Intravenous Artesunate for Imported Severe Malaria in Children Treated in Four Tertiary Care Centers in Germany

A Retrospective Study

Sabine Bélard, MD,† Judith Brand, MD,* Ulf Schulze-Sturm, MD,‡ Ales Janda, MD,§ Ulrich von Both, MD,¶ Costanza Tacoli, PhD,‖ Martin Alberer, MD,** Caroline Kempf, MD,†† Miriam S.Stegemann, MD,‡‡ Renate Krüger, MD,* Verena Varnholt, MD,* Martin Blohm, MD,‡ Karl Reiter, MD,§§ Thomas Zoller, MD,‡‡ Norbert Suttorp, MD, ‡‡ Marcus Mall, MD *† Horst von Bernuth, PhD,*¶¶‖‖ Alexander Gratopp, MD,* Johannes Hübner, MD, ¶ Markus Hufnagel, MD,§ Robin Kobbe, MD,‡ and Florian Kurth, MD‡‡*

Background: Intravenous artesunate (ivA) is the standard treatment for severe malaria. Data systematically evaluating the use of ivA in pediatric patients outside malaria-endemic regions are limited. The aim of this case series was to summarize efficacy and safety of ivA for imported severe malaria in children in Germany.

Methods: Our retrospective case series included pediatric patients with imported severe malaria treated with at least 1 dose of ivA (Artesun, Guilin Pharmaceutical; Shanghai, China) at 4 German tertiary care centers. Severe malaria was defined according to World Health Organization criteria.

Results: Between 2010 and 2018, 14 children with a median [interquartile range (IQR)] age of 6 (1;9.5) years were included. All children were of African descent. All but 2 patients had *Plasmodium falciparum* malaria; 1 child had *P. vivax* malaria and 1 child had *P. falciparum* and *P. vivax* co-infection. Median (IQR) parasitemia at admission in patients with *P. falciparum* was 9.5% (3;16.5). Patients were treated with 1–10 [median (IQR) 3 (3;4)] doses ivA. All but one patient received a full course of oral antimalarial treatment. Parasite clearance was achieved within 2–4 days, with the exception of 1 patient with prolonged clearance of peripheral parasitemia. Three patients experienced posttreatment hemolysis but none needed blood transfusion. Otherwise ivA was safe and well tolerated.

Conclusions: ivA was highly efficacious in this pediatric cohort. We observed episodes of mild to moderate posttreatment hemolysis in approximately one-third of patients. The legal status and usage of potentially life-saving ivA should be evaluated in Europe.

Key Words: severe malaria, intravenous artesunate, artemisinin, child, hemolysis

(*Pediatr Infect Dis J* 2019;38:e295–e300)

Severe malaria, which is primarily caused by *Plasmodium falciparum*, is a fatal disease if untreated. Malaria ranks among the top imported diseases in febrile patients returning from endemic countries.[1] Analysis from the GeoSentinel Surveillance Network shows that among pediatric patients presenting with fever after international travel, malaria is the most common specific diagnosis.[2] *P. falciparum* malaria requires immediate treatment, since delay in initiation of antiparasitic treatment results in increased mortality.[3]

Currently, artemisinin-based drugs are the mainstay for treatment of nearly all forms of malaria. Over the last 2 decades, artemisinins have provided a significant breakthrough for malaria control by virtue of their favorable safety profile and rapid, high antiparasitic activity against nearly all stages of the parasite.

In severe malaria, antiparasitic treatment should be administered parenterally.[3] In 2010 the World Health Organization (WHO) changed the recommendation from intravenous quinine to intravenous artesunate (ivA) as first-line therapy for severe malaria. This recommendation was based on the results of SEAQUAMAT and AQUAMAT studies showing a 22%–35% reduced mortality in patients treated with ivA when compared with intravenous quinine.[4,5]

In endemic areas, ivA is now the standard treatment for severe malaria in children and adults. Outside endemic settings, adoption of artesunate as first-line treatment was impeded by the fact that high-quality evidence on its superiority for imported malaria is missing and that ivA has not been licensed in Europe with no good manufacturing practice-conform product available at this time.[6] Hospital pharmacies and prescribing physician are therefore faced with needing to treat a life-threatening condition without approved access to the drugs currently considered most effective. This represents a conflict between drug efficacy on the one hand and legal challenges as well as drug quality on the other hand. Reports on delayed hemolysis after treatment with ivA, a phenomenon which seems to be particularly frequent in patients without

Accepted for publication June 6, 2019.

From the *Department of Paediatric Pulmonology, Immunology and Intensive Care Medicine, Charité - Universitätsmedizin Berlin, Berlin, Germany; †Berlin Institute of Health, Berlin, Germany; ‡Department of Paediatrics, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; §Division of Paediatric Infectious Diseases and Rheumatology, Department of Paediatrics and Adolescent Medicine, Medical Center, Faculty of Medicine, University of Freiburg, Freiburg, Germany; ¶Division Paediatric Infectious Diseases, Dr. von Hauner Children's Hospital, University Hospital, Ludwig Maximilians University, Munich, Germany; ‖Institute of Tropical Medicine and International Health, Charité - Universitätsmedizin Berlin, Berlin, Germany; **Division of Infectious Diseases and Tropical Medicine, University Hospital, LMU Munich, Munich, Germany; ††Department of Paediatric Gastroenterology, Nephrology and Metabolic Disorders, Charité- Universitätsmedizin Berlin, Berlin, Germany; ‡‡Department of Infectious Diseases and Pulmonary Medicine, Charité-Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany; §§Division of Paediatric Intensive Care, Dr. von Hauner Children's Hospital, University Hospital, Ludwig Maximilians University, Munich, Germany; ¶¶Labor Berlin, Immunology, Berlin, Germany; and ‖‖Berlin-Brandenburg Center for Regenerative Therapies, Charité - Universitätsmedizin Berlin, Berlin, Germany.

There was no project-specific funding. S.B. is currently a participant in the BIH-Charité Clinician Scientist Program funded by Charité - Universitätsmedizin Berlin and the Berlin Institute of Health.

The authors have no conflicts of interest to disclose.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (www.pidj.com).

Address for correspondence: Sabine Bélard, MD, Department of Paediatric Pulmonology, Immunology and Intensive Care Medicine, Charité - Universitätsmedizin Berlin, Berlin, Germany. E-mail: sabine.belard@charite.de.

ISSN: 0891-3668/19/3811-e295
DOI: 10.1097/INF.0000000000002417

previous episodes of malaria and which is pathophysiologically not entirely understood, further complicate this picture.[7,8]

Given the low number of patients with severe malaria in nonendemic countries, along with the documented superiority of artesunate over quinine in endemic countries, randomized controlled clinical trials to generate evidence for artesunate in nonendemic areas are questionably feasible. Therefore, documentation and analysis of experience with ivA in cases of imported severe malaria are of utmost importance. The number of reports on the use of ivA in adults in nonendemic areas has risen[9] but data on ivA in *children* with imported severe malaria remain limited.[7,10,11]

The aim of the current case series is to summarize documented efficacy and safety of ivA for imported severe malaria in children in Germany to evaluate the use of this drug for this nonendemic setting.

MATERIALS AND METHODS

Study Sites and Ethics

This retrospective case series included all patients with imported severe malaria who were treated between 2010 and 2018 with at least 1 dose of ivA at one of the following 4 German tertiary care centers: Department of Paediatrics, University Hospital Hamburg-Eppendorf (Hamburg); Department of Paediatrics and Adolescent Medicine, Medical Center, Faculty of Medicine, University of Freiburg (Freiburg); Dr. von Hauner Children's Hospital, University Hospital, LMU Munich; and the Department of Paediatrics, Charité-Universitätsmedizin (Berlin). The study was approved by the Ethics Committee of Charité-Universitätsmedizin Berlin (Approval number EA2/225/18). Ethical clearance for transfer of anonymized patient data was sought at the other participating centers according to local regulations.

Study Procedures and Definitions

ivA (Artesun) was obtained from Guilin Pharmaceutical (Shanghai, China) and stored at room temperature according to the manufacturer's instructions in all treatment centers. Severe malaria was defined according to WHO criteria,[3] with the exception that hyperparasitemia was defined as peripheral parasitemia >5% according to recommendations for nonendemic settings,[12] and hemoglobin <8 g/dL without lower threshold for parasitemia was defined as severe anemia at the site in Berlin according to site's internal standard operating procedures. To identify patients for inclusion, laboratory books and patient registries for the period March 2010 through May 2018 were screened. For patients with a positive blood result for *Plasmodium* spp., patient records were reviewed to document the type of antiparasitic therapy and to evaluate criteria for severe malaria. Clinical and laboratory data were extracted from patient records using a standardized questionnaire. Patient follow-up data were used to describe long-term outcomes and were analyzed in a descriptive way; given the study design follow-up was, however, not standardized. Posttreatment hemolysis was defined as an >10% increase in lactate dehydrogenase (LDH) concentration and/or an >10% drop in hemoglobin level, both associated with a haptoglobin concentration below the lower, age-dependent normal range at any time after Day 7 following start of treatment.[13]

Laboratory Methods

For 1 patient with considerably prolonged parasite clearance under treatment, analysis of *Kelch13* was performed as previously described.[14] In short, genomic *P. falciparum* DNA was extracted from full blood by QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany) and *Kelch13* propeller domain amplified by previously published polymerase chain reaction assays.[14] Polymerase chain reaction products were bidirectionally sequenced (Source BioScience, Berlin, Germany), and multiple nucleotide sequence alignments were analyzed using BioEdit version 7.2.5 (http://www.mbio.ncsu.edu/BioEdit/bioedit.html) and SnapGene version 3.1 (GSL Biotech, Chicago, IL) to detect polymorphisms. The *Kelch13* sequence of *P. falciparum* 3D7 (PF3D7_1343700) retrieved from PlasmoDB was used as reference.

RESULTS

Fourteen children treated with ivA for severe malaria were included. Children were 5 months to 17 years of age with a median [interquartile range (IQR)] age of 6 (1;9.5) years. All children were of African descent. Only 2 patients reported one or more previous episodes of malaria. Presented in Table 1 are baseline characteristics including demographics, country of disease acquisition, travel purpose, use of malaria prophylaxis, *Plasmodium* species, parasitemia, and criteria for severe malaria. One patient (case 4) with Hb 7.2 g/dL and 0.01% parasitemia was included according to local definitions of severe malaria at the Berlin site, although WHO criteria were not fulfilled. All but 2 patients had *P. falciparum* malaria; 1 child had *P. vivax* malaria and 1 child had *P. falciparum* and *P. vivax* co-infection. Median (IQR) parasitemia at admission in patients with *P. falciparum* was 9.5% (3;16.5).

The patients were treated with 1–10 [median (IQR) 3 (3;4)] doses of ivA. All but one patient (case 9) consecutively received a full course of oral artemether-lumefantrine (n = 10) or dihydroartemisinin-piperaquine (n = 1) or atovaquone-proguanil (n = 2); patients with *P. vivax* malaria also received a 14-day treatment course of primaquine (dosage 0.5 mg/kg/day). Parasite clearance was achieved between Day 2 and Day 4 after treatment initiation in patients for whom daily parasitology was performed, with the exception of 1 patient (case 9, Fig. 2) who had a significantly prolonged clearance of peripheral parasitemia. All patients except one with *P. vivax* mono-infection received initial treatment in a pediatric intensive care unit (PICU). Median (IQR) time until discharge from PICU and hospital was 2 (2;3) and 5.5 (4;8) days, respectively. All but one patient (case 9, Fig. 2) were cured without residual sequelae. Antimalarial treatment details and outcomes are presented in Table 2.

Posttreatment hemolysis was experienced by 3 of 9 patients who were followed up for more than 7 days. None of them required blood transfusion (BT) and no additional specific therapeutic actions were necessary. The courses of the laboratory markers for patients with posttreatment hemolysis are shown in Figure 1. ivA was well tolerated without any documented, drug-related adverse events.

One patient, a 7-year-old girl (Case 9, Fig. 2), presented with hyperparasitemia of 25%, together with renal and respiratory failure, acidosis, shock and rhabdomyolysis requiring organ replacement therapy and extensive supportive treatment. In this patient, parasitemia declined rapidly during the first 5 days but then persisted at around 5% of red blood cells for 5 more days, despite continued daily ivA treatment for 9 days. Thereafter, low-level parasitemia persisted further for a total of 22 days after initiation of treatment, but no resurgence of parasitemia was observed after termination of antiparasitic treatment on Day 9. On microscopy, parasites appeared pyknotic (Fig. 3). Molecular analysis of the propeller region of the *Kelch13* gene of parasites collected on Days 2, 4 and 5 of treatment revealed no mutation associated with artemisinin resistance.

This patient received 5 BTs during the first 10 days of therapy. Sharp declines in hemoglobin requiring further BT on Day 14 and Day 19 were related to clotting during renal replacement

TABLE 1. Baseline Characteristics of Children With Severe Imported Malaria Treated With Intravenous Artesunate, Germany 2010-2018

Case	Age (years)	Sex (female or male)	Body Weight (kg)	Country of Malaria Acquisition	Purpose of Travel	Malaria Prophylaxis	*Plasmodium* species	Parasitemia (%)	Criteria of Severe Malaria on Admission	Hemoglobin (g/dL)
1	0.4	f	7.5	Nigeria	VFR	Mefloquine (incomplete)	*P. falciparum*	18	Hyperparasitemia, anemia	7.3
2	1	f	10	Togo	VFR	Doxycyclin*	*P. falciparum*	24	Hyperparasitemia	8.9
3	1	f	11	Mozambique	NN	No	*P. falciparum*	9	Hyperparasitemia	9.3
4	1	m	12	Cameroon	VFR	Mefloquine	*P. falciparum*	0.01	Anemia*	7.2
5	4	m	17	Ghana	Deportation	No	*P. falciparum* *P. vivax*	3	Anemia, lactate acidosis	5.8
6	6	m	21	Ghana	VFR	Mefloquine (incomplete)	*P. falciparum*	16	Hyperparasitemia	10.0
7	6	m	25	Togo	VFR	Mefloquine	*P. falciparum*	3	Seizure†	10.1
8	7	m	22	Mozambique	VFR	No	*P. falciparum*	7	Hyperparasitemia	8.5
9	7	f	48	Nigeria	VFR	Chloroquine‡	*P. falciparum*	25	Hyperparasitemia, acidosis, impaired consciousness, hypoglycemia, renal impairment	10.1
10	9	f	37	Cameroon	NN	No	*P. falciparum*	12	Hyperparasitemia, anemia, impaired consciousness	6.9
11	9	f	38	Cameroon	VFR	No	*P. falciparum*	16	Hyperparasitemia, impaired consciousness, hypoglycemia, anemia	5.0
12	11	f	42	Nigeria	VFR	No	*P. falciparum*	10	Hyperparasitemia, pulmonary edema, renal impairment	7.8
13	15	m	50	Eritrea or Ethiopia	Asylum seeking unaccompanied minor	No	*P. vivax*	1	Prostration	6.2
14	17	m	62	Togo	Resident in Togo	No	*P. falciparum*	5	Hyperparasitaemia§	11.7

* Anemia was judged to be severe according to local standards at the Berlin site, although WHO criterion of severe malaria was not fulfilled in this patient.

† This child had one protracted episode of convulsion that ceased only after administration of intravenous lorazepam; parasitemia was 3% and the patient was unable to take oral medication due to its postictal impaired consciousness. Therefore, the site started intravenous artesunate.

‡ No further information on reasons for this prophylaxis available.

§ As living in an endemic area, severe malaria would be more appropriately classified if hyperparasitemia >10% (WHO).

VFR, visiting friends and relatives; NN: not known.

TABLE 2. Antimalarial Treatment and Outcome of Children With Severe Imported Malaria Treated With ivA, Germany 2010–2018

Cases	Doses ivA (n)	Dosage ivA per Injection (mg/kg)	First Day of Slide Negativity	Complications During or After Treatment	Days Until Discharge From PICU	Days Until Discharge From Hospital	Outcome (Days of Follow-up After Treatment Initiation)
1	4	2.0*	Day 4	BT on Day 2	2	5	Cured without residues (22)
2	3	2.4	Day 3	PTH	2	7	Cured without residues (21)
3	2	2.5	Day 2	PTH	2	4	Cured without residues (28)
4	3	2.5	Day 2	No	2	7	Cured without residues (28)
5	2	2.4	Day 3–4†	No	2	7	Cured without residues (23)
6	3	2.4	Day 3	PTH	3	10	Cured without residues (41)
7	3	2.4	Day 3–5†	No	3	6	Cured without residues (6)
8	3	2.4	Day 3	No	1	3‡	Cured without residues (3)
9	10	2.5	>3 weeks	multiple, see Figure 2	31	59	Critical illness myopathy, contractures, motoric retardation (2 years)
10	4	2.5	Day 3	No	4	5	Cured without residues (6)
11	5	2.4	Day 2	No	1	4	Cured without residues (21)
12	3	2.5	Day 2	Glomerulone-phritis	3	13	Cured without residues (124)
13	3	2.4	>2 Days	No	NA	5	Cured without residues (5)
14	1	2.0	Day 3	No	2	4	Cured without residues (4)

*Preceded by 1 tablet Malarone Junior

†Parasitology was not performed daily, days presented are the last day of positive parasitology and first day of negative parasitology.

‡Against medical advice

PTH, posttreatment hemolysis.

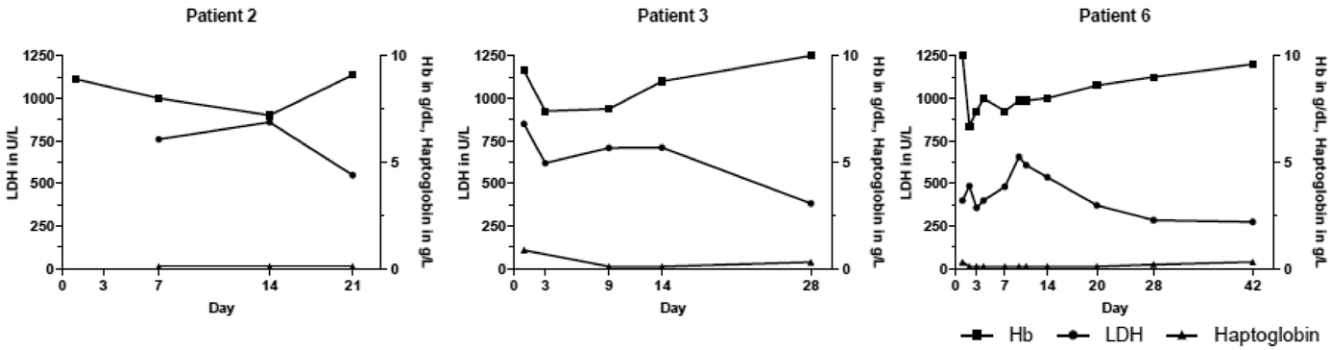

FIGURE 1. Course of hemoglobin, LDH and haptoglobin in 3 pediatric patients with severe malaria and posttreatment hemolysis after treatment with ivA.

therapy; no increase in LDH levels was observed making acute posttreatment hemolysis unlikely. Peripheral hypoperfusion during vasopressor treatment resulted in necrosis of a finger necessitating skin transplantation 5 weeks after treatment and consecutively she developed lymphedema. The patient developed critical illness myopathy with consecutive severe contractures requiring surgery and ongoing orthopedic support, as well as motor retardation and progressive obesity. Due to these conditions, she receives continuous medical support 3 years after the malaria episode; she is, however, well enough to attend a regular school.

DISCUSSION

Efficacy of ivA was excellent in this series of children of African descent with imported severe malaria. All patients survived. Overall, parasite clearance time was short, and the majority of patients could be discharged from hospital within a week of admission.

Data on ivA treatment in children outside endemic areas are limited: In a case series of 29 children in France treated with ivA for severe malaria, all cases showed rapid improvement and a favorable outcome without any significant adverse events.[11] A case series by Zoller et al,[7] and the TropNet Severe Malaria study,[15] each included 1 child with artesunate treatment. Both children were quickly cured without sequelae. A case series from the Netherlands and Belgium included 3 children,[10] one of whom was treated with parenteral quinine and artesunate in combination. This child experienced posttreatment hemolysis with a hemoglobin nadir of 6.1 g/dL on Day 8. A retrospective report from Spain mentions the switch from quinine plus clindamycine to ivA in 2 children with imported severe malaria.[16]

In recent years, episodes of delayed hemolysis have been reported with increasing frequency, particularly among nonimmune Caucasian-European adults treated with ivA for imported severe malaria.[17] In the present study, applying a sensitive definition,[13] posttreatment hemolysis occurred in 3 of 9 (30%) pediatric patients with *P. falciparum* infection and at least 3 weeks of follow-up, a rate that is comparable to data on European adults with severe malaria and artesunate treatment.[8,18] Posttreatment hemolysis occurred in young children with comparatively high parasite counts. However, it is notable that hemolytic reactions were mild. Neither BTs nor further therapeutic actions were required.

For African children in endemic areas, the phenomenon of posttreatment hemolysis appears to be far less frequent. Two

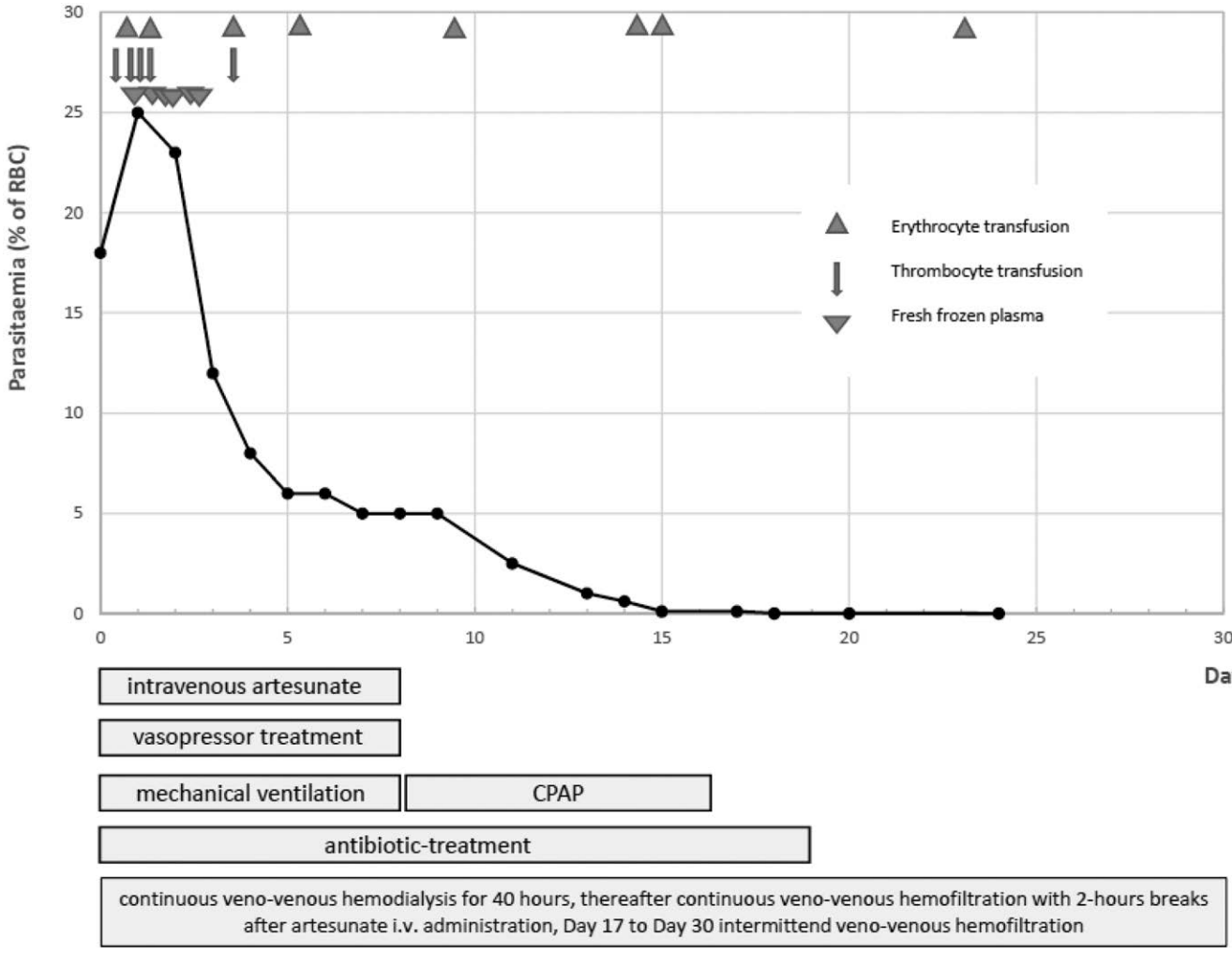

FIGURE 2. Course of parasitemia under ivA and supportive treatment in a child with severe imported malaria and multi-organ failure (case 9).

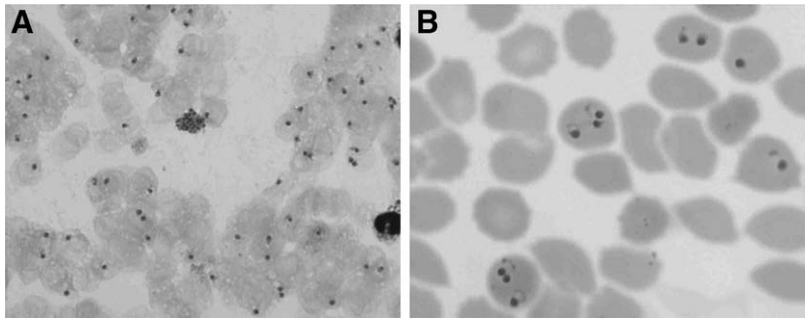

FIGURE 3. Thick and thin blood film showing persisting parasitemia under treatment with ivA in patient 9. Note the schizont (**A**) and the pyknotic parasites inside red blood cells (**B**).

prospective studies in Africa (using different definitions) found posttreatment hemolysis present in only 5%–7% of pediatric patients treated with ivA.[19,20] All patients in the present case series were of African descent. The data therefore indicate that delayed hemolytic reactions following treatment with ivA are unlikely to be linked with genetic factors but rather with the status of semi-immunity for instance. They clearly document the usefulness of close clinical and laboratory follow-up during the first month after ivA.

With the exception of posttreatment hemolysis, no adverse events, which clinically could be attributed to ivA, were documented in our case series of pediatric patients in Germany. The sequelae in case 9 are judged to be related to severe malaria and intensive care treatments; however, a (partial) contribution of the antimalarial treatment cannot be excluded. This provides further support for a good safety profile of parenteral artesunate, also in patients who reside outside endemic areas.[11] ivA is especially valuable because it does not share many disadvantages of quinine,

in particular, the potential cardiotoxicity, the narrow therapeutic range, and frequent transient side effects, such as hypoglycemia, deafness and visual disturbance.

All patients in this case series are of African descent. These patients—and in particular those who travel to their former home countries to visit friends and relatives—frequently are at higher risk for imported malaria.[21] This is based on multiple factors like travel to more remote areas (with higher mosquito infestation), longer stays in exposed areas and less use of malaria prophylaxis (either due to a false belief about the medical necessity of malaria prophylaxis, cultural barriers or limited financial funds for medical prophylaxis).[22] Among adults with a history of migration from malaria-endemic regions, the risk of developing severe malaria has been linked to a potential decline in semi-immunity among this patient population.[18] For children whose parents have a history of migration from malaria-endemic regions, but who themselves never have lived in malaria-endemic areas, the risk of developing severe malaria seems to be even more pronounced, at least according to our experience

In the most seriously diseased child (case 9) of this case series peripheral parasitaemia initially showed quick reduction, but reached an unusual plateau by Day 5 and declined only very slowly afterwards (Fig. 2). Possible causes considered included diminished parasite sensitivity to artesunate or insufficient blood levels of artesunate due to continuous hemofiltration. Molecular analysis revealed wild-type *Kelch13* propeller gene. No difference was achieved when hemofiltration was paused for 2 hours during and after ivA administration. Prolonged clearance of parasites has been reported in splenectomized patients with malaria.[23,24] However, the patient had neither history of splenectomy nor sonographic abnormalities of the spleen. Nevertheless, functional asplenia as underlying cause was supported by the fact that no resurgence in parasitemia was noted after termination of antiplasmodial treatment on Day 9. Possibly the capacity of the spleen to clear parasites had been exhausted by the high initial parasite load in this patient, leaving dead parasites circulating in the peripheral blood.

To the best of our knowledge, this series includes the first reported case of severe imported *P. vivax* malaria treated with ivA in children. One case of successful treatment of *P. vivax* malaria with ivA in a neonate has been reported from Indonesia where malaria is endemic.[25]

Our case series is limited by its retrospective design and a missing control group. All children were of African descent. This may limit generalization of our results to non-African children.

One patient (case 4) with severe anemia and 1 patient (case 7) with a single but protracted convulsion were included in this series; both were not strictly fulfilling WHO criteria of severe malaria but received ivA justified by a local predefined cutoff for severe anemia and a critical clinical condition. Indicators for post-treatment hemolysis were not investigated systematically, mild episodes may therefore have been missed in further patients. However, the present data strengthen the recommendation for the use of ivA as therapy in the treatment of severe malaria in children outside endemic areas and adds knowledge on posttreatment hemolysis in this patient population.

REFERENCES

1. Schlagenhauf P, Weld L, Goorhuis A, et al; EuroTravNet. Travel-associated infection presenting in Europe (2008-12): an analysis of EuroTravNet longitudinal, surveillance data, and evaluation of the effect of the pre-travel consultation. *Lancet Infect Dis.* 2015;15:55–64.
2. Hagmann S, Neugebauer R, Schwartz E, et al; GeoSentinel Surveillance Network. Illness in children after international travel: analysis from the GeoSentinel Surveillance Network. *Pediatrics*. 2010;125:e1072–e1080.
3. World Health Organization. *Guidelines for the Treatment of Malaria. 3rd edition*. Geneva;2015.
4. Dondorp A, Nosten F, Stepniewska K, et al; South East Asian Quinine Artesunate Malaria Trial (SEAQUAMAT) Group. Artesunate versus quinine for treatment of severe falciparum malaria: a randomised trial. *Lancet.* 2005;366:717–725.
5. Dondorp AM, Fanello CI, Hendriksen IC, et al; AQUAMAT Group. Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): an open-label, randomised trial. *Lancet*. 2010;376:1647–1657.
6. Cramer JP, López-Vélez R, Burchard GD, et al. Treatment of imported severe malaria with artesunate instead of quinine–more evidence needed? *Malar J*. 2011;10:256.
7. Zoller T, Junghanss T, Kapaun A, et al. Intravenous artesunate for severe malaria in travelers, Europe. *Emerg Infect Dis.* 2011;17:771–777.
8. Jauréguiberry S, Thellier M, Ndour PA, et al; French Artesunate Working Group. Delayed-onset hemolytic anemia in patients with travel-associated severe malaria treated with artesunate, France, 2011-2013. *Emerg Infect Dis*. 2015;21:804–812.
9. Roussel C, Caumes E, Thellier M, et al. Artesunate to treat severe malaria in travellers: review of efficacy and safety and practical implications. *J Travel Med*. 2017;24. doi: 10.1093/jtm/taw093.
10. Kreeftmeijer-Vegter AR, van Genderen PJ, Visser LG, et al. Treatment outcome of intravenous artesunate in patients with severe malaria in the Netherlands and Belgium. *Malar J.* 2012;11:102.
11. Levy M, Pham LL, Faye A, et al. Parenteral artesunate for severe imported *Plasmodium falciparum* malaria in children. *Pediatr Infect Dis J*. 2016;35:1053–1054.
12. Deutsche Gesellschaft für Tropenmedizin und Internationale Gesundheite e.V. *Leitlinie Malaria 2016*. Available at: https://www.dtg.org/empfehlungen-und-leitlinien/leitlinien.html. Accessed May 27, 2019.
13. Jauréguiberry S, Ndour PA, Roussel C, et al; French Artesunate Working Group. Postartesunate delayed hemolysis is a predictable event related to the lifesaving effect of artemisinins. *Blood*. 2014;124:167–175.
14. Ariey F, Witkowski B, Amaratunga C, et al. A molecular marker of artemisinin-resistant *Plasmodium falciparum* malaria. *Nature*. 2014;505:50–55.
15. Kurth F, Develoux M, Mechain M, et al; TropNet Severe Malaria Investigator Group. Intravenous artesunate reduces parasite clearance time, duration of intensive care, and hospital treatment in patients with severe malaria in Europe: the tropNet severe malaria study. *Clin Infect Dis*. 2015;61:1441–1444.
16. Sánchez BS, Tato LMP, Martín SG, et al; Cohort of Children With Malaria in Madrid, Spain. Imported malaria in children in Madrid, Spain, 2007-2013. *Enferm Infecc Microbiol Clin*. 2017;35:348–353.
17. Rolling T, Agbenyega T, Krishna S, et al. Delayed haemolysis after artesunate treatment of severe malaria - review of the literature and perspective. *Travel Med Infect Dis*. 2015;13:143–149.
18. Kurth F, Develoux M, Mechain M, et al. Severe malaria in Europe: an 8-year multi-centre observational study. *Malar J*. 2017;16:57.
19. Rolling T, Agbenyega T, Issifou S, et al. Delayed hemolysis after treatment with parenteral artesunate in African children with severe malaria–a double-center prospective study. *J Infect Dis*. 2014;209:1921–1928.
20. Fanello C, Onyamboko M, Lee SJ, et al. Post-treatment haemolysis in African children with hyperparasitaemic falciparum malaria; a randomized comparison of artesunate and quinine. *BMC Infect Dis*. 2017;17:575.
21. Antinori S, Napolitano M, Grande R, et al. Epidemiological and clinical characteristics of imported malaria in adults in Milan, Italy, 2010–2015. *Eur J Intern Med*. 2018;57:e13–e16.
22. Neave PE, Behrens RH, Jones CO. "You're losing your ghanaianess": understanding malaria decision-making among Africans visiting friends and relatives in the UK. *Malar J*. 2014;13:287.
23. Chotivanich K, Udomsangpetch R, McGready R, et al. Central role of the spleen in malaria parasite clearance. *J Infect Dis*. 2002;185:1538–1541.
24. Le TA, Davis TM, Tran QB, et al. Delayed parasite clearance in a splenectomized patient with falciparum malaria who was treated with artemisinin derivatives. *Clin Infect Dis*. 1997;25:923–925.
25. Tatura SNN, Wowor EC, Mandei JM, et al. Case report: severe *Plasmodium vivax* malaria mimicking sepsis in a neonate. *Am J Trop Med Hyg*. 2018;98:656–659.