CEBAM
Belgian Centre for Evidence-Based Medicine
Belgian Branch of the Dutch Cochrane Centre

Arthrite rhumatoïde et médicaments biologiques. Une vision de la première ligne.

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Février 2018 AFMPS, Bruxelles

R/ R.A. un paysage en évolution rapide

R/ R.A. un paysage en évolution rapide

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

MECHANISMS OF DISEASE

The Pathogenesis of Rheumatoid Arthritis

Iain B. McInnes, F.R.C.P., Ph.D., and Georg Schett, M.D.

N Engl J Med **2011**;365:2205-19.

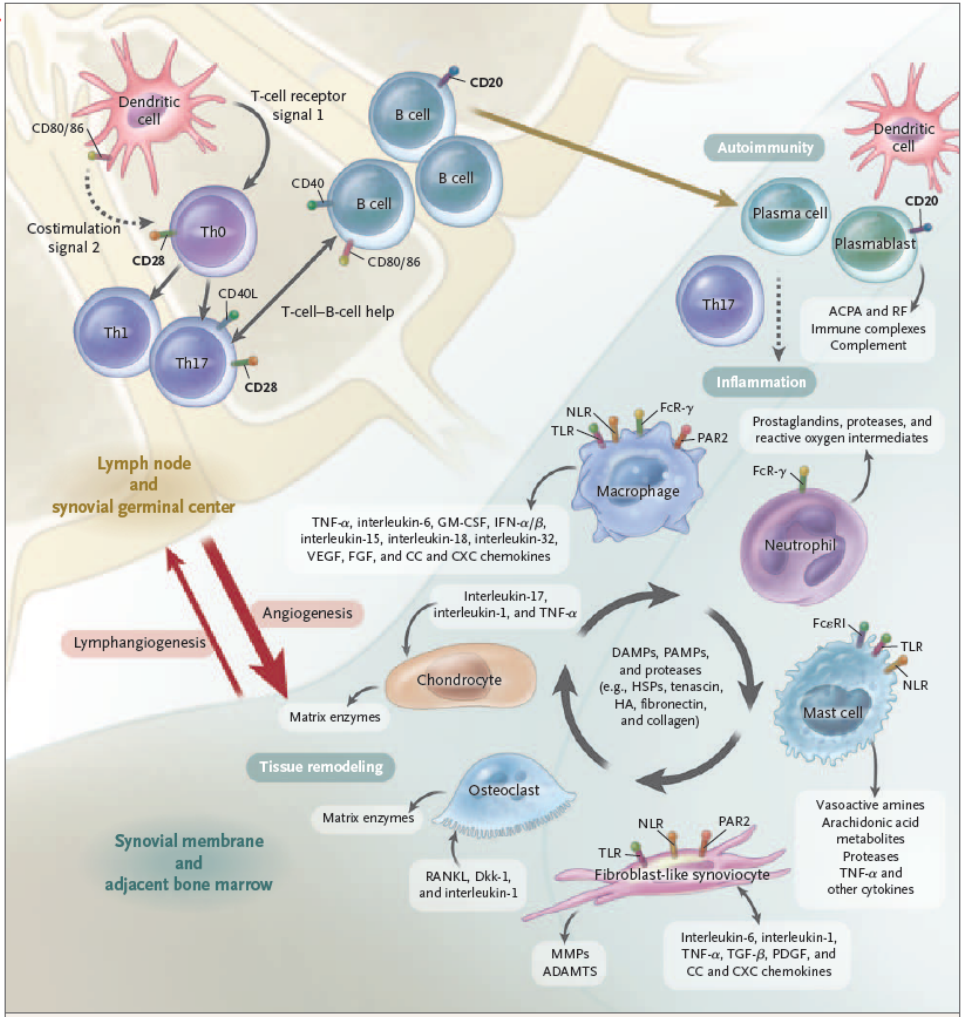

Figure 2. Adaptive and Innate Immune Processes within the Joint in Rheumatoid Arthritis.

Comment voir l'arbre au milieu de la forêt en tant que généraliste ?

Classique 4 types R/

- Symptomatique (analgésiques AINS)
- Corticostéroïdes (ARMM léger)
- ARMM (médicaments antirhumatismaux modificateurs de la maladie)
  - Base = méthotrexate (+ sulfasalazine + hydroxychloroquine) -> triple R/
- Médicaments biologiques (anticorps monoclonaux contre des cytokines spécifiques, protéines, …)

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Médicament s biologiques

Augmentation rapide du nombre de médicaments biologiques

Table 2. Key Molecules and Signal Mediators Implicated in the Pathogenesis of Rheumatoid Arthritis.*

Molecule or Signal Mediator	Key Disease-Relevant Functions	Status†
Cytokines		
TNF-α	Activates leukocytes, endothelial cells, and synovial fibroblasts, inducing production of cytokines, chemokines, adhesion molecules, and matrix enzymes; suppression of regulatory T-cell function; activation of osteoclasts; and resorption of cartilage and bone; mediates metabolic and cognitive dysfunction	Approved drug
Interleukin-1α and 1β	Activate leukocytes, endothelial cells, and synovial fibroblasts; induce matrix-enzyme production by chondrocytes; activate osteoclasts; mediate fever; enhance glucose metabolism; and reduce cognitive function	Approved drug
Interleukin-6	Activates leukocytes and osteoclasts; is involved in B-lymphocyte differentiation; regulates lipid metabolism, acute-phase response, and anemia of chronic disease; and is implicated in hypothalamic–pituitary–adrenal axis dysfunction and fatigue	Approved drug
Interleukin-7 and 15	Promote and maintain T-cell and natural killer–cell activation and T-cell memory, block apoptosis, and maintain T-cell–macrophage cognate interactions	Phase 2 trial completed
Interleukin-17A and 17F	Act synergistically to enhance activation of synovial fibroblasts, chondrocytes, and osteoclasts	More than one phase 2 trial with positive results
Interleukin-18	Promotes activation of Th1, neutrophils, and natural killer cells	
Interleukin-21	Activates Th17 and B-cell subsets	
Interleukin-23	Expands Th17	
Interleukin-32	Activates cytokine production by several leukocytes and promotes osteoclast differentiation	
Interleukin-33	Activates mast cells and neutrophils	
Growth and differentiation factors		
BLyS and APRIL	Activate B cells and have a role in the maturation of B cells and enhancement of autoantibody production	In phase 2 trial
GM-CSF and M-CSF	Enhance differentiation of granulocyte and myeloid-lineage cells in the bone marrow and synovium	In phase 1 trial
RANKL	Promotes maturation and activation of osteoclasts	Phase 2 trial completed
Intracellular signaling molecules and transcription factors		
JAK	Tyrosine kinase that regulates cytokine-mediated leukocyte maturation and activation, cytokine production, and immunoglobulin production	More than one phase 2 trial with positive results
Syk	Tyrosine kinase that regulates immune-complex–mediated and antigen-mediated activation of B and T cells and other Fc receptor–bearing leukocytes	More than one phase 2 trial with positive results
PI3K	Mediates signals that drive proliferation and cell survival	Phase 1 trial planned
BTK	Plays important role in the activation of B cells, macrophages, mast cells, and neutrophils, through regulation of B-cell receptor and Fc receptor signaling as appropriate	Phase 1 trial planned
NF-κB	Helps integrate inflammatory signaling and is important for cell survival	

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Table 3. Approved Immune-Targeted Therapies in Rheumatoid Arthritis.*

Agent	Class	Target	Structure	Comments
Adalimumab	Cytokine inhibitor	TNF-α	Human monoclonal antibody	TNF-α blockers were the first biologic agents approved for the treatment of rheumatoid arthritis; TNF-α blockade has become a central strategy of targeted antiinflammatory therapy in the disease.
Certolizumab pegol	Cytokine inhibitor	TNF-α	Pegylated humanized Fab′ fragment of an anti–TNF-α monoclonal antibody	
Etanercept	Cytokine inhibitor	TNF-α	TNF-α receptor–Fc fusion	
Golimumab	Cytokine inhibitor	TNF-α	Human monoclonal antibody	
Infliximab	Cytokine inhibitor	TNF-α	Chimeric monoclonal antibody	
Tocilizumab	Cytokine inhibitor	Interleukin-6 receptor	Humanized monoclonal antibody	This agent is considered the second major advar in cytokine blockade in rheumatoid arthritis; has profound effects on systemic features, acu phase response, and synovitis.
Anakinra	Cytokine inhibitor	Interleukin-1	Interleukin-1 receptor antagonist	Despite good antiinflammatory activity in inflan masome-driven disease (e.g., the Muckle–Wells syndrome, Still's disease, and gout), this agent has had only limited efficacy in rheumatoid arthritis.
Rituximab	Cell-depleting agent	CD20	Chimeric monoclonal antibody	This is the only approved cell-depleting agent fo rheumatoid arthritis; its use has reinforced the role of adaptive immunity, particularly humoral immune responses, in the disease.
Abatacept	Costimulation blocker	CD80 and CD86	CTLA4–Ig fusion protein	This agent disrupts the interaction of antigen-presenting cells with T cells, an effect that confirms the link between innate and adaptiv immune responses in rheumatoid arthritis.

tofacitinib

Qu'est-ce qui agit le mieux ?

Cochrane Database of Systematic Reviews

Methotrexate monotherapy and methotrexate combination therapy with traditional and biologic disease modifying anti-rheumatic drugs for rheumatoid arthritis: A network meta-analysis

Review Overview

Glen S Hazlewood ✉, Cheryl Barnabe, George Tomlinson, Deborah Marshall, Daniel JA Devoe, Claire Bombardier

First published: 29 August 2016

Qu'est-ce qui agit le mieux ?

preuve de qualité modérée à élevée que :

- la triple thérapie (méthotrexate + sulfasalazine+ hydroxychloroquine)
- méthotrexate + plus biologiques des ARMM
- méthotrexate + tofacitinib

ont eu une efficacité similaire chez des patients n'ayant jamais reçu de méthotrexate ou après une réaction inappropriée au méthotrexate.

Qu'est-ce qui agit le mieux ?

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 25, 2013 VOL. 369 NO. 4

Therapies for Active Rheumatoid Arthritis after Methotrexate Failure

James R. O'Dell, M.D., Ted R. Mikuls, M.D., M.S.P.H., Thomas H. Taylor, M.D., Vandana Ahluwalia, M.D., Mary Brophy, M.D., M.P.H., Stuart R. Warren, J.D., Pharm.D., Robert A. Lew, Ph.D., Amy C. Cannella, M.D., Gary Kunkel, M.D., Ciaran S. Phibbs, Ph.D., Aslam H. Anis, Ph.D., Sarah Leatherman, M.A., and Edward Keystone, M.D., for the CSP 551 RACAT Investigators*

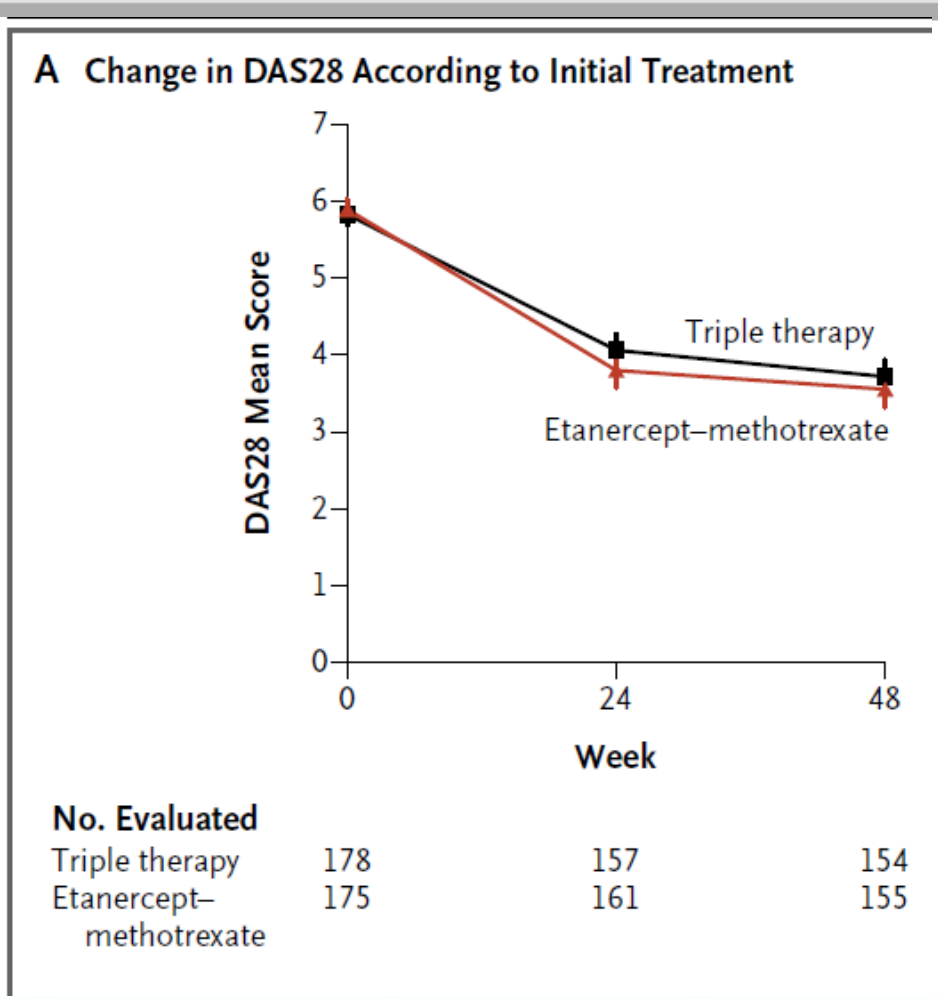
Qu'est-ce qui agit le mieux ?

Triple thérapie : Mtx + sulfasalazine à une dose de 1 g par jour pendant les 6 premières semaines, en diminuant la dose ensuite à 2 g par jour, et hydroxychloroquine, à une dose de 400 mg par jour, + injection de placebo

Contre :

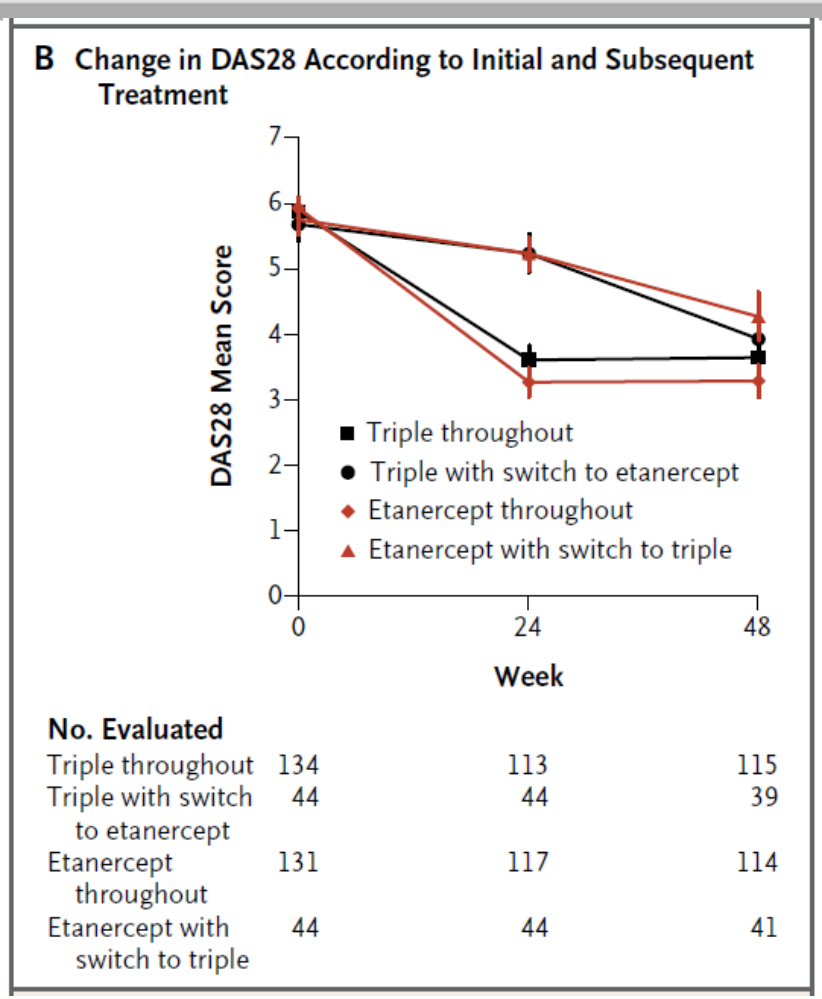
Mtx + Etanercept

(anti TNF α) + placebo par voie orale



Qu'est-ce qui agit le mieux ?

Passage à la thérapie alternative à 24 semaines en raison d'**une réaction cliniquement insignifiante survenue avec fréquence égale dans les deux groupes**, avec passage de 44 des 163 participants (27.0%) de la triple thérapie à la thérapie etanercept–méthotrexate et de 44 des 165 dans l'autre groupe



Qu'est-ce qui agit le mieux ?

Nos constatations suggèrent que la stratégie d'administrer d'abord la triple thérapie, avec un passage à l'etanercept–méthotrexate chez les patients qui ne donnent pas une réaction adéquate à la triple thérapie, permettra à un pourcentage important de patients d'être traités de façon plus économique, sans affecter négativement les résultats cliniques.

Effets secondaires

Cochrane Database of Systematic Reviews

Adverse effects of biologics: a network meta-analysis and Cochrane overview

Review Overview

Jasvinder A Singh ✉, George A Wells, Robin Christensen, Elizabeth Tanjong Ghogomu, Lara J Maxwell, John K MacDonald, Graziella Filippini, Nicole Skoetz, Damian K Francis, Luciane C Lopes, Gordon H Guyatt, Jochen Schmitt, Loredana La Mantia, Tobias Weberschock, Juliana F Roos, Hendrik Siebert, Sarah Hershan, Chris Cameron, Michael PT Lunn, Peter Tugwell, Rachelle Buchbinder

First published: 16 February 2011

Effets secondaires des médicaments biologiques

à court terme, taux plus élevés de

- graves infections,
- réactivation de TB,
- totaux AE et retraits dus aux AE.

Effets secondaires des médicaments biologiques

La sécurité à long terme (p. ex. cancer) des médicaments biologiques demande davantage de recherches, de préférence sans implication du secteur.

Les registres nationaux et internationaux et d'autres types de bases de données de grande ampleur sont des sources pertinentes pour l'apport de preuves complémentaires concernant la sécurité à court et à long terme des médicaments biologiques.

Expériences sur 3 patients.

Patient 1: V.A. 49a f : sacro-iliite HLA B27 -

V.A. 49 a HLA B27 neg pelvispondylite rhumatismale

2015 Rhumatologue

- plaintes de douleurs irradiantes vers le bas de la jambe droite par

  pseudoradiculopathie d'arthrose facettaire lombaire

- augmentation des douleurs dorsales avec douleurs pendant la nuit et **raideur matinale pendant une heure**, avec CRP légèrement augmentée

- **MRI** Déformation osseuse focale dans l'articulation SI gauche : évt début de SI-itis

- Proposition de thérapie temporaire :

  Ibuprofen + évt paracétamol. Kiné.

  Enbrel va être envisagé

Patient 1: V.A. 49a f : sacro-iliite HLA B27 -

V.A. 49 a HLA B27 neg pelvispondylite rhumatismale

2016 douleurs limitées, AINS de temps en temps.

2017 Consultation rhumatologue 25.04.2017

- sacro-iliite bilatérale active.
- Vu les douleurs inflammatoires (douleur pendant la nuit et raideur significative le matin), pas d'amélioration suffisante avec des AINS, vu augmentation répétitive de CRP, R/ **Enbrel**.

Juillet 2017 otite moyenne AB et arrêt très temporaire d'Enbrel.

Aujourd'hui : La patiente est OK

Patient 1: V.A. 49a f : sacro-iliite HLA B27 -

V.A. 49 a HLA B27 - SI

CRP

Datum		Resultaat	Eenheid	Referentie waarden
25/04/2017	+	8,5	mg/L	0,0 - 5,0
23/09/2014		< 5,0	mg/L	0,0 - 5,0
03/06/2014		< 5,0	mg/L	0,0 - 5,0
28/03/2014		-		
28/03/2014		< 5,0	mg/L	0,0 - 5,0
14/08/2013		-		
14/08/2013	+	7,9	mg/L	0,0 - 5,0
07/02/2013		-		
07/02/2013	+	14,0	mg/L	0,0 - 5,0
03/07/2012	+	1,2	mg/dL	0,0 - 0,5
01/03/2011		<0,5		
20/05/2010		0,5	mg/dL	0,0 - 0,5
22/10/2009		0,2	mg/dL	0,0 - 0,5
07/11/2008		0,4	mg/dL	0,0 - 0,5
15/10/2008	+	0,7	mg/dL	0,0 - 0,5

20/05/2010

Patient 2: F.C. 70a h : R.A.

- Polyarthrose +++ et R.A. actif R/Mtx et Enbrel

Octobre 2016 selon la lettre de rhumatologue

- Érysipèle récent dans le bas de la jambe droite, d'où traitement par antibiotiques. Enbrel suspendu par le généraliste.
  Proposition de thérapie :
  Je recommande donc au patient de recommencer l'Enbrel dans une semaine. Le patient est cependant très réticent à ce propos et n'ose pas reprendre ce médicament.
  J'essaie d'expliquer que les lésions d'érysipèle n'ont pas été provoquées par
  l'Enbrel mais que l'Enbrel doit légalement être suspendu en cas infection parce que l'Enbrel affaiblit le système immunitaire.

Patient 2: F.C. 70a h : R.A.

Pourtant, le patient préfère ne pas recommencer l'Enbrel. Dans le passé, il a développé
une intolérance gastro-intestinale aux Ledertrexate et Arava (léflunomide) si bien que la reprise de ces médicaments n'est actuellement pas une option.
Il est donc décidé temporairement de ne continuer qu'un AINS.

Je recommande pourtant, après quelques semaines, **de recommencer l'Enbrel.**

Je revois le patient pour contrôle 2 mois **après la reprise d'Enbrel.**

2017 HA recommencé en plus de Mtx plaquenil, le patient va bien. Ne consulte plus de rhumatologue.

Patient 3: VH,25a f. : HLA B27 + spondylartropathie

04/2016 Rhumatologue

VH 25 a une douleur inflammatoire variable à hauteur de la cuisse gauche. Je soupçonne une spondylartropathie positive HLA B27 R/Gambaran

Pas d'indication pour commencer anti-TNF vu CRP normale.

02/2017 rapport MRI

Divergences érosives à hauteur des deux SIG, gauche plus que droite. Œdème sous-chondral à hauteur de SIG bilatéral, gauche > droite, en raison de sacro-iliite active (selon les critères ASAS).

Patient 3: VH,25a f. : HLA B27 + spondylartropathie

09/2017 CT thorax : ganglions lymphatiques médiastinaux : les affections lymphoprolifératives ou granulomateuses (p. ex. sarcoïdose) doivent être exclues

Octobre 2017 : **début Cimzia**

11-2017. conseil pneumo : Glandes, éventuellement secondaires à sarcoïdose. Vu qu'il n'y a pas d'autres atteintes d'organes, position d'attente.

Contrôle CT 6 mois avant CT précédent

Aujourd'hui : Depuis le début de Cimzia (anti tnf), ses douleurs sont sous contrôle.

Conclusion sur la base de l'expérience de ces patients

Échantillon représentatif de notre population pt

- Dans ces trois cas, la triple thérapie n'a jamais commencé.
- Au moins dans une situation, activité inflammatoire très limitée
- Peu (pas) de participation du patient, dans une situation même le contraire

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Le monde tel qu'il est.

Ma question : est-ce un usage correct des médicaments biologiques ?

MERCI !