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

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Position statement TropNet 2005

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Berlin, Oct., 31st, 2005

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.

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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 **EMEA approval** of i.v.-artesunate, pre- or post-licensing study
- **New/modified position statement and criteria** for artesunate use on basis of network data

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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 ?

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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 ?

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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

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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)

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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

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Quinine or artesunate ?

Criteria used at MICU Charité, Berlin

Artesunate	**Quinine**
Pro • Parasitaemia >10% • Cardiac comorbidities • Blackwater fever • Complications under treatment with quinine • Not licensed, but **orphan drug status of EMEA**	**Pro** • Licensed for severe malaria • Reasonably safe in pregnancy • In pt. with parasitaemia <10% probably not inferior to artesunate in terms of survival
Con • Off-label use • Pregnancy • Potential post-treatment haemolysis of unknown origin	**Con** • QT prolongation, risk of tachyarrhythmia • Hypoglycemia • May trigger blackwater fever • Rarely: resistance

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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

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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

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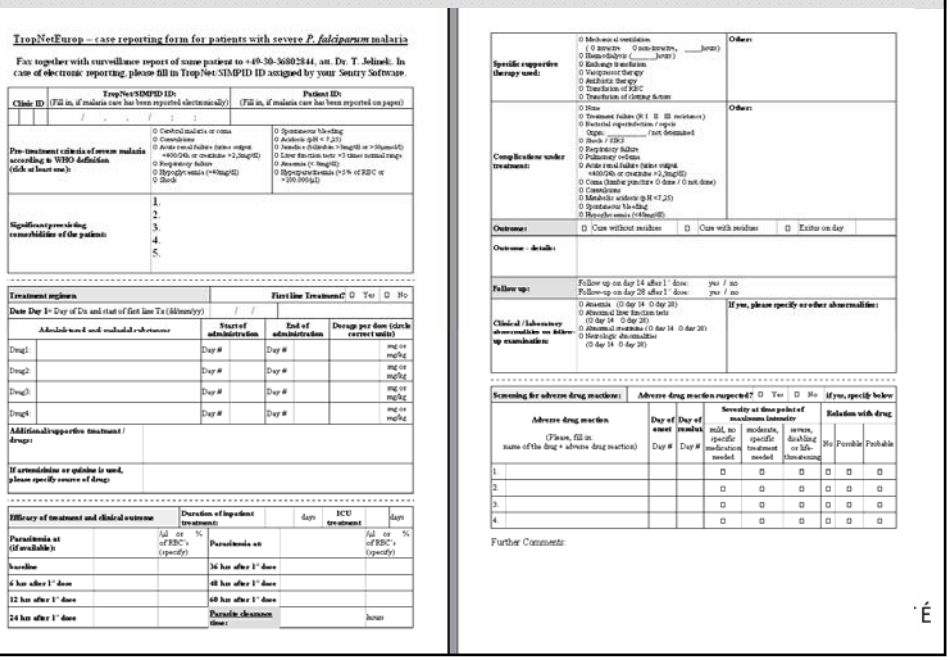
New severe malaria case reporting form



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

Fax together with surveillance report of same patient to +49-30-36802844, att. Dr. T. Jelinek: In case of electronic reporting, please fill in TropNet/SIMPID ID assigned by your Sentry Software.

TropNet/SIMPID ID: Clinic ID (Fill in, if malaria case has been reported electronically)	Patient ID: (Fill in, if malaria case has been reported on paper)
/ . . / : :	

Pre-treatment criteria of severe malaria according to WHO definition (tick at least one):	○ Cerebral malaria or coma ○ Convulsions ○ Acute renal failure (urine output <400/24h or creatinine >2,2mg/dl) ○ Respiratory failure ○ Hypoglycaemia (<40mg/dl) ○ Shock	○ Spontaneous bleeding ○ Acidosis (pH < 7,25) ○ Jaundice (bilirubin >3mg/dl) or >50µmol/l) ○ Liver function tests >3 times normal range ○ Anaemia (< 5mg/dl) ○ Hyperparasitaemia (>2 % of RBC or >200.000/µl)
Significant preexisting 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 (dd/mm/yy)	/ /			
Administered and cumulative dose	Start of administration	End of administration	Dosage per dose (circle correct unit)	
Drug1:	Day #	Day #		mg or mg/kg
Drug2:	Day #	Day #		mg or mg/kg
Drug3:	Day #	Day #		mg or mg/kg
Drug4:	Day #	Day #		mg or mg/kg
Additional/supportive treatment / drugs:				
If artemisinine or quinine is used, please specify source of drug:				

Efficacy of treatment and clinical outcome			Duration of inpatient treatment:		days	ICU treatment		days
Parasitemia at (if available):		/ul or % of RBC's (specify)	Parasitemia at:				/ul or % of RBC's (specify)	
baseline			36 hrs after 1st dose					
6 hrs after 1st dose			48 hrs after 1st dose					
12 hrs after 1st dose			60 hrs after 1st dose					
24 hrs after 1st dose			Parasite clearance time:				hours	

Specific supportive therapy used:	○ Mechanical ventilation (○ invasive ○ non-invasive, ____hours) ○ Hemodialysis (_____hours) ○ Exchange transfusion ○ Vasopressor therapy ○ Antibiotic therapy ○ Transfusion of RBC ○ Transfusion of clotting factors	Other:
Complications under treatment:	○ None ○ Treatment failure (R I II III resistance) ○ Bacterial superinfection / sepsis Organ: _____ (not determined ○ Shock / DIC ○ Respiratory failure ○ Pulmonary oedema ○ Acute renal failure (urine output <400/24h or creatinine >2,2mg/dl) ○ Coma (lumbar puncture ○ done / ○ not done) ○ Convulsions ○ Metabolic acidosis (pH <7,25) ○ Spontaneous bleeding ○ Hypoglycaemia (<40mg/dl)	Other:
Outcome:	☐ Cure without residues ☐ Cure with residues ☐ Exitus on day	
Outcome - details:		
Follow up:	Follow up on day 14 after 1st dose: yes / no Follow-up on day 28 after 1st dose: yes / no	
Clinical / laboratory abnormalities on follow-up examinations:	○ Anaemia (○ day 14 ○ day 28) ○ Abnormal liver function tests (○ day 14 ○ day 28) ○ Abnormal creatinine (○ day 14 ○ day 28) ○ Neurologic abnormalities (○ day 14 ○ day 28)	If yes, please specify or other abnormalities:

Screening for adverse drug reaction:	Adverse drug reaction suspected? ☐ Yes ☐ No					if yes, specify below
Adverse drug reaction (Please, fill in: name of the drug + adverse drug reaction)	Day of onset Day #	Day of resolut. Day #	Severity at time point of maximum intensity: mild, no specific medication needed	moderate, specific treatment needed	severe, disabling or life-threatening	Relation with drug: No	Possible	Probable
1.			☐	☐	☐	☐	☐	☐
2.			☐	☐	☐	☐	☐	☐
3.			☐	☐	☐	☐	☐	☐
4.			☐	☐	☐	☐	☐	☐

Further Comments:

Project website: www.artesunate.info

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

Thank you for contributing to the study !

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