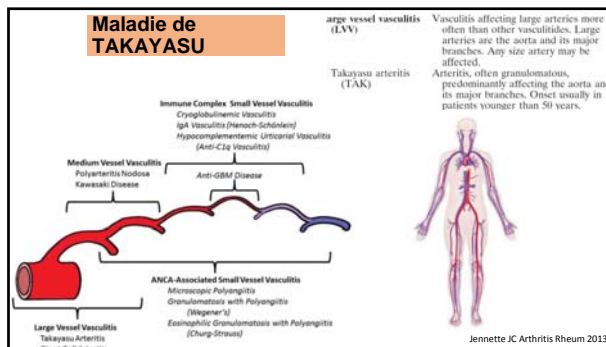


Takayasu en 2014

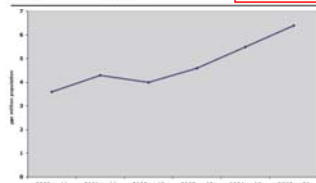
Arsene Mekinian

Service de Médecine Interne, Université Paris 13, AP-HP,
Hôpital Jean Verdier, 93140, Bondy, France.



Epidémiologie

Year	Place	Incidence/million	Prevalence/million
1962-64	Japan*	1-2	NR
1994	Japan*	NR	40
1969-94	Kuwait*	NR	7.6
		2.2 (overall)	9.5
1971-83	Ormskirk County, USA	2.6	NR
1968-75	Sweden	0.8	6.4
1966-82	Schleswig-Holstein, Germany	0.5	NR
1960-69	Vilnius, Lithuania	1.3	NR
2000-05	UK (GPRD), UK	0.8 (overall)	4.7
		0.3 (age <40 years)	0.4
2000-05	Norwich, UK	0.4	7.1

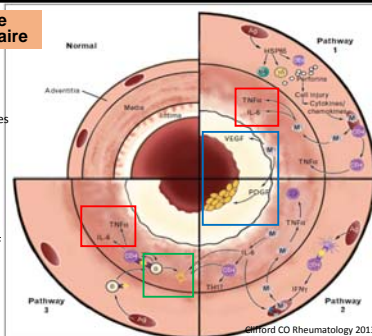


- Femme : ratio 1:9 (65-97% femmes)
- Age jeune < 40 ans (10% >40 ans)

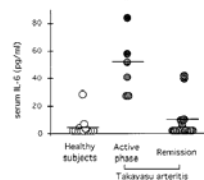
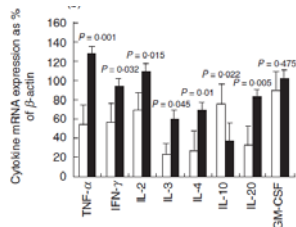
Watts R Rheumatology 2009

Physiopathologie de l'inflammation vasculaire

- Panarthritis segmentaire
- Infiltrat de macrophages et lymphocytes
- Granulomes +/- cellules géantes
- Médiadventitial
- Lymphocytes T / IFN γ -TNF α
- Macrophages TNF α / IL6 / VEGF-PDGF
- Cellules endothéliales
- Lymphocytes B

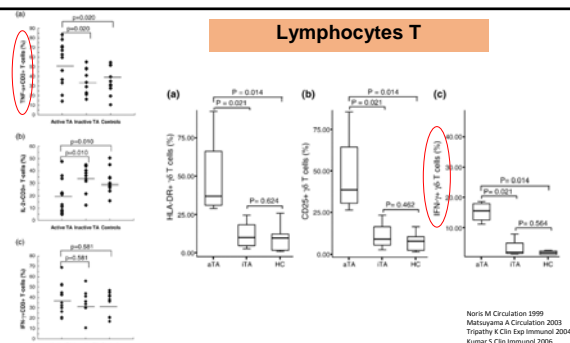


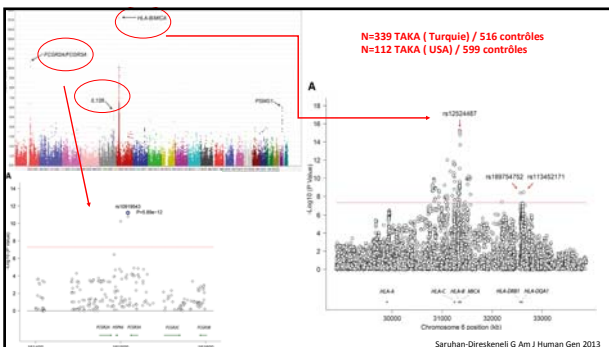
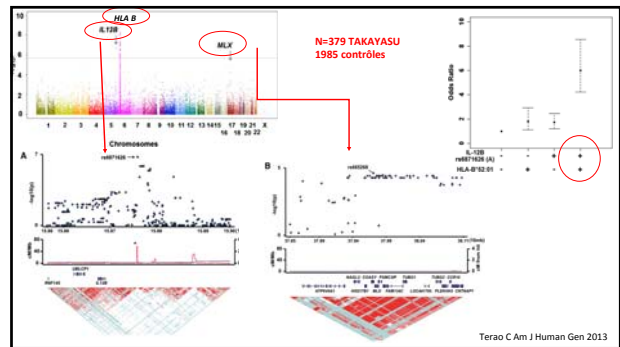
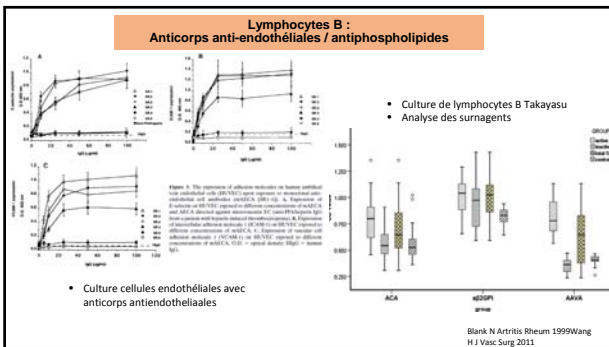
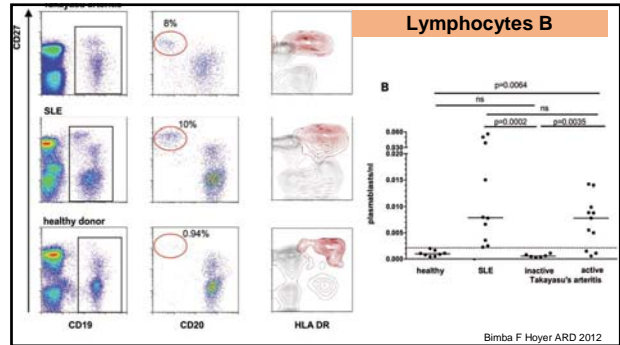
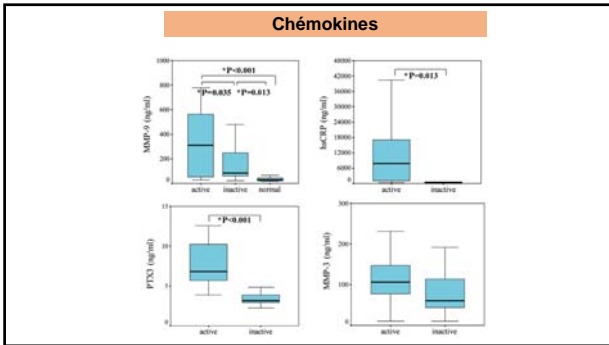
Cytokines pro-inflammatoires



Nishi M Circulation 1999
Matsuyama A Circulation 2003
Tripathy K Clin Exp Immunol 2004
Kumar S Clin Immunol 2006

Lymphocytes T






Atteinte systémique

Symptômes	Fréquences %
Asthénie	40-70%
Maigrissement	10-20%
Fièvre	20%
Arthralgies	10-30%
Érythème noueux	
Épisclérite	
MICI	

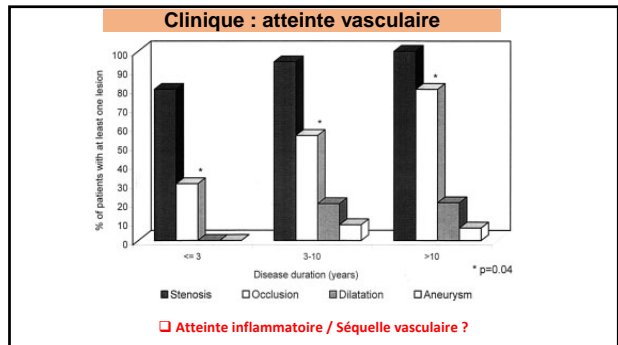
Biologie
VS > 20 mm
CRP > 10 mg/l
Fibrinogène > 4 g/l
Anémie
Haptoglobine
Orosomucoïde

Atteinte vasculaire

Territoire artériel atteint	Fréquence	Symptômes
Sous Clavière	57%	Claudication Raynaud Ischémie digitale
Carotides	40%	AIT / AVC / Troubles visuels
Aorte ascendante	29%	Insuffisance aortique
Arc aortique	36%	Insuffisance cardiaque
Aorte descendante	38%	Dissection aortique
Aorte abdominale	50%	HTA / angor mésentérique
Artères rénales	31%	HTA rénovasculaire
Artères ilio-fémorales	21%	Claudication / Ischémie
Coronaire	9%	Infarctus / insuffisance cardiaque

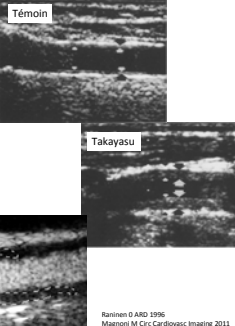


Clinique	%
Souffles	80-94%
Pouls abolis	80-94%
Anisotension (>10 mmHg)	75-80%
HTA rénovasculaire	40%
Rétinopathie	5-20%



Cartographie artérielle : Echographie Doppler = épaissement artériel

Artery	Layer of the artery	IMT thickness (mm)		P
		Patients with TA	Controls	
Right common carotid artery	Intima + media	1.23 (0.92)	0.74 (0.14)	0.001
	Adventitia	0.48 (0.21)	0.40 (0.10)	0.113
	Total	1.91 (0.42)	1.50 (0.32)	0.001
Left common carotid artery	Intima + media	1.75 (0.86)	0.74 (0.11)	0.000
	Adventitia	0.49 (0.18)	0.38 (0.16)	0.028
	Total	2.48 (0.99)	1.50 (0.32)	<0.001
Right subclavian artery	Intima + media	2.08 (1.26)	0.87 (0.14)	0.001
	Adventitia	0.49 (0.15)	0.51 (0.17)	0.991
	Total	2.87 (1.31)	1.38 (0.16)	0.001
Left subclavian artery	Intima + media	2.41 (1.06)	0.85 (0.17)	0.001
	Adventitia	0.87 (0.17)	0.50 (0.16)	0.114
	Total	2.99 (1.06)	1.35 (0.16)	0.000
Brenson artery	Intima + media	1.16 (0.60)	0.90 (0.18)	0.057
	Adventitia	0.51 (0.06)	0.52 (0.10)	0.375
	Total	1.66 (0.63)	1.42 (0.12)	0.066
Renal artery	Intima + media	1.04 (0.36)	0.85 (0.16)	0.045
	Adventitia	0.53 (0.15)	0.52 (0.09)	0.332
	Total	1.97 (0.48)	1.37 (0.17)	0.005
Abdominal aorta	Intima + media	1.92 (1.88)	2.20 (0.31)	0.001



Brenson © AARD 2006
Magnon M Crc Cardiovasc Imaging 2011

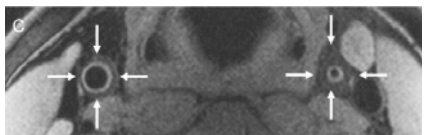
Cartographie des lésions artérielles : AngioTDM / IRM

Angio-TDM

- Epaissement artériel
- Rehaussement tardif
- Evaluation globale
- Irradiation / nephrotoxique
- Activité ?
- Suivi : nouvelles lésions artérielles

Angio-IRM

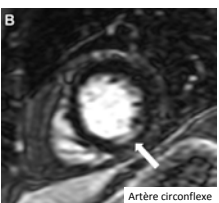
- Epaissement artériel
- Prise de contraste murale
- Evaluation globale
- Artéfacts
- Activité ?
- Suivi : nouvelles lésions artérielles



Cartographie des lésions artérielles : atteinte cardiaque

- Echographie cardiaque : atteinte valvulaire aortique (10-20%)
- Exploration atteinte coronaire
- Atteinte infra-clinique : IRM cardiaque ?

Variable	Patients With TA (n = 27)	Control Subjects (n = 80)	p
Age (yrs)	48 (34-61)	51 (4-59)	0.304
Female sex	19 (70.4)	48 (60)	0.368
Diabetes mellitus	4 (14.8)	26 (32.5)	0.088
Hypertension (history)	10 (37)	55 (68.3)	0.006
Dyslipidemia (history)	9 (33.3)	31 (38.8)	0.653
Tobacco use	7 (25.9)	16 (20)	0.590
Family history of CAD	3 (11.8)	NA	NA
Total cholesterol	1.7 (1.5-2.6)	1.73 (1.54-2.08)	0.235
g/L			
mg/dL	170 (150-260)	173 (154-208)	
Absolute cardiovascular risk (%)	5 (2-8)	5 (3-8.5)	0.219
LOE revealed on CMR	7 (25.9)	4 (5)	0.002



Comarmond C Am J Cardiol 2014

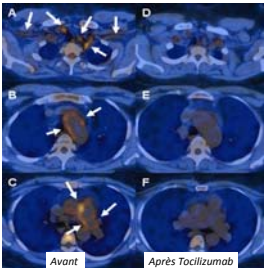
18 FDG-TEP/CT

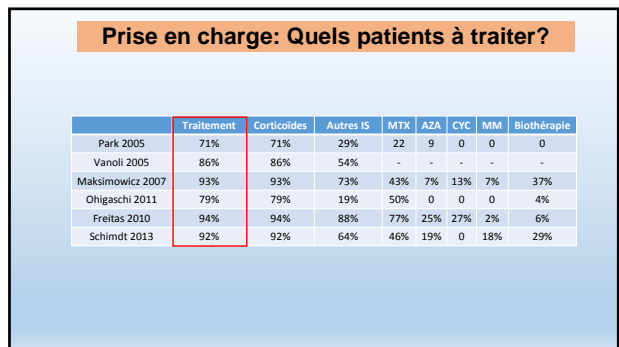
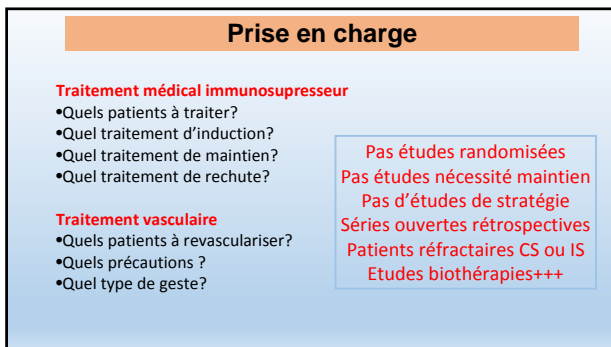
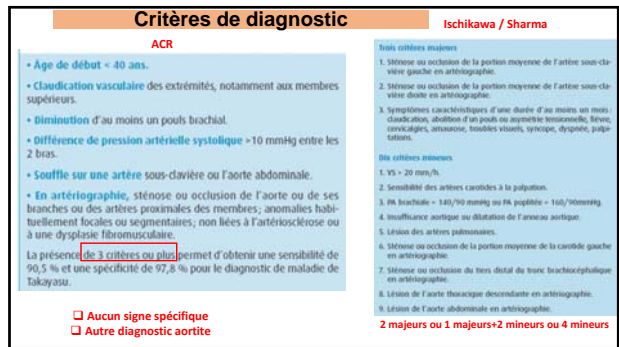
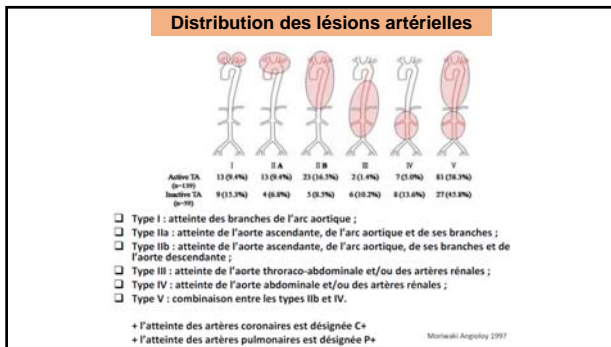
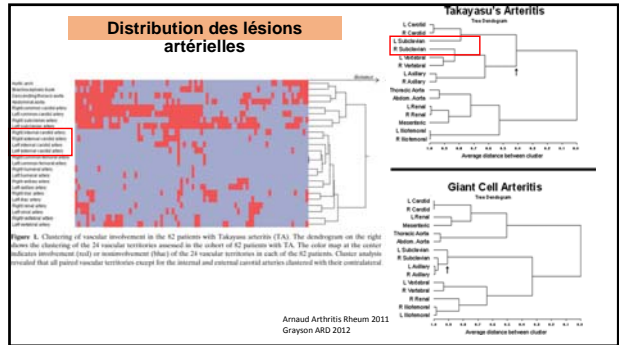
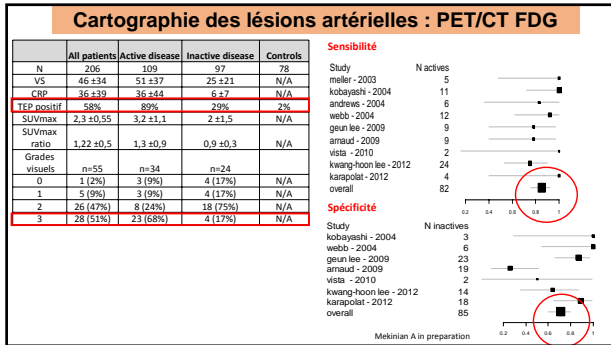
□ Femme 38 Ans

□ Douleur thoracique / Dyspnée
Scintigraphie pulmonaire : EP

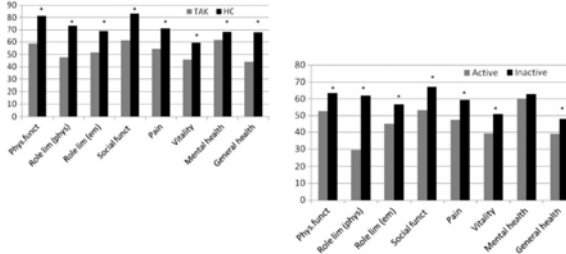
□ Claudication artérielle
Aortite diffuse angio-TDM

□ Echet Prednison- Methotrexate
Tocilizumab 8 mg/kg

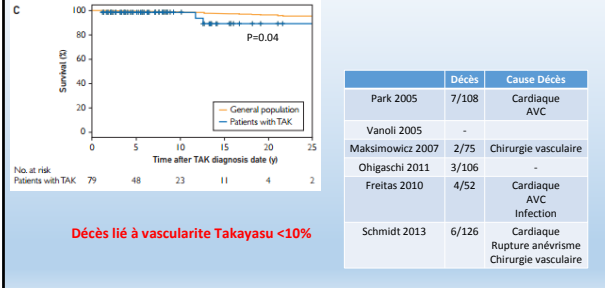




Qualité de vie



Survie et causes de décès

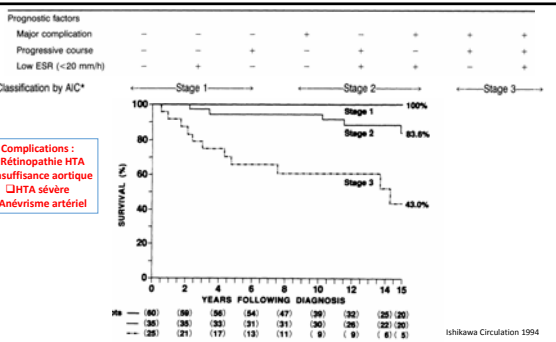
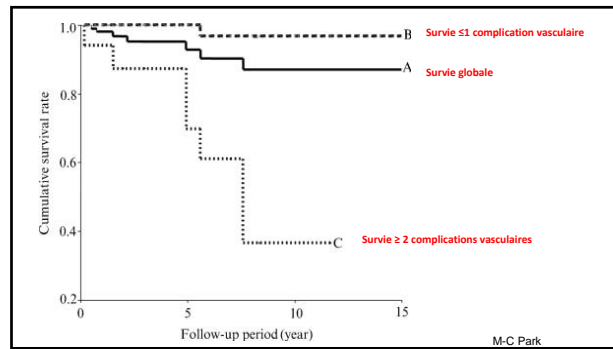


Décès lié à vasculite Takayasu <10%

Complications vasculaires

Study	Complications	Type
Park 2005	57%	Insuffisance aortique Insuffisance cardiaque Ischémie myocardique AVC HTA rénovasculaire Rétinopathie HTA
Schmidt 2013	24%	AVC Ischémie myocardique Dissection aortique Autre ischémie

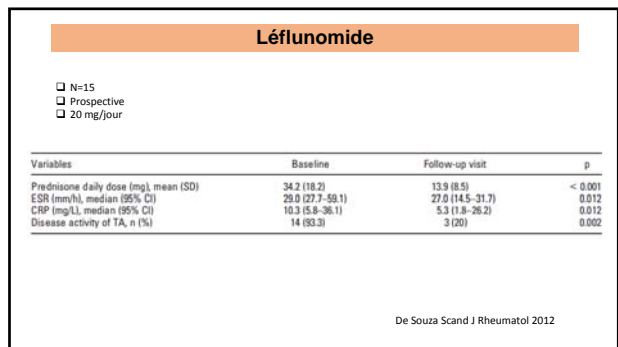
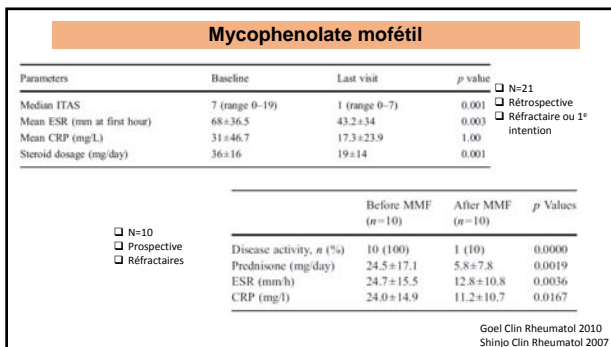
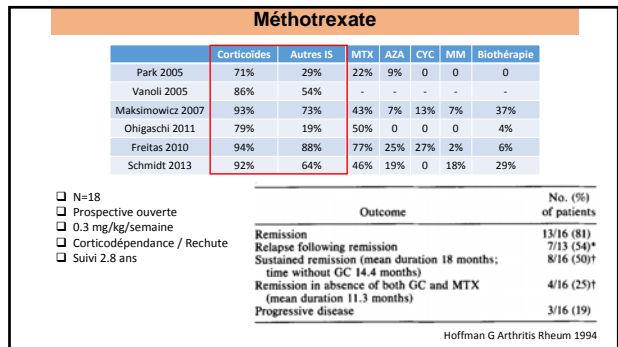
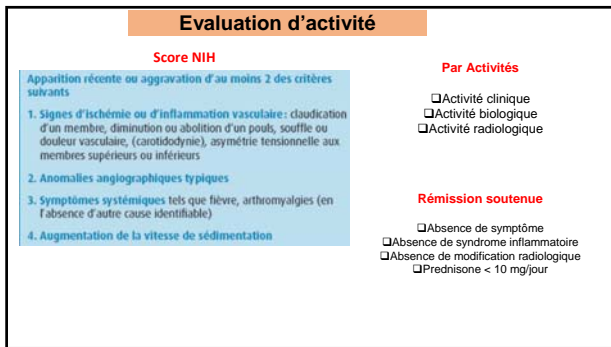
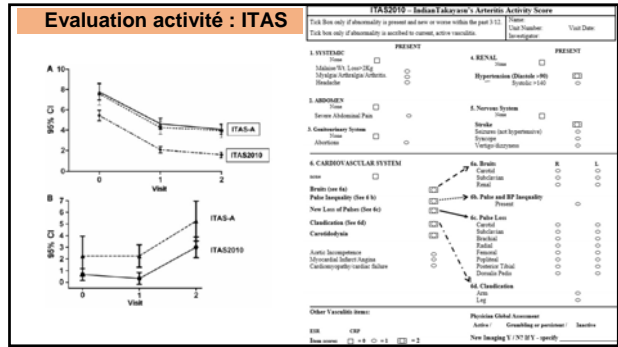
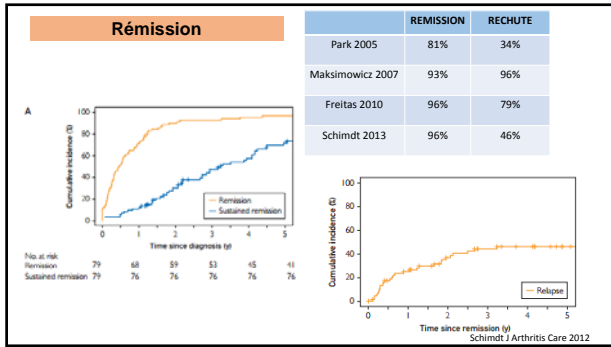
➔ Nouvelles lésions artérielles au cours de suivi chez 56% (41-71%)



Complications :
 □ Rétinopathie HTA
 □ Insuffisance aortique
 □ HTA sévère
 □ Anévrisme artériel

Takayasu active est à risque de nouvelles lésions artérielles

	Disease activity		p-value*	Angiographic change		p-value*
	With remission (n=74)	Without remission (n=17)		With progression (n=16)	Without progression (n=23)	
Age at diagnosis of TA, years	30.1 ± 11.7	31.0 ± 7.2	NS	31.4 ± 8.8	31.6 ± 9.7	NS
Lag time from symptom onset to diagnosis, months	5.6 ± 4.9	16.7 ± 5.9	0.039	15.4 ± 6.6	11.6 ± 7.8	NS
Elevated ESR, n	71 (95.9%)	17 (100%)	NS	16 (100%)	20 (87.0%)	NS
ESR level, mm/h	30.6 ± 31.1	75.5 ± 28.9	0.009	70.7 ± 22.5	41.0 ± 28.4	0.041
Elevated CRP, n	42 (56.9%)	12 (70.6%)	NS	12 (75.0%)	14 (60.9%)	NS
CRP level, mg/dL	1.8 ± 1.3	2.8 ± 1.1	NS	2.1 ± 0.8	1.9 ± 1.1	NS
Angiographic classification						
Type I	28 (37.9%)	8 (28.4%)	NS	4 (25.0%)	8 (34.8%)	NS
Type IIa	1 (1.4%)	0 (0%)	NS	0 (0%)	1 (4.3%)	NS
Type IIb	2 (2.7%)	2 (11.8%)	NS	0 (0%)	2 (8.7%)	NS
Type III	9 (11.9%)	1 (5.9%)	NS	1 (6.2%)	1 (4.3%)	NS
Type IV	11 (14.8%)	2 (11.8%)	NS	3 (18.8%)	5 (21.7%)	NS
Type V	27 (35.5%)	6 (35.3%)	NS	8 (50.0%)	6 (26.1%)	NS
Glucocorticoid therapy	67 (90.5%)	10 (58.8%)	0.004	11 (68.8%)	21 (91.3%)	NS
Immunosuppressive agent	28 (37.8%)	5 (29.4%)	NS	3 (18.8%)	15 (65.2%)	NS
Active disease at diagnosis	-	-	-	16 (100%)	14 (60.9%)	0.003
Achievement of remission	-	-	-	13 (81.3%)	14 (60.9%)	NS
Occurrence of first relapse	-	-	-	11 (68.8%)	5 (21.7%)	0.019
Achievement of remission	-	-	-	6 (37.5%)	4 (17.4%)	NS



Antagonistes TNFalpha : Infliximab

Number of evaluable patients	Baseline assessment (n = 15)	3-month evaluation (n = 15)	6-month evaluation (n = 13)	12-month evaluation (n = 11)
Clinical response				
Infliximab efficacy by physician, n (%)	-	13 (87)	10 (77)	8 (73)
Disease clinical activity, n (%)	11 (73)	3 (20)**	4 (31)*	3 (27)*
Infliximab-associated treatments				
CSs (prednisone), n (%)	14 (93)	12 (80)	11 (85)	10 (91)
CSs (prednisone, mg/day)	20 (0-30)	15 (0-20)**	7.5 (0-18)*	6 (0.5-30)*
Diagnosed dependence, n (%)	8 (53)	2 (13)*	0*	1 (9)*
MTX, n (%)	7 (46)	9 (60)	9 (69)	7 (64)
MTX, mg/week	15 (7.5-25)	15 (7.5-20)	15 (5-15)	15 (5-20)
AZA, n (%)	4 (27)	4 (27)	4 (31)	4 (36)
AZA, mg/day	125 (100-175)	125 (100-175)	100 (100-175)	100 (100-175)
Laboratory data				
Biological activity, n (%)	11 (73)	4 (27)*	4 (31)**	4 (42)**
ESR, mm/h	60 (12-100)	15 (6-32)*	10 (4-64)*	8 (2-60)
CRP, mg/l	30 (4-70)	5 (0-57)*	6 (0-50)*	9 (0-100)
Fibrinogen, g/l	5.5 (3-7.5)	3 (1-4.6)*	2.5 (0-6)*	2 (2-4)
Leucocyte count, 10 ⁹ /mm ³	11 (2.4-20)	6 (3.6-15)*	8 (4.2-15) ***	6 (3.8-16)

Mekinian Rheumatology 2012

Antagonistes TNFalpha

	N	Remission	Sustained remission	Relapses	New arterial lesions	CS cessation	Side effects	Follow-up (months)
Schmidt 2012	20	90%	50%	33%	0%	58%	33%	54
Hoffman 2004	15	93%	66%	NA	28%	66%	7%	12
Molloy 2008	25	88%	60%	62%	16%	60%	20%	28
Mekinian 2012	15	87%	60%	28%	NA	7%	30%	43

Hoffman Arthritis Rheum 2004
Molloy ARD 2008
Mekinian Rheumatology 2012
Schmidt Arthritis Care Res 2012

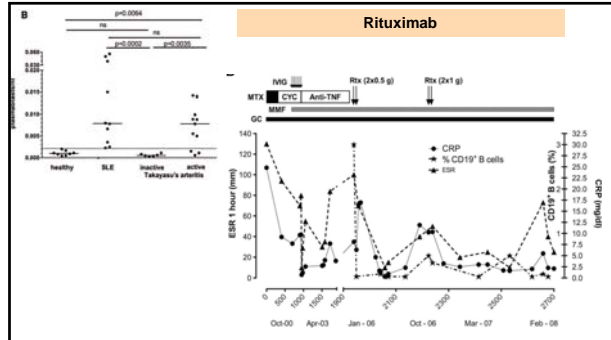
Tocilizumab

Characteristics of patients with TA from personal data (n = 5) and literature review (n = 39).

Number of evaluable patients	Baseline assessment (N = 44)	3 months after beginning tocilizumab treatment (N = 30)	8 months after beginning of tocilizumab treatment (N = 24)	Last visit (N = 44)
Tocilizumab treatment	44 (100)	28 (93)	12/15 (80%)	17/32 (53%)
Delay from baseline (months)	-	3 [2-3]	6 [4-6]	15 [8-33]
Clinical response				
Tocilizumab efficacy	-	13/14 (93%)	14/18 (78%)	33/44 (75%)
Drug alterations				
Disease clinical activity	41/42 (98%)	1/14 (7%)	3/18 (17%)	7/34 (20%)
Laboratory data				
Biological activity	38/39 (97%)	3/17 (18%)	3/17 (18%)	7/34 (20%)
ESR (mm/h)	42 [8-85]	4 [0-63]	5 [0-41]	4 [0-41]
C-reactive protein (mg/l)	21 [8-126]	0 [0-13]	0.5 [0-124]	0 [0.5-17]
Radiological data				
Radiological activity	15/22 (68%)	3/9 (33%)	3/17 (18%)	-
retrovascular spaces	3/9	-	3/7 (43%)	-
SUV max	3.8 [1.3-5.3]	-	-	-
Tocilizumab associated events	27/40 (68%)	27/30 (90%)	8/13 (62%)	18/27 (67%)
Stomach (prednisone, mg/day)	15 [3-75]	10 [3-30]	-	3 [0-30]

Abstror Autoimmun Rev 2013

Rituximab



Avant greffe moelle



Après greffe moelle



H Kato Bone Marrow Transplantation 2013

Recommandations EULAR 2009

Induction (3C):

- Prednisone 1 mg/kg/jour
- 10-15 mg/kg à 3 mois
- Durée plusieurs années

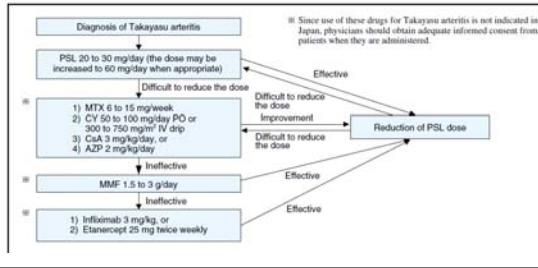
Maintien (3C):

- Immunosuppresseur associé :
 - Methotrexate (20-25 mg/sem)
 - Azathioprine (2 mg/kg/jour)
 - Cyclophosphamide

Mukhtyar C, ARD 2009

Recommendations Japanese Circulation Society 2008

JCS Guidelines for Management of Vasculitis Syndrome



Traitement vasculaire

- N= 79
- N=166 gestes vasculaires
- Chirurgie :
 - Remplacement prothétique
 - Remplacement non-prothétique
- Angioplastie avec / sans stent

	All (n=166)	Surgery (n=104)	Endovascular Repair (n=62)	P
Arterial lesion, n (%)	137 (82.5)	75 (72.1)	62 (100)	<0.0001
Stenosis	29 (17.5)	29 (27.9)	0	
Aneurysms				
Arterial territory, n (%)				
Aorta	31 (18.7)	18 (17.3)	13 (21.0)	0.68
Subclavian	24 (14.4)	19 (18.3)	5 (8.1)	0.11
Renal	22 (13.2)	6 (5.8)	16 (25.8)	0.0006
Carotid	19 (11.4)	15 (14.4)	4 (6.5)	0.14
Iliac	16 (9.6)	8 (7.7)	8 (12.9)	0.29
Mesenteric	11 (6.6)	9 (8.7)	2 (3.2)	0.21
Femoral	10 (6.0)	7 (6.7)	3 (4.8)	0.25
Colic. trunk	7 (4.2)	4 (3.8)	3 (4.8)	1
Axillary	6 (3.6)	5 (4.8)	1 (1.6)	0.41
Coronary	6 (3.6)	4 (3.8)	2 (3.2)	1
Humeral	5 (3.0)	4 (3.8)	1 (1.6)	0.65
Others	9 (5.4)	5 (4.8)	4 (6.5)	0.73

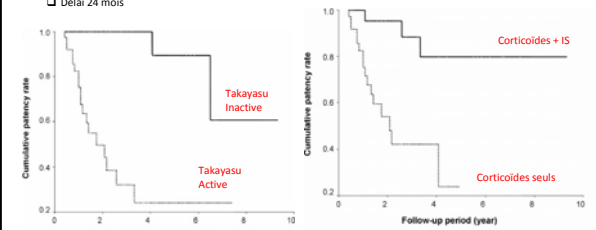
Saadoun Circulation 2012

Traitement vasculaire : complications

	All (n=79)	Surgery (n=35)	Endovascular Repair (n=31)	Univariate Analysis		Multivariate Analysis	
				OR (95% CI)	P	OR (95% CI)	P
Age at diagnosis				0.99 (0.94-1.04)	0.54		
Sex							
Male				1			
Female				0.62 (0.1-3.62)	0.59		
Geographic origin							
Europe				1			
North Africa				3.15 (0.65-15.8)	0.26		
Africa				1.53 (0.59-4.77)	0.79		
Cardiovascular risk factors							
Hypertension*				1			
Hyperlipidemia*				0.29 (0.06-1.48)	0.14		
Diabetes mellitus				0.24 (0.02-3.58)	0.31		
Overweight				1.58 (0.10-4.21)	0.64		
Smoking				0.31 (0.05-1.89)	0.21		
Control of blood pressure				0.37 (0.06-1.93)	0.19		
Biological inflammation				4.89 (1.26-19.77)	0.04	7.48 (1.42-39.35)	0.04
Treatments							
Corticosteroids				3.45 (0.85-7.06)	0.10		
Immunosuppressants				11.89 (2.8-48.88)	0.001	1.72 (0.23-1.72)	0.82
Aspirin				4.85 (1.3-21.49)	0.043		
Anticoagulants				32.89 (5.29-192.88)	<0.001	4.38 (0.58-33.05)	0.17
Statins				3.02 (0.58-15.46)	0.19		

Risque de restenose

- N= 63 interventions vasculaires (angioplasties / remplacement prothétique)
- Resténose = 32%
- Délai 24 mois



Park MC, Rheumatology 2006

Risque de restenose : antiagrégants ?

	Ischemic event (n=41)	No ischemic event (n=44)	P value
Age at diagnosis, years	30.6±11.3	28.5±10.1	0.699
Female, n (%)	13 (32.0)	30 (68.2)	1.000
Caucasian, n (%)	7 (17.1)	22 (49.7)	0.344
Time since TA diagnosis, months	118.8±101.3	148.8±107.8	0.324
Time since TA diagnosis, months	74.3±52.7	115.5±62.7	0.123
Diabetes/dyslipidemia/obesity	44 (107.3)	36 (80.9)	0.618
Antiplatelet agents, n (%)	2 (4.9)	38 (86.4)	<0.0001
Median aspirin dose, mg/day	300	300	0.982
Antiplatelet therapy, n (%)	3 (7.3)	3 (6.8)	0.939
Procedures, n (%)	12 (29.3)	31 (70.2)	0.621
Immunosuppressive drugs, n (%)	12 (29.3)	22 (49.7)	0.589
Statin therapy, n (%)	8 (19.5)	13 (29.3)	0.230
Risk factors for CVD, n (%)	19 (46.3)	31 (70.2)	1.000
Advanced age, n (%)	1 (2.4)	2 (4.5)	1.000
Tobacco use, n (%)	2 (4.9)	2 (4.5)	0.989
Systemic hypertension, n (%)	12 (29.3)	25 (56.8)	0.489
Low HDL-C, n (%)	2 (4.9)	9 (20.5)	0.391
Mean HDL-C, mg/dL	60.30±20.43	54.91±19.44	0.466
High LDL-C, n (%)	7 (17.1)	18 (40.9)	0.110
Diabetes, n (%)	1 (2.4)	3 (6.8)	1.000
Obesity, n (%)	2 (4.9)	6 (13.6)	1.000
Family history of premature CVD, n (%)	0 (0.0)	1 (2.3)	1.000
Mean number of risk factors for CVD, means±SD	2.06±0.86	1.77±0.80	0.290
Deaths, n (%)	0 (0.0)	0 (0.0)	0.001*

De Souza Circulation J 2012

JCS Guidelines of surgical treatment

I) General Descriptions

i) Surgical Treatment

Bypass surgery is the standard technique.⁴⁶ Surgery should be performed when inflammation is not present and the grafts should be anastomosed to intact vessels. Branches of the aortic arch are bypassed with artificial grafts, while the renal arteries are bypassed with artificial grafts or venous grafts.⁴⁷ Since the incidence of aneurysm at the site of anastomosis is high, patients should be followed for a long period of time after bypass surgery.

ii) Vascular Interventions

Bifurcated lesions often lead to restenosis, and stenting for such lesions does not improve the outcome.⁴⁸ Stenting is mainly indicated for discrete lesions and high-risk patients. It has been reported that the use of stents in the treatment of aortic coarctation may improve both the early and long-term outcomes of patients with Takayasu arteritis.⁴⁹⁻⁵¹

Etudes en cours

- TOCITAKA : tocilizumab / sevrage en corticoïdes à 6 mois (A Mekinian / O Fain)
- Régistre TAKAYASU en France
- Régistre de Biothérapies BIOTAKA (CRI / SNFMI / GEFA)
- Takayasu - grossesse (N Abisor / N Costedoat / GR2)