MALTHER study:
Therapy of uncomplicated falciparum malaria in Europe
- preliminary results -

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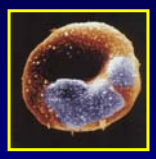


10th TropNetEurop Workshop
Verona, Italy
07/09/2009

Background

- in clinical terms, falciparum malaria is the most important 'tropical' disease imported into Europe
- current European standards of care are based on the respective national guidelines
- recommended therapies are based on data predominantly derived from therapeutic studies which have been performed in endemic areas

Background

- for epidemiological and biological reasons, those data are not always easily applicable to imported infections:

endemic areas	*non-endemic areas*
➢ large ethnically homogenous study cohorts	➢ small inhomogenous study cohorts
➢ comparable host immune status	➢ differences in host immune status
➢ comparable level of parasite drug resistance	➢ vast variations of parasite strains
➢ 'proper' trial design	➢ no 'prope' trials

Background

Therapeutic use of antimalarials in affluent, non-endemic countries remains to a certain extent empirical in character until present, as comparative studies between competing regimens are lacking.

Study objectives

To assess tolerance and efficacy of therapeutic regimens in use for the treatment of uncomplicated falciparum malaria imported into Europe

MALTHER study

- The overall aims are
  - ➢ to summarise data on treatment regimens in Europe
  - ➢ to harmonise treatment modalities for uncomplicated falciparum malaria
  - ➢ to optimise drug treatment strategies amongst participating centers
  - ➢ **to pave the way for more ambitious studies**

MALTHER study design

- Prospective
- Unrandomized
- Open-label
- Open time frame
- Observational

MALTHER study end points

- ***Primary***
  - ➢ Rate and severity of adverse events
- ***Secondary***
  - ➢ Clinical and parasitological cure rates on days 7 (28)
  - ➢ Duration of hospitalisation

MALTHER inclusion criteria

- confirmed uncomplicated falciparum malaria with or without (compliant or non-compliant) chemoprophylaxis performed
- no previous malaria therapy for the current episode of illness
- minimum age of 18
- informed consent, if non-routine procedures were performed at individual sites

MALTHER exclusion criteria

- age less than 18 years
- complicated/severe falciparum malaria
- refusal of informed consent

- pregnancy was not an exclusion criterion

MALTHER treatment principles

- treatment was performed, if feasible, in hospital
- post-discharge control examinations are recommended to be performed on day 28
- if not feasible, FU by telephone was at day 28 was attempted in order to detect R1 tx failures and possible late-onset Aes years
- Tx regimens as in routine use in participating European tx

MALTHER study documents

Online available - via TropNetEurop[1]/SIMPID[2] home pages:

- Study protocol
- Master ethics proposal
- Study software programs and tools
- ‚Help' documents (technical and medical)

[1]www.tropnet.net [2]www.simpid.de

MALTHER data analysis

- software instrument (Access database) based on routine surveillance instrument
- electronic data reporting to database scrutinized by TropNetEurop data manager

MALTHER study – n

- contributions from individual partner sites until end of recruitment – June 2009 -

BOB	F	135	29.80
MAS	F	116	25.61
TOR	I	41	9.05
BRE	I	39	8.61
FRK	D	35	7.73
ANT	B	26	5.74
TUE	D	12	2.95
BON	D	9	1.99
UDI	I	8	1.77
NEW	UK	7	1.55
ULM	D	7	1.55
BRT	D	4	0.88
FIR	I	3	0.66
POT	D	1	0.22

∑ **453**

MALTHER study – first results

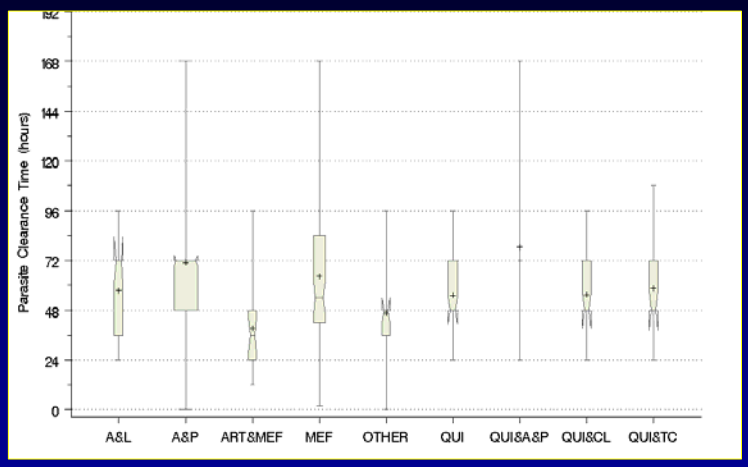
Therapeutic regimens used (first line t_x)

		1st line t_x	1st line t_x compl.	
A/P	249	54.97%	219/249	87.95%
M	69	15.23%	64/69	92.75%
Q	31	6.84%	25/31	80.65%
Ar/L	25	5.52%	23/25	92.00%
Ar/M	19	4.19%	19/19	100%
QC	19	4.19%	17/19	89.47%
QTC	16	3.53%	13/16	81.25%
Q/A/P	15	3.31%	15/15	100%
others*	10	2.21%	9/10	100%

A/P = Atovaquone/Proguanil (fixed combination); M = Mefloquine; Q = Quinine; C = Clindamycin; T = Doxycyclin; SP = Sulfadoxin-Pyrimethamine; Ar/L = Artemether/Lumefantrine (fixed combination); *e.g. Amodiaquine

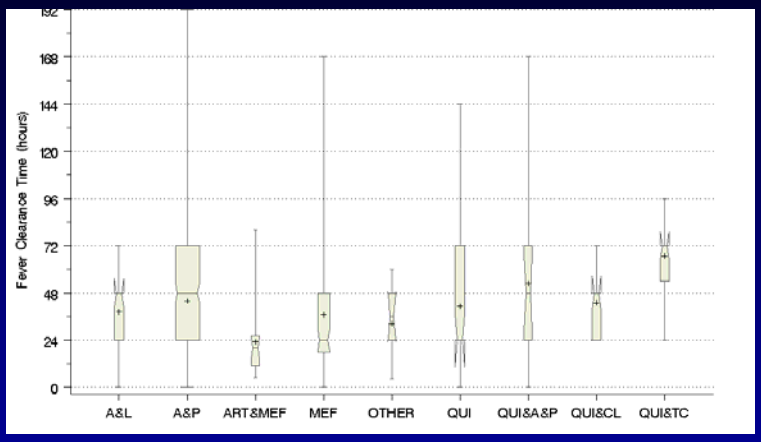
- detailed analysis of why tx was changed to follow -

PCT



Schematic Boxplot: Min; Last obs. within lower fence; Q1, Median; Q3, Last obs. within upper fence; Max; Mean = +; Box width varies with n
Kruskal-Wallis Test: $p < 0.0001$

FCT



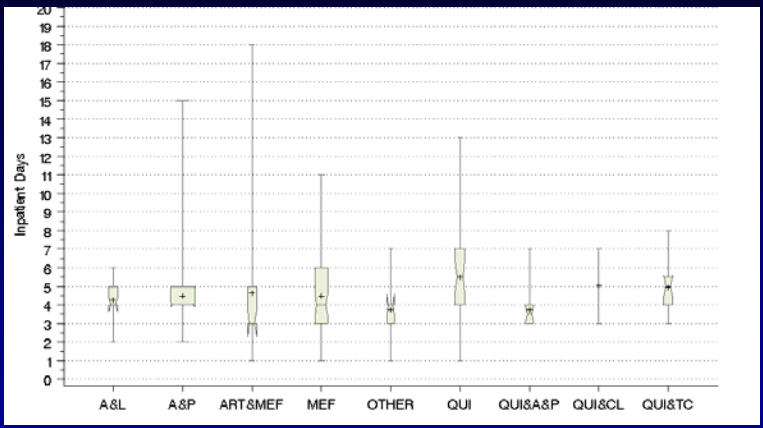
Schematic Boxplot: Min; Last obs. within lower fence; Q1, Median; Q3, Last obs. within upper fence; Max; Mean = +; Box width varies with n; Kruskal-Wallis Test: p = 0.0002

Cure on D 28 (1st line t_x)

Drug	yes		no		unknown		total
A/P	189	75.90%	2	0.80%	58	23.29%	249
M	54	78.26%	0		15	21.74%	69
Q	23	74.19%	0		8	25.81%	31
Ar/L	21	84.00%	1	4.00%	3	12.00%	25
Ar/M	8	42.11%	0		11	57.89%	19
QC	10	52.63%	0		9	47.37%	19
QTC	10	62.50%	0		6	37.50%	16
Q/A/P	13	86.67%	0		2	13.33%	15
others	7	70.00%	0		3	30.00%	10

Chi-Square p = 0.0478

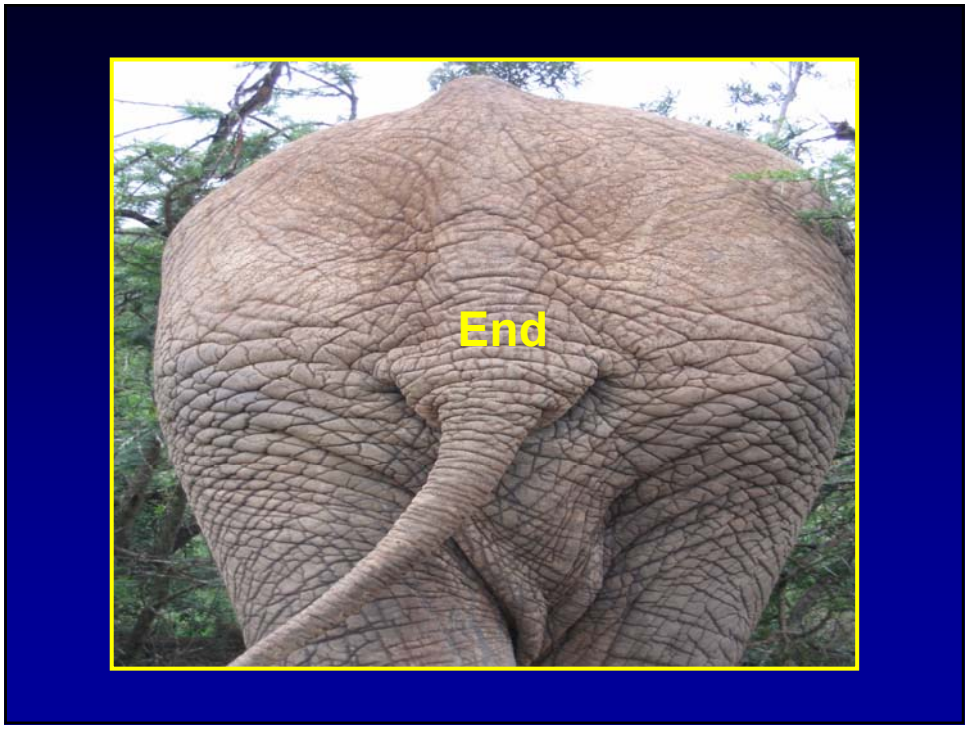
Inpatient days



Schematic Boxplot: Min; Last obs. within lower fence; Q1, Median; Q3, Last obs. within upper fence; Max; Mean = +; Box width varies with n
Kruskal-Wallis Test: p = 0.002

FACIT of interim analysis

- a comparative analysis of tx modalities of uncomplicated falciparum malaria across Europe is feasible and makes sense
- study may assist in optimizing tx and harmonizing guidelines
- study offers an excellent tool for AE recording
- study may serve as ‚proof of principle' that prospective tx studies across Europe are feasible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