Management of Chronic Sequelae of Arthritogenic Virus Infections: What’s New?

Prof Fabrice SIMON, MD, PhD
Department of Infectious Diseases and Tropical Medicine, LAVERAN Military Teaching Hospital & UMR 790 Unité des virus émergents, Medicine University MARSEILLE – FRANCE

Declaration of interest

I declare working as temporary senior consultant for
- PAHO and WHO (since 2010)
- Sanofi (2017)
- Valneva (since 2017)

Constellation of the main arthritogenic alphaviruses in 2019

What do the adult patients with post-chikungunya disorders really suffer from?

Chronic arthralgias and stiffness

Chronic stage, up to 6 years...

Rheumatic symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>CHIK+ 2008</th>
<th>CHIK+ 2012</th>
<th>CHIK- 2008</th>
<th>CHIK- 2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>83</td>
<td>70</td>
<td>35</td>
<td>17</td>
</tr>
<tr>
<td>Stiffness</td>
<td>82</td>
<td>53</td>
<td>18</td>
<td>14</td>
</tr>
<tr>
<td>Swelling</td>
<td>50</td>
<td>20</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>

Other symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>CHIK+ 2008</th>
<th>CHIK+ 2012</th>
<th>CHIK- 2008</th>
<th>CHIK- 2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>60</td>
<td>32</td>
<td>60</td>
<td>32</td>
</tr>
<tr>
<td>Headache</td>
<td>42</td>
<td>29</td>
<td>60</td>
<td>32</td>
</tr>
<tr>
<td>Depression</td>
<td>21</td>
<td>6</td>
<td>21</td>
<td>6</td>
</tr>
</tbody>
</table>

757 military policemen, Reunion Island, 2006
6 months after onset, 672 answerers: 31, 92%, mean age: 40 yo on the average.

Simon F, personal data

Marimoutou C et al. BMC Musc Dis 2015
French gendarmes cohort
Reunion exposure, 2006
Follow-up 2008-2012 period
Chronic stage, up to 6 years...

Long impaired quality of life

Two types of post-CHIK rheumatisms

Tenosynovitis, tendonitis, fascitis, bursitis, enthesitis...

Cumulative and centripetal evolution with time

The post-CHIK vicious circle

Multiple clinical and social consequences
The clinical paradox of post-CHIK status

For the majority of the patients

- Physical examination poorly contributive
- Biological testings frequently normal or subnormal
- Imaging: rare joint destruction

On the shelf and beyond

- "Symptomatic" treatments
  - Painkillers up to level 3, antineuropathic drugs
  - NSAIDs, corticosteroids
  - Physical therapy
  - Psychological support

- "Etiopathogenic" treatments
  - Antiviral drugs & anti-CHIKV monoclonal antibodies
  - Diseases modifying antirheumatic drugs: methotrexate, sulfasalazine, hydroxychloroquine, leflunomide, biological agents...

- Other treatments
  - Homeopathy
  - Phytotherapy

What should the ideal treatment do?

What are the targets for the treatment?

Antiviral drugs, including MAbs

Expected:
- Control of acute symptoms
- Prevention of chronicity

Anti-CHIK drugs, including MAbs

Expected:
- Etiopathogenic treatment of chronicity
Anti-inflammatory drugs

Acute D1-D21
Post-acute W4-W12
Chronic From M4…

Viremia
Viral sanctuary(?)
Clinical inflammation
Clinical impact

Expected:
Control of acute articular symptoms
Prevention of chronicity

Disease-modifying antirheumatic drugs (DMARDs)

Acute D1-D21
Post-acute W4-W12
Chronic From M4…

Viremia
Viral sanctuary(?)
Clinical inflammation
Clinical impact

Expected:
Etiopathogenic treatment of chronic joint inflammation

What are the good endpoints?

• Viral load…
• Number of tender joints
• Number of swollen joints
• Morning stiffness

• Clinically-assessed stiffness
• Pain
• Functional testings
• Quality of life
• Drug tolerance
• Social life

• CRP
• Rheumatoid factors
• …

The most important for the patients

An exponential number of papers on the treatment

PubMed, « chikungunya » & « treatment », 2019/06/06

Many scientific papers
(in vitro, animal studies)

Many cases reports
Few series

Experts’ opinions
Some clinical trials

Reviews
Meta-analyses

National & international guidelines
Numerous reviews of the literature

Very few relevant data for EBM in CHIK disease

Only few CT, very few RCT

Poor quality of the studies: numerous bias & low level of proof

Different methodologies → impossible comparison

Main criticisms: no randomization, pooling MSD&CIR, endpoints

Antiviral drugs and anti-CHIKV MAb

- Antiviral drugs active anti-CHIKV
  - Chloroquine: one RCT in Reunion 2006 → not efficient
  - Ribavirin +/- doxycycline: no RCT
  - Sofosbuvir: no RCT
  - Some other candidates being studied in vitro

- Anti-CHIKV Mab
  - One being developed: no RCT

- Efficacy at late stage speculative for both

Not recommended at any stage

Painkillers

- Analgesics
  - Paracetamol: hepatotoxicity when used on chronic liver disease or overdose
  - Dipyrone: initially recommended in Brazil, risk for medullar toxicity

- Opioids
  - For refractory pain only. Short use.

- Antineuropathic painkillers
  - To be added for patients with DN4 score >4


NSAIDs & corticosteroids

- Systemic NSAIDs
  - No class has been shown to be superior
  - Full dose x few weeks when possible
  - Avoid if patient with coronary diseases, renal failure, hypertension, risk for digestive bleeding...

- Corticosteroids
  - Caution: low dose, short time, no long-action (DXM)
  - Followed by NSAID to avoid clinical rebound
  - Long-term adverse effects in patients older than 40: osteoporosis, cataract

Recommended, with caution in older adults

Consider the diagnosis of CIR if refractory

Search for an alternative for long-term treatment

Methotrexate

- In vitro study suggests non benefit in acute stage

- Recommended as first-line treatment for RA (ARA, EULAR)
  - For patients fulfilling definition criteria
  - After 4-6 weeks

- Empirically used in post-CHIK RA by rheumatologists in Reunion island since 2005

- No well-designed RCT

- Some case series with positive results
  - Possible adverse effects
  - Some failure when started too late

Recommended as first-line treatment for CIR only

Requires biological follow-up
Experience of methotrexate in Reunion island, 2005-2010

<table>
<thead>
<tr>
<th>MTX Failure</th>
<th>MTX use</th>
<th>Biological agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>7</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>9</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>12</td>
<td>3</td>
<td>6</td>
</tr>
</tbody>
</table>

- 77% of de novo CIR received MTX
- 100% of RA, 80% of SA, <1/3 of UP
- 75% efficacy (54/72) vs 25% failure (18/72)
- Well tolerated
- 15% second line treatment with biotherapy (12/72) (TNF blockers, abatacept, rituximab or tocilizumab)

Experience of methotrexate in Reunion island, 2005-2010

<table>
<thead>
<tr>
<th>MTX Failure (n=48)</th>
<th>MTX Efficacy (n=64)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Means age (year)</td>
<td>40</td>
</tr>
<tr>
<td>Score M</td>
<td>6</td>
</tr>
<tr>
<td>Score P</td>
<td>13</td>
</tr>
<tr>
<td>Destructions</td>
<td>9</td>
</tr>
<tr>
<td>RA</td>
<td>10</td>
</tr>
<tr>
<td>SA</td>
<td>7</td>
</tr>
<tr>
<td>UP</td>
<td>1</td>
</tr>
<tr>
<td>Easy MTX introduction</td>
<td>4%</td>
</tr>
</tbody>
</table>

Biological agents

- Only few cases reports
  - Anti-TNF, rituximab, tocilizumab
- Not recommended as first-line treatment in RA
- Expensive and not always available vs MTX or HCQ

For confirmed CIR as second-line treatment only
Caution after a tropical stay (TB, strongyloidiasis)

Hydroxychloroquine

- Recommended in some CIR
- Contradictory data in the litterature
- Proposed in the Brazilian guidelines
- Requires monitoring of ocular and cutaneous adverse effects

To be prescribed by a rheumatologist/internist

Physical medicine

- Low level of proof for these tools that are use daily...
  - Poorly studied
- Only one RCT in Brazil: benefit of adjunctive Pilates
  - Reduction in pain, fatigue, and increase of QoL
- Safe and beneficial for many patients with post-CHIK disorders

Recommended at post-acute and chronic stage

Homeopathy, phytotherapy

- No proof of efficacy

Not recommended at any stage
What should I do now in my clinical practice?

**Experience-based guidelines for CHIK disease**

Free online

**Principle of the post-CHIK treatment**

SUFFERING

Dedicated case management

Self-remobilization

[Image: Arrow pointing to "Leave the chikungunya behind!"]

**Five pillars to manage persisting symptoms**

- Diagnosis time
- Orientation of complex cases to the specialists
- Control of the pain(s)
- Control of the inflammation(s)
- Physical therapies

**Persisting rheumatic disorders: clinical management**

Caution if...

- Intense acute stage
- Patient older than 40
- Corticodependance
- Hands involvement
- Any arthritis (synovitis)
- Criteria for CIR
- Arthralgia not improved after complete treatment for 6-8 weeks
- Diagnosis uncertainty and complex clinical situation
Persisting rheumatic disorders, diagnosis algorithm

Persisting rheumatic disorders, principles of treatment

Several techniques for physical therapy

- **Antalgic physiotherapy**
  - Tenosynovitis → cryotherapy/orthese (night)
  - Subcutaneous oedema → Scottish bath/massage

- **Activo-passive mobilization for painful and/or stiff joints**
- **Massage for the paravertebral muscles**
- **Transversal deep massages for plantar fasciitis**

- **Other technical tools**
  - Electrostimulation, ultrasounds with NSAIDs, infrared, shock waves...

Persisting symptoms

Trained physician

Drugs

Reconditioning

Rehabilitation and reconditioning

- Repetition of soft movements to reduce stiffness
  - Pilates

- **Balneotherapy**
  - Self-rehabilitation
    - During and after physiotherapy
    - The step before restarting a soft sport

In practice

- For all patients +++
  - Painkillers, physiotherapy, local treatment, psycho-social support, specific treatment if required & prolonged follow-up

- For non-CIR
  - Non-inflammatory features: NSAIDs for weeks
  - Polyarthralgia & pararticular oedema: NSAIDs, short corticotherapy
  - *Aspecific diffuse pain*: other cause ?
- For CIR: guidelines in rheumatology

Key-messages

- Chikungunya is not dengue
- Do not pool all the patients with chronic disorders
- Most suffering people don’t go to the hospitals
- There is no magic bullet for the treatment
- Trained doctors + drugs + physical therapy + mobilization
- Late is not lost
- Clinical improvement with simple treatment is frequent
- Well-designed studies for treatment are still needed
This lecture results from the multidisciplinary experience of the French Military Medical Service in collaboration with:
the University Hospitals of Reunion, Martinique and Marseille,
GPs from Guadeloupe,
the expert group for the French guidelines and the unit 190 on emerging viruses, Faculty of medicine, Marseille.
simon-f@wanadoo.fr
chikungunya.expertise@gmail.com

Some important questions to address

• Overview of the current evidence concerning the management of acute infection as well as chronic sequelae of arthritogenic viral infections

• Therapeutic value of different classes of drugs (NSAIDS, paracetamol, corticosteroids, MTX, TNF-alpha blockers, chloroquine...) in different arthritogenic viruses

• Prognostic markers