

Emilie JAVELLE, MD
Infectious and Tropical Diseases
Laveran Military Teaching Hospital
Marseille, France





I certify that I have no conflict of interest.



POST-CHIKUNGUNYA CHRONIC DISORDERS ***A 6-year experience from Reunion Island***

Clinical spectrum

Methotrexate use in the inflammatory forms



***Émilie Javelle, Anne Ribera, Isabelle Degasne,
Catherine Marimoutou, Fabrice Simon***



Post-CHIK rheumatisms in the 1980's

First reports by South African teams

- 12% of persistent joint pains 3 years after CHIK

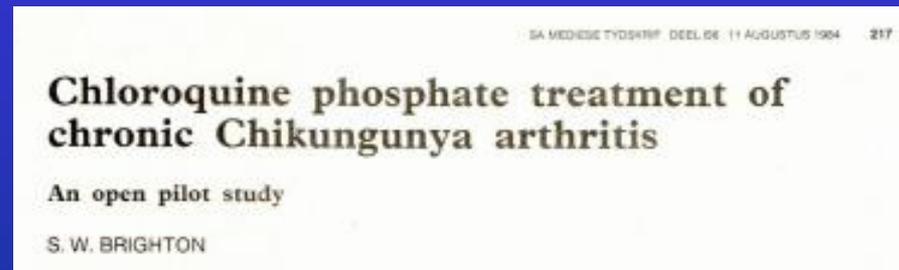
Brighton SW, S Afr Med J. 1983

- CHIK destructive polyarthritis

Brighton SW, Clin Rheumatol. 1984

- Chloroquine phosphate treatment

Brighton SW, S Afr Med J. 1984

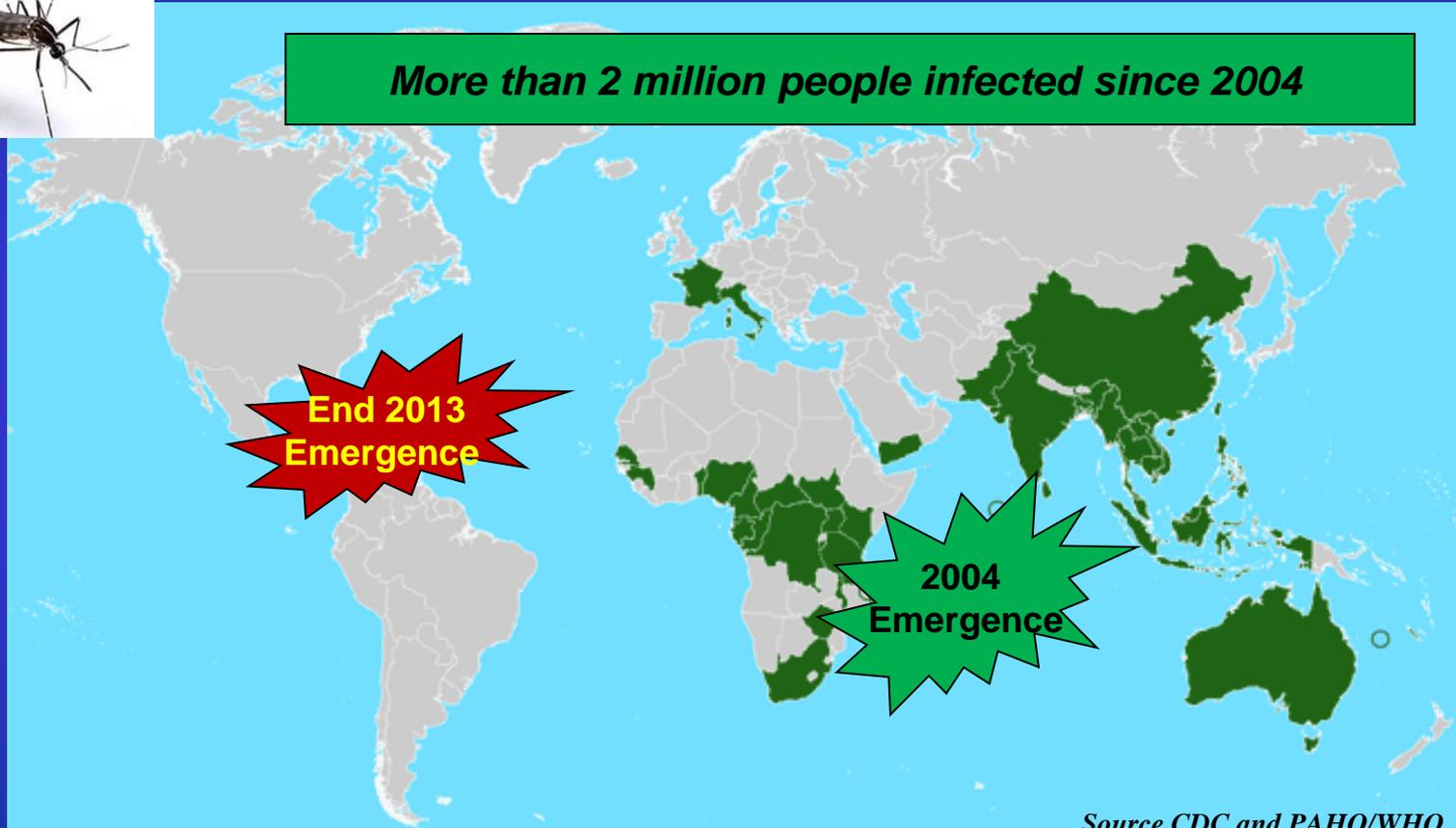




The current emergence



More than 2 million people infected since 2004



Source CDC and PAHO/WHO

May 2014 \approx 45 000 cases in the Americas

Modified from: Powers AM, Logue CH. Changing patterns of chikungunya virus: re-emergence of a zoonotic arbovirus. *J Gen Virol.* Sep 2007;88(Pt 9):2363-2377.



Post-CHIK long-lasting disorders

AREA (number of patients)	YEAR OF OUTBREAK	%	TIME AFTER CHIK ONSET	CHRONIC DISORDER	REFERENCES
Reunion (106)	2005-2006	52%	17 months	Chronic pains	de Andrade DC et al. BMC Infect Dis 2010
Reunion (88)	2005-2006	63,6%	18 months	Persistent arthralgia (yes/no)	Borgherini G et al. Clin Infect Dis 2008
Reunion (147)	2005-2006	57%	15 months	Joint manifestations (NRS scale)	de Andrade DC et al. PLoS Negl Trop Dis 2010
India Maharashtra (509)	2006	4,1% 1,6% 0,3%	12 months 24 months 12 months	Persistent rheumatism Chronic inflammatory arthralgia	
India Kerala (1396)	2007	75% 31% 30% 46,3% 17% 13% 6%	1 month 1 month 1 month 10 months 10 months 10 months 10 months	Rheumatism Swelling Asthenia Joint pain /swelling ACR rheumatoid arthritis criteria Asthenia Neuritis	Mathew AJ et al. Trans R Soc Trop Med Hyg 2010
India Oloor village in Kerala (1396)	2007	55% 8,3%	15 months 15 months	Musculoskeletal pain Chronic rheumatism (naïve to pain before CHIK)	Mathew AJ et al. Int J Clin Pract 2011
Indian Ocean and South East Asia (69)	Jan-Oct 2006	69% 13%	2 months 6 months	Persistent arthralgia	Taubitz W et al. Clin Infect Dis 2007
Sri Lanka Galagedara-Madige village in Kandy District (513)	Oct 2006	45% 24% 8% 2,7%	14 days 7 months 12 months 36 months	Arthritic disability	Kularatne SA et al. J Trop Med 2012
Italy (250)	2007	66,5%	12 months	Myalgia, asthenia, arthralgia	Moro ML et al. J Infect 2012
Japan (15 imported cases)	2005	6/15 (40%)		Persistent arthralgia 1/6 erosive arthritis and tenosynovitis	Mizuno Y et al. J Infect Chemother 2011

**Waning with time
Not down to zero
Inflammatory chronic
features : 5%**

Wide clinical spectrum





A wide clinical spectrum



F. Simon Collection

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No guidelines for post-CHIK treatment

- **Lack of evidence-based drug efficacy**

- **Choloroquine (200mg/d)**

Clinical trials CuraChik in France & India N°2010/091/000208

Chopra et al. Arthritis Rheum. 2013

- **Hydroxychloroquine (200mg/d) & sulfasalazine (1-2mg/d)**

Ganu et al. J Assoc Physicians India. 2011

- **Ribavirin (200 mg/d)**

Ravichandran et al. J Infect Dev Ctries. 2008

- **Recent use of methotrexate & TNF blockers in post-CHIK rheumatoid arthritis (RA)**

Bouquillard et al. Joint Bone Spine. 2009; Ganu et al. J Assoc Physicians India. 2011

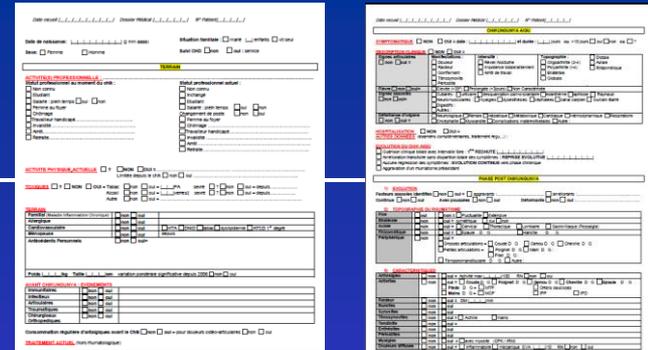


Aims of the present study

- **To describe post-CHIK rheumatic-musculoskeletal disorders (pCHIK RMSKD)**
 - Features, severity and burden
 - Focus on *de novo* Chronic Inflammatory Rheumatism (CIR)
- **To evaluate methotrexate (MTX) in post-CHIK chronic inflammatory rheumatism (pCHIK CIR)**
 - Factors associated with efficacy



Methods



- **Retrospective descriptive study**
- **Centers of Rheumatology, Saint Denis, La Réunion**
 - Dpt of Rheumatology, Felix Guyon University Hospital (AR, ID)
 - Private medical office (AR)
- **Data anonymously recorded from medical files**
 - From January to May 2012
 - Structured questionnaire developed for the study
 - Demographic, medical, clinical, biological, imaging, treatments



Population

- **Inclusion criteria**

- Patients referred to the rheumatologist for symptoms related to CHIK (2005-2006 outbreak) persisting more than 4 months
- CHIKV infection biologically confirmed

- **Definitions**

- **De novo pCHIK-RMSKD:** patients naïve for chronic or recurrent joint pains before acute CHIK (**vs preexisting RMSKD**)
- **De novo pCHIK-CIR subgroups:**
 - **RA** 2010 ACR/EULAR criteria
 - **SA** European Spondyloarthritis Study Group (ESSG)
 - **Undifferentiated Polyarthritis (UP)** at least 4 swelling joints & exclusion of other causes



Assessing severity of pCHIK RMSKD

- **Radiographic destructions**
- **Functional impairment**
 - Job invalidity or adjustment
 - Subjective significant reduction in daily activities
 - Psychiatrist follow-up or antidepressant drug introduction



Measuring MTX efficacy

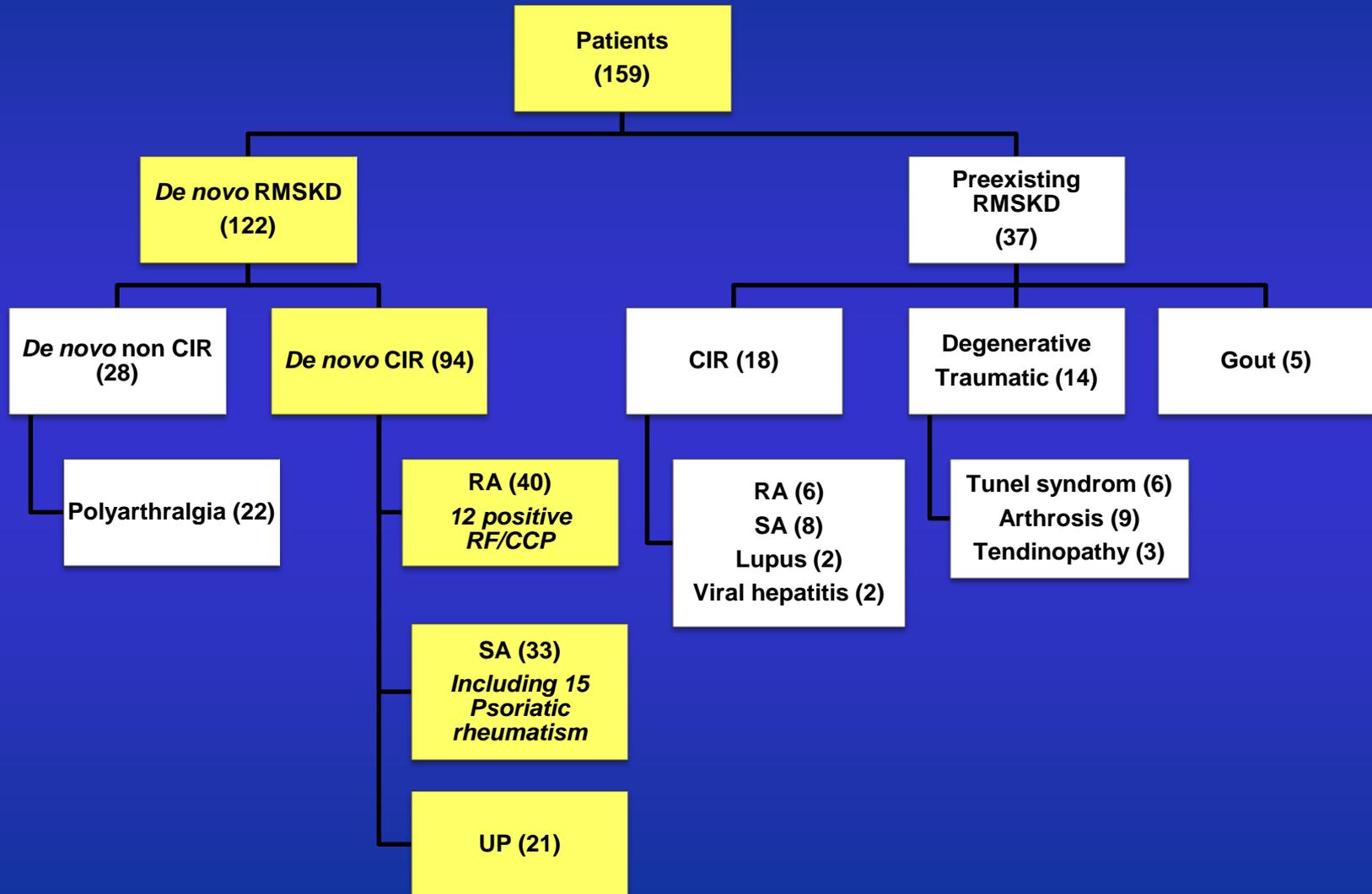
- **Definition for MTX failure**
 - MTX switch for others DMARDs (side effects included)
 - MTX association with others DMARDs
 - MTX efficacy if no MTX failure
- **Statistics**
 - MTX efficacy compared to MTX failure in
 - age, gender, type of rheumatism, destructive evolution
 - **Early time of MTX introduction** if delay ≤ 1 year (delayed if > 1 year)
 - Fisher exact test



RESULTS



Flow chart (effective)





Patients' characteristics

	TOTAL (n=159)	PREEXISTING CIR (n=18)	PREEXISTING NON CIR (n=19)	<i>de novo</i> pCHIK RA (n=40)	<i>de novo</i> pCHIK SA (n=33)	<i>de novo</i> pCHIK UP (n=21)	<i>de novo</i> NON CIR (n=28)
Median age	51 [12-80]	47 [23-73]	63 [30-71]	49 [33-70]	49 [13-74]	59 [46-80]	51 [12-69]
Sex M	38 (24)	4 (23)	8 (42)	10 (25)	10 (30)	1 (5)	5 (18)
Sex F	121 (76)	14 (77)	11 (58)	30 (75)	23 (70)	20 (95)	23 (82)
Tobacco +	18 (11)	1 (6)	3 (16)	5 (13)	6 (18)	1 (5)	2 (7)
Hypertension	50 (31)	7 (39)	7 (37)	11 (28)	8 (24)	9 (43)	8 (28)
Diabetes	17 (11)	3 (16)	1 (5)	4 (10)	3 (9)	2 (10)	4 (14)
Thyroid disorders	8 (5)	2 (11)	-	1 (3)	1 (3)	3 (14)	1 (3)
Acute RMSKD history	50 (31)	6 (33)	7 (37)	8 (20)	6 (18)	13 (62)	10 (36)
Acute CHIK ≥ 3weeks	105 (66)	10 (56)	8 (42)	27 (68)	25 (76)	15 (72)	20 (72)
Vitamin D deficiency	34 (21)	5 (28)	5 (26)	8 (20)	6 (18)	2 (10)	8 (29)

Underlying conditions

Women about 50 year-old
Long lasting acute CHIK disease & vitamin D deficiency
No significant differences in comorbidities



de novo pCHIK CIR treatment

	pCHIK RA (n=40)	pCHIK SA (n=33)	pCHIK UP (n=21)	TOTAL (n=94)
Start of MTX	40 (100)	26 (79)	6 (29)	72 (77)
MTX failure	10	7	1	18
MTX side effects	7	3	-	10
Biological agents	9	3	-	12



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)
Good tolerance
15% second line treatment with biologic agents (12/72)
(TNF blockers, abatercept, rituximab, tocilizumab)





MTX efficacy determinants

	MTX FAILURE (n=18)	MTX EFFICACY (n=54)
Mean age (year)	48	49
Sex M	5	13
Sex F	13	41
RA	10	30
SA	7	19
UP	1	5
Early MTX introduction	3 *	28 *

* $p = 0,01$ (Fisher test)

**Cut-off
One year**

**Early introduction significantly
associated with MTX efficacy**



The most severe pCHIK CIR



E. Javelle Collection



pCHIK RMSKD burden

	TOTAL (n=159)	PREEXISTING CIR (n=18)	PREEXISTING NON CIR (n=19)	<i>de novo</i> pCHIK RA (n=40)	<i>de novo</i> pCHIK SA (n=33)	<i>de novo</i> pCHIK UP (n=21)	<i>de novo</i> NON CIR (n=28)
Destructions	41 (25)	9 (50)	1 (5)	28 (70)	3 (10)	-	-
Job impairment	38 (24)	10 (56)	2 (10)	11 (27)	12 (36)	2 (10)	1 (3)
Daily activities reduction	108 (68)	14 (77)	11 (58)	34 (85)	27 (82)	11 (52)	11 (39)
Psychologic impact	26 (16)	3 (17)	1 (5)	7 (17)	8 (24)	3 (14)	4 (14)
Orthopedic brace	46 (29)	11 (61)	4 (21)	15 (37)	8 (24)	1 (5)	7 (25)

De novo chronic inflammatory rheumatism

1/3 destructive: 70% of the RA

RA & SA heaviest burden: 1/3 in job invalidity, 80% daily life impact

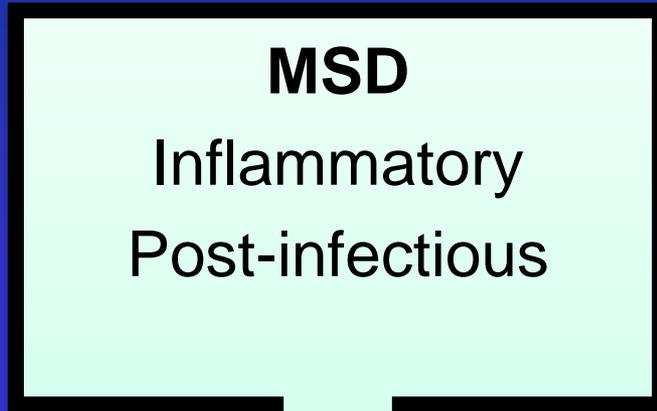


Limits and strengths of the study

- **Rheumatologist recruitment**
 - Overrepresentation of inflammatory rheumatisms
 - Specialized management & use of guidelines
- **Descriptive and retrospective study**
 - Not the best design to measure efficacy
 - Good size of the cohort and length of the case study (6 years)
 - Wideness of the rheumatic spectrum → individualized management
 - Interesting focus on the most incapacitated patients: CIR

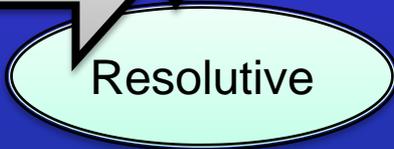


Two opposite clinical groups

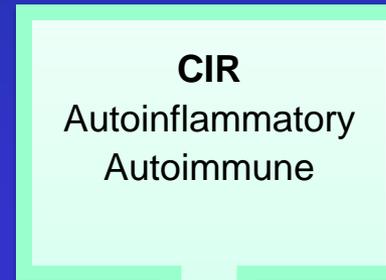


MSD
Inflammatory
Post-infectious

Anti-inflammatory drugs
Spare of tendons & muscles

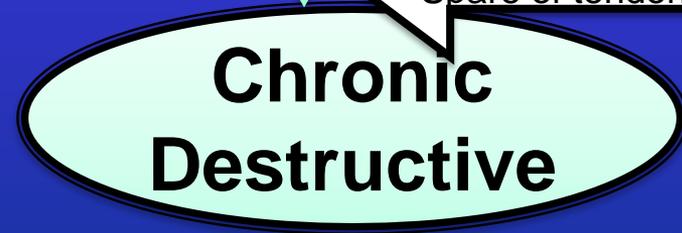


Resolutive



CIR
Autoinflammatory
Autoimmune

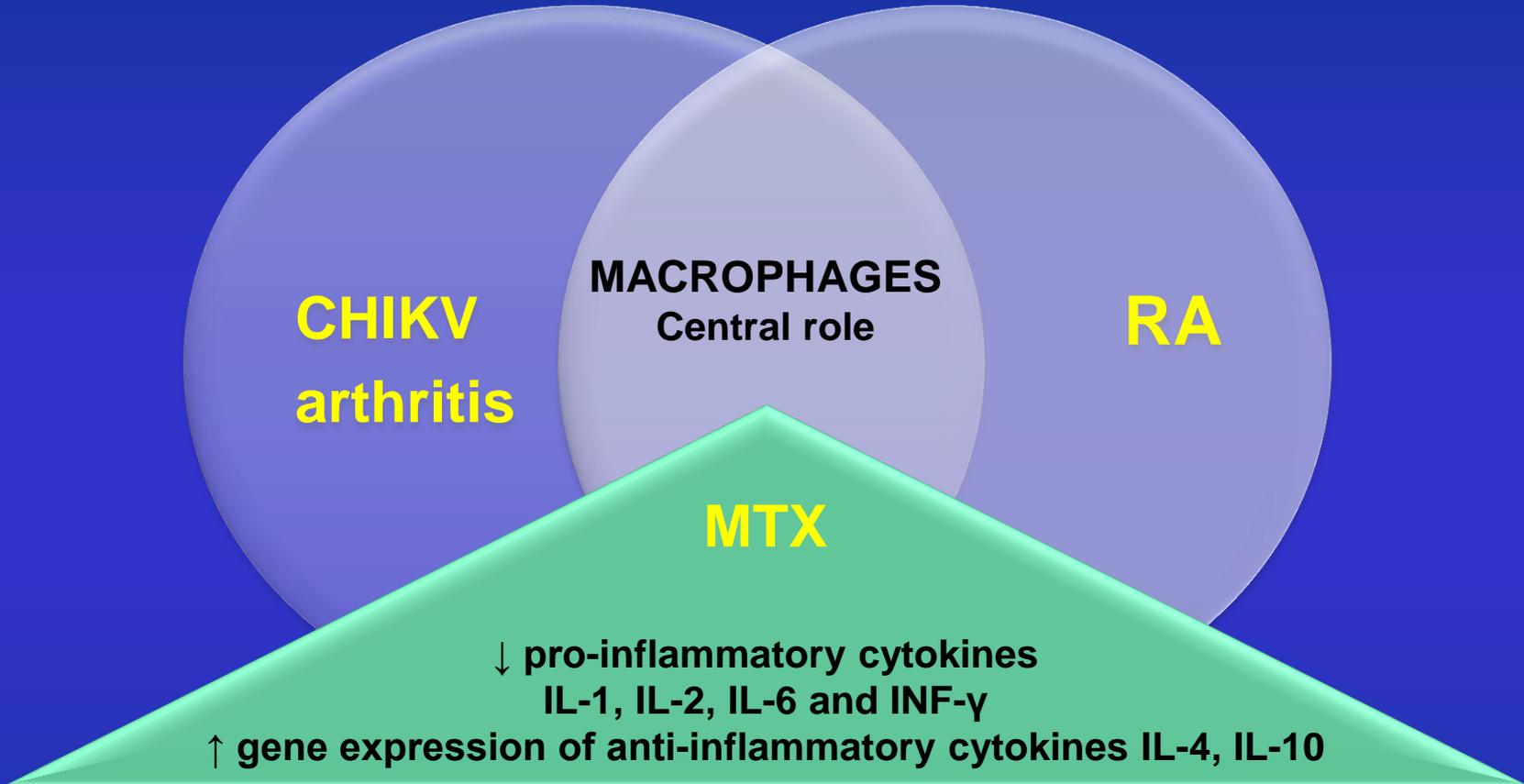
Immunomodulators
Spare of tendons & muscles



**Chronic
Destructive**



A rational use of MTX for pCHIK CIR



Szekanecz . Curr Opin Rheumatol. 2007
Hoarau et al. The Journal of Immunology 2010
Assunção-Miranda et al. Biomed Res Int. 2013
Hobl et al Clin Exp Rheumatol. 2011
Herrero et al Arthritis & Rheumatism. 2013



pCHIK CIR must be treated as any CIR

- **First-line treatment**

- Prevent from joint damages
- The greatest efficacy and tolerability (Disease Activity Score 28)
- Early start of MTX after diagnosis
- RA, SA and corticoresistant UP (our study)

- **Weekly low-dose**

- Up to 15 mg per week by the intramuscular route
- Oral switch and decreasing doses when maximum improvement
- Doses used in our study

Hoffmeister RT. Am J Med. 1983

Pincus et al. Clin Exp Rheumatol. 2003

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Management of pCHIK-RMSKD

Pay attention to post-menopausal women or long lasting acute stage



Correct vit D deficiency or microcrystalline disorders



Promptly recognize *de novo* Inflammatory Rheumatisms

Polysynovitis, stiffness, psoriasis

Search for validated clinical, biological criteria & radiographic destructions

≠ diffuse joint and muscular pain with spontaneous favorable outcome



Early start MTX

[4-8 months]

At a weekly low dose

Follow-up (RAPID3)



A large waterfall cascades down a rocky cliff in a lush green forest. The water is white and frothy as it falls, creating a misty spray at the bottom. The surrounding rocks are dark and covered in moss and ferns. The background is filled with dense green foliage, including various trees and plants. The overall scene is vibrant and natural.

***Thank you for
your attention***