Wrap-up: main findings, take home messages, future research

Disease and Health services: Clinical and epidemiological monitoring of treatment effectiveness

Disease and Parasites (India and Nepal): clinical samples and isolates from 2 cohorts of patients treated with SSG and MIL

Phenotyping: unique collection of parasites with variable susceptibility to SSG and MIL

Drug resistance markers

Targeted studies: candidate markers

Global studies: genome & metabome diversity

Epidemiological dynamics

Population genetics & fitness studies

Mathematical modelling of drug resistance

Translation of knowledge into practical tools for surveillance

Dissemination: health authorities

MIL efficacy

- Simple clinical and epidemiological tool for monitoring the effectiveness of Kala-Azar drug therapy in routine conditions
- Efficacy of MIL: similar results at 6 months follow-up in different settings (5-12 % TF)
- But, longer follow-up may reveal more relapses: 12-21 % TF
- Non response at the end of treatment (contrast with SSG) was not observed

MIL efficacy

Reason(s) of lower efficacy of MIL?

- True recrudescence and not reinfection
- Drug was OK
- Age = risk factor (lower exposure to MIL?)
- Not related to MIL-susceptibility of the parasite (no resistance found yet)
- No difference in MIL blood levels at end of tx (need for other parameter?)

Knowledge on drug-R

SSG-R

- Likely has emerged several times
- New mechanisms discovered: parasite manipulates the macrophage to extrude the drug (MDR)
- ‘Die-hard’ parasites, fitter, still abundant in the region
- Impact on other drugs?
- Imipramine could counter the SSG-R mechanism

Knowledge on drug-R

MIL-R

- No resistant strains among clinical isolates, well ‘tolerant’ ones: a few steps towards resistance?
- Studies on experimental strains: difficult to induce with *L.donovani* amastigotes
- Induction possible with promastigotes; molecular markers, but what is their value?

Knowledge on drug-R

PMM-R

- Studies on experimental strains: easy to induce with *L.donovani* amastigotes, stable phenotype
- Clinical impact of our findings?

Tools for monitoring drug-R

- Biological assays: amastigotes needed for most drugs, except MIL (simplified assay available)
- Serological assays: prototype under evaluation for tracking SSG-R
- Molecular tools: power of whole genome sequencing, translatable in simpler tools

Epidemiological findings

- Mathematical model of transmission: importance of asymptomatics; supports the fitness hypothesis (SSG-R)
- *L.donovani* = relatively homogeneous from genetic point-of-view (post-DDT epidemics?), but new variants very divergent were observed ('Yeti' strains in hills Nepal)
- Molecular tools available to track new epidemics

Take-home messages (1)

- Late treatment outcome monitoring should be extended to 12M; encourage PKDL patients for treatment ; optimal dosage for children
- **Monitoring** is best done by an outcome-based recording and reporting system as done in TB programs
- To reduce defaulters and treatment failures through insufficient adherence, **counseling** of VL patients on treatment adherence and management of side effects is crucial

Take-home messages (2)

- Existing network of ANMs/ASHAs are well placed to help in referral of suspected VL cases, supervision of treatment, and treatment outcome follow up
- To coordinate : reinforce the role of the Kala azar Treatment Supervisor (KTS) at block level

Take-home messages (3)

- Need to (keep on) monitoring drug susceptibility (all drugs, also new ones, also combinations); tools available
- MIL-resistance not yet detected
- SSG-resistance still present: clinical and epidemiological implications; argument against the re-introduction of SSG
- PMM-resistance easily induced in vitro: vigilance required if implemented in clinical practice

Take-home messages (4)

- full genome sequencing: more accessible, soon applicable directly in clinical samples; could become an element of surveillance (resistance or tracking the origin of new outbreaks); invest in infrastructure and people (bioinformatics)
- *L.donovani* from ISC is quite different from East Africa: results cannot a priori be extrapolated!!!

Take-home messages (5)

- Asymptomatically infected individuals play an important role in transmission
- Treatment of cases must be supplemented by vector control as a major factor towards disease elimination
- Quality assurance of vector control measures is important
- Role of arsenic in antimonial resistance?

Further research required (1)

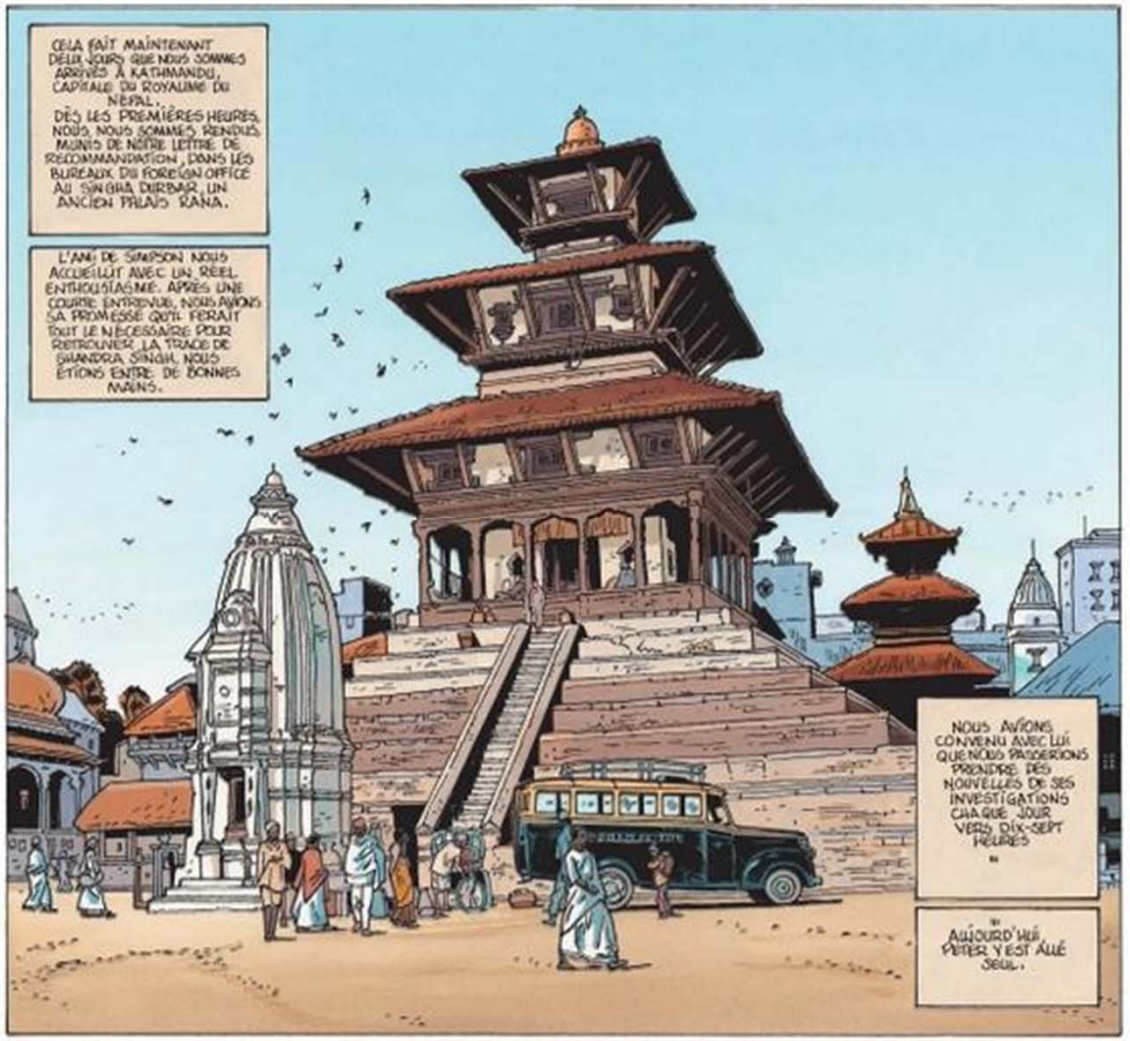
- Continue routine monitoring (up to 12 m); optimal MIL dosing algorithm
- Feasibility of other treatment schemes
- What explains MIL failure (why different results in different settings?): continue research on parasite, host, drug (PK/PD!!!), vector
- Legacy of SSG on other drugs: study long-term influence on efficacy of other drugs

Further research required (2)

- Drug discovery: (i) include SSG-R (and others) from the region, in panel for compound screening; (ii) induce resistance against new lead compounds (part of screening pipeline?)
- Imipramine: more research before possible VL clinical trial?
- PMM-R: mechanisms, markers (be proactive)

Further research required (3)

- WGS platforms for direct application in clinical samples, simplify data analysis, integrate with clinical databases, train people
- Revisit natural history of *L.donovani* (new variants, sandfly behaviour, asymptomatics, animals)
- Translate research (questions/tools) in other regions


CELA FAIT MAINTENANT DEUX JOURS QUE NOUS SOMMES ARRIVÉS À KATHMANDU, CAPITALE DU ROYAUME DU NÉPAL.
DÈS LES PREMIÈRES HEURES, NOUS NOUS SOMMES RENDUS, MUNIS DE NOTRE LETTRE DE RECOMMANDATION, DANS LES BUREAUX DU FOREIGN OFFICE AU SINGHA DURBAR, UN ANCIEN PALAIS RANA.
L'AMI DE SIMPSON NOUS ACCUEILLIT AVEC UN RÉEL ENTHOUSIASME. APRÈS UNE COURTE ENTREVUE, NOUS AVIONS SA PROMESSE QU'IL FERAIT TOUT LE NÉCESSAIRE POUR RETROUVER LA TRACE DE SHANDRA SINGH. NOUS ÉTIONS ENTRE DE BONNES MAINS.
NOUS AVIONS CONVENU AVEC LUI QUE NOUS PASSERIONS PRENDRE DES NOUVELLES DE SES INVESTIGATIONS CHAQUE JOUR VERS DIX-SEPT HEURES
AUJOURD'HUI, PETER Y EST ALLÉ SEUL.

धन्यवाद