

Treatment of severe malaria

TropNet Europ study

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Aims of the TropNet severe malaria/artesunate project

1. European database of patients with severe malaria
 2. Database of patients treated with i.v.-artesunate
- Inclusion of all patients regularly reported to the network fulfilling at least 1 WHO criterion for severe malaria, regardless of treatment regimen
- Observational study, open-label, not randomized



Position statement TropNet 2005

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Intravenous artesunate for treatment of patients with severe malaria: position statement of TropNetEurop

TropNetEurop recommends the application of i.v. artesunate in patients with severe malaria despite the unresolved issue of lacking GMP standards of the currently available artesunate formulation. A GMP-manufactured product of this drug should be introduced and distributed in Europe as soon as possible. The quality of the product used should be confirmed by international studies. Quality controls of single batches should be available. TropNetEurop will be monitoring patients who have received this drug.



Rationale (1)

- **TropNet** only European source of information on patients treated outside endemic areas under western-standard ICU conditions with significant patient numbers
- **Pharmacovigilance** system for the use of a unlicensed drug
- Information valuable for **EMA approval** of i.v.-artesunate, pre- or post-licensing study
- **New/modified position statement and criteria** for artesunate use on basis of network data



Rationale (2)

Can data from SEQUAMAT or other studies in developing countries be transferred to European patients ?

- Closer monitoring of patients
- Longer follow-up
- Higher probability to detect drug-related adverse reactions
- Different conditions of ICU care – influence on outcome ?



Regulatory issues – licensing in Europe and the U.S.

United States

- Treatment IND (investigational new drug) programme in place since July 2007
- Ongoing process of evaluation at FDA on basis of results from phase I&II studies

Europe

- Artesunate (iv) receives orphan drug designation from EMEA on 07 January 2008, involving
 - 10 year market exclusivity for the EU for the sponsor company
 - Protocol assistance from EMEA for designing studies towards licensing the drug
 - Fee reductions for application procedures at EMEA
 - Access to funds to further investigate the drug from the EU
- More pre- or post-marketing studies required for EMEA approval ?



Synopsis of current study database (1)

- 10 centres contributed: NEW, LED, VIK, BER, TRB, PAT, HEL, VIR, KRI, POZ, BEC
- 31 patients in database
 - 16 patients with new case reporting form
 - 7 patients with old case reporting form
 - 8 patients on regular TropNet surveillance questionnaire
- Treatment
 - 21 patients with iv Artesunate as first-line therapy
 - 3 patients with iv Artesunate as second-line therapy
 - 5 patients with iv quinine as first-line therapy
 - 1 patient with artemether as first-line therapy
 - 1 patient with mefloquine as first-line therapy



Synopsis of current study database (2)

- Outcome
 - 100% survival
 - Post-treatment haemolysis up to day 21 observed in 3 patients with i.v. artesunate of unknown cause (in 2 centres)



Next steps

- Aim: first preliminary data analysis after inclusion of 50 complete patient data sets of patients with i.v.-Artesunate (TropNet severe malaria reporting form)
- Publication of data following usual TropNet procedures
- Preparation of data for EMEA and manufacturer of GMP-artesunate
- Long-term goal: inclusion of 200 complete patient data sets (at least 100 with iv Artesunate as first-line therapy)
- Ongoing pharmacovigilance of artesunate use



Quinine or artesunate ?

Criteria used at MICU Charité, Berlin

Artesunate	Quinine
Pro <ul style="list-style-type: none"> • Parasitaemia >10% • Cardiac comorbidities • Blackwater fever • Complications under treatment with quinine • Not licensed, but orphan drug status of EMEA 	Pro <ul style="list-style-type: none"> • Licensed for severe malaria • Reasonably safe in pregnancy • In pt. with parasitaemia <10% probably not inferior to artesunate in terms of survival
Con <ul style="list-style-type: none"> • Off-label use • Pregnancy • Potential post-treatment haemolysis of unknown origin 	Con <ul style="list-style-type: none"> • QT prolongation, risk of tachyarrhythmia • Hypoglycemia • May trigger blackwater fever • Rarely: resistance



Availability of artesunate

- Non-GMP i.v. artesunate
 - Imported to Europe by IDIS pharma www.idispharma.com, see „contact“, 148€ for 8 vials of 60mg artesunate (Nov 2008)
- GMP i.v. artesunate
 - Manufacturing process complicated; problems with sterilisation of substance
 - Last year: commercial availability anticipated for 2010
 - Information by SigmaTau 09/2009: product probably not available before 2012



Inclusion of patients

1. Report of regular TropNet surveillance dataset by electronic reporting or fax
 2. If the patient meets at least one WHO criterion for severe malaria: Report of additional data on **TropNet severe malaria reporting form**, available from www.artesunate.info, and **transmission by fax to the TropNet data center** using the same number as for reporting the regular dataset
- Receipt of a TropNet severe malaria reporting form will be separately acknowledged by e-mail to the site manager within 4 weeks from the study centre



New severe malaria case reporting form

TropNetEurop – case reporting form for patients with severe *P. falciparum* malaria

Fill together with surveillance report of same patient to +49-50-56802544, an. Dr. T. Jelinek. In case of electronic reporting, please fill in TropNet-SIMPID ID assigned by your Sentry Software.

Child ID	TropNet-SIMPID ID	Patient ID
(Fill in, if malaria case has been reported electronically) (Fill in, if malaria case has been reported on paper)		
Pre-treatment criteria of severe malaria according to WHO definition (tick at least one): <input type="checkbox"/> Confirmed malaria or coma <input type="checkbox"/> Convulsion <input type="checkbox"/> Acute renal failure (serum creatinine >440 µmol/L or creatinine >2 mg/dl) <input type="checkbox"/> Respiratory failure <input type="checkbox"/> Hypoglycaemia (<2.5 mmol/L or <45 mg/dl) <input type="checkbox"/> Shock		
Significant pre-existing comorbidities of the patient: 1. 2. 3. 4. 5.		

Treatment regimen		First-line Treatment		Yes	No
Date Day 1: Day of Dx and start of first line Tx (Abbrevy)		/ /			
Adherence of oral antimalarials	Start of administration	End of administration	Dosage per dose (drugs correct units)		
Drug1	Day #	Day #	mg or mcg/kg		
Drug2	Day #	Day #	mg or mcg/kg		
Drug3	Day #	Day #	mg or mcg/kg		
Drug4	Day #	Day #	mg or mcg/kg		
Additional supportive treatment / drugs:					
If artesunate or quinine is used, please specify source of drug:					

Efficiency of treatment and clinical outcome	Duration of hospital treatment	days	ICU treatment	days
Parasitaemia at (if available)	At or % of FBC's (specify)	Parasitaemia at	At or % of FBC's (specify)	
baseline		36 hr after 1 st dose		
4 hr after 1 st dose		48 hr after 1 st dose		
12 hr after 1 st dose		48 hr after 1 st dose		
24 hr after 1 st dose		Parasitaemia clearance		hours

Specific supportive therapy used:	Other:
<input type="checkbox"/> Mechanical ventilation <input type="checkbox"/> 0 breaths / min <input type="checkbox"/> Blood pressure (mmHg) <input type="checkbox"/> End-tidal CO ₂ (mmHg) <input type="checkbox"/> Urinary output (ml/h) <input type="checkbox"/> Transfusion of RBC <input type="checkbox"/> Transfusion of plasma fraction	<input type="checkbox"/> None <input type="checkbox"/> Parenteral nutrition (0.1-0.35 kcal/ml) <input type="checkbox"/> Parenteral electrolytes / vitamins <input type="checkbox"/> Diuretics / Furosemide <input type="checkbox"/> Shock / SIRS <input type="checkbox"/> Respiratory failure <input type="checkbox"/> Pulmonary oedema <input type="checkbox"/> Acute renal failure (serum creatinine >440 µmol/L or creatinine >2 mg/dl) <input type="checkbox"/> Coagulopathy (INR >1.5 or aPTT >1.5x normal) <input type="checkbox"/> Cardiac arrest <input type="checkbox"/> Metabolic acidosis (pH <7.35) <input type="checkbox"/> Spontaneous bleeding <input type="checkbox"/> Neurological deterioration
Outcome:	<input type="checkbox"/> Case without sequelae <input type="checkbox"/> Case with sequelae <input type="checkbox"/> Exit on day
Outcome details:	
Follow up: Follow up on day 14 after 1 st dose: yes / no Follow up on day 28 after 1 st dose: yes / no Follow up on day 36 after 1 st dose: yes / no Follow up on day 48 after 1 st dose: yes / no Follow up on day 60 after 1 st dose: yes / no	
Clinical / laboratory follow-up examinations: (Day 14, Day 28, Day 36, Day 48, Day 60) (Day 14, Day 28, Day 36, Day 48, Day 60) (Day 14, Day 28, Day 36, Day 48, Day 60)	

Screening for adverse drug reactions	Adverse drug reaction reported	Yes	No	If yes, specify below
Adverse drug reaction (Please, fill in name of the drug + adverse drug reaction)	Day of onset	Day of resolution	Severity at onset (mild, moderate, severe, specific treatment needed)	Resolution with drug
1.				
2.				
3.				
4.				

Further Comments:

Project website: www.artesunate.info

Epidemiology, treatment and outcomes of severe malaria in Europe
A TropNetEurop study

www.artesunate.info
www.artesunate.eu

This website is part of:

28 April 2008 - Update on i.v.-artesunate

Availability of artesunate
Current situation in the U.S. - an investigational new drug (IND) program is in place and running where the CDC provides i.v.-artesunate upon request to hospitals from certain places throughout the country. So far, in all patients the drug was effective and no specific adverse reactions were observed. The drug distributed by the CDC is a lot produced four years ago as a study drug, manufactured under GMP standards by the Walter Reed Institute. The amount of drug available is limited and no new study drug or commercial drug is available. Although there is no specified shelf-life, the question of stability will become increasingly important for its use in the future.
Sigma-Tau, manufacturer of the future artesunate produced under GMP standards, has informed the network today that due to unforeseen technical problems in the manufacturing process, the commercial form of the drug will not be available before the 4th quarter of 2008.
In Europe, no i.v.-artesunate is available other than the drug imported from China (for details see "Artesunate availability (Wt)").

Press release from Sigma-Tau (Manufacturer of the future GMP artesunate)
Artesunate has received orphan drug status from the EMA on 07 January 2008. For more details on the orphan drug designation, please see below. Sigma-Tau has now issued a press release regarding the orphan drug status of i.v.-artesunate (Sigma-Tau press release).

Approval FDA and EMA - update
The process of FDA approval is underway and the available data from SE Asia (SEQUAMAT, using the Chinese non-GMP product) along with the phase I and II studies completed in the U.S. and in Africa (using the Walter-Reed Artesunate) are likely to be sufficient to confirm its efficacy. Whether more data on toxicity will be required, is still open at the time of writing. After all risks with manufacturing the drug are solved, the final approval is anticipated in early 2010.
In Europe, with the orphan drug designation artesunate has passed a first step towards approval at the EMA, but EMA approval is not expected before completion of the full FDA approval. In the meantime, the investigational use of the drug under strict pharmacovigilance is supported by the EMA orphan drug designation.

07 January 2008 - Artesunate receives orphan drug status from EMA
Artesunate (i.v. formulation for use in severe malaria) has received the Orphan Medicinal Drug Designation from the European Medicines Agency (EMA). This is not a marketing authorization, but the Orphan Drug status is an important step towards licensing this drug. This status for i.v.-artesunate includes:
- 10 year market exclusivity for the EU for the sponsor (Sigma-Tau)
- Protocol assistance from EMA for designing studies towards licensing the drug
- Fee reductions for application procedures at EMA
- Access to funds to further investigate the drug from the EU
Furthermore, this is an important step towards availability of the drug within the EU since the decision by the COMP expert committee gives investigators more solid legal basis for carrying out studies or including patients e.g. on a named-patient basis.
The full summary of EMA on artesunate can be accessed at:
http://www.ema.europa.eu/pdfs/files/summary/summary_0000100710.pdf
More information about EMA's COMP committee:

- Information about artesunate
- Availability of artesunate
- Study protocol
- Case report form

Thank you for contributing to the study !

CHARITÉ