Traitements des maladies rhumatismales

Le rhumatisme …

Les rhumatismes

• Arthrose : rhumatisme dégénératif, maladie dégénérative du cartilage

• Poly-arthrite rhumatoïde : maladie inflammatoire/auto-immune chronique, affecte préférentiellement les articulations + manifestations systémiques
• Spondylarthite ankylosante : maladie inflmmatoire chronique qui affecte en priorité les articulations sacro-illiaques et la colonne vertébrale.
• Rhumatisme articulaire aigu : rhumatisme inflammatoire

• Goutte : arthropathie inflammatoire, rhumatisme métabolique

Arthrose (osteoarthritis)

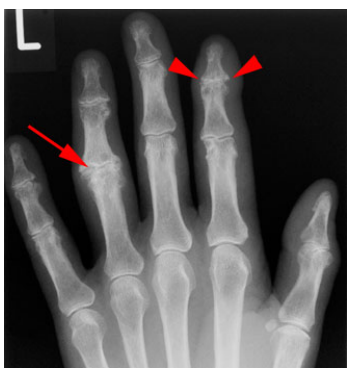
Rupture de l'équilibre dynamique entre dégradation et construction de la matrice cartilagineuse (dégradation majeure)

→Progressivité
→Douleur (gonflement)
→Perte de mobilité
→Genou, hanche, main

→Les lésions sont irréversibles!

Anabolisme
IGF I, IGF II

Catabolisme
TNFα, IL-1, protéinase



Arthrose symptomatique du genou : 13% population >60 ans
Arthrose symptomatique de la hanche : 4¨% population 55-74 ans
Arthrose de la main : 3-5% hommes > 70 ans
△ Seuls 15% population avec une arthrose démontrée par radiographie présente une arthose symptomatique

http://radiologie.charite.de/images/gallery/gelenk/arthrose.jpg

Arthrose (osteoarthritis)

TABLE 1

Endogenous and exogenous risk factors for osteoarthritis of the knee[*1]

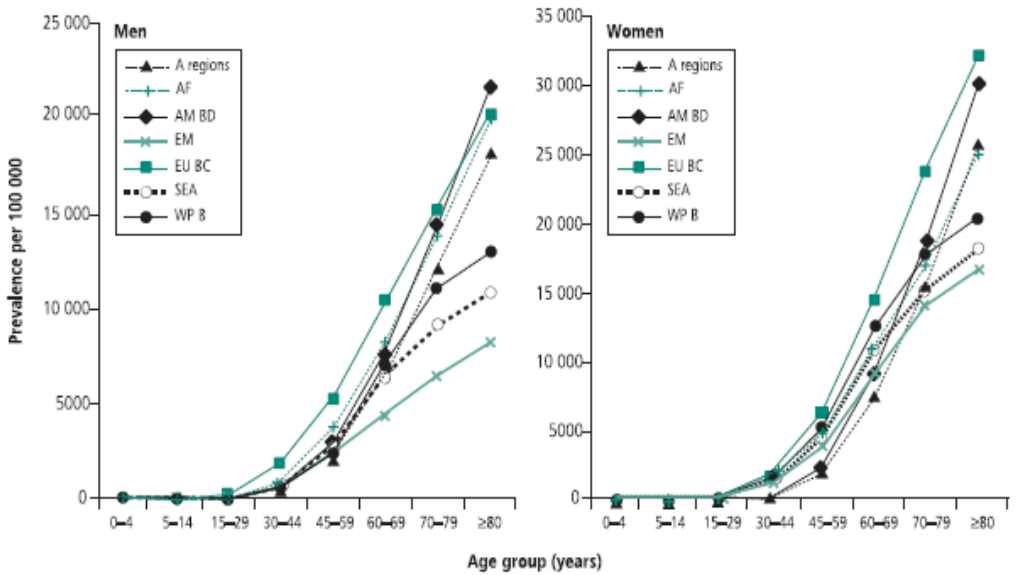
Endogenous	Exogenous
Age	Macrotrauma
Sex	Repetitive microtrauma
Heredity	Overweight
Ethnic origin (more common in persons of European descent)	Resective joint surgery
Post-menopausal changes	Lifestyle factors (alcohol, tobacco)

Etiologies of secondary osteoarthritis of the knee[*1]

- Post-traumatic
- Congenital/malformation
- Malposition (varus/valgus)
- Postoperative
- Metabolic
  - Rrickets
  - Hemochromatosis
  - Chondrocalcinosis
  - Ochronosis
- Endocrine disorders
  - Acromegaly
  - Hyperparathyroidism
  - Hyperuricemia
- Aseptic osteonecrosis

Dtsch Arztebl Int 2010; 107(9): 152–62

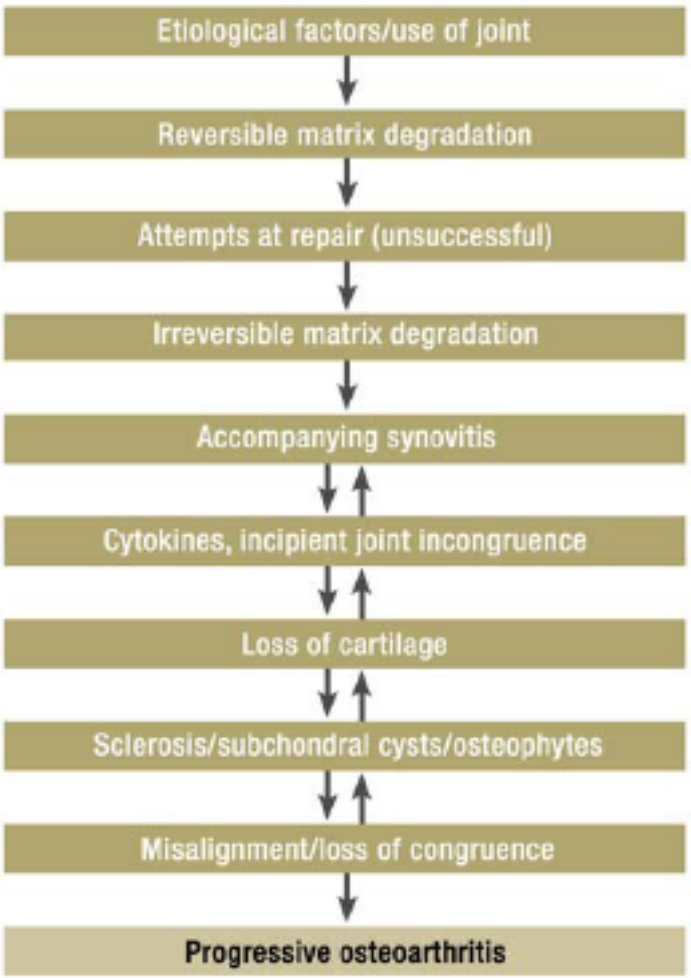
Fig. 1. **Prevalence of osteoarthritis of the knee, by age group, sex, and region, 2000** (16). A regions = developed countries in North America, Western Europe, Japan, Australia, and New Zealand. AF = countries in sub-Saharan Africa. AM BD = developing countries in the Americas. EM = countries in the Eastern Mediterranean and North African regions. EU BC = developing countries in Europe. SEA = countries in South-east Asia. WP B = countries in the Western Pacific region



WHO

Arthrose (osteoarthritis)

FIGURE 2



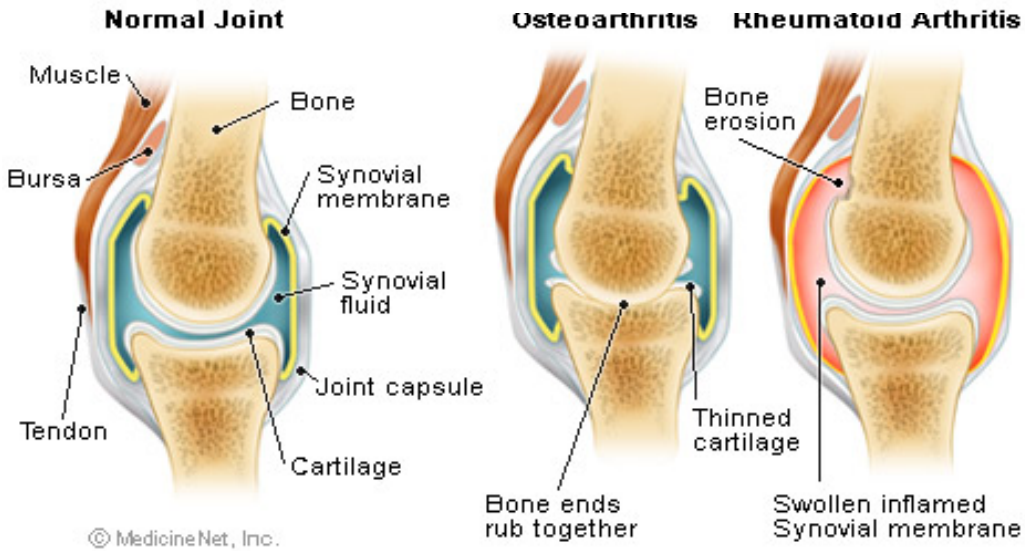
is as: Dtsch Arztebl Int 2010; 107(9): 152–62
DOI: 10.3238/arztebl.2010.0152

BOX 2

Specific historical features of osteoarthritis*[1]

- Pain
  - Pain at the beginning of movement
  - Pain during movement
  - Permanent / nocturnal pain
  - Need for analgesics
- Loss of function
  - Stiffness
  - Limitation of range of movement
  - Impairment in everyday activities
  - Need for orthopedic aids
- Other symptoms
  - Crepitation
  - Elevated sensitivity to cold and/or damp
  - Stepwise progression

*[1]Historical criteria for osteoarthritis in use at the Department of Orthopaedic and Trauma Surgery, University of Cologne



Normal and Arthritic Joints

http://www.webmd.com/osteoarthritis/guide/osteoarthritis-causes

Arthrose : traitement

Objectifs :

- soulager la douleur !
- améliorer la qualité de vie
- améliorer la mobilité
- retarder la progression

Mesures générales:

- Education du patient
- Modification des habitudes de vie
- Perte de poids (qd indiqué)
- Suppression des facteurs de “stress” pour les articulations.
- Physiothérapie et autres mesures non-pharmacologiques (éducation au mouvement, exercices adaptés, acupunctures, …)

Ex : préférer le ski de fond au ski alpin
utiliser des chaussures avec semelles adaptées (shock absorbing)

BOX 4

EULAR stepwise recommendations for the conservative treatment of osteoarthritis of the knee*[1]

1. Optimal management requires a combination of non-pharmacological and pharmacological treatment modalities
2. The treatment of knee osteoarthritis should be tailored according to risk factors, severity of pain, presence or absence of joint effusion, and degree of osteoarthritic damage
3. Non-pharmacological treatment: weight loss, orthopedic aids, physical and physiotherapeutic measures
4. Paracetamol is the analgesic of first choice for long-term use, if effective
5. Topical applications (e.g., non-steroidal anti-inflammatory drugs [NSAID]) are effective
7. Opioid analgesics can be used effectively if paracetamol or NSAID are ineffective or poorly tolerated
8. Symptomatic slow-acting drugs for osteoarthritis (SYSADOA) are an effective symptomatic treatment
9. Intra-articular injection of corticosteroids to treat effusions and severe pain

10. Chirurgie

*modified from (9); EULAR, European League Against Rheumatism

AINS p.o. :
1-4sem max

+associations

. Pendelton AN, Arden N, Dougados M, et al.: EULAR recommendations for the management of knee osteoarthritis: report of a task force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCICIT). Ann Rheum Dis Dec 2000; 59: 936–44.

Arthrose : traitements qui modifient la progression de l'arthrose

Symptomatic, slow-acting drugs for osteoarthritis (SYSADOA)
Disease-modifying osteoarthritis drugs (DMDOA)

Agents "chondroprotecteurs" → ciblent la matrice et les chondrocytes

DMDOA :

retarder la progression
arrêter la progression
régénérer le tissu lésé

Prévenir le développement de la maladie en développement

Importance d'aussi diminuer les manifestations cliniques (douleur, …)

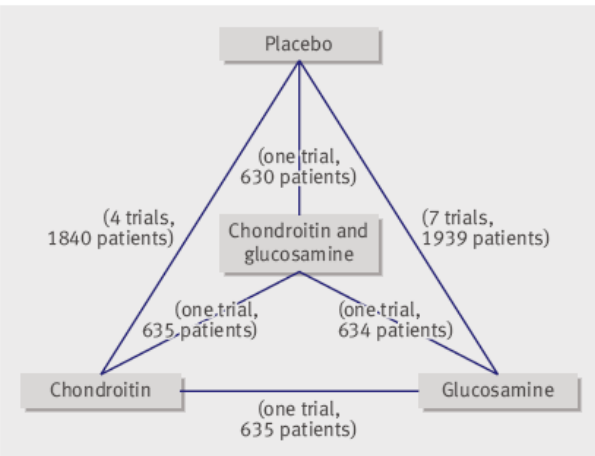
Arthrose : traitements

Constituents du cartilage:

• Chondroitine : polysaccharide formant un gel responsable de la résistance à la compression
• Glucosamine : → glucosaminoglycans
→Résorbés après ingestion par voie orale

Limite la perte de cartilage?

Efficacité mise en doute !



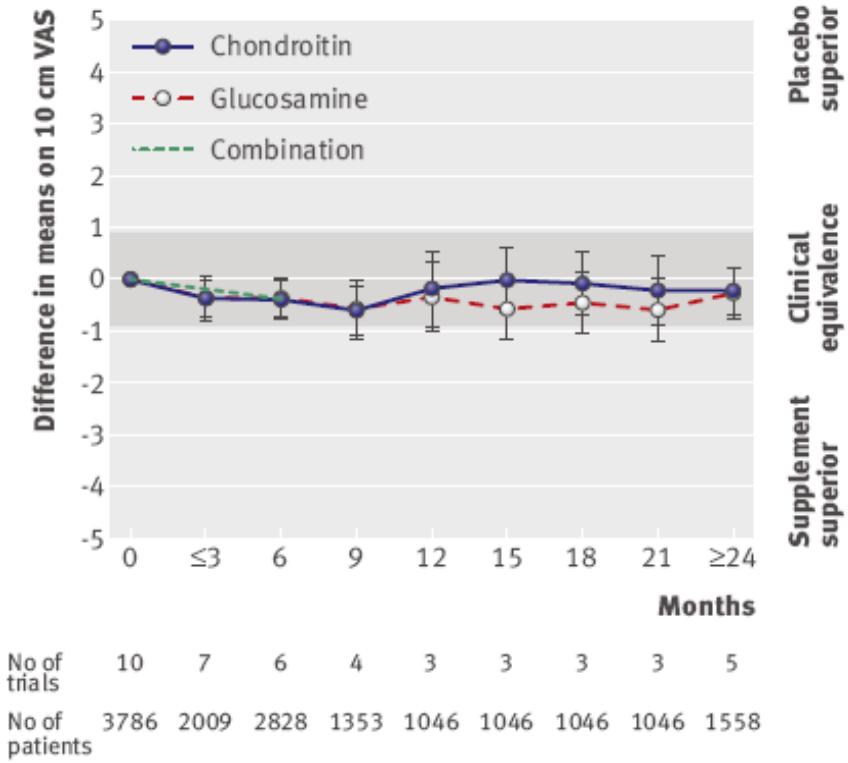


Fig 2| Differences in pain intensity measured on visual analogue scale (VAS) between experimental interventions and placebo over time. Shading represents area of clinical equivalence. Negative values indicate benefit of experimental interventions compared with placebo

BMJ 2010;341:c4675
doi:10.1136/bmj.c4675

Arthrose : Nouvelles perspectives

Table 1 | Human clinical trials of DMOADs

Study	Drug	ROA (concentration)	*n* (study duration)	Primary endpoint	Sponsor
Spector *et al.*[108]	Risedronate	Oral (5 or 15 mg daily)	284 (1 year)	Differences in symptoms and function on WOMAC	Proctor and Gamble
Bingham *et al.*[109]	Risedronate	Oral (5 or 15 mg per day or 35 mg per week in Europe and 50 mg per week in North America)	2,483 (2 years)	Semiflexed knee fluoroscopy, WOMAC	Proctor and Gamble
Brandt *et al.*[22]	Doxycycline	Oral (100 mg twice daily)	431 (2.5 years)	Semiflexed knee fluoroscopy, WOMAC	NIH
Clegg *et al.*[110] Reginster *et al.*[111] Pavelka *et al.*[112]	Glucosamine hydrochloride	Oral (1,500 mg daily)	1,583 (24 weeks)[110] 212 (3 years)[111] 202 (3 years)[112]	Semiflexed knee (no fluoroscopy), WOMAC	NIH,[110] Rottapharm[111,112]
Clegg *et al.*[110]	Chondroitin sulfate	Oral (1,200 mg daily)	1,583 (24 weeks)	Semiflexed knee (no fluoroscopy), WOMAC	NIH
Kahan *et al.*[113]	Chondroitin sulfate	Oral (800 mg daily)	622 (2 years)	Structure: minimal knee JSW	IBSA, Genévrier
Raynauld *et al.*[114]	Licofelone	Oral (200 mg twice daily)	355 (2 years)	Cartilage volume changes, meniscal lesion and subchondral bone hypersignal	Merckle GMBH, ArthroLab
Krzeski *et al.*[87]	MMP inhibitor (PG-116800)	Oral (25, 50, 100 or 200 mg twice daily)	401 (1 year)	Semiflexed knee fluoroscopy, WOMAC	Proctor and Gamble
Dougados *et al.*[23]	Diacerein	Oral (50 mg twice daily)	507 (3 years)	Minimal hip JSW on plain radiographs	Negma
Lequesne *et al.*[81]	Avocado–soybean unsaponifiables	Oral (300 mg daily)	163 (2 years)	Decrease of the JSW on plain anteroposterior radiographs of the pelvis	Pharmascience Laboratories
Listrat *et al.*[115] Jubb *et al.*[116]	Intra-articular hyaluronans	Intra-articular injection (20 mg hyalgan weekly for 2 or 3 weeks)	36 (1 year)[115] 273 (1 year)[116]	Reduction in mean JSW of the medial compartment	Fidia,[115] Société Française de Rhumatologie,[115] Sanofi-Aventis[116]

Data obtained from Le Graverand-Gastineau, M. P. *Curr. Drug Targets* 11, 528–535 (2010).[20] Abbreviations: DMOAD, disease-modifying osteoarthritis drug; JSW, joint-space width; MMP, matrix metalloproteinase; qMRI, quantitative MRI; ROA, route of administration; WOMAC, Western Ontario and McMaster Universities arthritis index.

Hunter, D. J. *Nat. Rev. Rheumatol.* advance online publication 16 November 2010; doi:10.1038/nrrheum.2010.178

Arthrose : Nouvelles perspectives

Key points

- Current therapeutic approaches for osteoarthritis (OA) are largely palliative
- Modifying the structural progression of OA has become a focus of drug development
- Numerous challenges face those involved in disease-modifying OA drugs (DMOADs) development
- A number of DMOADs are currently in phase II and III clinical trials

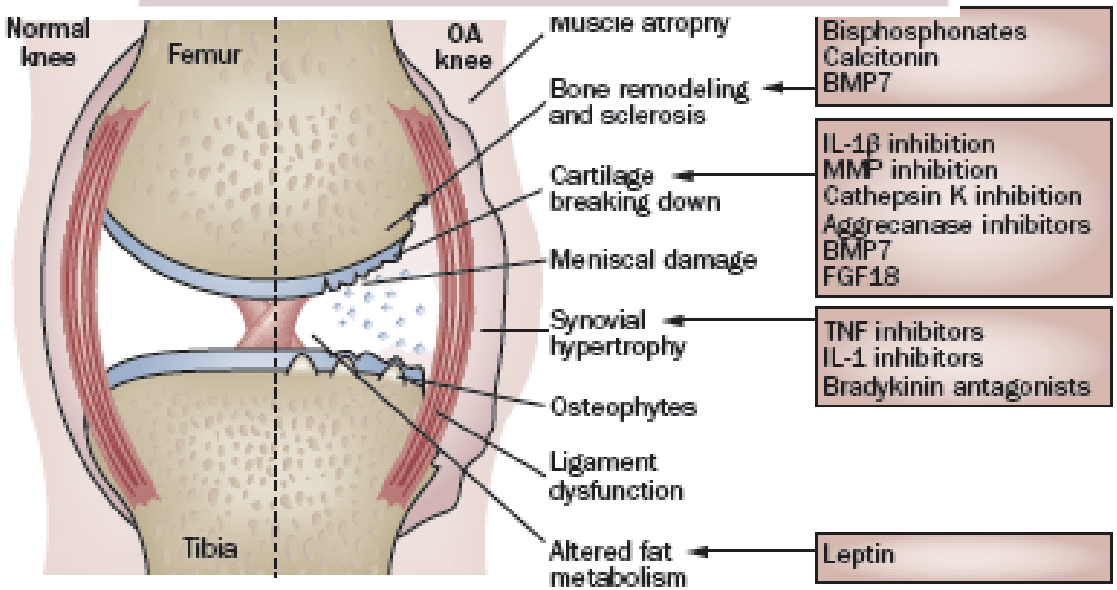
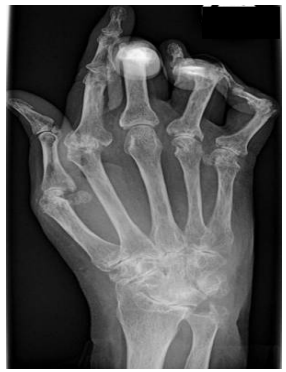


Figure 1 | Schematic of the knee joint depicting the synovial joint tissues affected in OA. Consistent with the theory that OA is a disease of the whole synovial joint, current DMOAD development is now targeting synovial-joint tissue structures including bone, cartilage and synovium. Some of the agents that target these relevant tissues are listed. Abbreviations: BMP, bone morphogenetic protein; DMOAD, disease-modifying OA drug; FGF, fibroblast growth factor; IL, interleukin; MMP, matrix metalloproteinase; OA, osteoarthritis; TNF, tumor necrosis factor.

Hunter, D. J. *Nat. Rev. Rheumatol.* advance online publication 16 November 2010; doi:10.1038/nrrheum.2010.178

Arthrite rhumatoïde

http://www.internat.sanofi-aventis.com/



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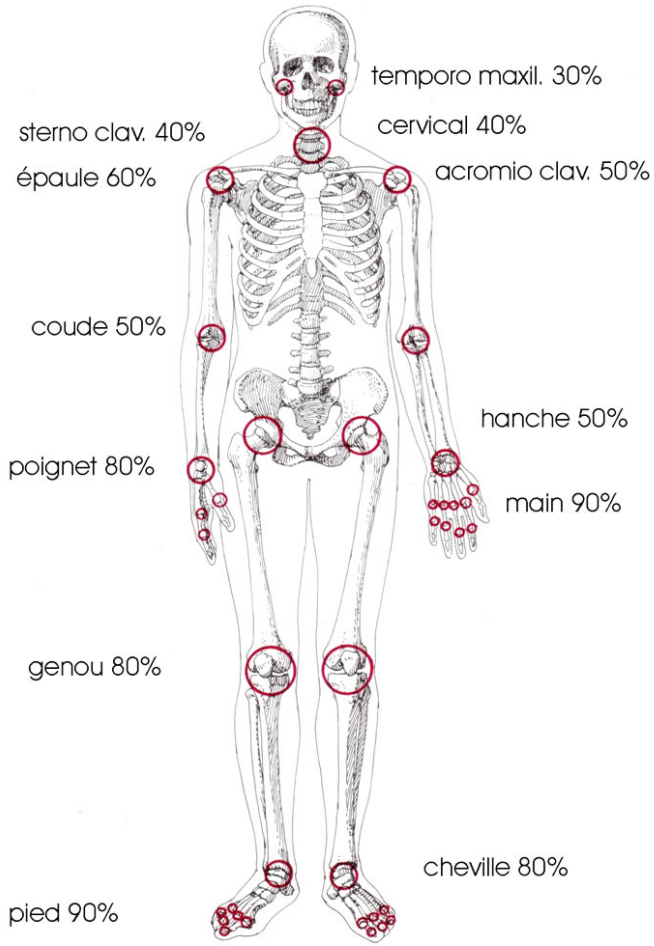


Maladie inflammatoire des articulation la plus fréquente :

- 0.5-1% population des pays industrialisés
- douleur, raideur, gonflement des articulations
  - →inflammation de la synovie
  - → envahissement des tissus cartilagineux et osseux
- perte de mobilité, diminution de la qualité de vie
- mort prématurée (risque multiplié par 2 de présenter une insuffisance cardiaque)
- facteurs génétiques

http://www.arthrites.be/images/squelette.jpg

Arthrite rhumatoïde

Perte de la tolérance

Auto-anticorps :
-Facteur rhumatoide (RA33, IgM, IgA)
-ACPA (anticorps dirigés contre les peptides citrulinés (vimentine, fibrinogène)

Lymphocytes B
Lymphocytes T
Macrophage-like synoviocytes
Fibroblaste-like synoviocytes

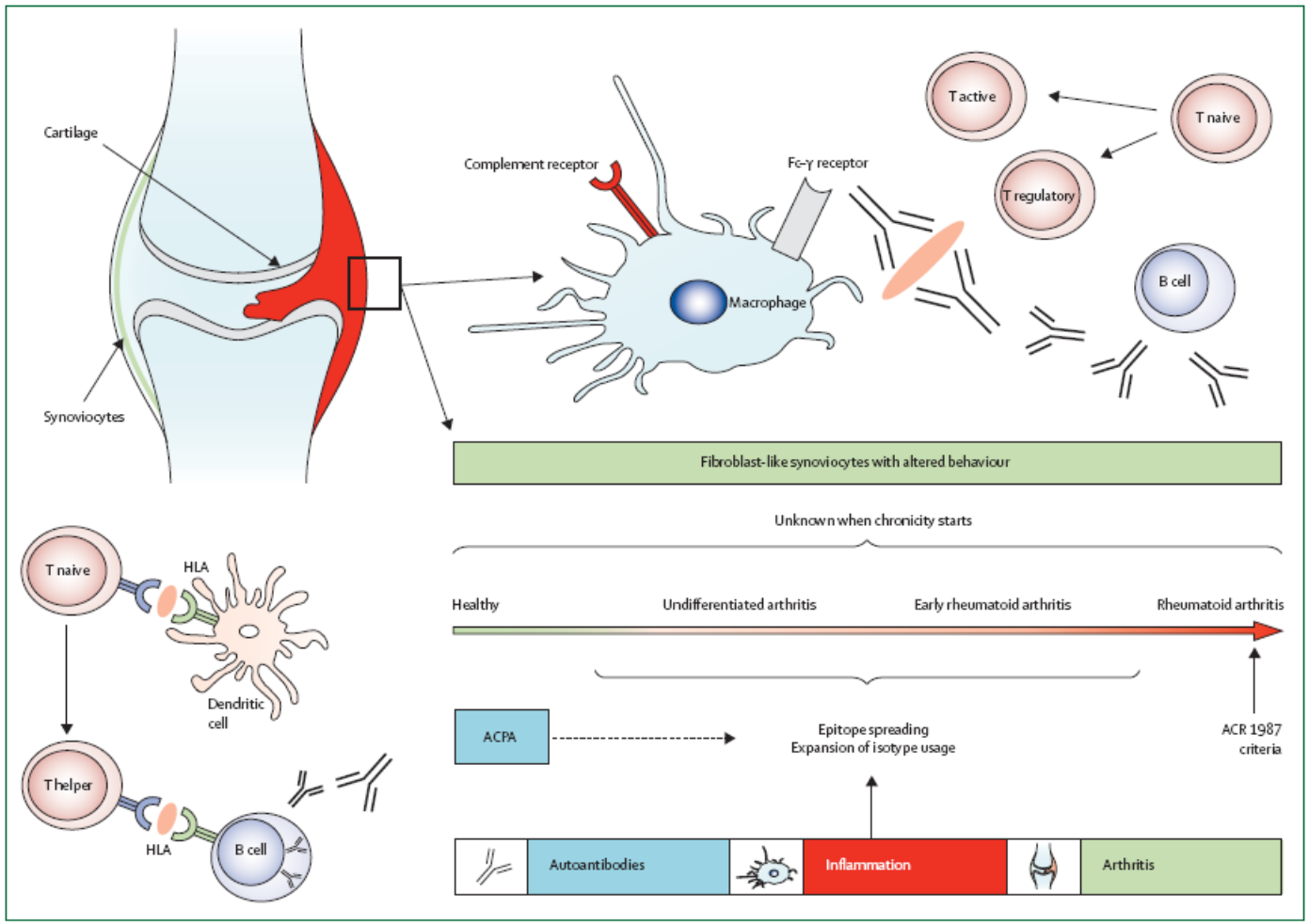


Figure 1: Key pathological changes in the synovium in rheumatoid arthritis
The joint consists of two bones covered by cartilage and aligned by a capsule. The inner surface of the capsule consists of fibroblast-like synoviocytes that produce synovial fluid. In a joint affected by rheumatoid arthritis, the synovium is swollen due to an infiltrate consisting of fibroblast-like and macrophage-like synoviocytes, macrophages, several populations of T cells, and B cells. Macrophages are activated to produce all kind of proinflammatory products (eg, tumour necrosis factor) partly by immune complexes binding to Fc-γ receptors and complement receptors on their surface. Evolution of chronicity in joint inflammation is controlled by so-called master switches, and prediction models suggest a pathway of autoantibodies, inflammation, and arthritis. Autoantibodies binding to citrullinated antigens (ACPA) have confined specificity and limited isotype use in healthy individuals, but epitope spreading and expansion of isotype usage happens in those with rheumatoid arthritis. ACR=American College of Rheumatology.

Arthrite rhumatoïde

Inflammation synovie
Destruction du cartilage
Atteinte de la structure osseuse

<u>Cytokines :</u>
TNFalpha,
IL-1
IL-6

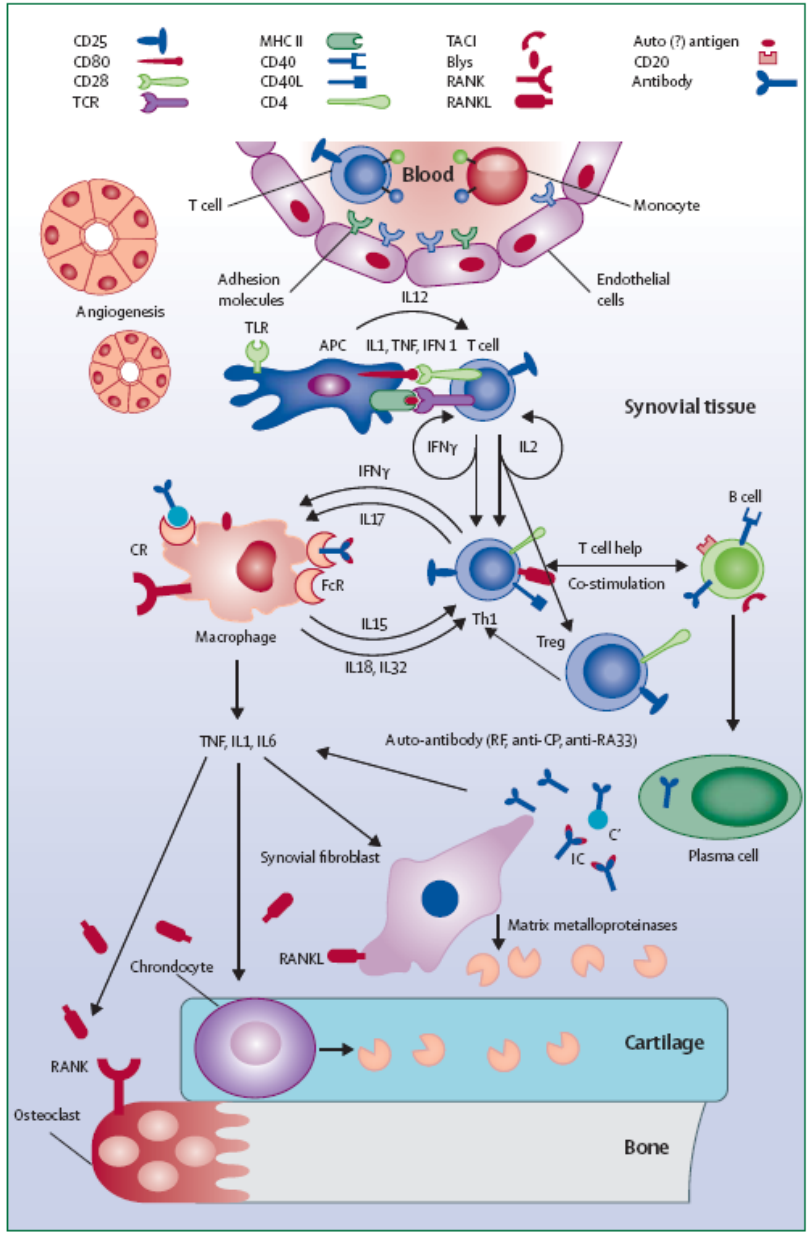


Figure 1: Current views on pathogenesis of rheumatoid arthritis
Arrows show some of many interactions in rheumatoid arthritis pathogenesis. Schematic depiction of events presumably occurring in synovial membrane, aswell as articular cartilage and subchondral bone, which are surrounded by aggressive rheumatoid synovitis. Blys=B lymphocyte stimulator. C'=complement. CP=citrullinated peptide. CR=complement receptor. FcR=receptor for the Fc portion of IgG. IC= immune complex. IFN=interferon. IFN1=type 1 interferons. IL=interleukin. RF=rheumatoid factor. TACI=transmembrane activator and calcium-modulator and cyclophilin ligand interactor. TCR=T-cell receptor. Th1=T-helper 1 cell. TLR=Toll-like receptor. Treg=regulatory T cell.

Arthrite rhumatoïde

Table 1 2010 ACR/EULAR Classification Criteria for Rheumatoid Arthritis[49]

Joint Involvement	Serology	Duration	Acute Phase Reactants
1 Large joint (0 points)	Negative RF and CCP (0 points)	Less than 6 weeks (0 points)	Abnormal ESR or CRP (1 point)
2-10 Large joints (1 point)	Low titer positive CCP or RF (2 points)	6 or more weeks (1 point)	
1-3 small joints (2 points)	High titer CCP or RF (3 points)		
4-10 small joints (3 points)			
More than 10 joints (with at least one small joint) (5 points)			
Total Possible Points			
5	3	1	1

Patients receive the highest point level for each domain: 6 points is defined as definite RA, though those with lower scores may obtain more points with time and subsequently be defined as having RA.

Ann Rheum Dis. 2010 June 1; 69(6): 964–975.

Arthrite rhumatoïde : traitements

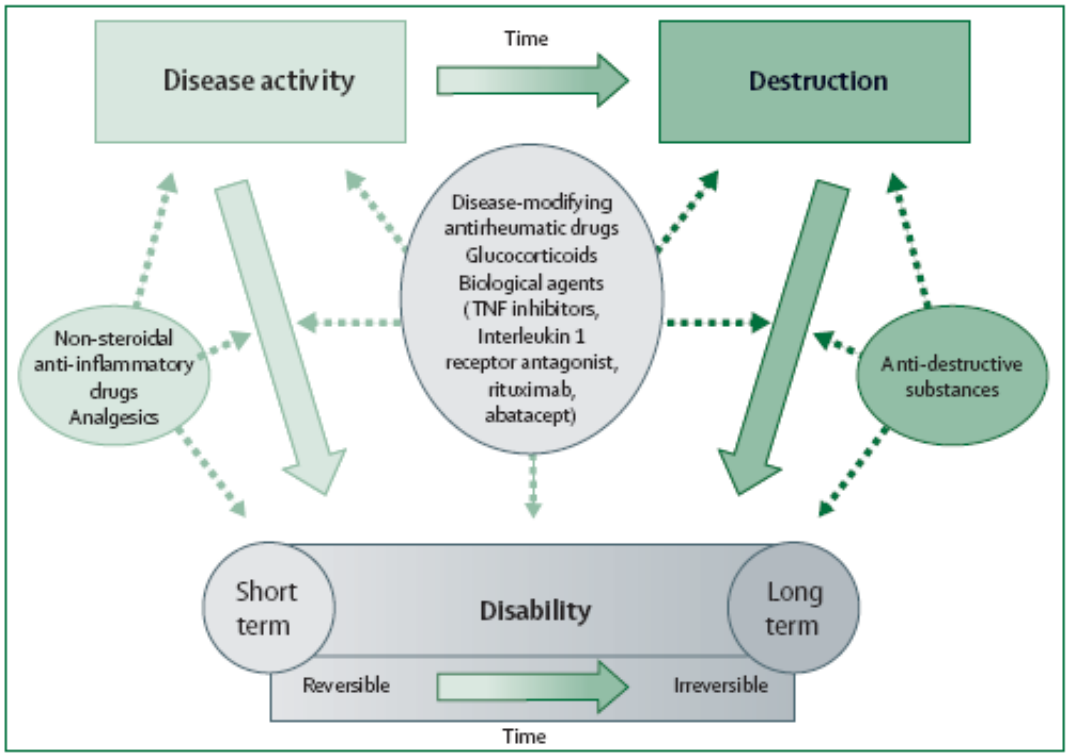


Figure 2: Inter-relationship between disease activity, joint damage, and reversible or irreversible functional limitation,[54,55] and differences in effectiveness of various therapeutic principles
Dotted arrows indicate inhibition.

Lancet 2007; 370: 1861–74

Objectif du traitement : arrêter ou limiter la progression de la maladie

Arthrite rhumatoïde : traitements

Analgésiques
Paracetamol
AINS

→ Ne modifient pas l'activité de la maladie

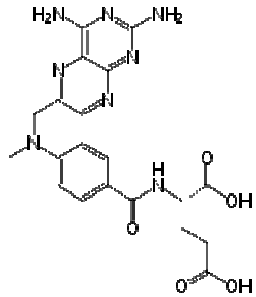
Glucocorticoïdes → Peuvent être considérés comme des DMARDs mais leur toxicité limite leur utilisation

DMARDS synthéthiques

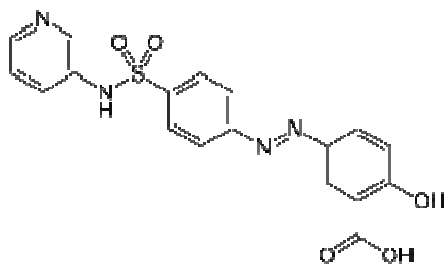
DMARDS biologiques → Anti-TNF
Anti CD20, inhibiteur de l'activtion lymphocyte T, anti-IL6

→ Nouvelles recommendations EULAR

DMARDs synthétiques

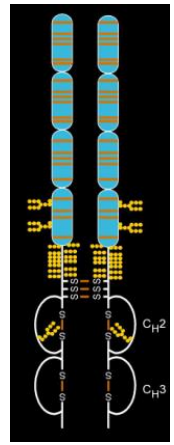


- Methotrexate :
  - Analogue de l'acide folique
  - Utilisé à des doses inférieures (jusque 25mg/semaine/po) °/° propriétés antitumorales
  - Inhibe l'amino-imidazole-carboxymide-transformylase, la thymidylate synthétase et la dihydrofolate réductase (↘ chimiotactisme des PMN)
  - Traitement combiné à une prise d'acide folique (5mg/semaine)
  - EI : nausées, vomissements, toxicité hématologique et hépatique.
- Leflunomide :
  - Inhibe la dihydro-orotate-déshydrogénase → ↘ synthèse des ribonucléotides → inhibe la prolifération des lymphocytes T et la production d'auto-anticorps par les lymphocytes B
  - EI : nausées, vomissements, toxicité hématologique et hépatique, perte de cheveux, …
  - Teratogène !!!!
- Sulfasalazine :
  - Métabolite actif (sulfapyridine)
  - Inhibition de la prolifération des lymphocytes B, inhibition de la production du FR ,…
  - 2-3g/j



- Sels d'or : (plus disponibles en Belgiques)
  - Aurothiomalate , aurothiglucose, aurafine
  - Pas anti-inflammatoire mais diminueraient l'activité des macrophages
- Antimalariques (chloroquine, hydroxychloroquine, azathioprine, …)

DMARDs biologiques



- Anti-TNF : etanercept
  - Adalimumab
    - Anticorps monoclonal recombinant humain
    - Administration par voie ss-cutanée
  - Etanercept
    - Protéine de fusion constituée de deux moitiés de récepteur TNFa soluble liées au fragment Fc de l'IgG1 humaine
    - Administration par voie ss-cutanée
  - Infliximab
    - Anticorps monoclonal chimérique IgG1 (humain 75%-murin 25%)
    - Administration IV
- EI:
  - Risque infectieux (tuberculose)
  - Risque accru de maladies associées à une démyélinisation?
  - △ administration de vaccins vivants

DMARDs biologiques : nouvelles molécules

- Rituximab :
  - Anticorps monoclonal chimérique anti- CD20 (exprimé spécifiquement par lymphocyte B matures et pré –B.
  - ↘ cellules CD20+
- Abatacept :
  - protéine de fusion impliquant le domaine Fc de IgG1 humain et le domaine extracellulaire de CTLA4
- Tocilizumab :
  - Anti-IL-6 receptor

TNF inhibiteurs seuls ou en association

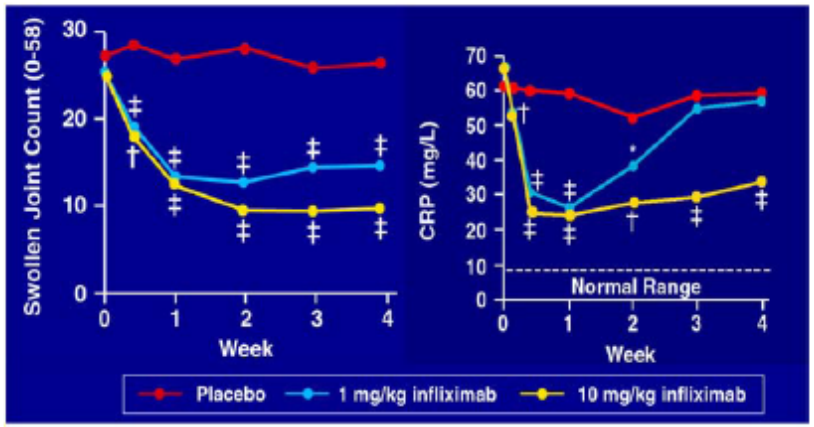


Fig. 1. Reduction in swollen joint counts and CRP in the first randomized controlled clinical trials of a TNF inhibitor in RA. A single infusion of two doses of infliximab or placebo was compared.

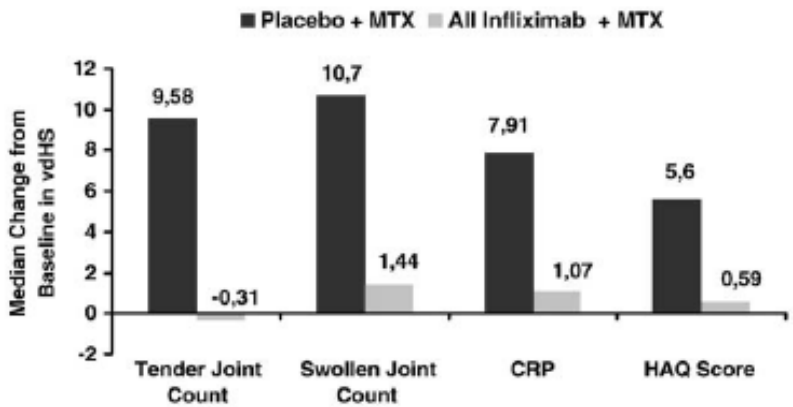


Fig. 4. Dissociation or uncoupling of the inflammatory from the destructive activity of RA. While usually clinical signs of inflammation are highly correlated with progression of joint damage, as seen in the control arms (placebo + methotrexate) of this trial, infliximab + methotrexate retarded progression of joint damage even if clinical signs of inflammation remained highly active, as seen in this subanalysis of the ATTRACT trial, where only patients who did not improve the indicated variables at all between baseline and endpoint were analyzed.

European Journal of Pharmacology 623 (2009) S5–S9

MTX diminue notamment le dvpt d'anticorps anti-antiTNF

Arthrite rhumatoïde

Table 1 Recommendations for the management of rheumatoid arthritis with non-biological and biological disease-modifying antirheumatic drugs.

Overarching principles	
A	Rheumatologists are the specialists who should primarily care for patients with RA
B	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
C	RA is expensive in regards to medical costs and productivity costs, both of which should be considered by the treating rheumatologist.

Final set of 15 recommendations for the management of RA	
1	Treatment with synthetic DMARDs should be started as soon as the diagnosis of RA is made
2	Treatment should be aimed at reaching a target of remission or low disease activity as soon as possible in every patient; as long as the target has not been reached, treatment should be adjusted by frequent (every 1–3 months) and strict monitoring
3	MTX should be part of the first treatment strategy in patients with active RA
4	When MTX contraindications (or intolerance) are present, the following DMARDs should be considered as part of the (first) treatment strategy: leflunomide, SSZ or injectable gold
5	In DMARD naïve patients, irrespective of the addition of GCs, synthetic DMARD monotherapy rather than combination therapy of synthetic DMARDs may be applied
6	GCs added at low to moderately high doses to synthetic DMARD monotherapy (or combinations of synthetic DMARDs) provide benefit as initial short-term treatment, but should be tapered as rapidly as clinically feasible
7	If the treatment target is not achieved with the first DMARD strategy, addition of a biological DMARD should be considered when poor prognostic factors are present; in the absence of poor prognostic factors, switching to another synthetic DMARD strategy should be considered
8	In patients responding insufficiently to MTX and/or other synthetic DMARDs with or without GCs, biological DMARDs should be started*; current practice would be to start a TNF inhibitor (adalimumab, certolizumab, etanercept, golimumab, infliximab)† which should be combined with MTX*
9	Patients with RA for whom a first TNF inhibitor has failed, should receive another TNF inhibitor, abatacept, rituximab or tocilizumab
10	In cases of refractory severe RA or contraindications to biological agents or the previously mentioned synthetic DMARDs, the following synthetic DMARDs might be also considered, as monotherapy or in combination with some of the above: azathioprine, ciclosporin A (or exceptionally, cyclophosphamide)
11	Intensive medication strategies should be considered in every patient, although patients with poor prognostic factors have more to gain
12	If a patient is in persistent remission, after having tapered GCs, one can consider tapering biological DMARDs‡, especially if this treatment is combined with a synthetic DMARD
13	In cases of sustained long-term remission, cautious titration of synthetic DMARD dose could be considered, as a shared decision between patient and doctor
14	DMARD naïve patients with poor prognostic markers might be considered for combination therapy of MTX plus a biological agent
15	When adjusting treatment, factors apart from disease activity, such as progression of structural damage, comorbidities and safety concerns should be taken into account

Symbols *, † and ‡ refer to levels of evidence provided in table 2.
DMARD, disease-modifying antirheumatic drug; GCs, glucocorticoids; MTX, methotrexate; RA, rheumatoid arthritis; SSZ, sulfasalazine; TNF, tumour necrosis factor.

Spondylarthrite ankylosante

Table 2 Classification Criteria for Spondyloarthritis and Ankylosing Spondylitis

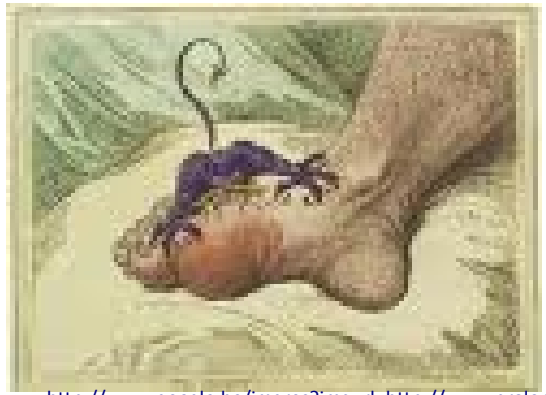
	Modified New York Criteria for Ankylosing Spondylitis[3]*	European Spondylarthropathy Study Group[4]	Amor Criteria[5]
Definitive diagnosis	Radiologic criteria is associated with at least one of the following clinical criteria: • Back pain and stiffness for more than 3 months that improves with exercise but is not relieved by rest • Limitation of motion of the lumbar spine in both the sagittal and frontal planes • Limitation of chest expansion relative to normal values correlated for age and sex	Inflammatory spinal pain or synovitis (asymmetric or predominantly in the lower limbs), together with at least one of the following: • Positive family history • Psoriasis • Inflammatory bowel disease • Urethritis • Alternating buttock pain • Enthesopathy • Sacroiliitis	Diagnosis of SpA if 6 or more points are amassed (exclusion criteria not included): • Inflammatory back pain (1 point) • Unilateral buttock pain (1 point) • Alternating buttock pain (2 points) • Enthesitis (2 points) • Peripheral arthritis (2 points) • Dactylitis (sausage digit) (2 points) • Acute anterior uveitis (2 points) • HLA-B27 positive • History of SpA (2 points) • Good response to NSAIDs (2 points)
Radiologic criteria	Presentation of sacroiliitis greater or equal to grade 2 bilaterally or grade 3-4 unilaterally†	Sacroiliitis (bilateral with a grade of 2-4 or unilateral with a grade of 3-4)	

*Criteria yield sensitivity of 83%, specificity of 98%; †Required. AS, ankylosing spondylitis; ESSG, European Spondylarthropathy Study Group; HLA-B27, human leukocyte antigen-B27; MRI, magnetic resonance imaging; NSAIDs, nonsteroidal anti-inflammatory drugs; SpA, spondyloarthritis; uSpA, undifferentiated spondyloarthritis.

Bulletin of the NYU Hospital for Joint Diseases 2008;66(3):203-9

Bonne réponse aux inhibiteurs TNF, peu d'interet d'associer le MTX

Goutte :
Rhumatisme métabolique
Epidémiologie



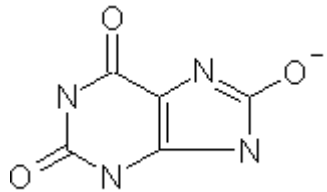
http://www.google.be/imgres?imgurl=http://www.gralon.net/articles/vignettes/thumb-la-goutte-

Table 1
Contribution of common forms of arthritis to burden of pain carried by U.S. adults

Diagnosis	Prevalence in US (approx)	Male-female ratio	Age range of peak incidence	Mechanism of pain
Gout	3 million (6.1 million lifetime prevalence)	4:1 until age 65 y 3:1 after age 65 y	Men: 40-60 y Women: after middle age	Urate crystal-induced inflammation of joints and other synovial tissues
Osteoarthritis	26.9 million	1:1.2-1.4	Incidence increases with age until ~80 y.	Focal and progressive loss of hyaline cartilage of joints
Rheumatoid arthritis	1.3 million	~1:2	Women and men 60-70 y	Autoimmune disease, chronic inflammatory polyarthritis
Systemic lupus erythematosus	<500 000	1:6-10	Primarily women aged 15-40 y	Autoimmune disease with many clinical manifestations

Source: http://www.cdc.gov/arthritis/resources/spotlights/dsArthritis.htm.

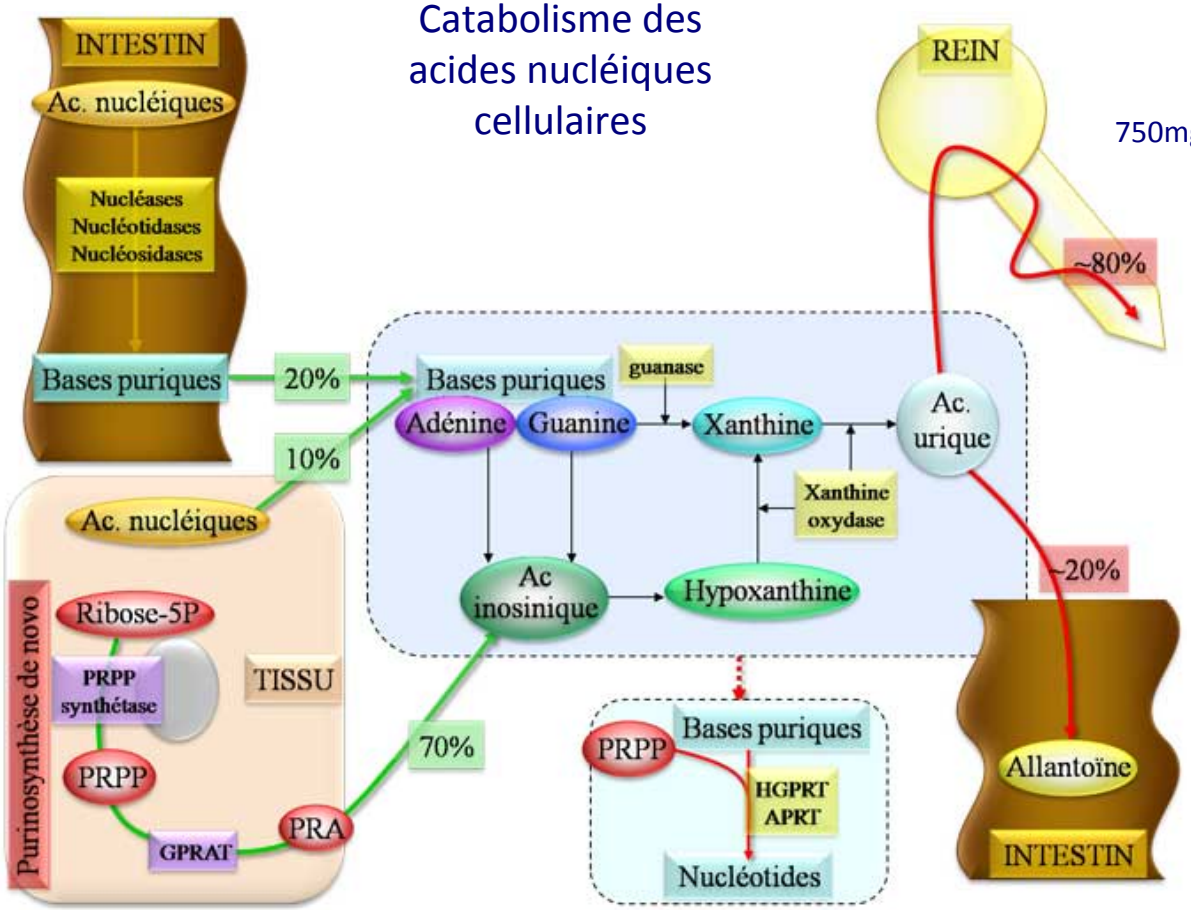
Goutte : L'acide urique



Urate

Catabolisme des acides nucléiques alimentaires

Catabolisme des acides nucléiques cellulaires



Purinoynthèse de novo

http://www.memobio.fr/html/bioc/bi_ur_me.html

Uricolyse
(Flore intestinale)

Goutte : L'acide urique → hyperucricémie

Purinoynthèse de novo

Catabolisme des acides nucléiques alimentaires

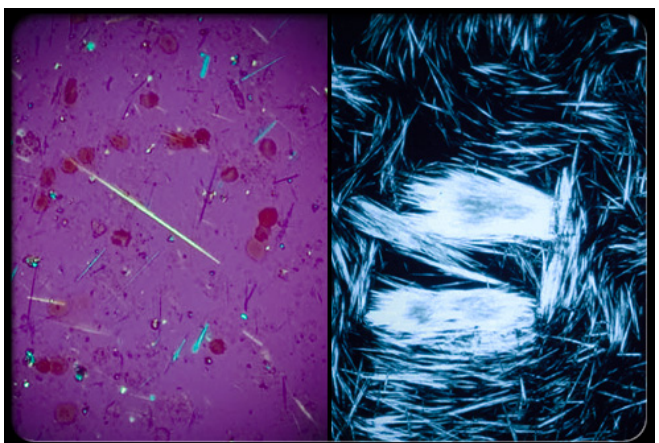
Catabolisme des acides nucléiques cellulaires

Pool miscible d'acide urique
(plasmatique et tissulaire)
Normal : 1200mg
(turnover 700mg/j)
Pool Pathologique : 1600-4000mg

Uricolyse
(Flore intestinale)

Elimination urinaire:
- Filtration glomérulaire
- Sécrétion
- Réabsorption

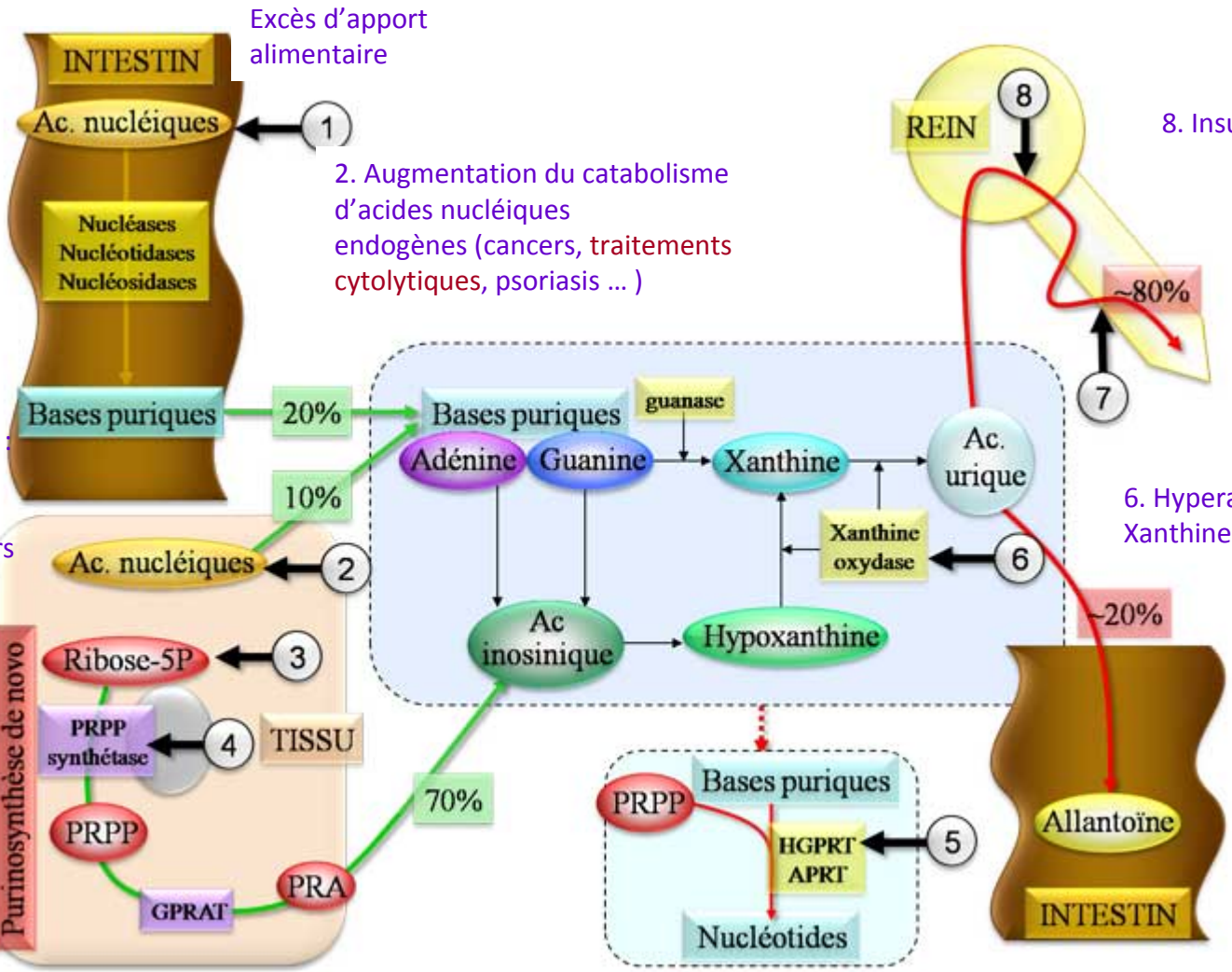
Hyperuricémie: > 70mg/l (60mg/l chez la femme)



Needle-shaped urate crystals diagnostic of gout from an acutely inflamed joint (left) as seen under polarized microscopy and unpolarized microscopy (right). http://www.medicinenet.com/gout_pictures_slideshow/article.htm

Goutte : L'acide urique

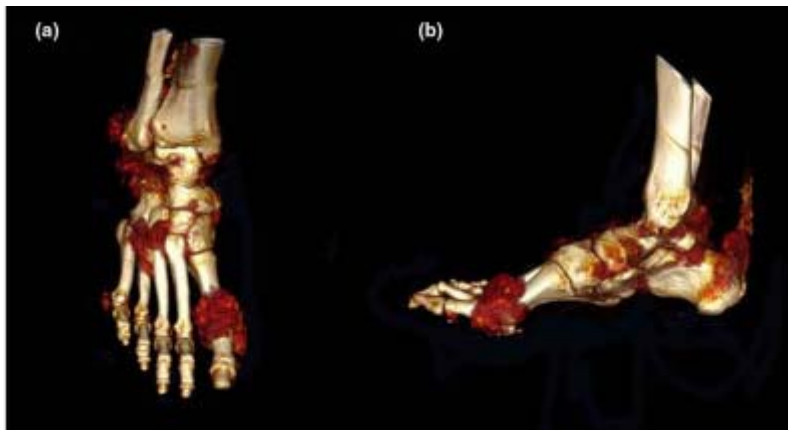
7. -Défaut de sécrétion tubulaire de l'acide urique
- Inhibition compétitive la sécrétion tubulaire de l'acide urique par les corps cétoniques, les lactates, les diurétiques thiazidiques, le furosémide, les salicylés …



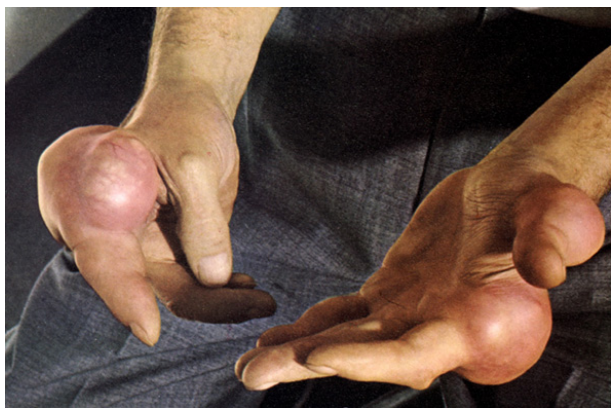
5. Déficit partiel ou complet en HGPRT(syndrome de Lesch-Nyhan

http://www.memobio.fr/html/bioc/bi_ur_me.html

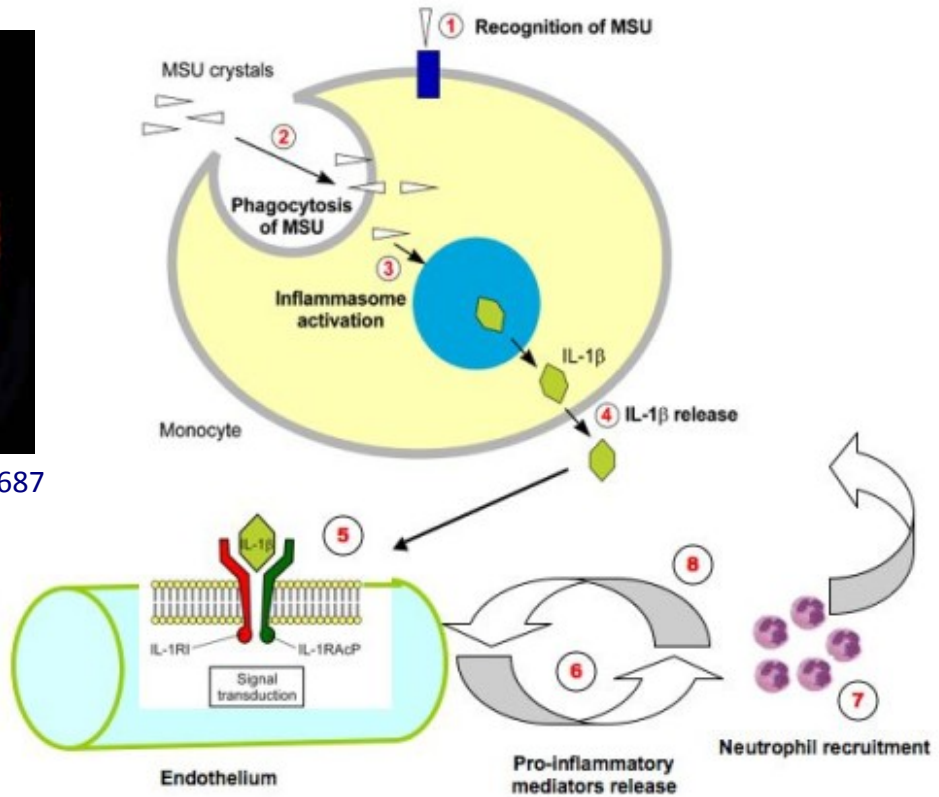
Goutte : manifestations cliniques



Arthritis Research & Therapy 2009 **11**:232 doi:10.1186/ar2687



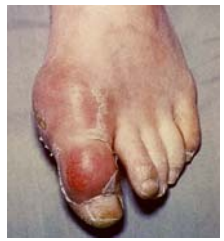
http://www.medecine.ups-tlse.fr/



Arthritis Research & Therapy 2010, **12:**206doi:10.1186/ar2952

Hyperucicémie : manifestations cliniques

- Accès de goutte aigu :



http://www.medecine.ups-tlse.fr/

Le plus souvent , atteinte de l'articulation métatarsophalangienne du gros orteil

→ douleur d'apparition brutale svt nocture, lancinante

→ Impotence fonctionnelle

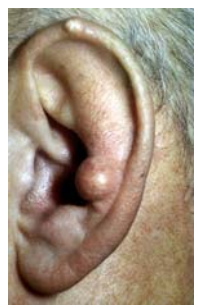
→ (altération de l'état général)

→ Résolution spontannée en +/- 1sem → le traitement accélère la résolution

- Atteintes d'autres articulations (genou, poignet, …) , atteintes extra-articulaires (tendinites)

- Lithiases rénales

- Goutte chronique :
  - Tophus
  - Manisfestations articulaires
  - Manifestations rénales : lithiases et néphopathie goutteuse



http://www.medecine.ups-tlse.fr/

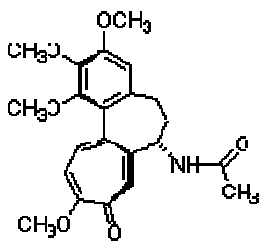
Traitements

Traitements de crise :

- AINS : tous sauf AAS! (voir cours précédant)
- Colchicine : alcaloïde du croccus

Seulement 50% diminution de la douleur après 2-3 j → Les nouveaux traitements anti-inflammatoires sont en cours d'évaluations ….

- Pas d'action analgésique par ailleurs !
- Pas d'action sur le métabolisme ou l'élimination de l'acide urique



- inhibe la migration leucocytaire et la phagocytose
- inhibe la polymérisation des microtubules et la mitose cellulaire

- effets indésirables : nausées, vomissements, diarrhées, (dépression médullaire)

- métabolisée par CYP3A4!!!

- Contre-indications : Grossesse, insuffisance rénale ou hépatique

- Posologie : ≠ protocoles

Ex : 3 mg le premier jour, puis 2 mg pendant 2 j, puis 1 mg pendant 7 j
Ou 1mg suivi de 0,5mg toutes les 2-3h jusqu'à disparition de la douleur ou apparition d'effets indésirables
△Max 6-8mg/j

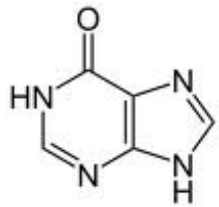
Traitements de fond

→ traitements hypo-uricémiants
→ inhibiteurs de la xanthine-oxydase

Si plus de 3 crises par an
Si apparition de tophus
Si élévation exagérée de l'uricémie (avec atteintes tissulaires inévitables)
Objectifs : [ac urique]pl < 60mg/l

Ne commencer un traitement de fond qu'à distance d'une crise
Associer un traitement de crise lors de l'installation du traitement de fond

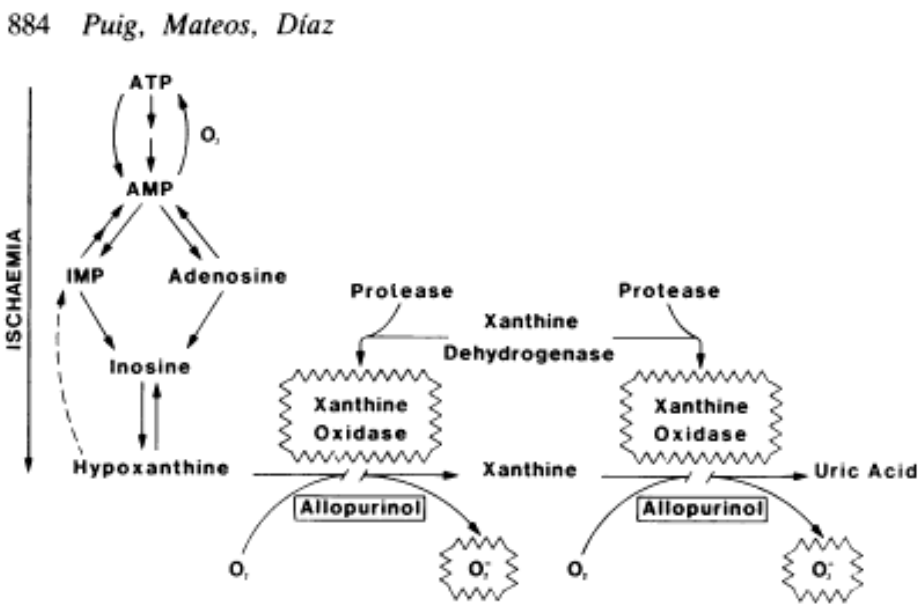
Traitements : Inhibiteurs de la xanthine-oxydase

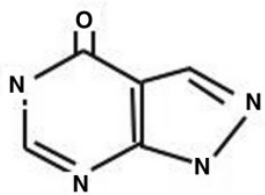


Hypoxanthine

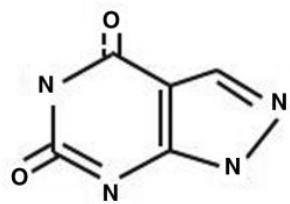
Allopurinol : isomère de l'hypoxanthine → inhibiteur de la synthèse d'acide urique

→ Métabolisé en alloxanthine (aussi inhibiteur de la xanthine oxydase)
→ traitement chronique → à vie?
→ Réactions d'hypersensibilité à l'allopurinol (épidermolyse)
→ Réévaluation de la posologie (100 mg/j puis ↗ de 100mg /j toutes les 1 à 4 sem jusque [ac urique] < 6mg/dl (max 600mg/dl) sauf si insuffisance rénale

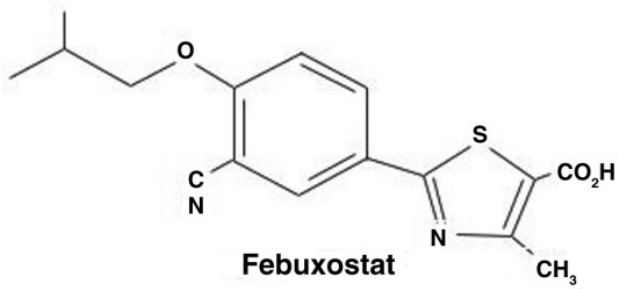




Allopurinol



Oxypurinol

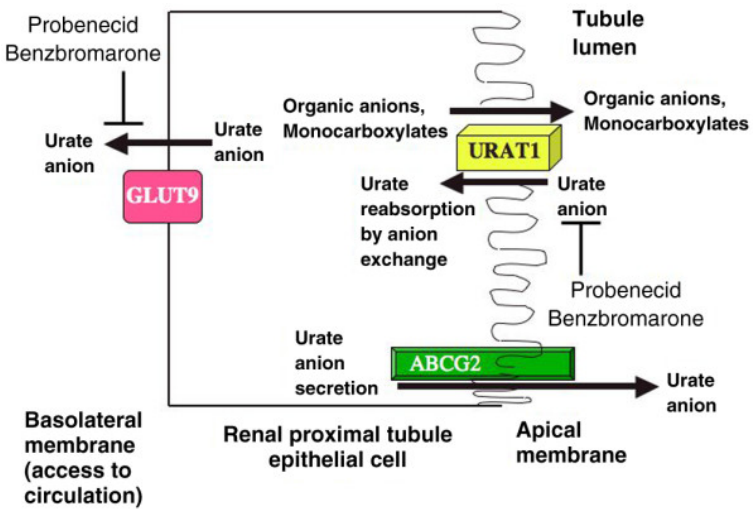


Febuxostat

Approuvé par FDA EMEA

Traitements de fond → Uricosuriques

inhibiteurs de la réabsoption proximale de l'acide urique

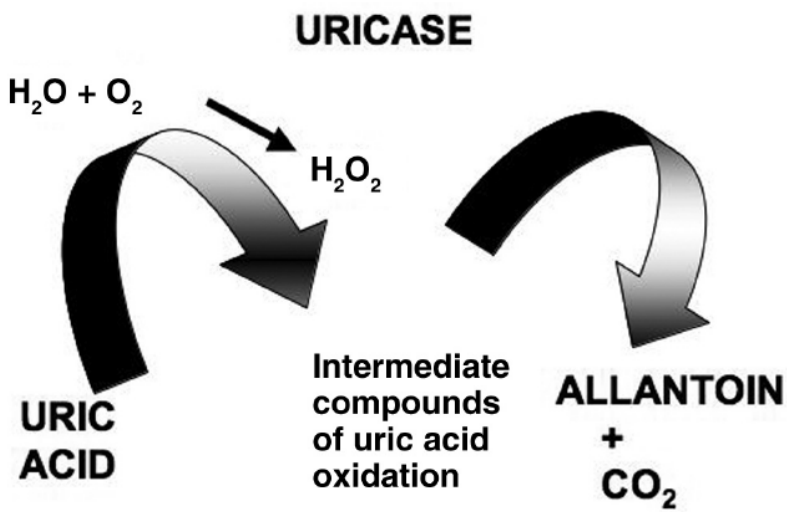


Arthritis Res Ther. 2009;11(4):236. Epub 2009 Jul 23

- Probénécid (en magistrale)
- Benzbromarone

↗ risque de lithiase urique

Goutte et uricase



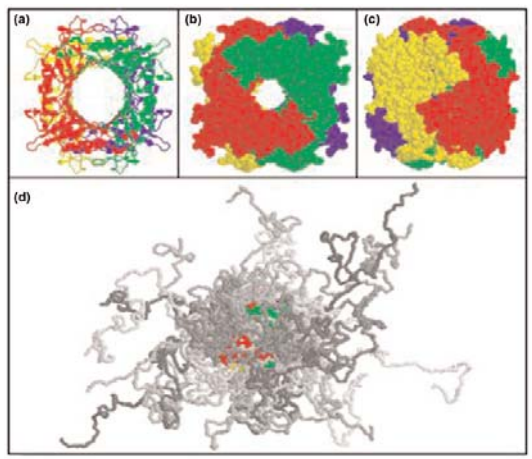
→ Urate oxydase recombinante (rasburase)

→ hautement antigénique

→ induit un stress-oxydatif…

→ Réservée au traitement et à la prophylaxie des hyperuricémies associées aux traitements chimiothérapeutiques

PEG-uricase : ↘ immunogénicité et ↗ la demi-vie



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