Updates in the Diagnosis and Therapy of Rheumatoid Arthritis

Updates MSD
18 octobre 2010

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Case presentation

- 49-year old female without previous medical history
- Joint pain since 6 months: hands, feet, knees
- Morning stiffness: 1h
- 10 painful and swollen joints

What is your differential diagnosis?
What tests should you prescribe?

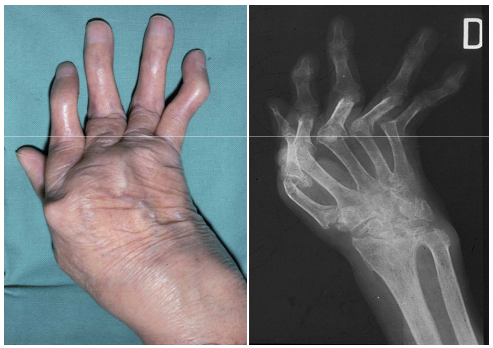
Results

- ESR: 30 mm/h, CRP 21 mg/L
- RF IgM: negative; RF IgA: negative
- Anti-CCP: 200 (N<50)
- ANA: 160 (N<80), anti-dsDNA: negative
- Hb 11g/L
- X-rays: normal

S'agit-il d'une PR?

- Critères cliniques
- Quels tests et quelle sensibilité/ spécificité
- Algorythme diagnostic

Rheumatoid Arthritis



Frequency: 1%
Female:male 3:1
Higher incidence 40-60 yr

ACR 1987 Classification Criteria

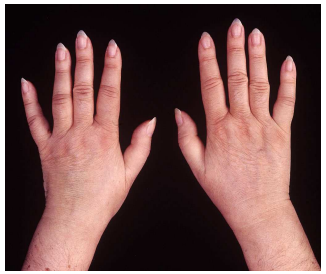
1. **Morning stifness ≥ 1 h**
2. **Arthritis ≥ 3 joints**
3. **Arthritis wrists, hands**
4. **Symetrical arthritis**
5. **Rheumatoid nodules**
6. **Rheumatoid factors**
7. **Erosions (X-rays)**

Sensibilité 91%, spécificité 89%

2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative

Table 3 The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for RA

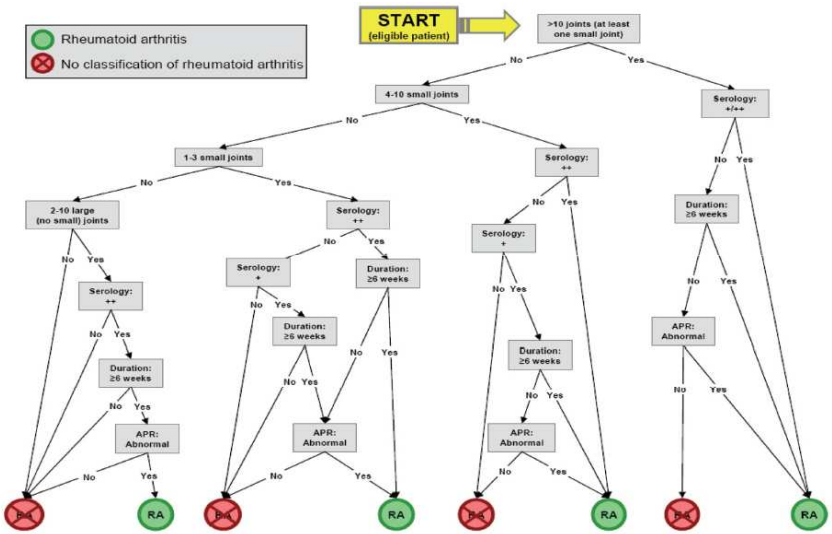
	Score
Target population (Who should be tested?): Patients who	
1) have at least 1 joint with definite clinical synovitis (swelling)*	
2) with the synovitis not better explained by another disease†	
Classification criteria for RA (score-based algorithm: add score of categories A-D; a score of ≥6/10 is needed for classification of a patient as having definite RA)‡	
A. Joint involvement§	
1 large joint¶	0
2–10 large joints	1
1–3 small joints (with or without involvement of large joints)**	2
4–10 small joints (with or without involvement of large joints)	3
>10 joints (at least 1 small joint)††	5
B. Serology (at least 1 test result is needed for classification)‡‡	
Negative RF *and* negative ACPA	0
Low-positive RF *or* low-positive ACPA	2
High-positive RF *or* high-positive ACPA	3
C. Acute-phase reactants (at least 1 test result is needed for classification)§§	
Normal CRP *and* normal ESR 0	0
Abnormal CRP *or* normal ESR 1	1
D. Duration of symptoms¶¶	
<6 weeks	0
≥6 weeks	1



Diagnosis of RA: 6 points

Ann Rheum Dis 2010;**69**:1580–1588. doi:10.1136/ard.2010.138461

Diagnosis Algorythm



Anti-CCP

Tests	Sensitivity (95% IC)	Specificity (95% IC)
Anti-CCP	0.56 (0.49-0.63)	0.90 (0.86-0.93)
IgM FR	0.73 (0.67-0.79)	0.82 (0.77-0.87)
IgA FR	0.63 (0.56-0.70)	0.90 (0.86-0.94)
CCP + IgM FR	0.48 (0.41-0.55)	0.96 (0.93-0.98)
CCP + IgA FR	0.44 (0.37-0.51)	0.98 (0.96-1.00)
IgM + IgA FR	0.59 (0.52-0.66)	0.94 (0.91-0.97)
CCP + IgM + IgA FR	0.41 (0.34-0.48)	0.98 (0.97-1.00)

196 patients with rheumatoid arthritis
239 patients with other inflammatory and non-inflammatory rheumatic diseases

S. Bas et al *Rheumatology* 2003

High Predictive Value of anti-CCP

Similar results in non-Caucasian subjects

Table 2 Serological and immunogenetic characteristics in RA patients, controls with inflammatory rheumatic diseases, and healthy individuals

Laboratory values	RA	IRD (n = 56)	HI (n = 51)	Sensitivity (n = 50)	Specificity	PPV	NPV	AUC (ROC) (95%) CI
RF IgM (%)	43	3 (6)	4 (8)	77	93	86	88	0.85 (0.79 to 0.91)
RF IgA (%)	47	8 (16)	0 (0)	84	92	85	91	0.88 (0.82 to 0.94)
Anti-CCP2 (%)	46	1 (2)	1 (2)	82	98	96	91	0.90 (0.85 to 0.96)
Anti-CCP3 (%)	43	4 (8)	1 (2)	77	95	90	88	0.86 (0.80 to 0.92)
SE 1 or 2 copies (%)	17	7 (14)	5 (10)	30	88	59	70	0.59 (0.52 to 0.66)
- SE 1 copy (%)	15	7 (14)	5 (10)	27	88	56	68	0.57 (0.51 to 0.64)
- SE 2 copies (%)	2	0 (0)	0 (0)	4	100	100	65	0.52 (0.49 to 0.54)

Anti-CCP, anti-cyclic citrullinated peptides; AUC, area under the curve in the ROC analysis; HI, healthy individuals; IRD, inflammatory rheumatic diseases; RA, rheumatoid arthritis; RF, rheumatoid factor; Sensitivity, the percentage of RA patients who would be identified as having RA by the laboratory tests (*positive test results*); Specificity, the percentage of control patients (IRD and HI together) who would be identified as not having RA by the laboratory tests (*negative test results*); PPV, positive predictive value or the proportion of RA patients with *positive test results* who are correctly diagnosed as having RA; NPV, negative predictive value or the proportion of control patients with *negative test results* who are correctly diagnosed as not having RA; SE, shared epitope

Singwe-N'gandeu et al. *Arthritis Res Ther 2009*

EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs

Josef S Smolen,[1,2] Robert Landewé,[3] Ferdinand C Breedveld,[4] Maxime Dougados,[5] Paul Emery,[6] Cecile Gaujoux-Viala,[5,7] Simone Gorter,[3] Rachel Knevel,[4] Jackie Nam,[6] Monika Schoels,[2] Daniel Aletaha,[1] Maya Buch,[6] Laure Gossec,[5] Tom Huizinga,[4] Johannes W J W Bijlsma,[8] Gerd Burmester,[9] Bernard Combe,[10] Maurizio Cutolo,[11] Cem Gabay,[12] Juan Gomez-Reino,[13] Marios Kouloumas,[14] Tore K Kvien,[15] Emilio Martin-Mola,[16] Iain McInnes,[17] Karel Pavelka,[18] Piet van Riel,[19] Marieke Scholte,[14] David L Scott,[20] Tuulikki Sokka,[21] Guido Valesini,[22] Ronald van Vollenhoven,[23] Kevin L Winthrop,[24] John Wong,[25] Angela Zink,[26] Désirée van der Heijde[4]

OVERARCHING PRINCIPLES

1. Rheumatologists are the specialists who should primarily care for patients with rheumatoid arthritis (RA)
2. Treatment of patients with RA should aim at the best care and must be based on a shared decision between the patient and the rheumatologist
3. RA is expensive in regards to medical costs and productivity costs, both of which should be considered by the treating rheumatologist

Ann Rheum Dis 2010;**69**:964–975. doi: 10.1136/ard.2009.126532

Principes généraux de prise en charge

- Prise en charge précoce utile?
- Quelle cible de traitement ?
- Prise en charge physique?
- Prise en charge médicamenteuse?

Principles of RA Management

- Control pain and avoid subsequent damage and disability
- Take into account patient's expectations and risk factors of adverse events
- Take into account the presence of signs of aggressive disease
  - Serological markers (Anti-CCP, Rheumatoid factors)
  - Early structural damage
  - Clinical presentation (number of inflamed joints)
  - High inflammatory response (high C-reactive protein / ESR levels)

Ann Rheum Dis 2010;**69**:964–975. doi: 10.1136/ard.2009.126532

Recommendations for the management of RA

Treatment with synthetic disease modifying anti-rheumatic drugs (DMARDs) should be started as soon as the diagnosis of RA is made

Treatment should be aimed at reaching a target of remission or low disease activity as soon as possible; treatment should be adjusted by frequent (1-3 months) and strict monitoring

Methotrexate (MTX) should be part of the first treatment strategy

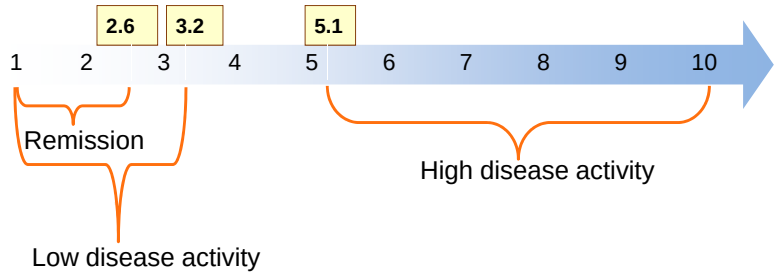
Ann Rheum Dis 2010;**69**:964–975. doi: 10.1136/ard.2009.126532

Disease Activity Score

DAS28 = 0.56 * √(TJC 28) + 0.28 * √(SJC 28) + 0.70 * ln (ESR) + 0.014 * GH

[where **TJC = tender joint count**; **SJC = swollen joint count**; **ESR = erythrocyte sedimentation rate**; **GH = general health assessment**]

DAS28 provides a number on a scale from 0 to 10 which indicates the current activity of the disease



How to achieve these objectives ?

1. **To measure** – Disease Activity Score (tender and swollen joints + ESR/CRP)
2. **Non-pharmacological means**
   - Education
   - Occupational therapy
   - Physical therapy (balneotherapy, thermotherapy, exercise)
3. **Pharmacological therapies**
   - Disease Modifying Antirheumatic drugs (DMARDs)
   - Glucocorticoids (systemic or local injections)
   - Non-steroidal antiinflammatory drugs (NSAIDs)

Non-pharmacological interventions

Balneotherapy: 6 RCT, 355 patients,
Positive findings but studies were methodologically flawed
Verhagen et al. Cochrane Database Syst Rev 2003

Aerobic exercise: 14 RCT, 1040 patients
Improved QoL, function (HAQ), pain (VAS)
Baillet et al Arthritis Res Ther 2010

Thermotherapy: 3 RCT, 79 patients
No effect on objective measures but high level of patient preference
No difference for heat or ice
Welch et al. Cochrane Database Syst Rev 2001

Occupational therapy: 15 studies (6 controlled studies)
Positive effect on functional ability
Steultjens et al. Cochrane Database Syst Rev 2004

Tai chi: 4 RCT (206 patients)
No significant on most outcomes of disease activity
Significant improvement of in ankle plantar flexion
Han et al. Cochrane Database Syst Rev 2004

Quels médicaments?

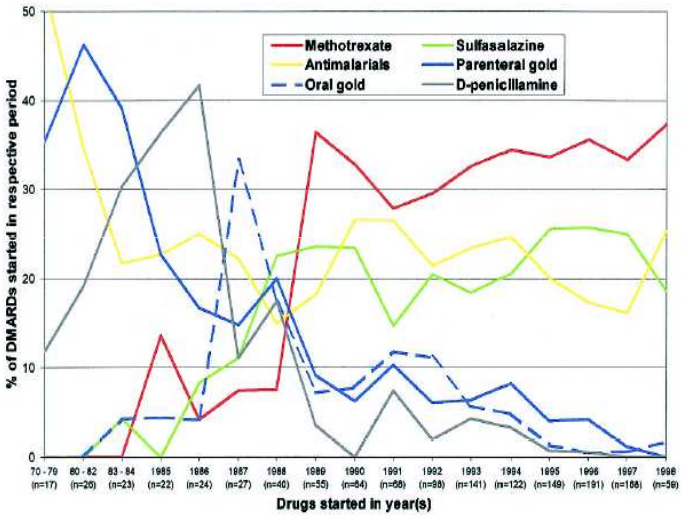
- **Que doit savoir l'interniste non rhumatologue?**
- **Principes généraux du traitement**
- **Suivi des effets secondaires**
- **Complications/ précautions**

Methotrexate

First trial in RA in 1951

- Greatest experience - open- RCT- comparative trials
- Long term treatment, functional and X-Ray evolution
- High retention rate (50% after 5 yrs)
- Easy to dose - 10 mg/wk to 25 mg/wk
- Oral or parenteral (sc/im)
- Toxicity well described
- Monitoring guidelines
- Folic and folinic acid to reduce toxicity
- Decreases the mortality of RA
- Low cost

Evolution of DMARDs Use From 1970 to 2000



Leflunomide

Biologicals

Alateha & Smolen. *Rheumatology* 2002

Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study)

- 110 RA patients randomized to
  - Routine care
  - Intensive care (monthly DAS assessement followed by change of therapy (DMARDs and CS) to achieve DAS < 2.4)

	Intensive group (n=55)	Routine group (n=55)
Women	39 (71%)	38 (69%)
Age (years)	51 (15)	54 (11)
Disease duration (months)	19 (16)	20 (16)
Rheumatoid-factor positive	41 (75%)	40 (73%)
Disease activity score	4·9 (0·9)	4·6 (1·0)
Swollen joint score (0–44)	12 (4)	11 (4)
Ritchie articular index	23 (10)	22 (12)
Pain score (0–100)	62 (20)	59 (20)
Patient global assessment (0–100)	69 (21)	62 (23)
Physician global assessment (0–100)	70 (18)	65 (18)
C-reactive protein (mg/L)	44 (53)	38 (50)
Erythrocyte sedimentation rate (mm/h)	45 (31)	34 (27)
Health assessment questionnaire score*(0–3)	2·0 (0·8)	1·9 (0·7)
Short form-12 physical summary†	28 (7)	28 (8)
Short form-12 mental health summary†	39 (13)	39 (13)
Median total Sharp score (IQR)	21·5 (10–39·5)	24·5 (13·25–47)
Total Sharp score	28 (23)	32 (27)

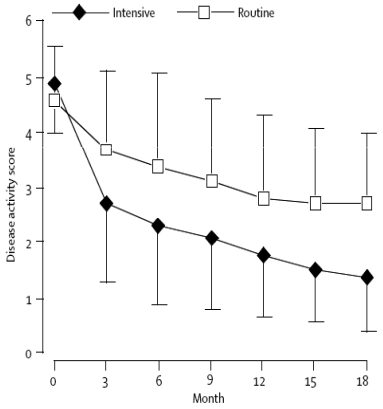
Data are mean (SD) or number of patients (%), unless otherwise indicated. *0=no disability, 3=maximum disability. †Population mean=50.

Table 1: **Baseline characteristics**

C. Grigor et al. *Lancet* 2004; 364: 263-69

The TICORA study
At 18 months

- Intensive group had a significantly better outcome regarding:
  - Function
  - Erosion score
  - Pain score
  - Global assessement
  - ESR and CRP

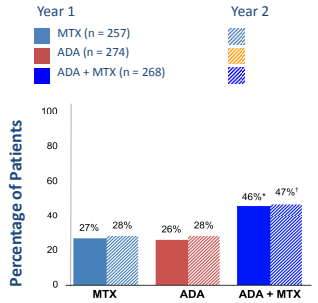


Biological Agents Licensed for the Management of Rheumatoid Arthritis

- Tumor Necrosis factor (TNF)-alpha antagonists
  - Infliximab, Adalimumab, Golimumab
  - Certolizumab pegol
  - Etanercept
- Interleukin-6 receptor antagonist
  - Tocilizumab
- B Lymphocyte depleting agent
  - Rituximab
- Co-Stimulation Inhibitor (inhibition of T cell activation)
  - Abatacept

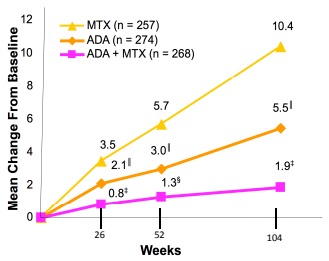
Clinical and Radiographic Responses

Improvement in Signs and Symptoms: ACR 70



Nonresponder imputation
*$P < 0.001$ for ADA + MTX vs MTX; †$P < 0.001$ for ADA + MTX vs ADA

Inhibition of Radiographic Progression: mTSS



Linear extrapolation methodology
‡$P < 0.001$ vs ADA and vs MTX; §$P = 0.002$ vs ADA and $P < 0.001$ vs MTX; ‖$P < 0.001$ vs MTX

F. Breedveld et al. *Arthritis Rheum* 2006

Prediction Model of Rapid Radiographic progression Derived From the ASPIRE Trial

		IFX + MTX			MTX mono				
28 Swollen Joint Count	>17	8 (5,14)	11 (7,16)	14 (9,20)	33 (22,47)	40 (30,51)	47 (36,59)	>=3	CRP (mg/dL)
	10-17	8 (5,12)	10 (7,14)	13 (9,18)	31 (21,44)	38 (28,48)	45 (34,56)		
	<10	7 (4,12)	9 (6,15)	12 (7,19)	29 (18,44)	35 (24,49)	42 (29,57)		
	>17	6 (4,10)	8 (6,11)	10 (7,15)	17 (11,26)	22 (16,30)	27 (19,37)	0.6-3	
	10-17	6 (4,8)	7 (6,10)	10 (7,13)	16 (11,23)	20 (16,26)	25 (19,33)		
	<10	5 (3,8)	7 (4,10)	9 (6,13)	15 (9,23)	19 (13,27)	23 (16,33)		
	>17	4 (2,8)	6 (3,10)	8 (4,13)	8 (4,15)	11 (6,19)	14 (7,24)	<0.6	
	10-17	4 (2,7)	5 (3,8)	7 (4,11)	7 (4,13)	10 (6,16)	12 (7,21)		
	<10	4 (2,7)	5 (3,8)	6 (4,11)	7 (4,13)	9 (5,15)	11 (6,20)		
		<80	80-200	>200	<80	80-200	>200		
		RF ___ (U/mL)			RF ___ (U/mL)				

Risk of RRP (%)
<10%
10-19%
20-29%
30-39%
≥40%

NNT=3

3 patients with these characteristics need to be treated with IFX + MTX in order to avoid that one patient treated with only MTX will progress rapidly.

SJC Swollen joint count; RF Rheumatoid factor; ESR Erythrocyte sedimentation rate; RRP Rapid radiographic progression; NNT Number needed to treat

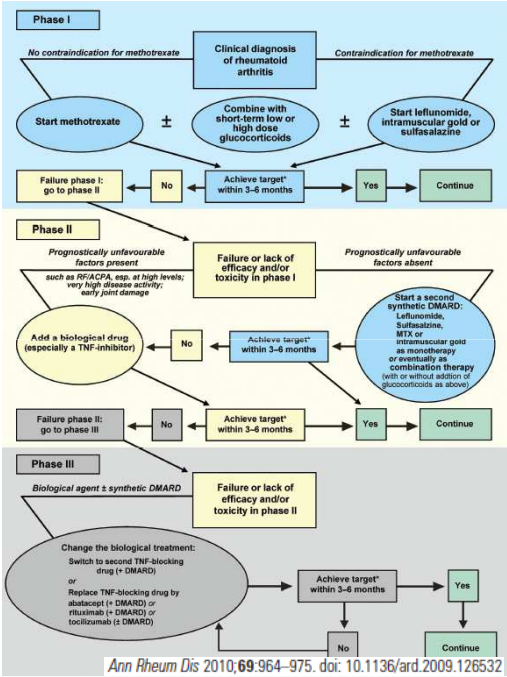
Vastesaeger et al. *Rheumatology* 2009

If treatment target is not achieved by the first DMARDs, biological therapy should be started; current practice would be to start a TNF inhibitor, which should be combined with MTX

Patients for whom the first anti-TNF has failed should receive another TNF inhibitor or another biological agent

Intensive medication should be considered in every patient

If a patient is in persistent remission, one can consider tapering biological treatment especially if this therapy is combined with a synthetic DMARD



Glucocorticoids

Systemic glucocorticoids (GC) added at low to moderate doses to synthetic DMARDs provide benefit as initial short-term treatment, but should be tapered rapidly as clinically feasible

Ann Rheum Dis 2010;**69**:964–975. doi: 10.1136/ard.2009.126532

Low dose GC < 10 mg/day (best dosage: 5 to 7.5 mg/day)

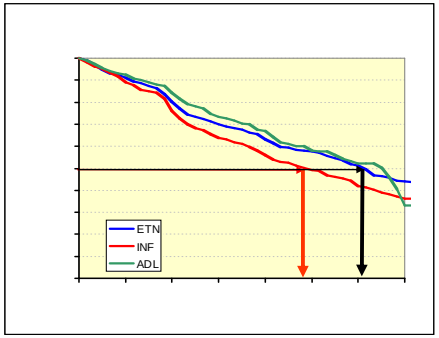
Intra-articular GC administration should be considered if a few joints remain active despite appropriate DMARD therapy (no more than 4x/year).
Do not forget the systemic effects of intra-articular glucocorticoids

Long-term follow-up

- Treatment maintenance
- Disease-related (or treatment-related) complications
  - Infections
  - Cancer
  - Cardiovascular events
  - Osteoporosis
  - Vasculitis
  - Lung disease
  - Eye disease
  - Felty's syndrome

Maintenance of Therapy with TNF Antagonists in RA Patients

- Median duration on anti-TNF 31 months (IQR 12-68)
- Age does not influence the time to discontinuation
- Ineffectiveness is the leading cause of treatment discontinuation
- Highest discontinuation rates in infliximab-treated patients, mainly because of allergic reactions



Genevay et al. *Arthritis Care Res* 2006
Martin du Pan et al. *Arthritis Care Res* 2009

Case presentation

Following the diagnosis of rheumatoid arthritis, MTX was started at a dosage of 15 mg weekly sc

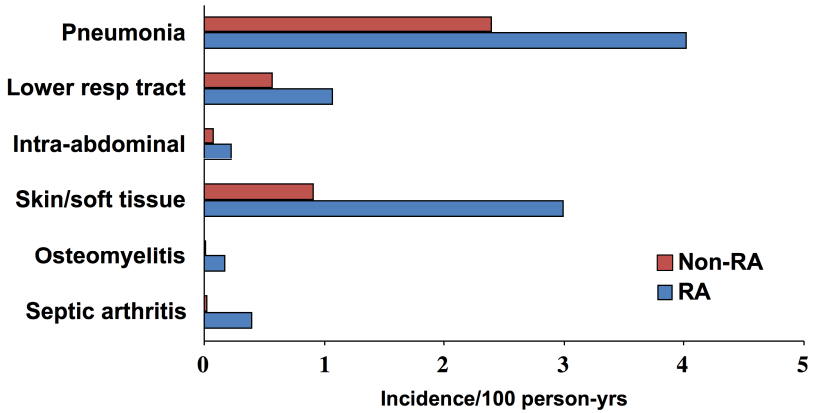
After 3 month the disease was still active (DAS28: 4.9)
Etanercept was started in combination with MTX
After 3 months: there was a very good clinical response (DAS28: 2.5)

After 10 months, the patient complained of severe acute left knee pain. On physical examination, the joint was swollen

A quoi le médecin traitant doit-il/ elle être attentif?
Complications/ précautions

- Complications/ risques infectieux
- Complications oncologiques
- Complications cardiovasculaires
- Autres

Incidence of Infections in Subjects With/Without RA



Doran MF, et al. *Arthritis Rheum*. 2002;46(9):2287-93.

Treatment for Rheumatoid Arthritis and the Risk of Hospitalization for Pneumonia

16'788 patients followed for 3.5 yrs

Prednisone	Hazard ratio 1.7 [95% confidence interval 1.5-2.0]
≤ 5 mg/day	HR 1.4
5-10 mg/day	HR 2.1
> 10 mg/day	HR 2.3
Leflunomide	HR 1.2 [95% confidence interval 1.0-1.5]
Methotrexate	HR 1.0 [95% confidence interval 0.8-1.2]
Etanercept	HR 0.8 [95% confidence interval 0.6-110]
Infliximab	HR 1.1 [95% confidence interval 0.9-1.4]
Adalimumab	HR 1.1 [95% confidence interval 0.6-1.9]

F. Wolfe et al. *Arthritis Rheum* 2006

Serious Infections in Rheumatoid Arthritis Patients on Anti-TNF Therapy

	DMARD	Anti-TNF
Persons-years	1'352	9'868
Incidence rate ratio [95% CI]		1.28 [0.94-1.76]
Adjusted for prednisone use		
Co-morbidities		1.03 [0.68-1.57]
Skin infections		4.28 [1.06-17.17]
Lung		0.77 [0.46-1.31]
No difference between the three anti-TNF agents		

19 cases bacterial intracellular infection only in anti-TNF treated patients

10 *M. Tb*, 2 *Legionella*, 3 *Listeria*, 1 *M. fortuitum*, 3 *Salmonella*

W.G. Dixon et al *Arthritis Rheum* 2006

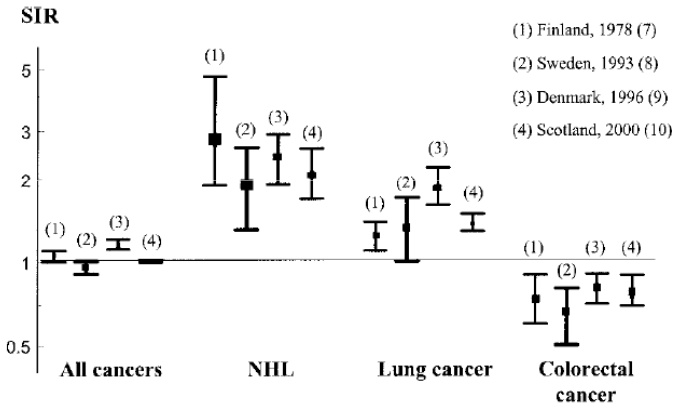
Vaccination

Patients with RA **should** be vaccinated against seasonal influenza
Patients with RA treated with biological agents **should** receive pneumococcal vaccine

Patients with RA treated with MTX, leflunomide, immunosuppressants, or biological agents **should not** receive live vaccines

Vaccination against H1N1 adjuvanted vaccines was safe
Immune response after one dose was lower than controls but patients achieved similar responses after 2 doses of vaccine

Rheumatoid Arthritis and Malignancy



Symmons and Silman *Arthritis Rheum* 2004

Results from Other Registries

Three US and Canada registries
1152 RA patients treated with biologic agents
OR= 1.37 [95% CI 0.71-2.60] for hematological cancer
OR= 0.91 [95% CI 0.65-1.26] for solid tumors

National Data Bank for Rheumatic Diseases (USA)
13000 patients (49'000 patients-yrs)
Anti-TNF treated patients had increased **skin cancer**
melanoma OR= 2.3, non melanoma OR=1.5

Lymphoma and Leukemia in RA Patients

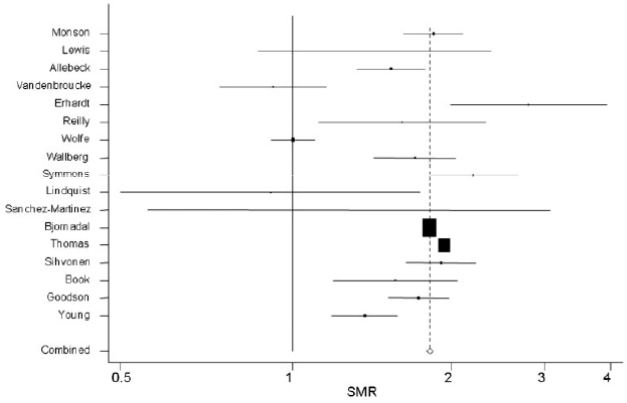
Three RA cohorts (Sweden) Prevalent (admitted in hospital 1990-2003)
Incident (diagnosed 1995-2003)
Anti-TNF (1999-2003)

Disease	prevalent (n=53'067)		incident (n=3703)		exposed to aTNF (n=4160)	
	n	SIR (95%CI)	n	SIR	n	SIR
Total	481	1.7 (1.5-1.8)	15	1.6 (0.9-2.6)	11	2.1 (1.1-3.8)
Lymphoma (w CLL)	319	1.9 (1.7-2.1)	11	2.0 (1.0-3.5)	9	2.9 (1.3-5.5)
Myeloma	45	0.8 (0.6-1.1)	0	0 (0-2.2)	0	0 (0-4.4)
Leukemia (all but CLL)	107	2.1 (1.7-2.5)	4	2.2 (0.6-5.7)	2	2.0 (0.2-7.3)

No difference after adjustment for age, sex, disease duration

Askling et al *Ann Rheum Dis* 2005

Meta-analysis on CV Related Standardized Mortality Ratio in RA Patients



C. Meune et al. *Rheumatology* 2009

Cardiovascular Morbidity and Mortality in Women Diagnosed with Rheumatoid Arthritis

Nurses'Health Study:

- 114'342 women free of CV disease at baseline in 1976
- 527 cases of incident RA
- 3622 cases of MI and strocke

TABLE 2. Age-Adjusted and Multivariable Relative Risks for Cardiovascular End Points According to Presence of Rheumatoid Arthritis in Nurses' Health Study, 1977 to 1996

Cardiovascular End Point	Rheumatoid Arthritis	No Rheumatoid Arthritis	*p*
Person-years of follow-up	6259	2 381 418	...
Myocardial infarction			
Incidence/100 000 person-years	272	96	...
No. of cases	17	2279	...
Age-adjusted relative risk* (95% CI)	2.07 (1.28 to 3.34)	1.0	0.002
Multivariable relative risk† (95% CI)	2.00 (1.23 to 3.29)	1.0	0.005
Stroke			
Incidence/100 000 person-years	112	55	...
No. of cases	7	1319	...
Age-adjusted relative risk (95% CI)	1.47 (0.70 to 3.08)	1.0	0.31
Multivariable relative risk (95% CI)	1.48 (0.70 to 3.12)	1.0	0.31

*Relative risk compared with participants without rheumatoid arthritis. Adjusted for age in 5-year categories.

†Relative risk compared with participants without rheumatoid arthritis. Adjusted for age in 5-year categories, hypertension, diabetes, high cholesterol level, parental history of myocardial infarction before age 60 years, body mass index, cigarette use, physical activity, alcohol use, aspirin use, menopausal status, hormone replacement therapy use, oral glucocorticoid use, nonsteroidal antiinflammatory drug use, folate intake, omega-3 fatty acid intake, and vitamin E supplement intake.

D.H. Solomon et al. *Circulation* 2003

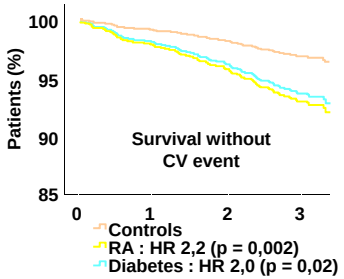
CV Risk and Rheumatoid arthritis

cohort CARRE

- Population-based study in the Netherlands
  - Cohort CARRE : 335 RA with a CV follow-up of 3 yrs
  - Comparison with 1 852 matched controls of the cohort HOORN (metabolic risk factors)
- Evaluation of CV event risk factors (Myocardial infarction, stroke, CV-related death)

	HR ajusted* (IC_{95})
General population All RA	1,0 2,0 (1,2-3,4)
Diabetic controls Type 2 diabetes RA without diabetes	1,0 1,4 (0,8-2,6) 1,9 (1,1-3,5)

* Ajusted for age, sex, blood pressure, cholesterol, smoke, statins use, aspirin use



- **CV risk in RA similar to type 2 diabetes**
- **RA is an independent CV risk factor as diabetes**

Peters et al. ACR 2008

Take home messages

- La polyarthrite rhumatoïde est une maladie grave et il est par conséquent important de faire un diagnostic précoce
- Le traitement de fond doit être commencé dès que le diagnostic est posé
- L’objectif du traitement est la rémission et tout doit être mis en œuvre pour arriver à ce but
- Il faut connaître les complications associées à la maladie et aux traitements