M) throughout France, which increases the robustness of our findings. The use of IPTW method assured the comparability of the groups on measured confounders such as older age, non-African origin, presence of neurological impairment, respiratory distress, circulatory collapse, abnormal bleeding, acidosis, hyperlactatemia >5 mmol/L, hypoglycemia <2.2 mmol/L, renal failure, platelet count below 10 G/L and hyperparasitemia above 10%. All those factors were associated to death in univariable analysis which is consistent with literature [17, 18]. Adding the variable annual activity of the center in the propensity score allowed us to take in consideration the indication bias since centers with a high number of cases admitted per year switched faster to artesunate.

Being treated in a center receiving more than 12 malaria cases per year was a protective factor from death in univariable analysis. We assume that such centers do better, mainly due to a better experience in handling patients with severe malaria. In our work African patients had a higher probability to receive AS. This could be explained by the fact that the African immigrant's population usually tend to live near the biggest cities in France and AS was introduced faster in large hospitals than in smaller ones. The time factor was also taken into consideration as most of patients who received Q were in early stages of the study while the number of patients that received AS increased gradually by time specially after 2014.

Nevertheless this study had limitations. Imported malaria is not a mandatory notifiable infectious disease in France and cases out the NRC-M network might have been missed. Moreover the surveillance system relies on motivation of physicians and parasitologists to report data to the NRC-M, consequently available data were not complete. In addition, propensity score allows to control the two groups only on measured confounders which is a limitation of this approach. However, most important confounding factors were taking into account in our study except for the presence of other comorbidities than being immunocompromised, this was due to lack of data on this factor in our database. As this study was based on the intention-to-treat principle, patients who had switched treatment were analyzed in their initial group and this might have minimized the difference observed between the groups on measured endpoints, however data on time at switch was very limited. Another limitation of this study was that it didn't compare safety with regard to the treatment received. However, AS use was proved to be safe and well tolerable in France and other non-endemic countries with less frequent episodes of hypoglycemia and cardiotoxicity despite reported cases of PADH [7, 8, 27].

In conclusion, this work suggests that a high level of intensive care can achieve a very low mortality rate regardless of the curative treatment. In view of the good tolerance of artesunate and its ease of use with regard to quinine, the current therapeutic transition is strengthened. Moreover, artesunate reduces the length of stay in ICU and this in turns supports the actual therapeutic transition happening in France and advocates for the implementation of ICU in developing countries.

Notes

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Figure 1. Flowchart of treated patients, French cohort 2011-2017.

As a second line treatment in artesunate group: 151 patients have received non-artemisinin based combination therapy such as Atovaquone + Proguanil (Malarone®), Chloroquine (Nivaquine®), Halofantrine (Halfan®), Doxycycline (Doxypalu®), Méfloquine (Lariam®) and Quinine per os, 573 have received artemisinin-based combination therapy such as Artemether + Lumefantrine (Coartem®, Riamet®), Dihydroartémisinine + pipéraquine (Eurartésim®) and Artemether IM (Paluther®) and 8 patients have switched to quinine while 320 haven't received a second line treatment or data was missing for them. In the quinine group, as a second line treatment, 107 have received non-artemisinin based combination therapy, 44 have received artemisinin based combination therapy and 140 patients have switched to artesunate while 169 haven't received a relay. Two patients died after day 28 thus were censored in survival analysis. Misclassified patients are those who received the 2 treatments, but had missing data on criteria and dosing at admission.

Figure 2. Kaplan Meier plots shows the time since initiation of the treatment to A.death, B. discharge from the hospital, C.discharge from the ICU in quinine and artesunate group with quinine group used as reference