Maladie de Still et biothérapie

Charlotte Jacquemin (DES)

25 avril 2014

HÔPITAUX UNIVERSITAIRES
PARIS NORD VAL DE SEINE
Bichat - Claude Bernard

Mme R. 38 ans

Janvier 2010:

- Clinique:
  - polyarthralgies (chevilles, coudes, poignets)
  - Fièvre fluctuente
  - éruption cutanée
  - odynophagie
  - polyADP
- Biologie:
  - Syndrome inflammatoire
  - Ferritinémie=2399, ferritine glycosylée=14% .
  - immuno -
- Complication pulmonaire: syndrome interstitiel. DLCO=62%
- Biopsie cutanée: vasculite leucocytoclasique compatible avec une maladie de Still

Diagnostic: Maladie de Still
Traitement: Cortancyl 0.5mg/kg=40mg puis décroissance progressive en 1an.
Evolution: Rémission

Octobre 2013

- Clinique:
  - odynophagie
  - Fièvre+frissons fluctuents
  - Polyarthralgies migratrices (chevilles, genoux, épaules, poignets)
  - Éruption cutanée urticariforme (décolleté, bras, cuisse) à recrudescence vespérale
- Biologie:
  - CRP=150
  - Ferritinémie=2111 µg/L
  - Ferritine glycosylée=11%
- Complication: pas d'atteinte pulmonaire. Minime décollement péricardique

Diagnostic: Nouvelle poussée de Maladie de Still

Traitement: Kineret 100mg/jour

Evolution:

- Efficacité spectaculaire du Kineret, mais effet suspensif
- Switch Cortancyl 30mg/jour: efficace, mais corticodépendance à 20mg
- Introduction Méthotrexate permettant décroissance du cortancyl.

Généralités

- Maladie inflammatoire
- Rare (1/100.000 à 1/1.000.000 cas)
- 1 homme pour 2 femmes
- Formes adulte et juvénile
- 16-35 ans
- Evolution par poussées uniques ou successives, ou chronique
- Etiologie inconnue
- Diagnostic d'exclusion

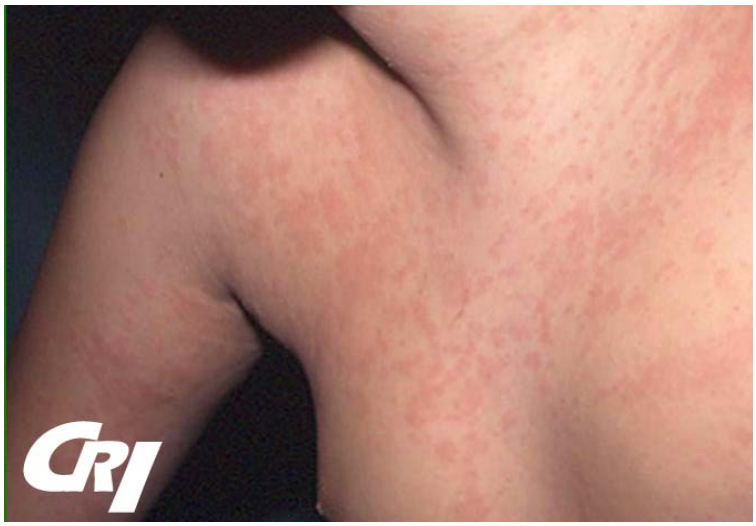
- Clinique hétérogène:
  - Signes généraux: fièvre intermittente, vespérale + AEG
  - Atteinte articulaire: arthralgies ou arthrites
  - Atteinte cutanée: maculo-papules rose saumon, transitoires
  - Autres symptômes aspécifiques: odynophagie(2/3), myalgies diffuses, polyADP, douleur abdo
- Atteinte systémique:
  - Cardiaque: péricardite>myocardite >>valvulopathies
  - Pulmonaire: épanchement pleural>atteinte parenchymateuse
- Perturbations biologiques:
  - Hyperleucocytose: PNN>80%
  - Sd inflammatoire
  - Perturbation du bilan hépatique
  - Hyperferritinémie + fraction glycosylée effondrée.
- Complications: SAM, amylose, CIVD

Table 1 - Classification criteria for adult-onset Still´s disease proposed by Yamaguchi et al

Major criteria	Minor criteria
Temperature of > 39°C for > 1 wk	Sore throat
Leukocytosis > 10 000/mm³	Lymph node enlargement
Typical rash	Splenomegaly
Arthralgias > 2 wk	High transaminases
	Negative ANA, RF

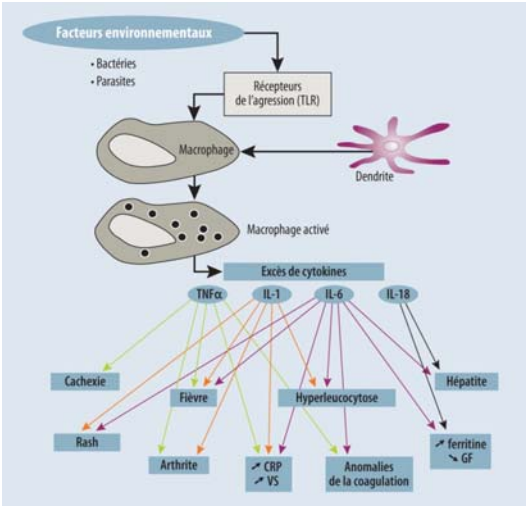
After excluding infections, malignancies, and other rheumatic diseases, adult Still´s should be considered if 5 criteria (2 of which being major ones) are met. ANA = antinuclear antibody; RF = rheumatoid factor

Eruption saumonée



Physiopathologie

Augmentation de la sécrétion IL1β, IL6, IL 18, TNFα, IFNγ



Quelle prise en charge thérapeutique?

AINS	20%	
Corticoides	80%	
Méthotrexate	Ciclosporine, azathioprine,...	70%
Biothérapie	⇒Quelle biothérapie?	

-Anti TNF?

-Anti IL1?

-Anti IL6?

-Rituximab?

Les anti TNFα (1)

- **Infliximab**

2 études prospectives:

- 4 patients suivis 18, 13, 13 et 5 mois
- 3-5mg/kg toutes les 4-12 semaines
- Rémission complète (dont un maintien 8 mois après arrêt du traitement)

Kokkinos A, and al. ; Successful treatment of refractory adult-onset Still's disease with infliximab. A prospective, non-comparative series of four patients. Clin Rheumatol 2004

- 6 patients. 3-5mg/kg. S0, S2, S4, S6, toutes les 6-8 sem.
- Rémission pour tous les patients. Suivi 5-28 mois

Kraetsch HG, and al. ; Successful treatment of a small cohort of patients with adult onset of Still's disease with infliximab: first experiences. Ann Rheum Dis 2001

Case-reports: 8 évolutions favorables. 2 réactions allergiques. 1 hépatite fulminante.

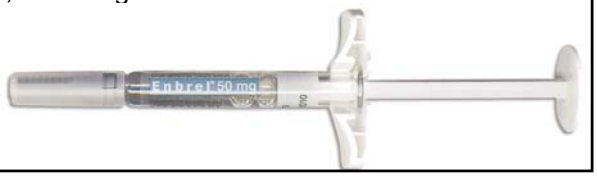
Les anti TNFα (2)

- **Etanercept**

12 patients suivis 6 mois
7 améliorations ACR 20 dont 4 ACR 50 et 2 ACR 70 à 6 mois
2 aggravations sous traitement

Husni ME and al. Etanercept in the treatment of adult patients with Still's disease. Arthritis Rheum 2002

Case-reports: 7 évolutions favorables; 1 angio-oedème périorbitaire, 1 SAM, 1 méningite à Listeria



Etanercept vs Infliximab

20 patients (10 IFX, 5 ETN, 5 les deux)

suivis en moyenne 13 mois

5 rémissions complètes (1ETN, 4 IFX)
16/25 rémissions partielles
17/25 arrêt de traitement pour manque d'efficacité (11) ou effet indésirable (4)

Fautrel B, and al. Tumour necrosis factor α blocking agents in refractory adult Still's disease: an observational study of 20 cases. Ann Rheum Dis 2005

Etanercept vs Infliximab

Table 2 Patients' outcome under anti-TNF alpha therapy

No.	Sex	Main clinical expression	ASD duration (years)	Age	Main symptoms	Therapy Type	Associated drug	Response	Remaining symptoms	Follow up
1	F	Systemic	2	33	Fever, arthralgia, rash	Etanercept 25 mg ×2/week	PDN 80 mg/day	Remission	None	5 months. Anti-TNF stopped (other: drug availability)
2	F	Articular	5	55	Fever, polyarthritis, rash	Etanercept 25 mg ×2/week	AZA 100 mg/day PDN 30 mg/day	Partial response	Isolated fever	12 months. Anti-TNF stopped (lack of efficacy)
						Infliximab 5 mg/kg	AZA 100 mg/day MethylPDN 1g PDN 30 mg/day IV Ig	Partial response	Isolated fever	10 months. Anti-TNF stopped (lack of efficacy)
3	M	Articular	7	55	Polyarthritis	Etanercept 25 mg ×2/week		Failure	Polyarthritis	3 months. Anti-TNF stopped (lack of efficacy)
4	F	Articular	5	36	Fever, polyarthritis, fatigue	Etanercept 25 mg ×2/week	PDN 20 mg/day	Partial response	Oligoarthritis	43 months. Anti-TNF ongoing
5	F	Articular	17	29	Polyarthritis	Infliximab 3 mg/kg	MTX	Failure	Polyarthritis	1 month. Anti-TNF stopped (side effects)
6	F	Systemic	2	74	Fever, arthralgia, rash	Infliximab 3 mg/kg	PDN 20 mg/day MTX 15 mg/week	Partial response	Rash, arthralgia	1 month. Anti-TNF stopped (side effects)
7	M	Articular	17	28	Fever, polyarthritis, myalgia	Infliximab 3 mg/kg	PDN 40 mg/day MTX 7.5 mg/week	Failure	Fever, arthritis, myalgia Polyarthritis, myalgia	2 months. Anti-TNF stopped (side effects)
					Rash	Etanercept 25 mg ×2/week	PDN 40 mg/day MTX 7.5 mg/week	Partial response	Rash, arthralgia	1 month. Anti-TNF stopped (side effects)
8	F	Articular	6	61	Polyarthritis, rash	Infliximab 3 mg/kg	PDN 10 mg/day MTX 17.5 mg/week	Remission	None	44 months. Anti-TNF ongoing
9	F	Articular	4	44	Polyarthritis	Infliximab 3 mg/kg	PDN 50 mg/day MTX 15 mg/week	Partial response	Few arthritis	34 months. Anti-TNF ongoing
10	F	Systemic	2	73	Fever, arthralgia, fatigue	Infliximab 3 mg/kg	PDN MTX 15 mg/week	Partial response	Arthralgia, fatigue	12 months. Anti-TNF stopped (lack of efficacy)
11	F	Articular	21	32	Fever, polyarthritis, rash	Etanercept 25 mg ×2/week	PDN 15 mg/day MTX 7.5 mg/week	Partial response	Few arthritis	10 months. Anti-TNF stopped (lack of efficacy)
						Infliximab 3 mg/kg	PDN 12 mg/day MTX 7.5 mg/week	Partial response	Few arthritis	7 months. Anti-TNF stopped (lack of efficacy)
12	M	Articular	12	29	Fever, polyarthritis, rash	Infliximab 3 mg/kg	MTX 15 mg/week	Remission	None	12 months. Anti-TNF stopped(lack of efficacy)
13	F	Articular	2	18	Polyarthritis	Etanercept	PDN 10 mg/day	Partial response	Few arthritis	35 months. Anti-TNF ongoing
					Fatigue	25 mg ×2/week	MTX 10 mg/week			
14	M	Articular	3	25	Polyarthritis, rash	Infliximab 3 mg/kg	PDN 10 mg/day MTX 15 mg/week	Remission	None	16 months. Anti-TNF ongoing
15	F	Articular	12	29	Fever, arthralgia	Infliximab 3 mg/kg	PDN 5 mg/day MTX 12.5 mg/week	Remission	None	36 months. Anti-TNF ongoing
16	F	Systemic	14	37	Fever, arthralgia, rash	Infliximab 3 mg/kg	PDN 20 mg/day AZA 150 mg/day	Partial response	Arthralgia, rash	9 months. Anti-TNF stopped (lack of efficacy)
17	M	Articular	5	18	Fever, polyarthritis	Etanercept 25 mg ×2/week	PDN 20 mg/day	Partial response	Few arthritis	9 months. Anti-TNF stopped (lack of efficacy)
						Infliximab 3 mg/kg	PDN 15–20 mg/day MT X 7.5 mg/week	Partial response	Few arthritis	3 months. Anti-TNF ongoing (lack of efficacy)
18	F	Articular	11	46	Fever, polyarthritis	Etanercept 25 mg ×2/week	PDN 15– 20 mg/day MTX 20 mg/week	Partial response	Few arthritis	6 months. Anti-TNF ongoing
19	F	Systemic	7	32	Fever, polyarthritis, rash	Etanercept 25 mg ×2/week	PDN 15– 20 mg/day	Failure	Fever, arthritis, rash	3 months. Anti-TNF stopped (lack of efficacy)
					Sore throat	Infliximab 3 mg/kg	PDN 15– 20 mg/day	Partial response	Few arthritis, rash	4 months. Anti-TNF stopped (other: serious burn)
20	F	Articular	15	60	Fever, polyarthritis, rash	Infliximab 3 mg/kg	PDN 45 mg/day MTX 17.5 mg/week	Partial response	Few arthritis	8 months. Anti-TNF ongoing

PDN, prednisone; AZA, azathioprine; MethylPDN, methylprednisolone; IV Ig, intravenous polyvalent immunoglobulin; MTX, methotrexate.

Fautrel B, and al. Tumour necrosis factor α blocking agents in refractory adult Still's disease: an observational study of 20 cases. Ann Rheum Dis 2005

Les anti TNFα (3)

- **Adalimumab**

3 cas favorables dont 2 compliqués secondairement de SAM. 1 échec

Anti-IL6

- **Tocilizumab**
  - Étude observationnelle en France entre 2006 et 2009, tous les patients recevant le tocilizumab.
  - Cohorte de 14 patients, tous en échec d'anakinra
  - 12 patients en échec d'au moins 1 anti TNF
  - 11 patients traités à M6
  - Effets indésirables: 1 angiodermite nécrosante. 1 douleur thoracique + frissons lors des perfusions. 1 recrudescence des symptômes.

Puéchal X, and al. Tocilizumab in refractory adult Still's disease. Arthritis Care Res 2011

Table 2. Outcome measures for patients with adult Still's disease treated with tocilizumab*

	Baseline assessment (n = 14)	3-month evaluation (n = 14)†	6-month evaluation (n = 14)‡
Recurrent systemic flares, no. (%)	7 (50)	1 (7)	1 (7)
Tender joint count§	10.5 ± 7.4	4.8 ± 6.7	3.9 ± 5.9
Swollen joint count§	7.9 ± 6.8	4.4 ± 4.4	2.9 ± 3.6
Patient global assessment by 100-mm VAS	61.9 ± 26.9	33.1 ± 23.2	24.6 ± 25.9
DAS28	5.61 ± 1.49	3.21 ± 1.76	2.92 ± 2.17
Prednisone dosage, mg/day	23.3 ± 20.9	13.0 ± 6.5	10.3 ± 4.9
ESR, median (range) mm/hour	36.5 (2–120)	8.0 (1–98)	12.5 (1–91)
CRP level, median (range) mg/dl	5.2 (0.3–27.2)	0.5 (0.1–14.7)	0.6 (0.02–23.0)
Leukocyte count, gm/liter	10.65 ± 5.56	9.80 ± 6.00	9.03 ± 3.01
Serum ferritin level, ng/ml	1,939 ± 4,685	132 ± 105	209 ± 144

* Values are the mean ± SD unless otherwise indicated. VAS = visual analog scale; DAS28 = Disease Activity Score in 28 joints; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein.
† Including 1 patient who withdrew from the study at 2 months.
‡ Including 3 patients who withdrew before the 6-month end point.
§ Tender and swollen joint counts on the 28 articles included in the DAS28 (17).

Puéchal X, and al. Tocilizumab in refractory adult Still's disease. Arthritis Care Res 2011

Case reports: 26 cas rapportés avec évolution favorable

Tocilizumab vs Infliximab vs Etanercept

Étude rétrospective,16 patients: 9 IFX, 4 ETN, 11 TCZ
durée moyenne de suivi 7,1 an
IFX: 4/9 rémissions. 1/4 ETN. 10/11 TCZ

Patient	Age (years)/ sex	Duration of disease before treatment with first biologic agent (year)	Clinical course pattern[a]	First biologic agent/response	Second biologic agent/response	Third, fourth biologic agent/response	Outcome at the last visit	Therapy at the last visit	Follow-up period (years)[b]	Remission period (months)	Adverse events
1	48/F	0.2	–	TCZ/unknown	–	–	Active	PSL, TCZ	0.2	–	
2	38/M	1.7	PS	IFX/effective	–	–	Inactive	PSL, MTX, IFX	3.6	24	
3	23/M	8.2	CA	IFX/ ineffective	ETN/ ineffective	–	Inactive	PSL, TAC	9.3	–	
4	22/F	2.0	PS	TCZ/effective	–	–	Inactive	Drug free		105	
5	17/F	6.6	PS	TCZ/effective	–	–	Inactive	PSL, TCZ	5.3	62	
6	16/F	1.5	PS	TCZ/effective	–	–	Inactive	TCZ	5.2	49	Urinary infection
7	22/F	11.4	PS	IFX/ ineffective	TCZ/effective	–	Inactive	PSL, TCZ	15.4	Unknown	
8[c]	32/F	9.4	PS	IFX/effective	ETN/ ineffective	IFX, TCZ/ effective	Inactive	PSL, MTX, TCZ	12.3	14	Liver disfunction (TCZ)
9	23/F	0.2	PS	IFX/ ineffective	–	–	Active	PSL	5.1	–	Bacterial meningitis
10	17/F	10.5	PS	IFX/effective	–	–	Inactive	Drug free	6.3	30	
11	24/F	6.8	PS	TCZ/effective	–	–	Inactive	DEX, MTX, TCZ	6.3	6	Stomatitis
12	52/M	1.1	CA	TCZ/effective	–	–	Inactive	TCZ	1.8	Unknown	
13	54/F	1.2	PS	IFX/ ineffective	TCZ/effective	–	Inactive	PSL, TCZ	2.1	7	
14	55/F	9.8	PS	ETN/ ineffective	TCZ/effective	–	Inactive	PSL, TCZ	12	Unkown	
15	50/F	4.4	CA	ETN/effective	–	–	Inactive	ETN	6.2	44	Weight loss
16	27/F	9.4	CA	IFX/ ineffective	TCZ/effective	–	Inactive	PSL, MTX, TCZ	15.3	13	Fever (IFX)

IFX Infliximab, *ETN* etanercept, *TCZ* tocilizumab, *PSL* prednisolone, *DEX* dexamethasone, *TAC* tocilizumab, *MTX* methotrexate

[a] Patients followed up for >1 year were assessed. *CA* Chronic articular, *PS* polycyclic systemic

[b] Duration from the first visit to the last visit

[c] In Patient 8, infliximab was the first drug given, with good response both to systemic and articular symptoms; due to the patient's desire to become pregnant, it was switched to etanercept with no response, and thereafter switched back to infliximab with good response again. Six months later, in accordance with the desire to become pregnant tocilizumab replaced infliximab

Suematsu R, and al. Therapeutic response of patients with adult Still's disease to biologic agents: multicenter results in Japan. Mod Rheumatol Jpn Rheum Assoc 2012

Anti IL1

Kineret® (anakinra) A biologic alternative

- **Kineret**

Étude rétrospective de cohorte

28 patients en échec de DMARDs, dont 14 en échec d'une autre biothérapie (11 ETN, 9 IFX, 3 ADA, 2 RTX)

46% atteinte articulaire chronique. 54% atteinte systémique.

Diminution des doses chez 6 patients: 2 rémissions prolongées, 4 rechutes

Effets indésirables: réaction au point d'injection.

Table 2. Therapeutic response at the last followup (mean 23 months)

	No. (%)	Anakinra discontinuation	
		No.	Reasons
Primary failure	0		
Complete remission	16 (57)	4	Side effects: 1 Remission: 3
Partial remission	8 (29)	4	Side effects: 1 Procreation desire: 1 Unsatisfactory response: 2
Loss of efficacy	4 (14)	4	Loss of efficacy after a period of complete remission: 4

Giampietro C, and al. Anakinra in Adult-Onset Still's Disease: Long-Term Treatment in Patients Resistant to Conventional Therapy: Long-Term Efficacy and Safety of Anakinra in AOSD. Arthritis Care Res 2013

Kineret

- 25 patients (16 sous DMARDs, 9 en monothérapie)
- Durée moyenne de suivi: 15 mois

- **21 rémissions complètes (84%)**. 3 rémissions partielles (12%). 1 échec (4%).
- 1 rechute traitée par ajout de MTX. 1 rechute suite à diminution des doses.
- **Pas de différence significative entre bi- et monothérapie**
- Diminution des doses (1jour/2) chez 7 patients: rémission moyenne de 12 mois.
- Arrêt du traitement chez 8 patients en rémission: 2 rechute à 1 mois. 6patients en rémission après une durée médiane de 6,5 mois.
- Effets indésirables: 3 urticaires (arrêt). 7 infections.

Laskari K, and al. Efficacy and long-term follow-up of IL-1R inhibitor anakinra in adults with Still's disease: a case-series study. Arthritis Res Ther 2011

Case-reports: 50 cas d'évolution favorable sous ttt, 1 Hépatite aigue, 1 SDRA, 1 décès par cardiomyopathie

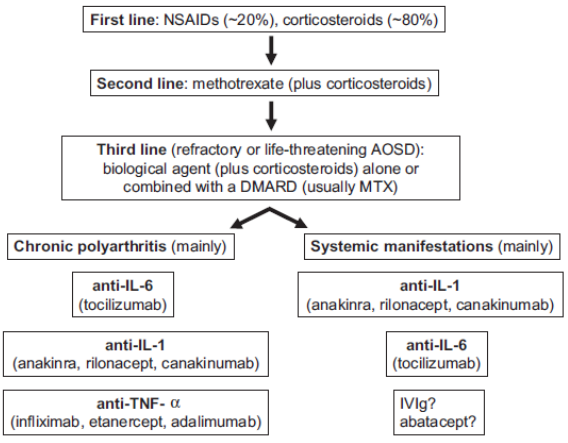
Anti IL1 & autres

- **Canakinumab**
  2 cas rapportés: efficacité après échec de l'anakinra et rilonacept
- **Rilonacept**
  3 cas rapportés: efficacité après échec anakinra
- **Abatacept**
  2 cas rapportés: efficacité
- **Rituximab**
  3 cas rapportés: efficacité

Conclusion

- Plusieurs biothérapies efficaces
- Anti IL6 et anti IL1 (anakinra) > anti TNF?
- Manque d'essai contrôlé randomisé
- Futur: anti IL18?

Conclusion (2)



Pouchot J, Arlet J-B. Biological treatment in adult-onset Still's disease. Best Pract Res Clin Rheumatol 2012