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

Reumatoïde Artritis en Biologicals. Blik vanuit eerste lijn.

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Huisarts, docent ACHG KU Leuven
Directeur CEBAM

Februari 2018 FAGG, Brussel

R/ R.A. snel evoluerend landschap

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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.

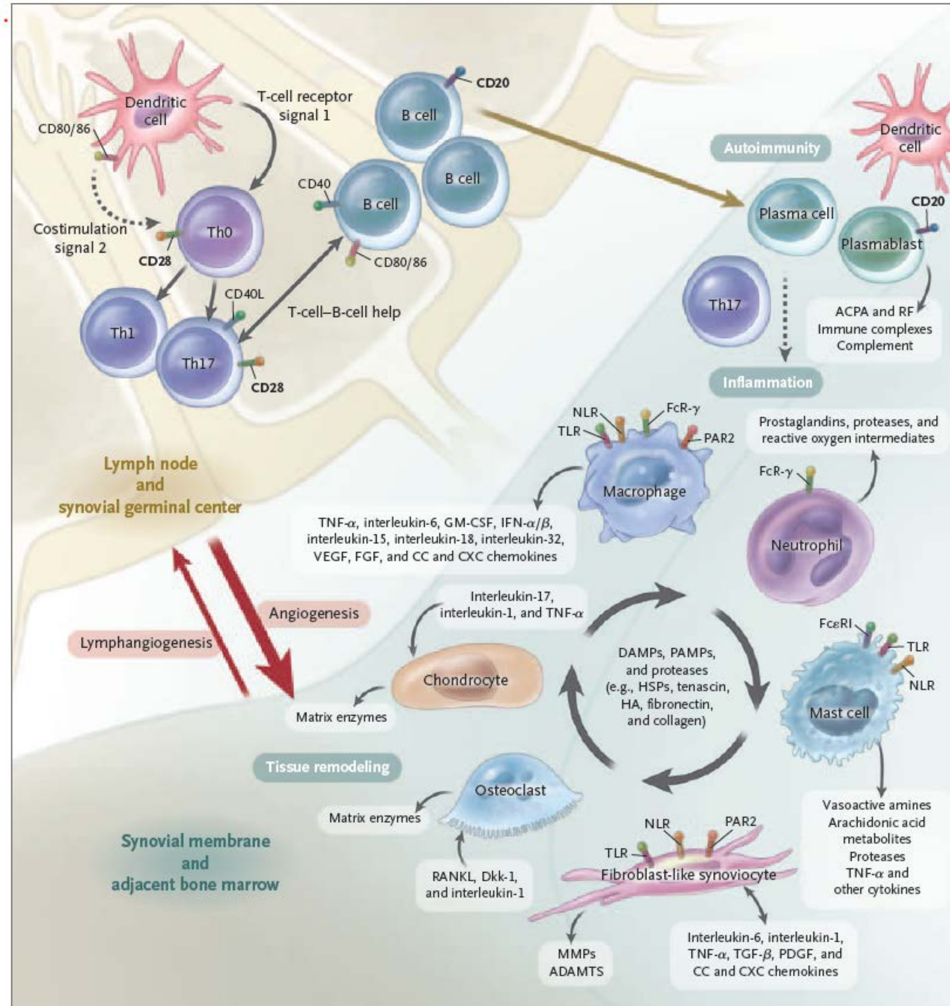

Figure 2. Adaptive and Innate Immune Processes within the Joint in Rheumatoid Arthritis.

Hoe als HA door het bos de bomen zien?

Klassiek 4 types R/

- Symptomatisch (NSAID- analgetica)
- Corticosteroïden (beetje DMARD)
- DMARD's (Disease Modifying Antirheumatic Drugs)
  - Basis = methotrexaat (+ sulfasalazine + hydroxychloroquine) -> triple R/
- Biologicals (monoclonale antistoffen tegen specifieke cytokines, eiwitten, …)

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Klassiek 4 types R/

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- Cortico roïden D)
- DMARD Drugs)
  - – ychloroquine) -> triple R/
- B egen specifieke
  cyt

Biologicals

Snelle toename aantal biologicals

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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Snelle toename aantal biologicals
tientallen drugs in de pipeline

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Snelle toename aantal biologicals:per klasse

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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; i 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

Wat werkt beter?

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

Wat werkt beter?

moderate to high quality evidence that:

- triple therapy (methotrexate + sulfasalazine+ hydroxychloroquine)
- methotrexate + most biologic DMARDs
- methotrexate + tofacitinib

were similarly effective in methotrexate-naïve patients or after an inadequate response to methotrexate.

Wat werkt beter?

The NEW ENGLAND JOURNAL of MEDICINE

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

Therapies for Active Rheumatoid Arthritis after Methotrexate Failure

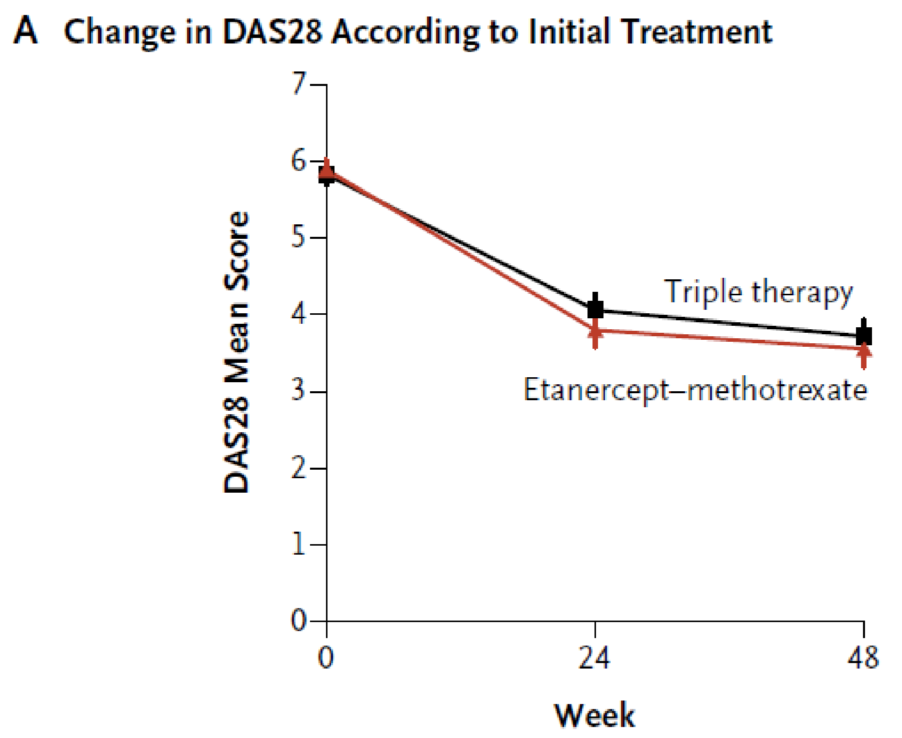
James R. O'Dell, M.D., Ted R. Mikuls, M.D., M.S.P.H., Thomas H. Taylor, M.D., Vandana Ahluwalia, M.D., Mary Brophy, M.D., M.P.H., Stuart R. Warren, J.D., Pharm.D., Robert A. Lew, Ph.D., Amy C. Cannella, M.D., Gary Kunkel, M.D., Ciaran S. Phibbs, Ph.D., Aslam H. Anis, Ph.D., Sarah Leatherman, M.A., and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

Wat werkt beter?

Triple-therapy: Mtx + sulfasalazine at a dose of 1 g daily for the first 6 weeks, with the dose increased thereafter to 2 g daily, and hydroxychloroquine, at a dose of 400 mg daily, + placebo injectie

Vs:

Mtx + Etanercept (TNF α blokker) + placebo per os

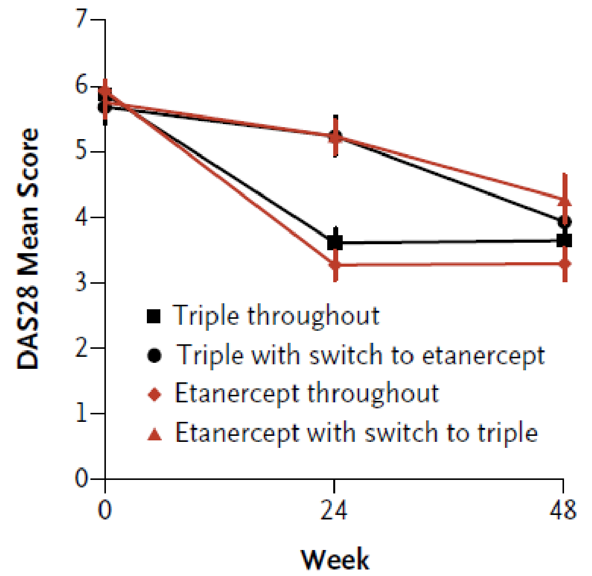


No. Evaluated	0	24	48
Triple therapy	178	157	154
Etanercept–methotrexate	175	161	155

Wat werkt beter?

Switching to the alternative therapy at 24 weeks owing to **a clinically insignificant response occurred with equal frequency in the two groups**, with 44 of 163 participants
(27.0%) switching from triple therapy to etanercept–methotrexate therapy and 44 of 165 in the other group

B Change in DAS28 According to Initial and Subsequent Treatment



No. Evaluated			
Triple throughout	134	113	115
Triple with switch to etanercept	44	44	39
Etanercept throughout	131	117	114
Etanercept with switch to triple	44	44	41

Wat werkt beter?

Our findings suggest that a strategy of first administering triple therapy, with a switch to etanercept–methotrexate in patients who do not have an adequate response to triple therapy, will allow a substantial percentage of patients to be treated in a more cost-effective way without adversely affecting the clinical outcomes.

Nevenwerkingen

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

Nevenwerkingen biologics

in the short term higher rates of

- serious infections,
- TB reactivation,
- total AEs and withdrawals due to AEs.

Nevenwerkingen biologics

There is a need for more research regarding the long-term safety (eg cancer) of biologics; preferably without industry involvement.

National and international registries and other types of large databases are relevant sources for providing complementary evidence regarding the short- and longer-term safety of biologics.

Ervaringen met 3 patiënten.

Patiënt 1: V.A. 49j vr. : sacroiliitis HLA B27 -

V.A. 49 j HLA B27 neg pelvis spondylarthropathie

2015 Reumatoloog

- pijnklachten irradiërend naar het rechteronderbeen door pseudoradiculopathie vanuit laaglumbale facetartrose
- toenemende rugpijnklachten met nachtelijke pijn en **ochtendstijfheid gedurende een uur** met licht verhoogd CRP
- **MRI** Focale botomvorming in de linker SI gewricht: evt beginnende SI-itis

- Voorlopig therapievoorstel :

  Ibuprofen + evt paracetamol. Kine.

  Enbrel zal worden overwogen.

Patiënt 1: V.A. 49j vr. : sacroiliitis HLA B27 -

V.A. 49 j HLA B27 neg pelvisspondylarthropathie

2016 beperkte klachten, NSAID op en af.

2017 Raadpleging Reumatoloog 25.04.2017

- actieve bilaterale sacro-iliitis.
- Gezien inflammatoire pijnklachten (nachtelijke pijn en significante ochtendstijfheid), onvoldoende beterschap met NSAID's, gezien herhaaldelijk verhoogd CRP, R/ **Enbrel**.

Juli 2017 otitis media AB en stop Enbrel zeer tijdelijk.

Heden: Patiënte is OK

Patiënt 1: V.A. 49j vr. : sacroiliitis HLA B27 -

V.A. 49 j 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

Patiënt 2: F.C. 70j m: R.A.

- Polyartrose +++ en actieve R.A. R/Mtx en Enbrel

Oktober 2016 uit brief Reumatoloog

- Recent erysipelas rechter onderbeen waarvoor behandeling met antibiotica. Enbrel werd gestaakt door huisarts.

  Therapievoorstel:
  Ik adviseer aan patiënt dan ook om te herstarten met Enbrel over een week doch patiënt zelf staat daar zeer weigerachtig tegenover en durft met deze medicatie niet herstarten.
  Ik probeer uit te leggen dat de erysipelas laesies niet zijn veroorzaakt door de Enbrel maar dat de Enbrel wettelijk gestaakt moet worden bij een infectie omdat Enbrel het immuunsysteem onderdrukt.

Patiënt 2: F.C. 70j m: R.A.

Toch wil patiënt liefst niet herstarten met Enbrel. In het verleden toonde hij een gastro-intestinale intolerantie voor Ledertrexate en Arava (leflunomide) zodat het momenteel ook geen optie is om met deze medicijnen terug te beginnen. **Voorlopig wordt er dan besloten om alleen een NSAID te continueren**.

Ik adviseer dan toch, over een aantal weken, **te herstarten met Enbrel.**

Ik zie pt terug ter controle 2 maanden **na het herstarten van Enbrel.**

2017 HA startte naast Mtx plaquenil op, patiënt gaat goed. Bezoekt geen reumatoloog meer.

Patiënt 3: VH,25j vr. : HLA B27 + spondylartropathie

04/2016 Reumatoloog

VH 25 j wisselend inflammatoire pijn thv de linker bilregio. Ik vermoed door een HLA B27 positieve spondylartropathie R/Gambaran

Geen indicatie voor het opstarten van anti-TNF gezien normaal CRP.

02/2017 verslag MRI

Erosieve afwijkingen ter hoogte van beide SIG, links meer dan rechts. Subchondraal oedeem thv de SIG bilateraal, links > rechts, ikv actieve sacro-iliitis (volgens de ASAS criteria).

Patiënt 3: VH,25j vr. : HLA B27 + spondylartropathie

09/2017 CT thorax : lymfeklieren mediastinaal: lymfoproliferatieve of granulomateuze aandoeningen (bv. sarcoïdose) dienen te worden uitgesloten

Oktober 2017 : start Cimzia

11-2017. advies pneumo : Klieren, mogelijk secundair aan sarcoidose. Gezien geen andere orgaanaantasting, afwachtende houding. Controle CT 6 mnd na vorige CT

Heden: Sinds opstarten van Cimzia (tnf blokker) zijn haar klachten onder controle.

Conclusie op basis van deze patiëntenervaringen

Representatief staal van onze pt populatie

- In deze drie gevallen in geen enkel geval opstarten van triple therapie
- Minstens in één situatie zeer beperkte inflammatoire activiteit
- Weinig (geen) inspraak van patiënt, in één situatie zelfs ronduit omgekeerde

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De wereld zoals ze is.

Mijn vraag: is dit correct gebruik van biologicals?

DANK!