Sarilumabi reumasairauksien ja muiden sairauksien hoidossa

Pekka J Nykänen
Reumatologi

Maaliskuu 2022 (Päivitys)

Biologisten ja synteettisten reumalääkkeiden käsikirja

Ajanvaraus vastaanotolle tästä

Linkki artikkeliin tosilitsumabista, joka on toinen IL-6 reseptorin antagonisti

Infektiot

- Bakteeri
  - Staphylococcus aureus
  - Streptococcus
  - Mycobacterium chelonae

Luuydin

Sarilumabi ja raskaus

Interleukiini 6 (IL-6) ja sen reseptori

IL-6 on 26 kilodaltonin (kDa) suuruinen glykopeptidi, jonka geeni sijaitsee kromosomissa 7. IL-6:n proteiiniosan paino on 20 kDa. Sokeriosan lisääminen proteiinin nostaa sen painon tasolle 21-26 kDa (Tanaka 2014).

(dalton on biokemiassa käytössä oleva epävirallinen atomimassayksikkö, joka on yksi kahdestoistaosa hiiliatomin (12C) massasta).
(glykopeptidi on hiilihydraattia sisältävä peptidi. Peptidi on peptidisidoksilla toisiinsa liittyneiden aminohappojen ketju).
(kromosomi on DNA-molekyylistä ja siihen kytkeytyneistä valkuaisaineista koostuva tuman osa, joka on solun jakautumisvaiheessa kiertynyt tiiviiksi sauvamaiseksi kappaleeksi).
IL-6:a valmistettiin kloonauksella ensimmäisen kerran vuonna 1986.
IL-6 on sytokiini, jolla on monia biologia vaikutuksia:

- immuunivasteen säätely
- tulehdus
- luukudoksen aineenvaihdunta
- veren solujen synty ja kehitys (hematopoeesi)
- kemokiinien ja adheesiomolekyylien tuotanto muissa soluissa
- maksasoluissa akuutin vaiheen proteiinien muodostus (CRP)

(kemokiinit ovat pienimolekyylisiä aineita, jotka aiheuttavat kaikkien tai joidenkin valkosolujen liikkumisen niitä kohti)
(adheesiomolekyyli on solupinnan molekyyli (mm. integriinit, selektiinit), joka sitoo solua toisiin soluihin tai sidekudoksen säikeisiin)

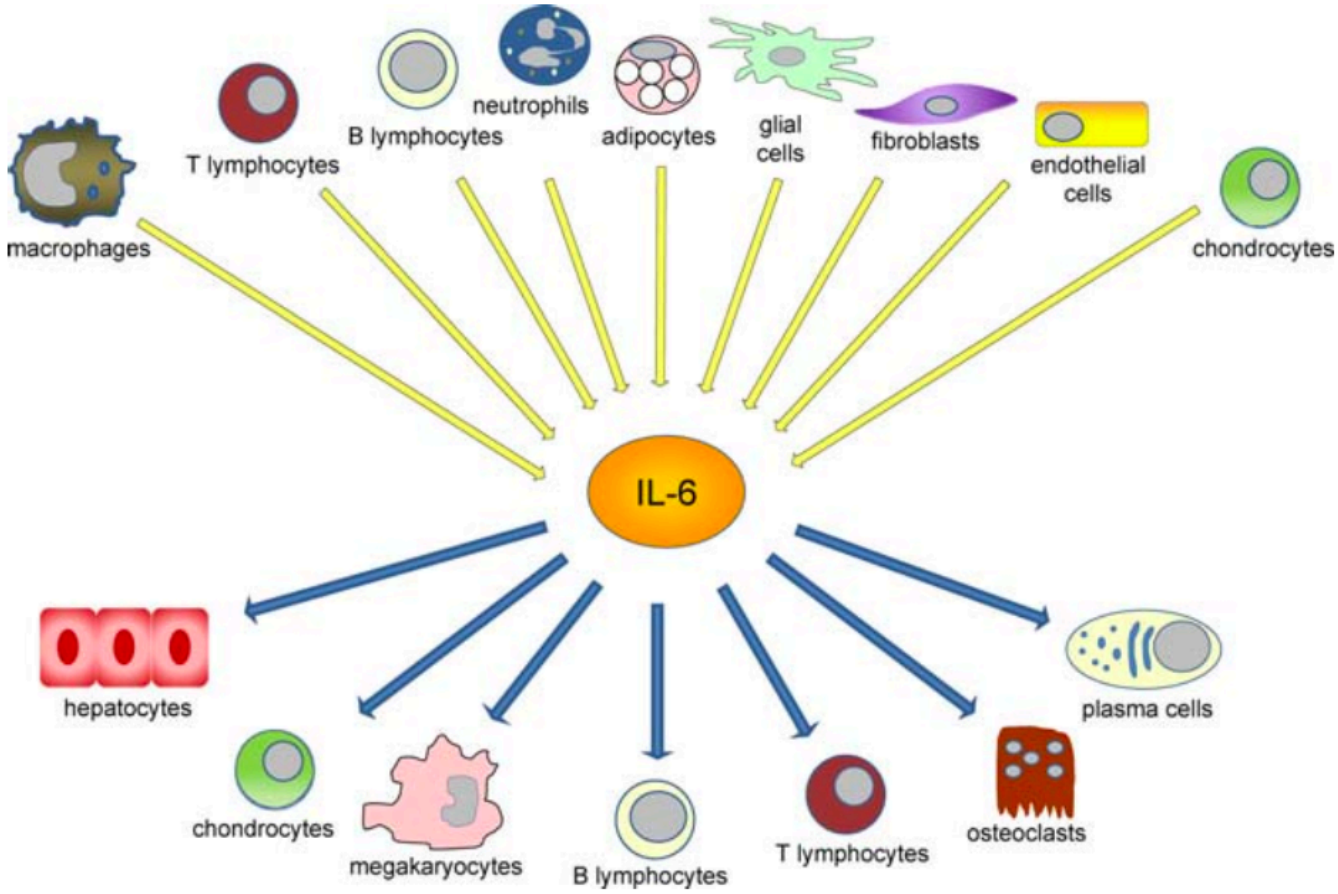
(Sytokiini on monentyyppisten solujen tuottamia, solujen välisinä viestiaineina toimivia pienimolekyylisiä proteiineja (esim. interferonit, interleukiinit, lymfokiinit, kasvutekijät)

Normaalioloissa IL-6:n pitoisuus seerumissa on hyvin matala (1-5 pg/ml) mutta tulehduksen yhteydessä voi pitoisuus nousta 100000 kertaiseksi (Mesquida 2014).

IL-6:a muodostuu

- T-soluissa
- B-soluissa (B-imusolu)
- Makrofageissa (syöjäsolu)
- Monosyyteissä (muuttuu kudoksessa makrofagiksi)
- Mastosyyteissä (syöttösolu)
- Neutrofiilisissä granulosyyteissä (neutrofiili)
- Eosinofiilisissä granulosyyteissä (eosinofiili)
- Gliasoluissa (hermotukisolu)
- Sidekudossoluissa (fibroblasti)
- Rustosoluissa (kondrosyytti)
- Rasvasoluissa (adiposyytti)
- Osteoblasteissa (osteosyytin varhaismuoto)
- Endoteelisoluissa (verisuonen sisäpinnan solu)

Katso alapuolella keltaisten nuolten yläpuolella olevat solut, jotka tuottavat IL-6:a.
Siniset nuolet näyttävät solut, joihin IL-6 vaikuttaa.



(

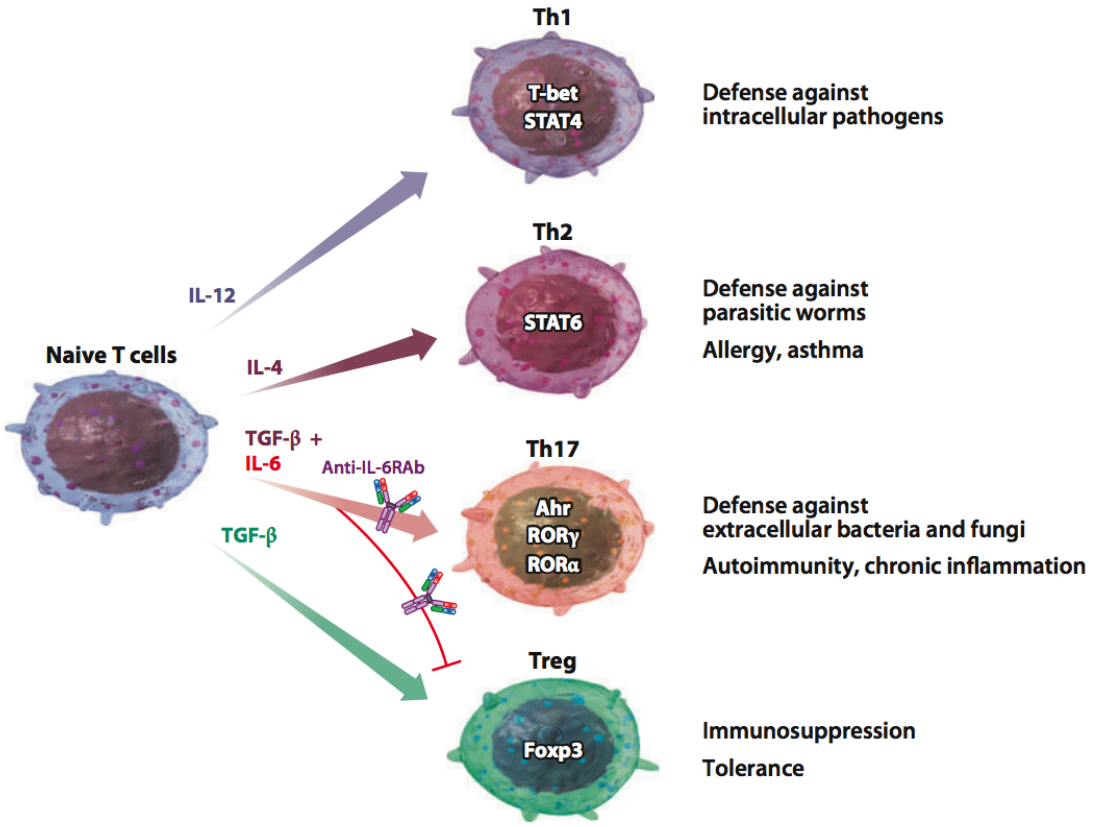
Fig. 1. Origin and cell targets of IL-6. Non-exhaustive representation showing the broad array of cells capable of producing IL-6 (top). There is also a wide variety of target cells (bottom).

(Assier 2010)

Interleukiini 17 (= IL-17) tuottavia CD4 positiivisia lymfosyyttejä sanotaan Th17 soluiksi.

Transformoiva kasvutekijä beta (= transforming growth factor = TGF beta) yhdessä IL-6:n kanssa indusoi patogeenisten Th17 solujen muodostuksen.

Kun TGFbeta vaikuttaa yksinään (ilman IL-6:n vaikutusta) indusoi CD4+CD25+ T regulatory (Treg) soluja, joissa on forkhead box P3 (FOXP3) positiivinen.



Anti-interleukin-6 receptor antibody (anti-IL-6RAb) may be able to repair Th17/Treg imbalance. When $CD4^+$ naïve T cells are primed, a specific cytokine directs their differentiation into an effector T cell subset. IL-6 in combination with TGF-β preferentially induces Th17 development, whereas IL-6 inhibits TGF-β-induced Treg differentiation, thus leading to Th17/Treg imbalance. This imbalance is pathologically important for the development of autoimmune and chronic inflammatory diseases. Anti-IL-6RAb may be able to repair this imbalance. Abbreviations: Ahr, aryl hydrocarbon receptor; Foxp3, forkhead box P3; ROR, retinoid-related orphan receptor; STAT, signal transducer and activator of transcription; T-bet, Th1-specific T box transcription factor; TGF-β, transforming growth factor β; Th17, IL-17-producing T helper cells; Treg, regulatory T cells.

Tanaka 2012

IL-6:n viestin (signaali) välittyminen kohdesolun sisälle

Signaalin välittymiseen on kaksi tietä (Al-Shakarchi 2013).

1. IL-6 tarttuu solun pinnalla olevaan IL-6 reseptoriin (=IL6R=CD126) (membrane bound IL-6 reseptor = mIL-6R). Sen molekyylipaino on 80 kDa.
   IL-6:n ja mIL-6R:n muodostama yhdiste (kompleksi) tarttuu solun
   pinnalla kahteen glykoproteiini 130:een (=gp130=CD130).

2. IL-6 tarttuu soluvälitilassa liukoisessa muodossa olevaan IL-6 reseptoriin (sIL-6R). IL-6:n ja sIL-6R:n muodostama kompleksi sitoutuu solun pinnalla kahteen glykoproteeiini 130:een ja tämä uusi kompleksi välittää signaalin solun sisälle. Liukoisen IL-6 reseptorin molekyylipaino on 50-55 kDa.
IL-6 reseptori on tietyissä soluissa kuten maksasoluissa (hepatosyytti) ja valkosoluissa. Sen sijaan liukoista IL-6-reseptoria (= sIL-6R) on seerumissa. Se sitoutuu IL-6:een ja tämä yhdistelmä tarttuu kohdesolun gp130:een (gp = glykoproteiini).
IL-6:n ja sIL-6R:n muodostama liukoinen kompleksi kykenee vaikuttamaan myös sellaisiin soluihin, joiden pinnalla ei ole IL-6:n reseptoria.

IL-6 aktivoi soluja sitoutumalla aluksi Alfa-reseptoriin (IL-6 R = CD 126), joka dimerisoituu gp130:n kanssa. Sen jälkeen aktivoituvat reseptoriin liittyvät kinaasit (JAK1, JAK2 ja Tyk2). Sen jälkeen fosforyloituvat glykoproteeini 130:n solunsisäiset osat, mikä vaikuttaa STAT1 ja STAT 3 aktiviteettiin. (Jones 2011).

IL-6 nivelreumassa

IL-6:a muodostuu runsaasti nivelreumassa nivelpussin sisäkerroksen soluissa (synoviaalisolu) ja syöjäsoluissa (makrofagi). Nivelreumapotilaiden veressä on IL-6:n ja sIL-6R:n määrä lisääntynyt.
Myös nivelnesteessä on IL-6:n pitoisuus koholla nivelreumassa (Alten 2011)

IL-6 vaikuttaa nivelreumassa usealla alueella:

- IL-6 edistää T-solujen aktivaatiota
- IL-6:n vaikutuksesta B solu muuttuu vasta-ainetta (immunoglobuliini) muodostavaksi plasmasoluksi.
- IL-6 edistää tulehdussolujen siirtymistä nivelkalvolle

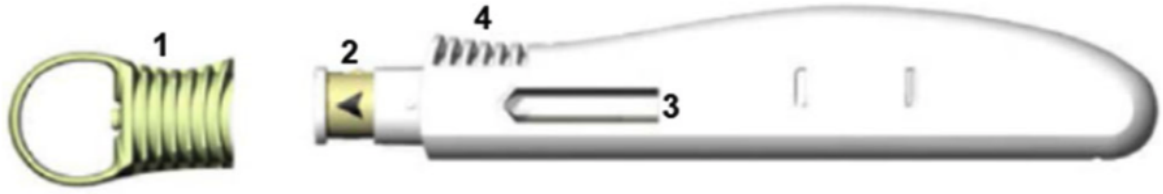
- IL-6 edistää yhdessä TNF-alfan ja IL-1:n kanssa verisuonten uudismuodostusta (angiogeneesi) nivelkalvolla
- IL-6 lisää maksassa akuutin vaiheen proteiinien muodostusta (CRP ja seerumin A amyloidi =SAA)
- IL-6 aiheuttaa osaltaan nivelreumapotilaan anemiaa lisäämällä maksassa hepsidiinin muodostusta. Hepsidiini on maksan tuottama proteiini, jonka tuotanto lisääntyy mm. tulehduksessa ja joka estää raudan imeytymistä suolesta ja sen vapautumista maksasta ja makrofageista.
  (Al-Shakarchi 2013)

Pelechas (2019 Kokotekstinä)

The IL-6 molecule sarilumab

Despite the advances in RA treatment, patients are still in a need of new treatment options. Sarilumab is expected to work in this direction. It is a human, IgG1 monoclonal antibody produced in Chinese Hamster Ovary cells by recombinant DNA technology that binds to the α-subunit of the membrane-bound and soluble IL-6 receptors inhibiting IL-6 signaling.[19]

Kivitz (2018 Kokotekstinä) totesivat sarilumabi-kynän käytön olevan helppoa nivelreumapotilailla.



Sarilumab pen. Visual features of the prefilled, single-use, disposable, buttonless, ergonomic sarilumab pen include (1) an easy-to-remove needle cap, (2) a needle cover that is automatically positioned after injection to help prevent needlestick injuries, (3) a transparent window that turns yellow when the injection is complete, and (4) strips to facilitate grip

Tutkijoiden johtopäätös:

“In this study, patients with rheumatoid arthritis successfully completed self-injections with a single-use, disposable, prefilled, buttonless, ergonomic sarilumab pen. Patients reported satisfaction with the sarilumab pen and found the pen easy to use. In addition, patients were very confident regarding the use of such a pen for self-injection in the future. Safety and efficacy appeared to be generally similar between the pen and syringe groups and consistent with observations from other clinical trials of sarilumab. In conclusion, this study demonstrated the ease of use and robustness of sarilumab 150 and 200 mg q2w administered via pen when used by patients with rheumatoid arthritis in an unsupervised real-world setting.”

Avci ja Burmester (2024 Kokotekstinä)

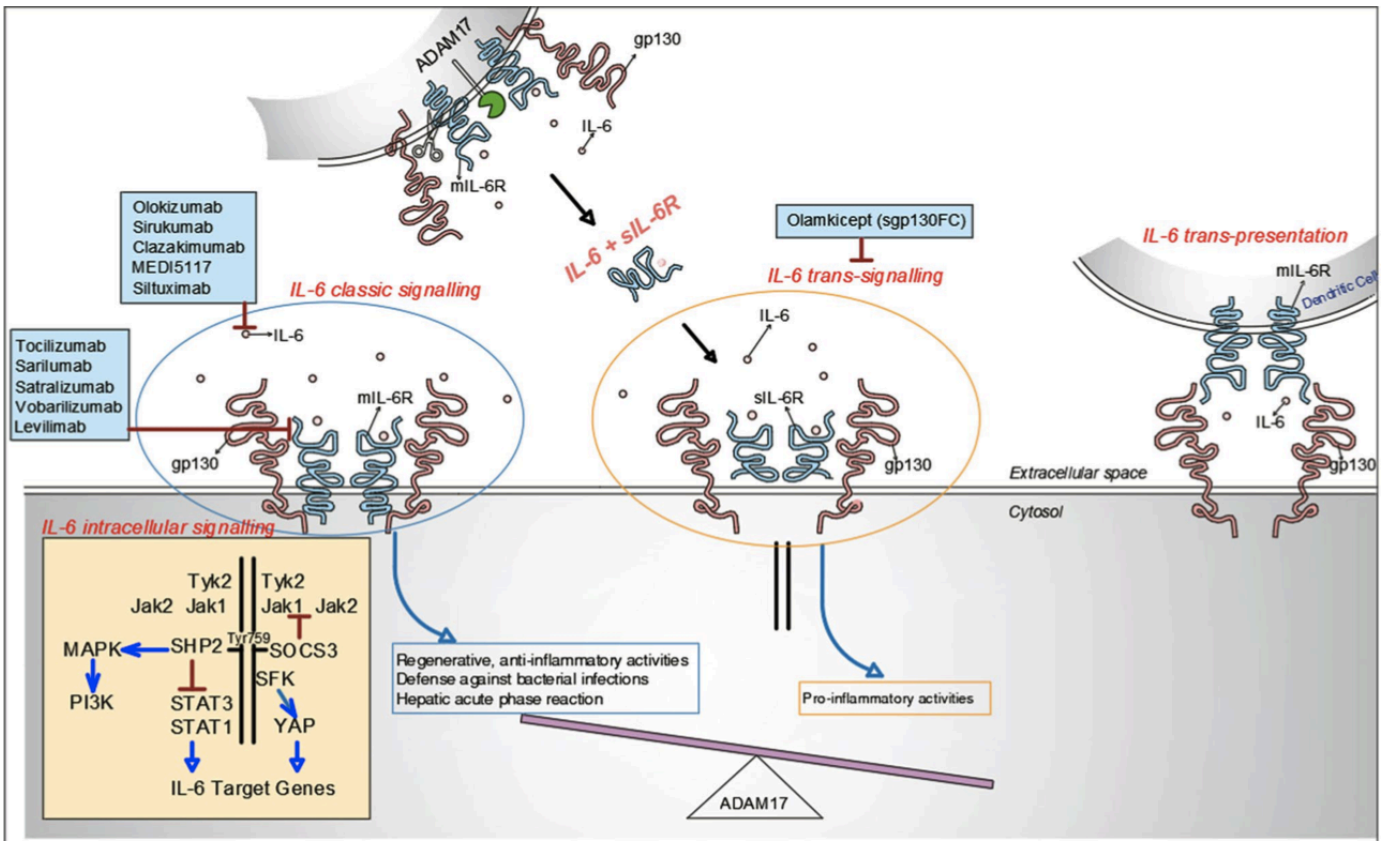
Key Points

The role of the interleukin (IL)-6 pathway in the treatment of rheumatoid arthritis has the potential to progress with different inhibitions of this pathway such as IL-6 cytokine blockade and trans-signaling blockade, in addition to IL-6 receptor blockers.

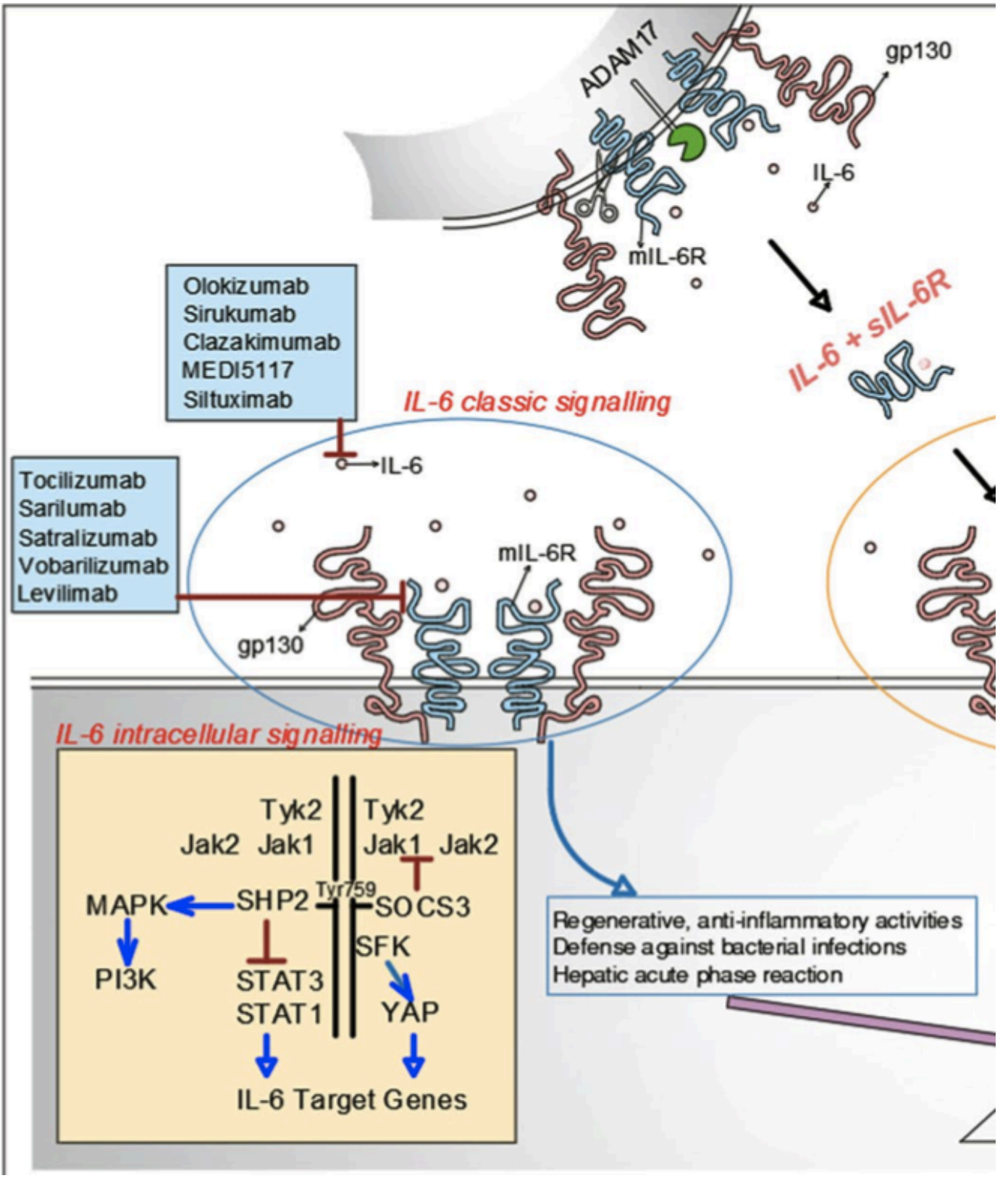
The favorable efficacy/safety profile of tocilizumab has prompted the rapid development of biosimilars and new potent IL-6 receptor inhibitors.

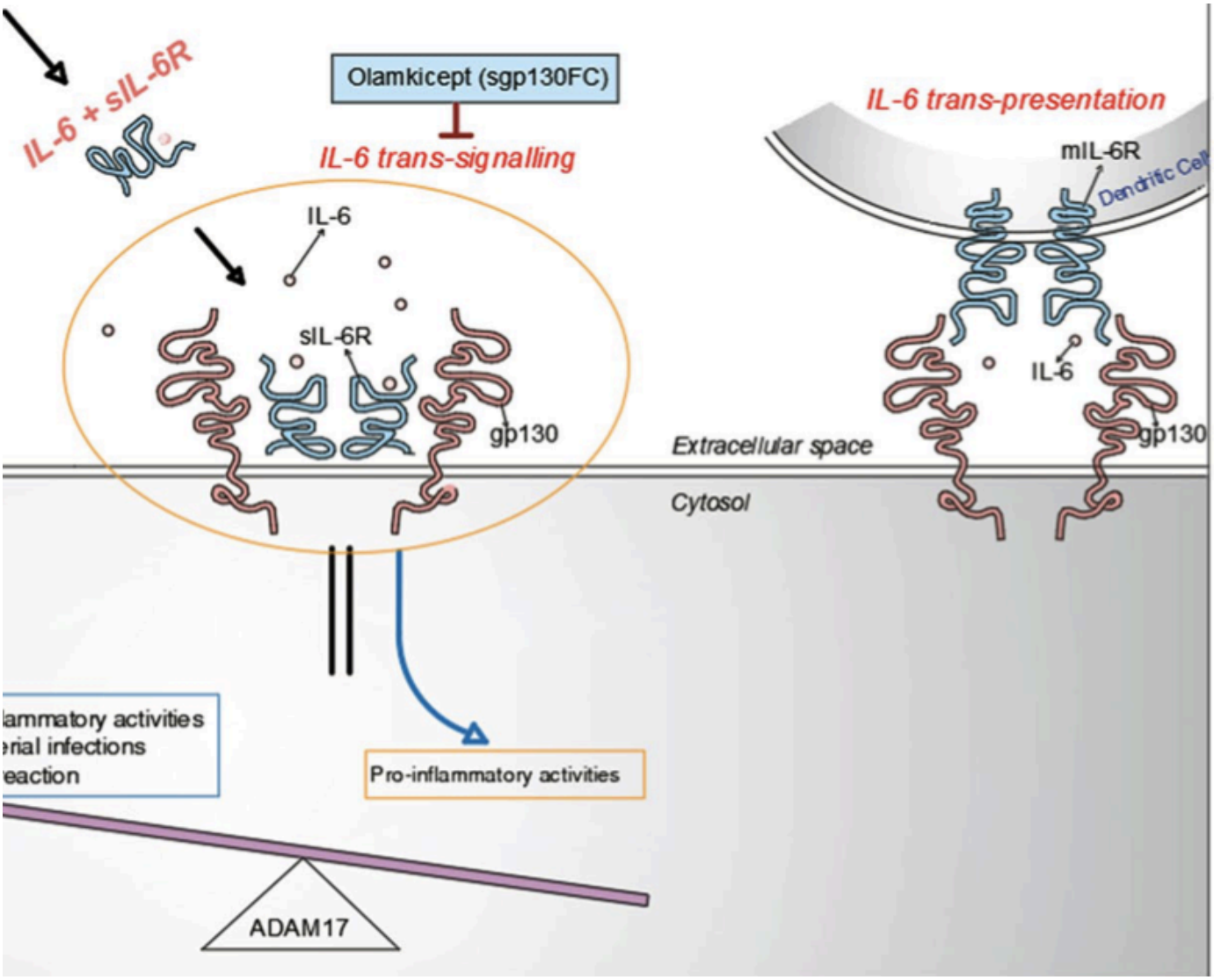
The potential impact of modalities targeting different antigenic sites of the IL-6 cytokine on efficacy and safety data highlights the importance of both clinical and basic research in revealing the true potential of this pathway.

The efficacy demonstrated by olokizumab in phase III studies, along with its open-label extension safety data, has shown that direct IL-6 inhibitors may also have an important place in this field.


ADAM17
gp130
IL-6
mIL-6R
IL-6 + sIL-6R
Olokizumab
Sirukumab
Clazakimumab
MEDI5117
Siltuximab
IL-6 classic signalling
Olamkicept (sgp130FC)
IL-6 trans-signalling
IL-6 trans-presentation
Tocilizumab
Sarilumab
Satralizumab
Vobarilizumab
Levilimab
sIL-6R
Dendritic Cell
Extracellular space
Cytosol
IL-6 intracellular signalling
Tyk2
Jak2
Jak1
MAPK
SHP2
Tyr759
SOCS3
SFK
PI3K
STAT3
STAT1
YAP
IL-6 Target Genes
Regenerative, anti-inflammatory activities
Defense against bacterial infections
Hepatic acute phase reaction
Pro-inflammatory activities
ADAM17

Suurennos:

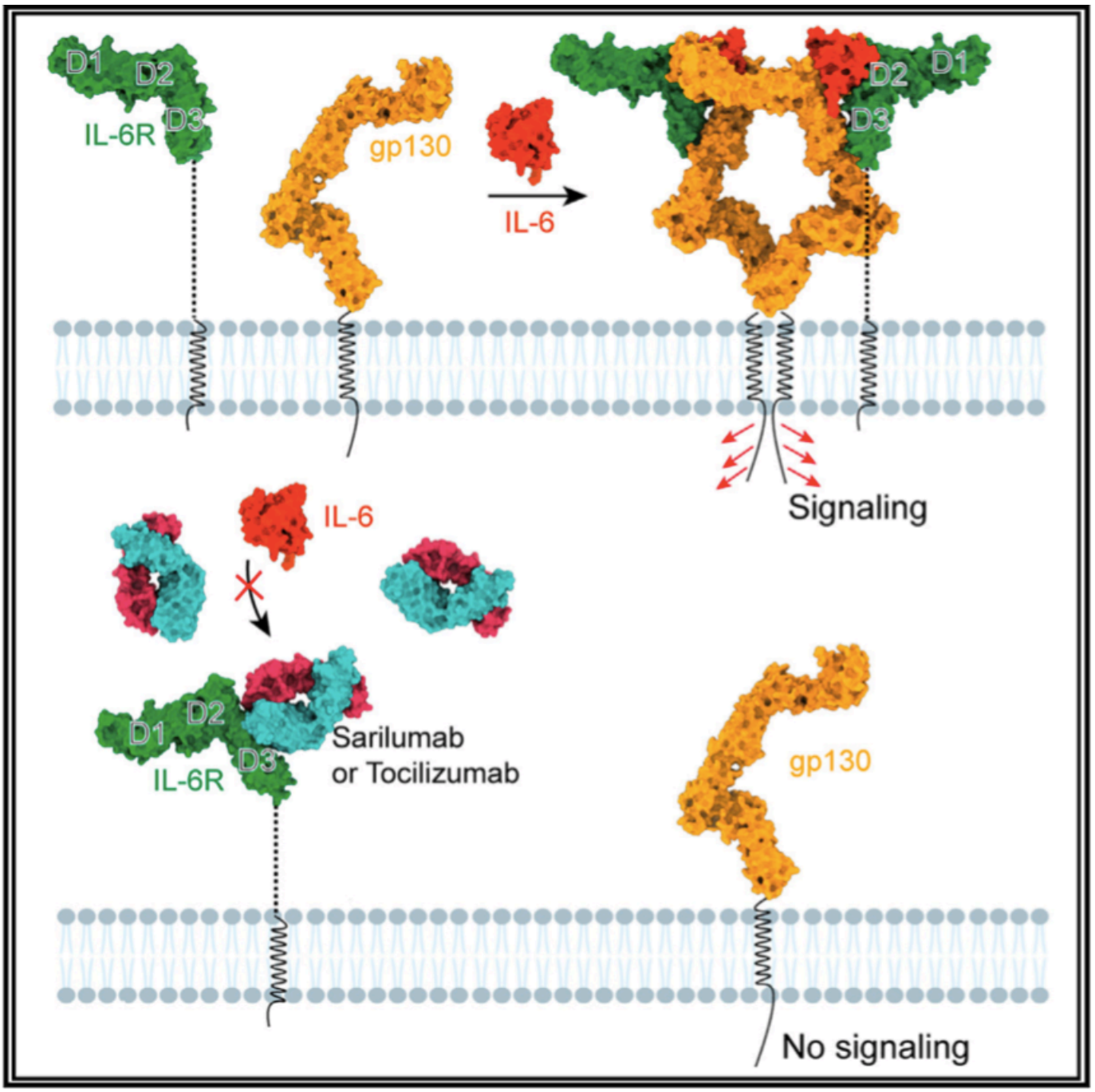

ADAM17
gp130
IL-6
mIL-6R
IL-6 + sIL-6R
Olokizumab
Sirukumab
Clazakimumab
MEDI5117
Siltuximab
IL-6 classic signalling
IL-6
Tocilizumab
Sarilumab
Satralizumab
Vobarilizumab
Levilimab
mIL-6R
gp130
IL-6 intracellular signalling
Tyk2
Tyk2
Jak2
Jak1
Jak1
Jak2
Tyr759
MAPK
SHP2
SOCS3
SFK
PI3K
STAT3
STAT1
YAP
IL-6 Target Genes
Regenerative, anti-inflammatory activities
Defense against bacterial infections
Hepatic acute phase reaction



Interleukin (IL)-6 signaling cascade. Interleukin-6 demonstrates its biological activities only by binding to its specific receptor, IL-6R. This cytokine-receptor complex then associates with the IL-6R β-subunit, gp130, leading to intracellular signaling. Classical IL-6 receptor signaling occurs in cells that express IL-6R and gp130. IL-6 receptor can be proteolytically cleaved from the cell membrane by ADAM17, generating sIL-6R. This mechanism of trans-signaling allows IL-6 to act on cells that lack IL-6R. Both modes of IL-6 receptor signaling lead to gp130 activation of Janus kinases 1 and 2 and

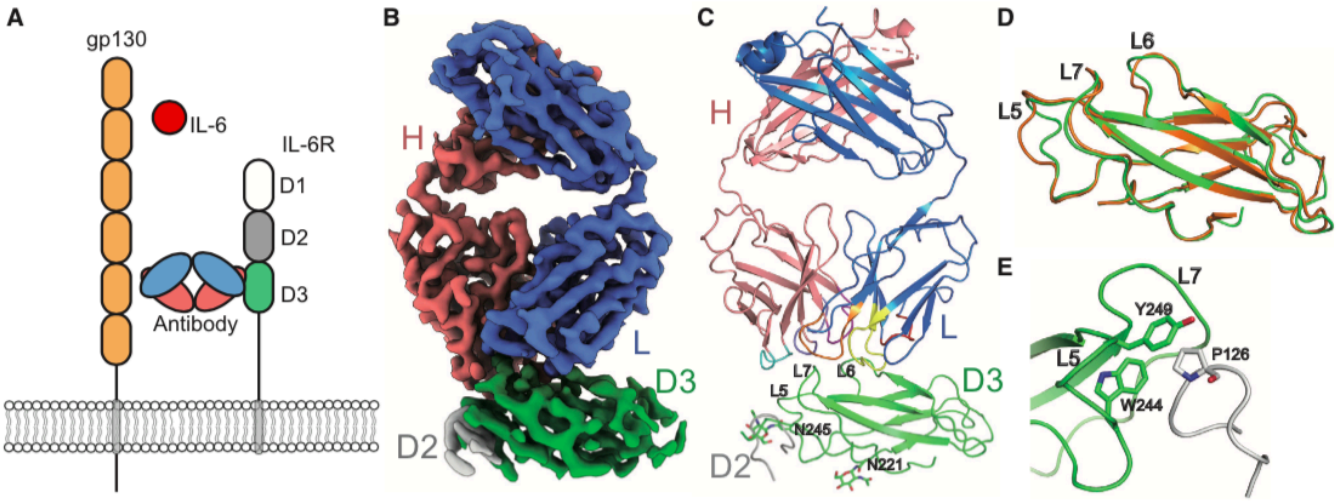
tyrosine kinase 2, and a series of proximal tyrosine residues that activate the STAT1, STAT3, MAPK, and PI3K cascade. In addition to the JAK/STAT pathway, IL-6 signaling also stimulates SFK-dependent signaling, which probably leads to the activation of different transcriptional regulators including YAP. Phosphorylation of the tyrosine motif 759 in the cytoplasmic tail of gp130 is important for negative regulation of IL-6 signal transduction. SHP2 and SOCS3 bind to this phosphotyrosine and attenuate the IL-6 downstream JAK/STAT signaling. In trans-presentation, mIL-6Rα in complex with IL-6 is presented by dendritic cells and sensed by gp130 molecules expressed on T cells. *ADAM17* a disintegrin and metallopeptidase domain 17, *IL-6* interleukin-6, *IL-6R* interleukin-6 receptor, *Jak* Janus kinase, *MAPK* mitogen-activated protein kinase, *mIL-6R* membrane bound IL-6R, *PI3K* phosphatidylinositol-4,5-bisphosphate 3-kinase, *SFK* Src-fam- ily kinase, *SHP2* Src homology 2-containing protein tyrosine phos- phatase 2, *sIL-6R* soluble IL-6R, *SOCS3* suppressor of cytokine sign- aling 3, *STAT* signal transducer and activator of transcription, *Tyk2* Tyrosine kinase 2, *Tyr759* tyrosine residue 759, *YAP* YES-associated protein”

Wang ja kollegat (2024 Kokotekstinä)


D1
D2
D3
IL-6R
gp130
IL-6
D2
D1
D3
Signaling
IL-6
D2
D1
D3
IL-6R
Sarilumab
or Tocilizumab
gp130
No signaling

Highlights

- The structures of Fabs with an ~10 kDa portion of the antigen are determined by cryo-EM
- Both tocilizumab and sarilumab bind to the D3 domain of IL-6R
- Sarilumab and tocilizumab inhibit IL-6/IL-6R signaling by competing for the IL-6 binding site



Cryo-EM analysis of the sarilumab Fab/IL-6R complex

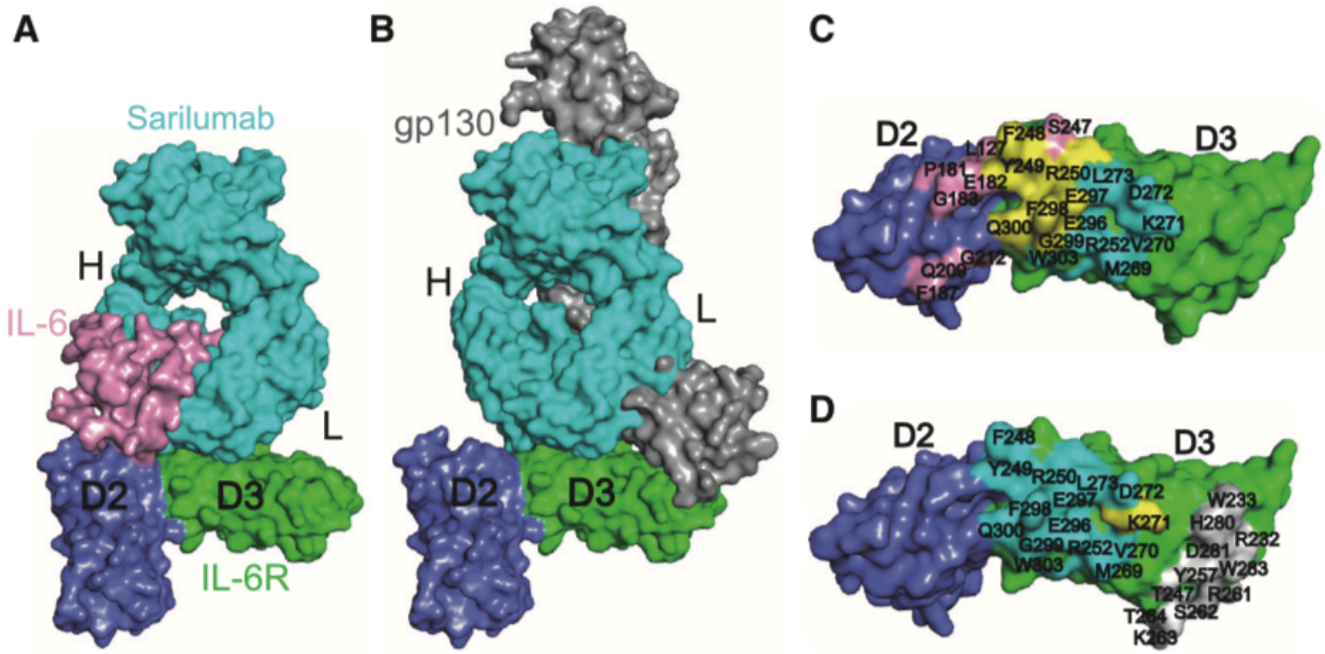
(A) Schematic representation of the IL-6 signaling pathway inhibited by sarilumab.

(B) Cryo-EM reconstruction of the sarilumab Fab/IL-6R complex with each chain colored individually. H, heavy chain; L, light chain; D2 or D3, the second or third domain of IL-6R.

(C) Cartoon representation of the sarilumab fab/IL-6R complex.

(D) Structural comparison of the D3 domain of the

sarilumab Fab/IL-6R structure (green) and the IL-6R structure (orange, PDB: 1N26). L5, L6, and L7 indicate loop 5, loop 6, and loop 7, respectively.
(E) The interactions between the D2 loop (gray) and the D3 domain (green).



Competitive binding of sarilumab with IL-6
(A and B) Superposition of the sarilumab Fab/IL-6R complex with the IL-6/IL-6R (A) or gp130/IL-6R (B) structure by aligning IL-6R. The IL-6/IL-6R and gp130/IL-6R structures were derived from PDB: 1P9M. IL-6, gp130, and sarilumab are colored pink, gray, and cyan, respectively. The D2 and D3 do- mains of IL-6R from 1P9M are shown in blue and green, respectively. IL-6R in the sarilumab Fab/IL- 6R complex is omitted for clarity.

(C) The binding surfaces of IL-6 (pink) and sarilumab (cyan) on IL-6R. The overlapping binding surface is colored yellow.
(D) The binding surfaces of sarilumab (cyan) and gp130 (gray) on IL-6R. The overlapping binding surface is colored yellow.

Tutkijoiden johtopäätökset:

In the present study, we report the structures of IL-6R in com- plex with the therapeutic antibodies sarilumab and tocilizumab. The Fabs of sarilumab and tocilizumab interact with the D3 domain of IL-6R, and the tightly associated D2 loop is essential for stabilizing the binding site. The binding sites of both anti- bodies partly overlap with that of IL-6, which explains the inhib- itory effect. Future antibodies may be designed to target the IL-6 binding surface between the D2 and D3 domains or the gp130 binding surface on the D3 domain. Several other bio- logics targeting IL-6R are known: satralizumab has been approved for treating neuromyelitis optica spectrum disor- der,20,21 and NI-120122 and vobarilizumab23 (a nanobody) are under development. The IL-6R binding mechanisms of these biologics need further investigation.

Therapeutic antibodies are a rapidly growing class of drugs that have been used to treat various human diseases,24 including cancer, autoimmunity, chronic inflammatory diseases, and infectious diseases.

Structural studies provide key information about antibody binding mechanisms and are helpful for rational antibody design.25–31 In the current Fab/antigen structures, only a portion of the multidomain receptor IL-6R (12.4 kDa in the sarilumab Fab/IL-6R structure; $8.5 kDa in the tocilizumab Fab/IL-6R structure) exhibited ordered structures, although the full extracellular domain of IL-6R was used for complex forma- tion. Importantly, membrane receptors and ligands containing either a multidomain or a small extracellular structure, such as PD-L1 and PD-1, constitute one of the most important protein classes targeted by therapeutic antibodies.24 Structural studies of Fabs interacting with a small portion of these receptors or ligands (10 kDa), as exemplified by the current study, would be one typical usage scenario of cryo-EM analysis in future therapeutic antibody development.”

Sarilimumabin farmakologia

Sarilimumabin farmakokinetiikka

Pelechas ja kollegat (2019 kokotekstinä)

Regarding the pharmacokinetics of the drug, it has a C_{max} of 2–4 days after administration reaching a steady state within 14–16 weeks. The half-life is concentration-dependent. Thus, for the 150 mg dose is <8 days while for the 200 mg dose it can reach up to 10 days. No dose-adjustments are required for patients with hepatic or renal impairment as it is not excreted by the hepatic or renal systems. Non-detectable levels of the drug can be achieved 28 days after discontinuation for the 150 mg dosage scheme or 43 days after the discontinuation of the 200 mg dosage scheme.[20]

Xu ja kollegat (2019 Kokotekstinä)

Key Points

Using data from 1770 patients with rheumatoid arthritis treated with sarilumab in clinical trials, a population-pharmacokinetic model was developed to describe the pharmacokinetics of sarilumab and impact of patient characteristics on pharmacokinetic variability

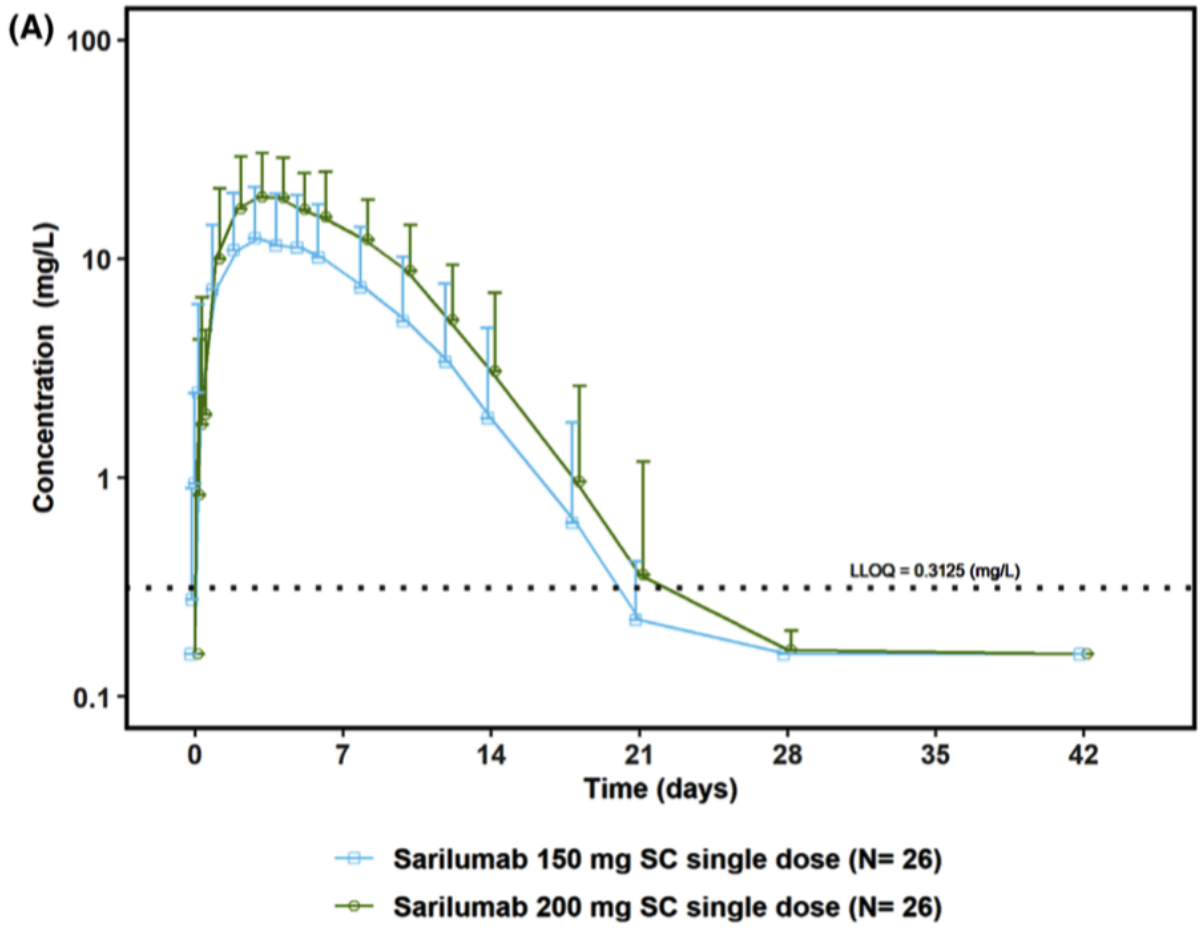
The pharmacokinetics of sarilumab is described by a two-compartment model with first-order absorption and parallel linear and nonlinear Michaelis–Menten elimination

We found limited clinical relevance of body weight on sarilumab exposure; no adjustment in sarilumab dose is required for body weight or any other patient characteristics assessed

Tutkijoiden johtopäätökset:
“The pharmacokinetics of sarilumab was described by a two- compartment model with first-order absorption and parallel linear and nonlinear (M–M) elimination, which allowed for characterization of sarilumab pharmacokinetics in the target patient population of patients with RA, and estimation of exposure in individual patients. Compared with sarilumab 150 mg

q2w, the 200-mg q2w dose resulted in more pro- nounced saturation of the nonlinear clearance pathway over the dosing interval and, hence, a greater than dose-proportional increase in exposure over this dose range. Increas- ing the sarilumab dose by one-third from 150 mg q2w to 200 mg q2w resulted in a twofold increase in AUC0–14d. Body weight, ADA status, sarilumab drug product, albumin, sex, CrCl, and baseline CRP, but not age, race, concomitant treatments, or liver function tests, were identified as significant covariates influencing sarilumab pharmacokinetics. Evidence indicates that the impact of these covariates on exposure does not translate into clinically meaningful differences in efficacy or safety. Therefore, no adjustment in the sarilumab dose is required for body weight or any of the other patient characteristics assessed, including age, sex, and race. “

Paccaly ja kollegat (2021 Kokotekstinä)



Paccaly ja kollegat (2021 Kokotekstinä)

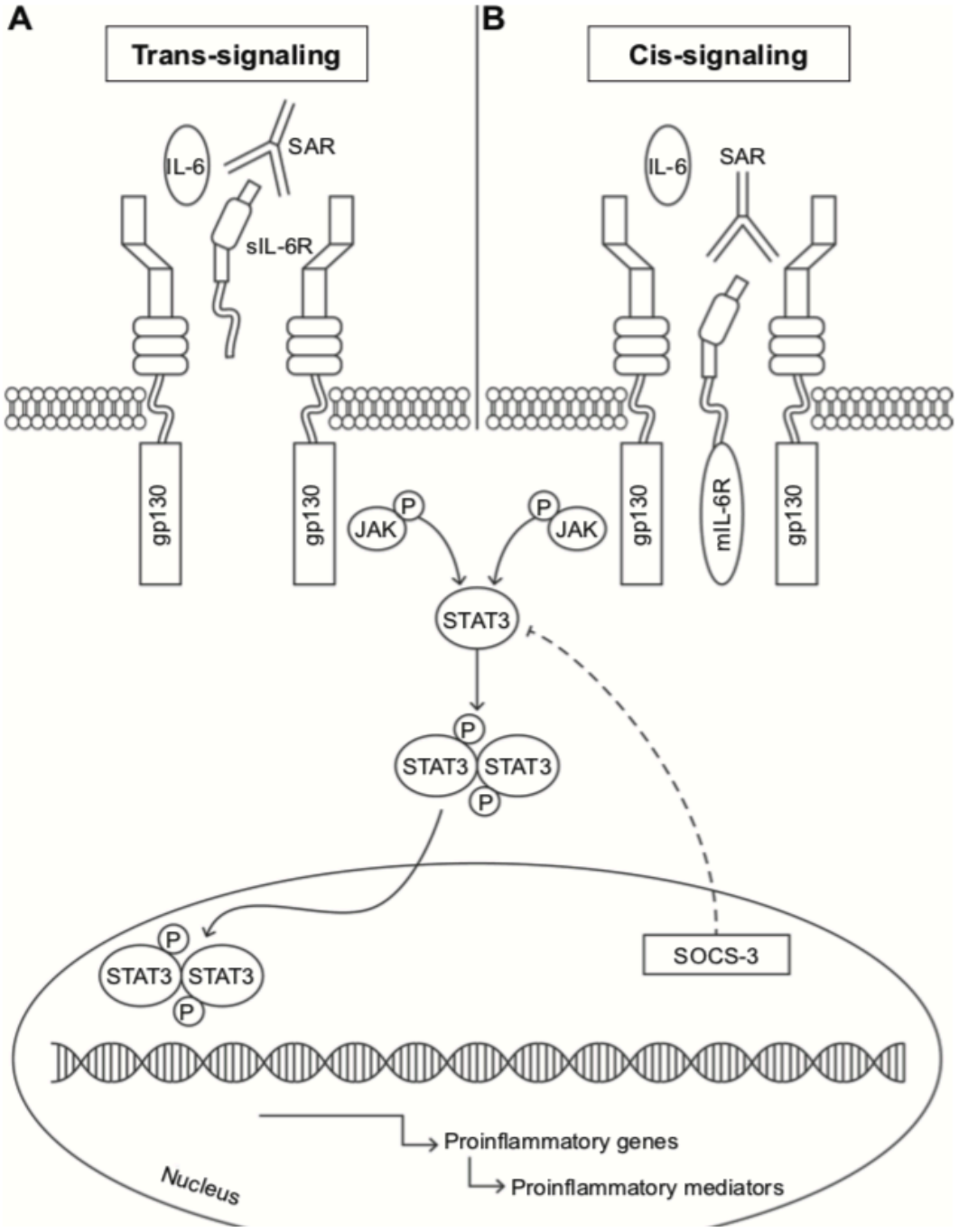
Tutkijoiden johtopäätökset:
“In summary, the drug concentration-time profiles following single doses of subcutaneous sarilumab (150 and 200 mg) and intravenous tocilizumab (4 and 8 mg/kg) were indicative of target-mediated drug disposition and concentration-dependent elimination. Maximal drug effect on the pharmacodynamic biomarkers (IL-6, sIL-6R, CRP, and absolute neutrophil count) was achieved at the low and high doses evaluated here. The pharmacokinetic and pharmacodynamic data provide support for the elevation in IL-6 and sIL-6R values in

serum as being a secondary effect of IL-6R blockade because of loss of IL-6R-mediated clearance. Overall, despite differences in pharmacokinetic, the onset of the increases in IL-6 and sIL-6R was similar for subcutaneous sarilumab and intravenous tocilizumab. A rapid decrease in CRP and in absolute neutrophil count occurred, with an onset that was similar regardless of the dose and route of administration of the anti-IL-6R drug. Maximal decrease in CRP (indicator of efficacy) correlated with circulating drug concentrations, while there was maximal decrease in absolute neutrophil count saturated with drug concentrations. The effect on absolute neutrophil count is in agreement with the hypothesis that anti- IL-6R drugs promote neutrophil margination from the systemic circulation to the vascular walls or other tissue. Exploratory markers for joint inflammation (CRPM (= CRP metabolite), C1M, and C3M) decreased in a dose-dependent manner. The effect of both anti-IL-6R drugs, subcutaneous sarilumab and intravenous tocilizumab, on pharmacodynamic biomarkers and safety is consistent with previous study results of rheumatoid arthritis patients administered an IL-6 inhibitor.”

Kim (2015 Kokotekstinä)

Name	Manufacturer	Clinicalstage	Target	Structure
Tocilizumab	JW Pharmaceutical	IV	sIL-6R mIL-6R	 humanized mAb
Sarilumab	Sanofi/Regeneron	III	sIL-6R mIL-6R	 human mAb

Raimondo ja kollegat (2017 Kokotekstinä)

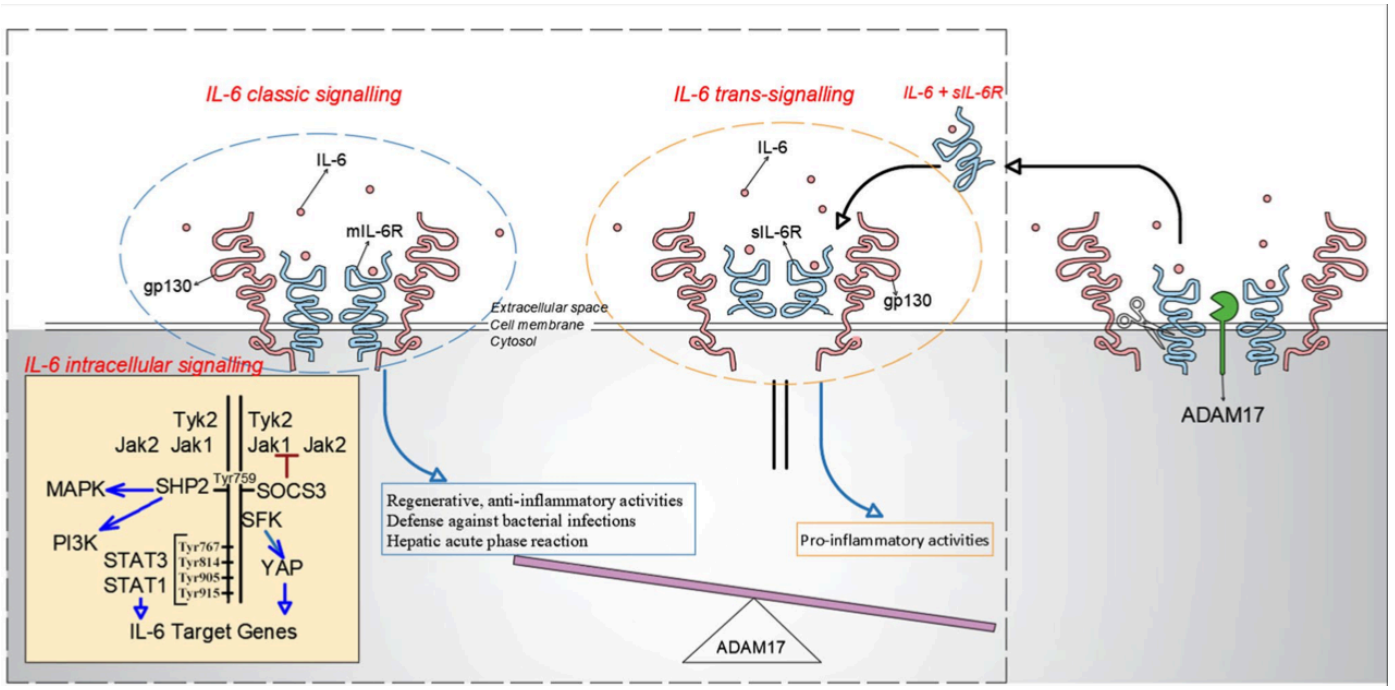


IL-6 receptor trans and cis-signaling pathway and its blockade by sarilumab.

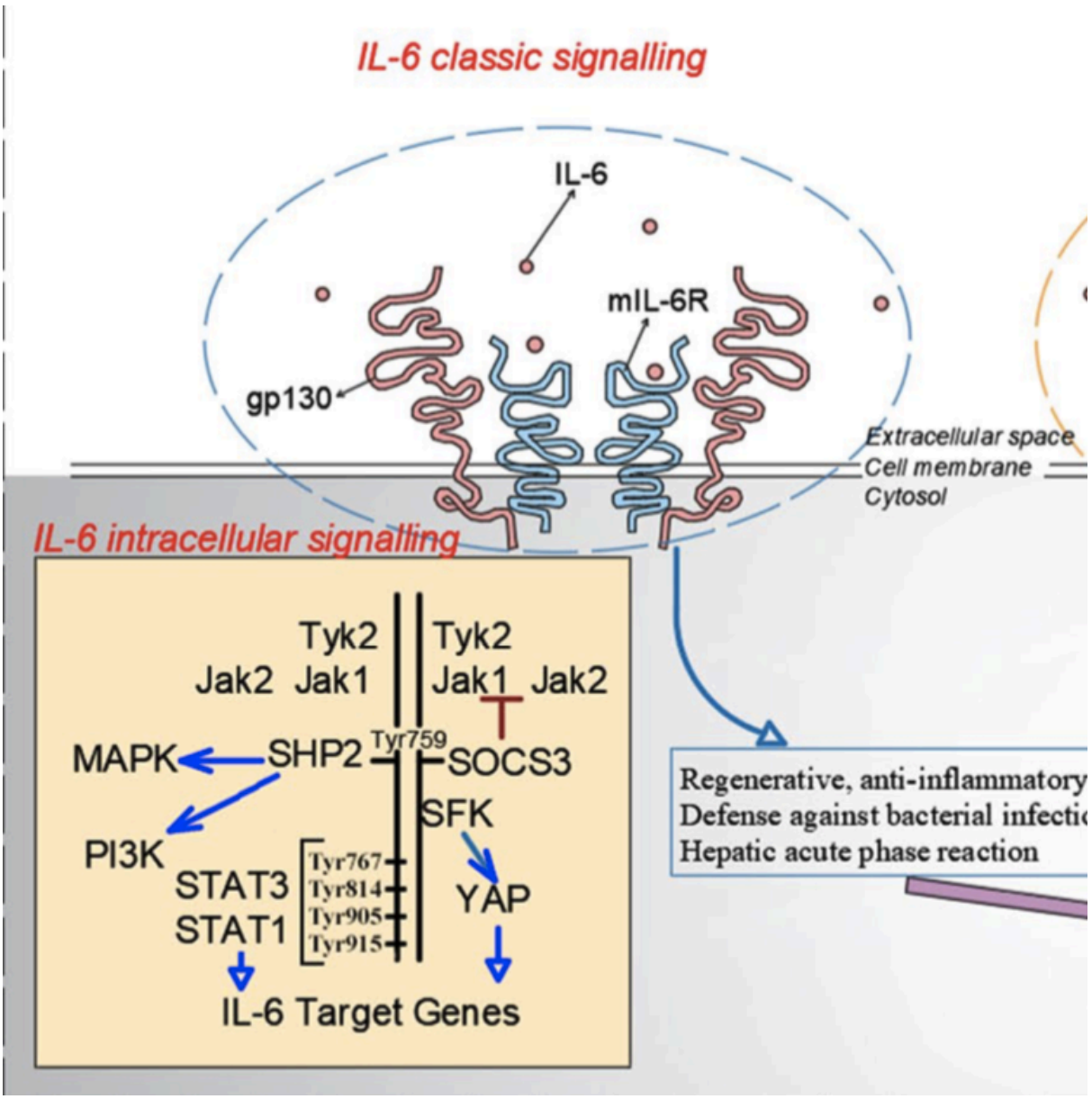
Abbreviations: gp130, glycoprotein 130; IL-6, interleukin-6; JAK, Janus family tyrosine kinase;

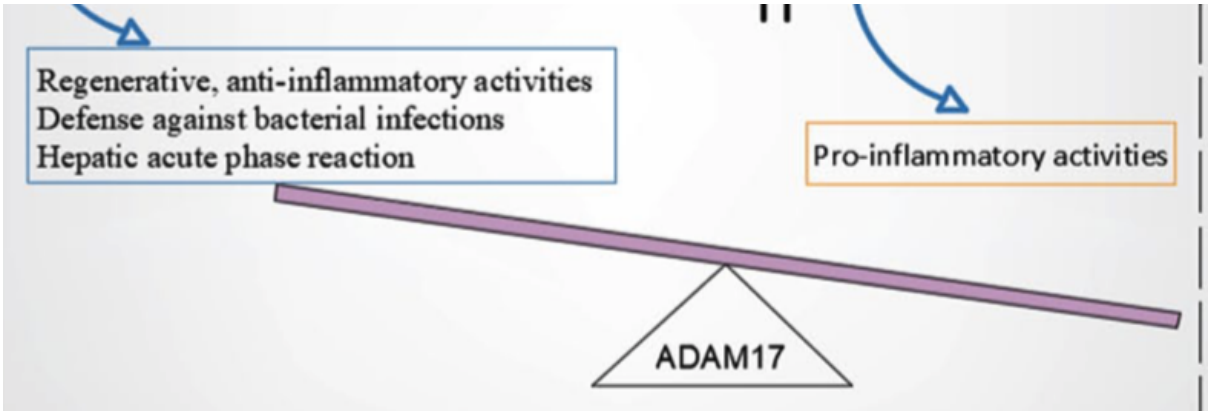
mIL-6R, membrane-bound interleukin-6 receptor; SAR, sarilumab; sIL-6R, soluble interleukin-6 receptor; STAT, signal transducer and activator of transcription; SOCS-3, suppressor of cytokine signaling 3; P, phosphoryl group.

Avci ja kollegat (2018 Kokotekstinä)



Kuvan suurennokset:


IL-6 classic signalling
IL-6
mIL-6R
gp130
Extracellular space
Cell membrane
Cytosol
IL-6 intracellular signalling
Tyk2
Jak2
Jak1
Tyk2
Jak1
Jak2
MAPK
SHP2
Tyr759
SOCS3
SFK
PI3K
STAT3
STAT1
Tyr767
Tyr814
Tyr905
Tyr915
YAP
IL-6 Target Genes
Regenerative, anti-inflammatory
Defense against bacterial infecti
Hepatic acute phase reaction


Regenerative, anti-inflammatory activities
Defense against bacterial infections
Hepatic acute phase reaction
Pro-inflammatory activities
ADAM17

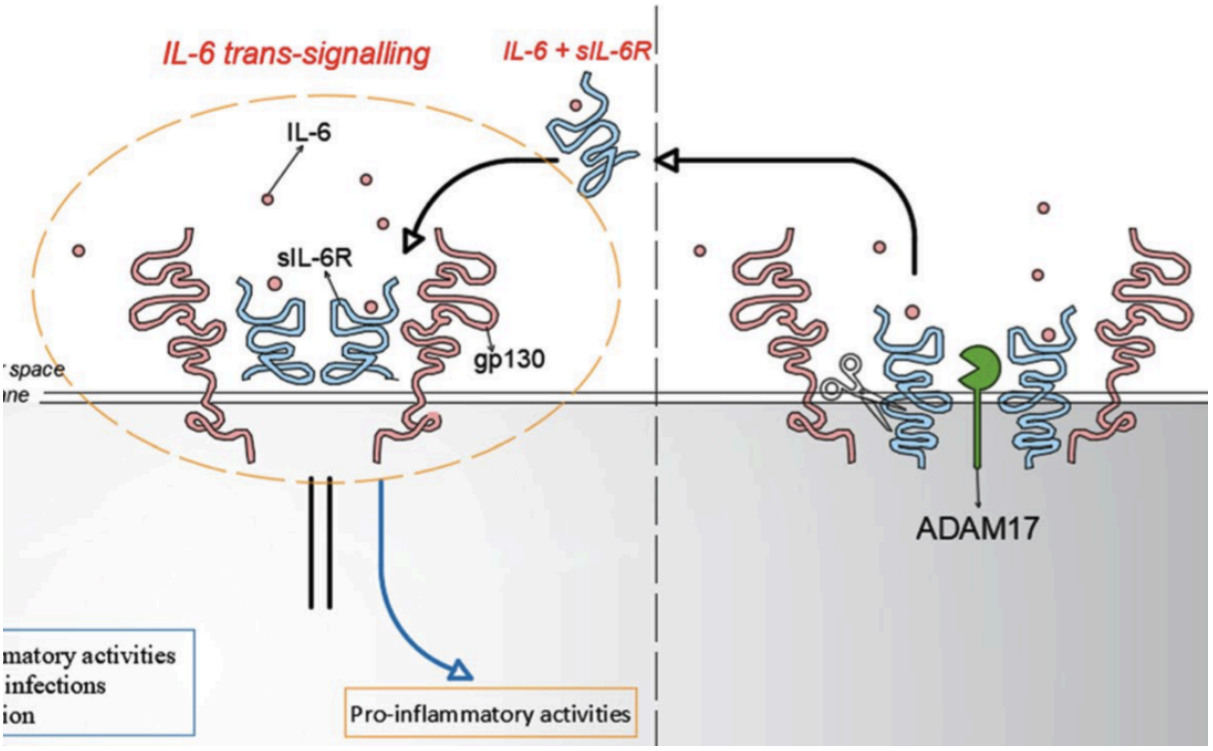


Fig. 1 IL-6 signaling cascade. IL-6 demonstrates its biological activities only by binding to its specific receptor, IL-6R. This cytokine-receptor complex then associates with the IL-6R β-subunit, gp130, leading to its dimerization and intracellular signaling. Classical IL-6 receptor signaling occurs in cells that express IL-6R and gp130. IL-6R can be proteolytically cleaved from the cell membrane by ADAM17, generating sIL-6R. This mechanism of trans-signaling allows IL-6 to act on cells that lack IL-6R. Both modes of IL-6 receptor signaling lead to gp130 activation of Janus kinases 1 and 2 and Tyrosine kinase 2, and a series of proximal tyrosine residues that activate STAT1, STAT3, MAPK and PI3K cascade. Besides the JAK/ STAT pathway, IL-6 signaling also stimulates SFK-dependent signal- ing, which probably leads to the activation of different transcriptional regulators including YAP. Phosphorylation of the tyrosine residue 759 in the cytoplasmic tail of gp130 is important for negative regu- lation of IL-6 signal transduction. SHP2 and SOCS3 bind to this phosphotyrosine and attenuate the IL-6 downstream JAK/STAT sign- aling. *ADAM17* a disintegrin and metallopeptidase domain 17, *IL-6* interleukin-6, *IL-6R* interleukin-6 receptor, *Jak* Janus kinases, *MAPK* mitogen-activated protein kinase, *mIL-6R*

membrane bound IL-6R, *PI3K* phosphatidylinositol-4,5-bisphosphate 3-kinase, *SFK* Src-fam- ily kinase, *SHP2* Src homology 2-containing protein tyrosine phos- phatase 2, *sIL-6R* soluble IL-6R, *SOCS3* suppressor of cytokine sign- aling 3, *STAT* signal transducer and activator of transcription, *Tyk2* Tyrosine kinase 2, *Tyr759* tyrosine residue 759, *YAP* YES-associated protein

Vasta-aineiden muodostus sarilimumabia kohtaan nivelreumassa

Tanaka ja kollegat (2021 Kokotekstinä)

Tutkijoiden johtopäätös:

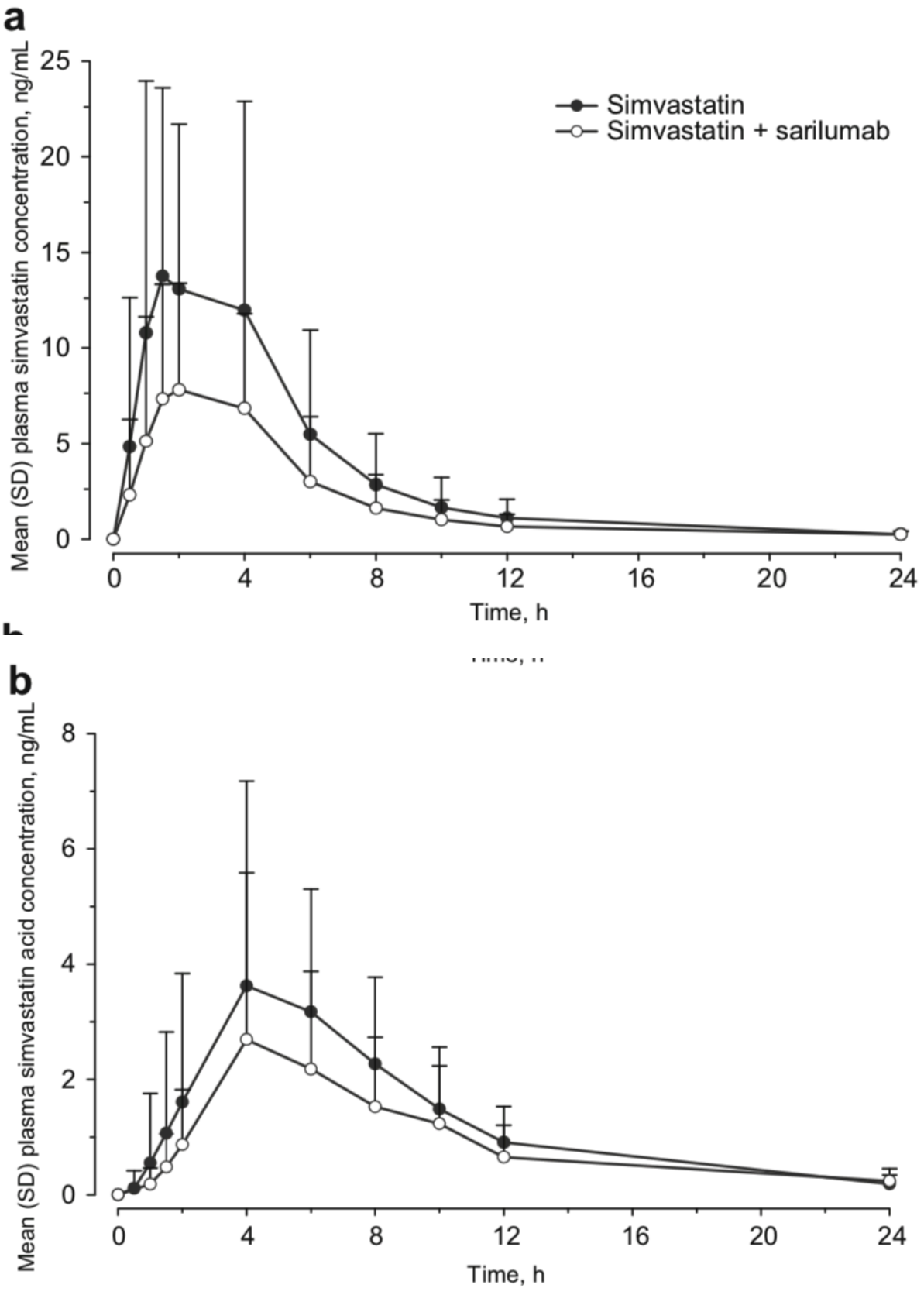
“In conclusion, when sarilumab was administered as monotherapy or in combination with MTX or non-MTX csDMARDs in Japanese patients with RA, treatment-emergent ADAs occurred infrequently at a low titre and did not alter the safety or efficacy of sarilumab 150mg or 200mg q2w. These results support the use of sarilumab at the recommended dose of 200 mg q2w as monotherapy or in combination with csDMARDs in Japanese patients with RA.”

Sarilumabin vaikutus muiden lääkeaineiden metaboliaan

Sarilumabi ja simvastatiini

Bong Lee ja kollegat (2017 Kokotekstinä) antoivat 19 nivelreumaa sairastavalle simvastatiinia (40 mg) vuorokausi ennen sarilimumabin (200 mg) antamista sekä toisen annoksen simvastatiinia (40 mg) seitsemän vuorokautta sarilimumabin antamisen jälkeen. Simvastatiinin antamisen jälkeen mitattiin koehenkilöiden plasman simvastatiinipitoisuus sekä simvastatiinin aineenvaihduntatuotteen hydroksisimvastatiinin plasmapitoisuus.

Tulokset: Sarilimabi pienensi plasmassa simvastatiinin ja hydroksisimvastatiinin pitoisuutta.



Mean a simvastatin and b b-hydroxy-simvastatin acid plasma concentration–time profiles after administration of simvastatin 40

mg 1 day before and 7 days after subcutaneous injection of sarilumab 200 mg (N = 19). Pharmacokinetic parameters for two patients were not calculated because of sample stability issues during bioanalysis. SD standard deviation

Tutkijoiden johtopäätös:

Sarilumab treatment resulted in a reduction in exposure of simvastatin, consistent with reversal of IL-6- mediated CYP3A4 suppression in patients with active RA, as was reported for tocilizumab with simvastatin and for sirukumab with midazolam.

Key Points
Interleukin (IL)-6 levels are elevated in inflammatory conditions, including rheumatoid arthritis (RA), leading to reduced cytochrome P450 (CYP) 3A4 activity and higher CYP3A4 substrate concentrations.
Sarilumab, a human monoclonal antibody blocking the IL-6 receptor-α (IL-6Rα), restores CYP3A4 activity, which results in decreased exposure of the sensitive CYP3A4 substrate simvastatin and its active metabolite β-hydroxy-simvastatin acid in patients with active RA.
These findings are consistent with those reported for the IL-6R antagonists tocilizumab and sirukumab.

Sarilumabi nivelreuman hoidossa

June ja Olsen (2016 Kokotekstinä)

Tutkijoiden johtopäätökset:
“Phase II and III clinical trials have established that sarilumab is an effective treatment for patients with moderate to severe rheumatoid arthritis who have had an incomplete response to methotrexate. The efficacy and safety profiles are very similar to the available IL6 targeting drug tocilizumab, and include significant decreases in progression of structural damage. Sarilumab was not effective in AS, which is also similar to findings with tocilizumab. This is despite the fact that circulating IL-6 levels correlate with disease features in AS, and is another reminder that predictions based on biologic data do not always translate into therapeutic effects. Infections were the most common adverse events with sarilumab , similar to findings with TNF

blockade, while neutropenia, transaminitis and elevated cholesterol are more specific for the IL6 pathway.”

Scott (2017 Abstrakti)

Boyce ja kollegat (2018 Abstrakti) esittivät yhteenvetoartikkelin sarilumabin käytöstä nivelreuman hoidossa.

Tutkijoiden johtopäätökset:
“Data from 4 clinical studies demonstrate that sarilumab (150 and 200 mg every 2 weeks) plus methotrexate was more effective than placebo plus methotrexate and that

monotherapy with sarilumab 200 mg every 2 weeks was more effective than adalimumab monotherapy in patients with rheumatoid arthritis who cannot take methotrexate. The risks for adverse effects were similar among sarilumab, adalimumab (monotherapy), and placebo groups, but placebo was associated with fewer withdrawals caused by adverse effects. In comparison with historical data, the overall efficacy, safety, and cost of sarilumab appear to be similar to those for tocilizumab and other biologic disease-modifying anti-rheumatic drugs. Therefore, sarilumab is an effective biologic disease-modifying anti-rheumatic drug that may be used as an alternative to tocilizumab, other biologic disease-modifying anti-rheumatic drugs , or tofacitinib in patients with moderate to severely active rheumatoid arthritis who have not responded adequately to prior conventional synthetic disease-modifying anti-rheumatic drugs therapy or TNFis. Additional long-term data are needed to confirm the efficacy, safety, cost, and place of sarilumab in rheumatoid arthritis .”

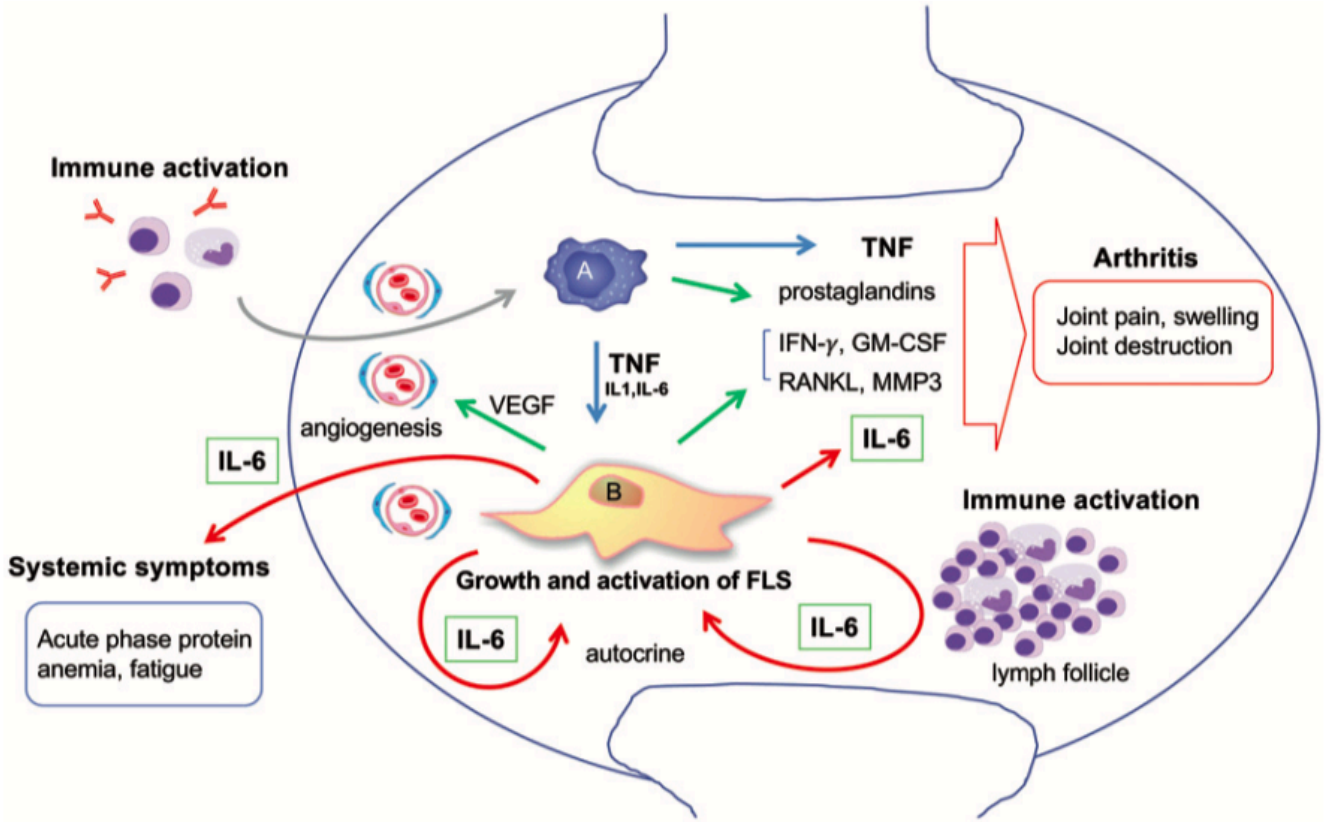
Avci ja kollegat (2024 Kokotekstinä)

Key Points

- The role of the interleukin (IL)-6 pathway in the treatment of rheumatoid arthritis has the potential to progress with different inhibitions of this pathway such as IL-6 cytokine blockade and trans-signaling blockade, in addition to IL-6 receptor blockers.
- The favorable efficacy/safety profile of tocilizumab has prompted the rapid development of biosimilars and new potent IL-6 receptor inhibitors.
- The potential impact of modalities targeting different antigenic sites of the IL-6 cytokine on efficacy and safety data highlights the importance of both clinical and basic research in revealing the true potential of this pathway.
- The efficacy demonstrated by olokizumab in phase III studies, along with its open-label extension safety data, has shown that direct IL-6 inhibitors may also have an important place in this field.

Kaavakuva IL-6:n osallistumisesta nivelreumassa niveltulehdukseen

Ogata ja kollegat (2019 Kokotekstinä)



The pathogenic role of IL-6 in RA synovitis. There are the two main cellular components in the synovium. Type A synoviocytes are bone marrow derived macrophage-like cells. Type B synoviocytes are residential fibroblast like cells also known as FLS. In the rheumatoid synovium, FLS mainly contributes to arthritis by producing IL-6, RANKL, MMP3, GM-CSF, IFN-c, and VEGF. TNF and IL-6 stimulate FLS autocrinally and induce tumor-like proliferation of FLS. Local arthritic symp- toms are generated by the collaboration of IL-6 with TNF- and FLS-derived cytokines. Systemic symptoms are caused by IL-6. IL-6 also contributes to immune acti- vation and leads to synovitis, resulting in a vicious circle.

Ogata ja kollegat (2019 Kokotekstinä)

Favalli (2020 Kokotekstinä)

Key Summary Points

Interleukin-6 (IL-6) plays an important role in the development of rheumatoid arthritis (RA) disease state within the joint.

Beyond the joint, IL-6 is also linked to extra-articular manifestations and common comorbidities in patients with RA.

Interleukin-6 receptor (IL-6R) blockade treatment with the humanized monoclonal antibody (mAb) tocilizumab, and more recently with the human mAb sarilumab, has been shown in clinical studies to be an important advancement for treating RA-associated disease manifestations within and beyond the joint.

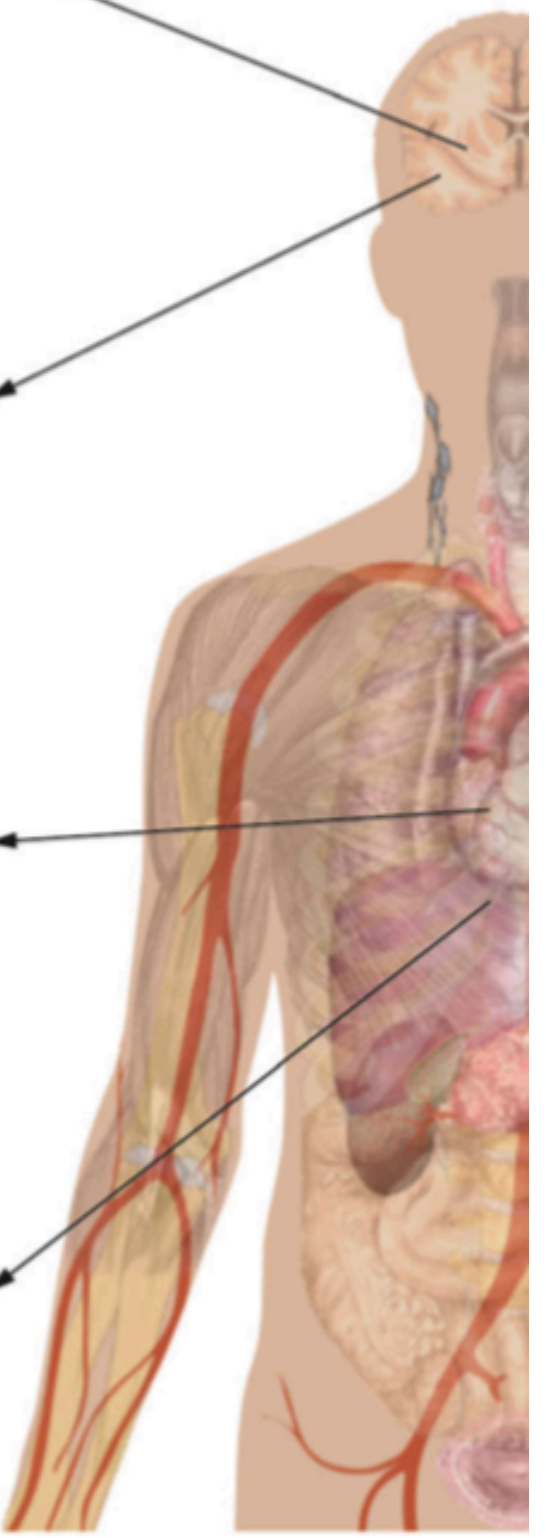
The benefits of IL-6R blockade seem to extend to improvements in many of the extra-articular manifestations of the condition, such as pain, fatigue, and anemia, as well as potentially beneficial effects on certain comorbidities, such as improvements in glycemic control in patients with RA and comorbid diabetes, improvements in bone mineral density in patients with RA prone to osteoporosis, and improvements in mood disorders.

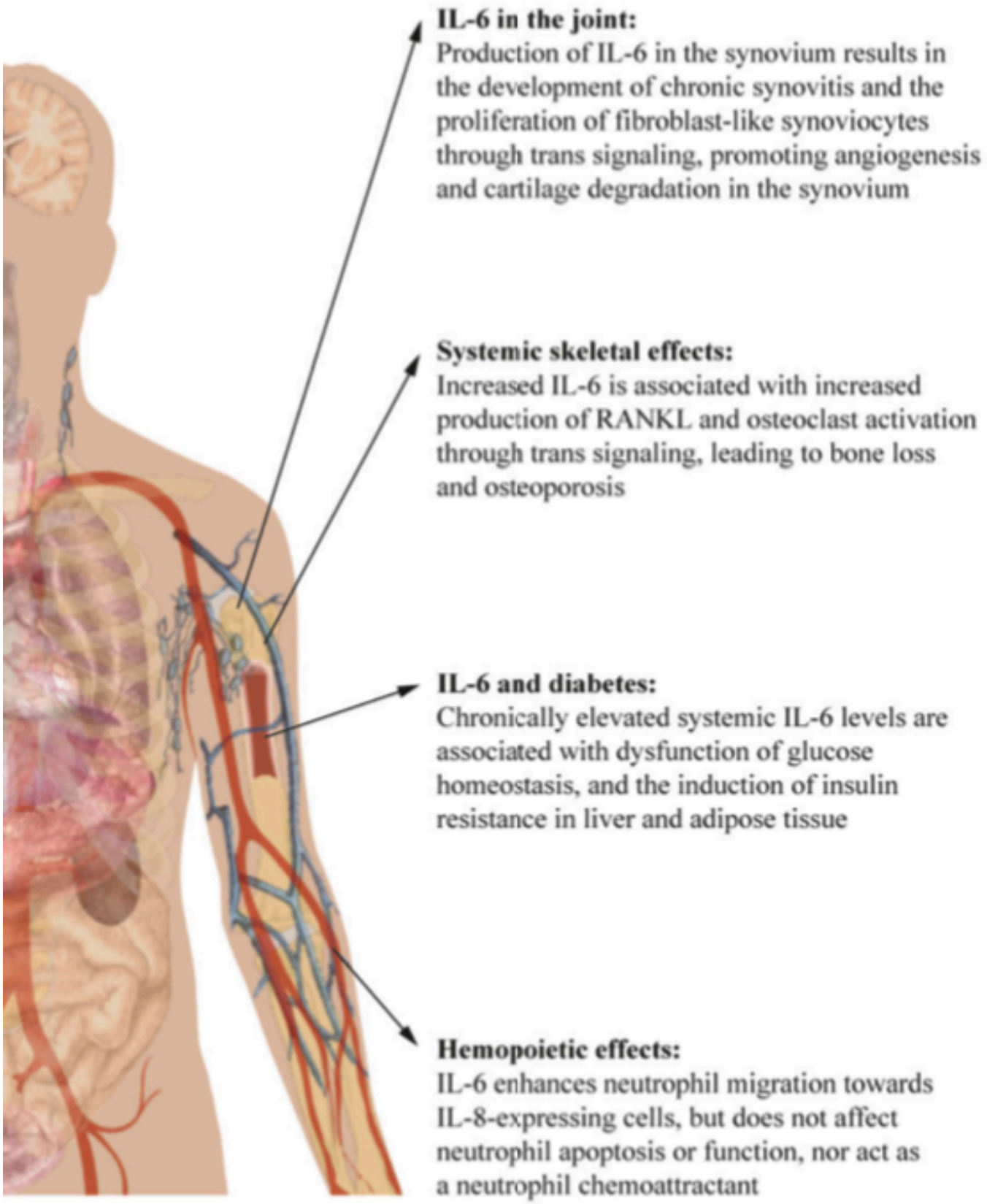
IL-6 and mood:
Elevated IL-6 levels have been associated with major depressive disorder. Hyperactivation of the HPA axis by IL-6 signaling is a possible mechanism for mood disorders and depression

CNS effects:
IL-6 production correlates with reports of fatigue in patients with RA, possibly influenced through dysregulation of the HPA axis

Cardiovascular effects:
IL-6-induced chronic elevation of acute-phase proteins like CRP, promote atherosclerosis and increase the risk of cardiovascular disease

IL-6 in the liver:
Elevated IL-6 enhances classic and trans signaling in hepatocytes to promote production of the acute-phase reactant CRP; IL-6 may contribute to RA-associated anemia through dysregulation of hepcidin expression





IL-6 as a pleiotropic cytokine.

CNS central nervous system,

CRP C-reactive protein,

HPA hypothalamic–pi- tuitary–adrenal,

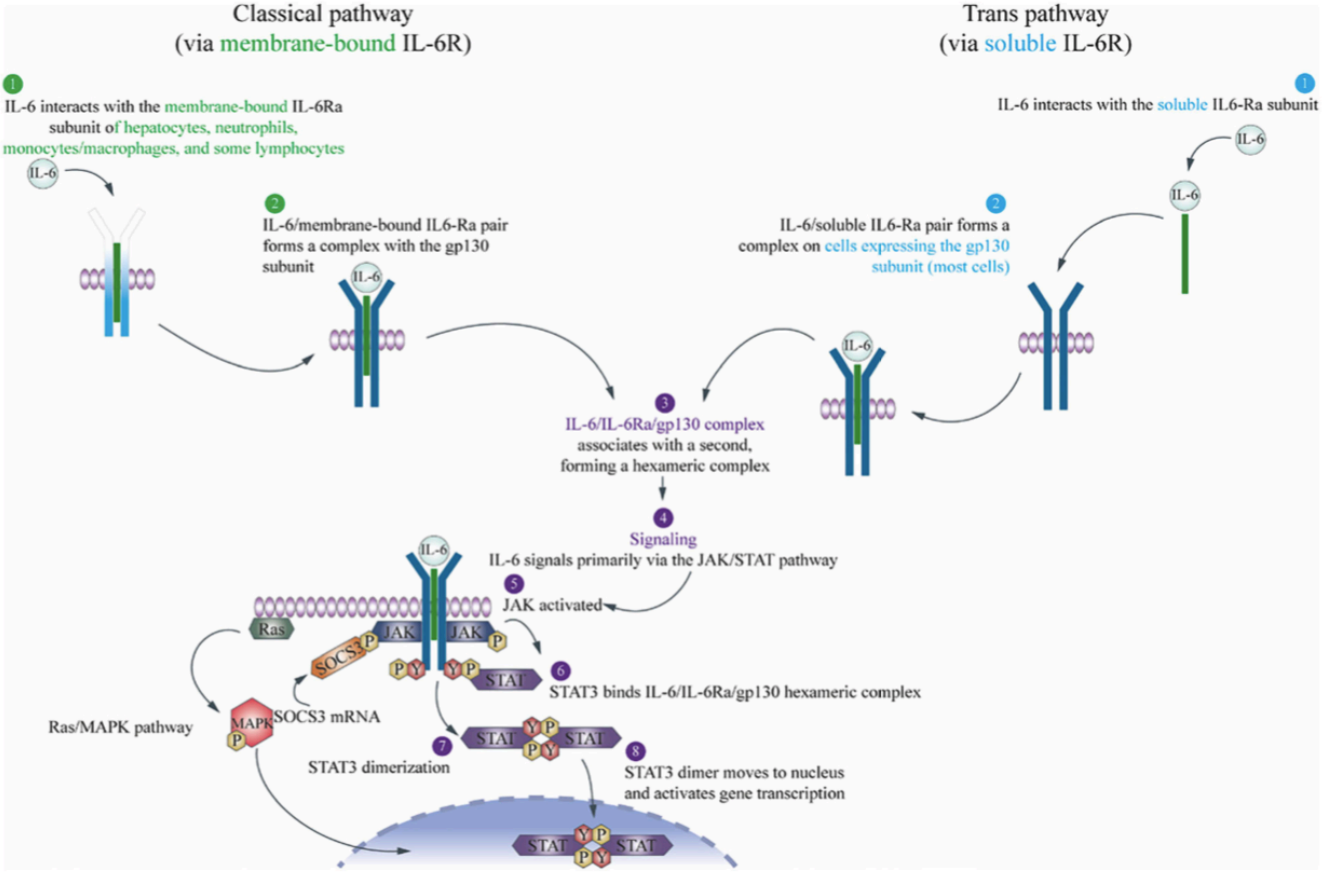
IL-6 interleukin-6,

IL-8 interleukin-8,

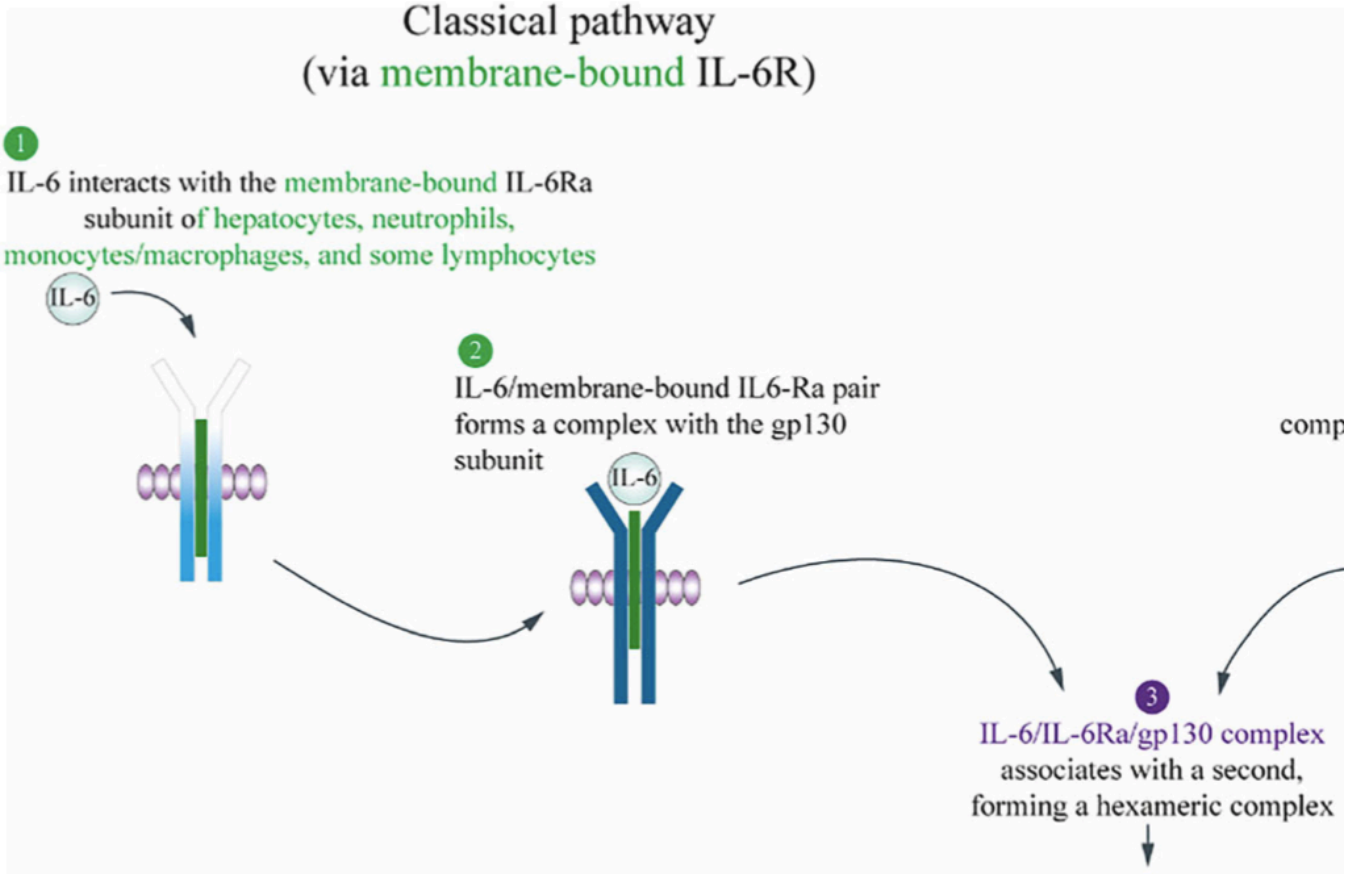
RA rheumatoid arthritis,

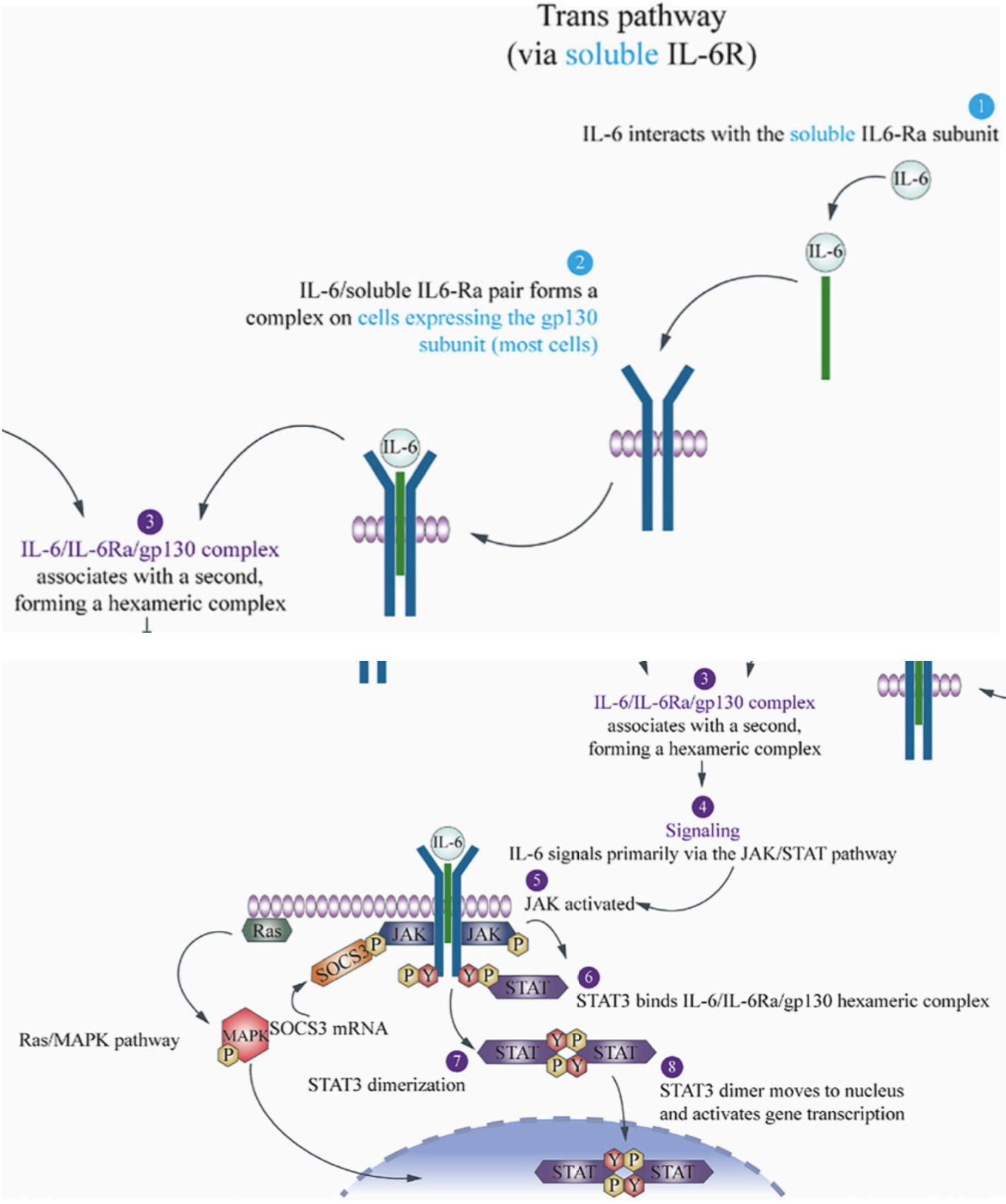
RANKL Receptor Activator of Nuclear Factor-kappaB Ligand.

Favalli (2020 Kokotekstinä)


Classical pathway
(via membrane-bound IL-6R)
Trans pathway
(via soluble IL-6R)
1
IL-6 interacts with the membrane-bound IL-6Ra subunit of hepatocytes, neutrophils, monocytes/macrophages, and some lymphocytes
IL-6
2
IL-6/membrane-bound IL6-Ra pair forms a complex with the gp130 subunit
IL-6
1
IL-6 interacts with the soluble IL6-Ra subunit
IL-6
IL-6
2
IL-6/soluble IL6-Ra pair forms a complex on cells expressing the gp130 subunit (most cells)
IL-6
3
IL-6/IL-6Ra/gp130 complex associates with a second, forming a hexameric complex
4
Signaling
IL-6 signals primarily via the JAK/STAT pathway
IL-6
5
JAK activated
Ras
JAK
JAK
P
SOCS3
P
Y
P
Y
STAT
6
STAT3 binds IL-6/IL-6Ra/gp130 hexameric complex
Ras/MAPK pathway
MAPK
P
SOCS3 mRNA
7
STAT3 dimerization
STAT
Y
P
P
Y
STAT
8
STAT3 dimer moves to nucleus and activates gene transcription
STAT
Y
P
P
Y
STAT

Suurennos:


Classical pathway
(via membrane-bound IL-6R)
1
IL-6 interacts with the membrane-bound IL-6Ra subunit of hepatocytes, neutrophils, monocytes/macrophages, and some lymphocytes
IL-6
2
IL-6/membrane-bound IL6-Ra pair forms a complex with the gp130 subunit
IL-6
comp
3
IL-6/IL-6Ra/gp130 complex associates with a second, forming a hexameric complex


Trans pathway
(via soluble IL-6R)
1
IL-6 interacts with the soluble IL6-Ra subunit
IL-6
IL-6
2
IL-6/soluble IL6-Ra pair forms a
complex on cells expressing the gp130
subunit (most cells)
IL-6
3
IL-6/IL-6Ra/gp130 complex
associates with a second,
forming a hexameric complex
3
IL-6/IL-6Ra/gp130 complex
associates with a second,
forming a hexameric complex
4
Signaling
IL-6 signals primarily via the JAK/STAT pathway
IL-6
5
JAK activated
Ras
JAK
JAK
SOCS3
P
P
Y
Y
P
STAT
6
STAT3 binds IL-6/IL-6Ra/gp130 hexameric complex
Ras/MAPK pathway
MAPK
P
SOCS3 mRNA
7
STAT3 dimerization
STAT
Y
P
STAT
P
Y
8
STAT3 dimer moves to nucleus
and activates gene transcription
STAT
Y
P
STAT
P
Y

The classical (or cis-) and trans-signaling pathways of IL-6.

gp130 glycoprotein 130,

IL-6 interleukin-6,

IL- 6Ra interleukin-6 receptor alpha,

JAK Janus kinase

MAPK mitogen-activated protein kinase,

P phosphate,

SOCS3 suppressor of cytokine signaling 3,

STAT3 signal transducer and activator of transcription 3,

Y tyrosine

Favalli (2020 Kokotekstinä)

Tutkijoiden johtopäätökset:

“Rheumatoid arthritis is a chronic, debilitating autoimmune dis- order characterized by inflammation of the synovial joint tissues. Rheumatoid arthritis pathogenesis is driven by a complex network of proinflammatory cells and cytokines, and among the actors involved in the network of rheumatoid arthritis , IL-6 seems to be the most pleiotropic cytokine with the greatest number of downstream influences. IL-6 can bind to various cell types around the body, and

increased production of IL-6 can lead to heightened activation of cells within the joint, contributing to the rheumatoid arthritis disease state. However, beyond the joint, IL-6 is also known to con- tribute to various extra-articular manifestations and life-threatening comorbidities tightly linked to an existing rheumatoid arthritis condition.

IL-6R blockade treatments have been shown to cause clinically important improvements in rheumatoid arthritis clinical endpoints in patients with mild to severe activerheumatoid arthritis . The leading approved IL-6R inhibitors, sarilumab and tocilizumab, have produced statistically significant improvements in the signs and manifestations of rheumatoid arthritis when used as monotherapy or in combination with csDMARDs, as defined by the ACR, CRP and ESR, CDAI, and radiographic progression measures, cementing IL-6R blockade as a robust treatment option for rheumatoid arthritis . However, beyond the joint, the extra-articular manifestations linked to rheumatoid arthritis including anemia, morning stiffness, pain, weight and body composition, and comorbidities linked to rheumatoid arthritis that include osteo- porosis, CVD and pulmonary disease, infections, depression, T2D, and malignancies have also previously been investigated as IL-6 treatment targets. Clinical evidence in a range of clinical studies has indicated that use of IL-6R blockade with sarilumab or tocilizumab can improve these IL-6-linked conditions

to varying extents, to ultimately improve patient disease states and quality of life. To this end, such findings indicate that sarilumab and tocilizumab can be supported as important treatments for certain extra-articular manifestations and comorbidities of rheumatoid arthritis , in addition to manifestations within the joint. The impacts of IL-6R blockade treatment effects can be observed when explored from both a clinician’s perspective through clinical efficacy outcome measures, and also when viewed from a patient’s perspective through the use of patient-reported outcome assessments, which measure variables including pain, physical functioning, and sleep disturbance.”

Avoimet tutkimukset

Crotti ja kollegat (2018 Kokotekstinä)

Tutkijoiden johtopäätös:
“Providing additional information beyond the usual domains commonly assessed in randomized controlled trials, patient reported outcomes are undoubtedly of great and rising interest in the assessment of rheumatoid arthritis and may be a promising tool for a more holistic evaluation of rheumatoid arthritis . In fact, understanding a patient’s perception of the disease is crucial for the right application of shared decision-making, suggested as an overarching principle by European League Against Rheumatism recommendations on the management of rheumatoid arthritis . Nevertheless, besides the proven psychometric properties, more data are needed for weighing the real predictive capacities of patient reported outcomes on short- and long-term outcomes and for managing potential confounding factors and

discordance between patient and physician perceptions of the disease. Pain and fatigue are reported as the most important symptoms by the majority of rheumatoid arthritis patients, and together with physical function are the most frequently evaluated patient reported outcomes . The link between those patient reported outcomes and depression or anxiety is well described in rheumatoid arthritis , where IL6 plays a crucial role in inducing and worsening mood disturbances by both increasing inflammation and directly affecting nociceptive neurons and the HPA axis. As previously reported for other IL6 blockers, the panel of patient reported outcome data in sarilumab-treated patients is very encouraging toward more comprehensive control of both articular and extra-articular manifestation of rheumatoid arthritis . In particular, sarilumab was highly effective in improving HAQ-DI, SF36 components, and FACIT-F in all rheumatoid arthritis subpopulations, from Mtx- to TNF-inadequate-response patients. Moreover, in the head-to-head comparison provided by the MONARCH study, the effect of sarilumab monotherapy was significantly greater than adalimumab in ameliorating the same patient-reported outcomes, suggesting the potential superiority of IL6 over TNF blockade in the management of patient-related disease outcomes. Additional data from observational real-life research are needed for further confirmation of the potential role of sarilumab in the holistic control of rheumatoid arthritis.”

Choy ja kollegat (2019 Kokotekstinä)

Tutkijoiden johtopäätökset:
“The present indirect comparison was conducted following best practice guidelines and demonstrated that sarilumab SC 200 mg monotherapy has superior efficacy compared with adalimumab, as well as csDMARDs alone, and comparable or better efficacy and similar safety compared with other bDMARDs and tsDMARDs in the csDMARD-IR patient populations. Compared with tocilizumab 8 mg/kg IV, sarilumab 200 mg had similar efficacy and safety.”

Emery ja kollegat (2020 Kokotekstinä)
Tutkijoiden johtopäätös:
“In conclusion, switching from double-blind tocilizumab intravenous or sarilumab subcutaneous to open-label sarilumab subcutaneous produced no new safety concerns and demonstrated sustained clinical efficacy over 96 weeks, as shown by the durability of treatment effect. The safety profile of sarilumab in the open-label extension was generally consistent with that seen in the randomized controlled trial, with long-term sarilumab treatment, and with the anticipated profile of an IL-6 inhibitor.”

“Switching from intravenous to subcutaneous interleukin-6 receptor inhibitor therapy produced no new safety concerns, and clinical efficacy was sustained over 96 weeks of follow-up. These findings alleviate potential concerns over switching route of administration with interleukin-6 receptor inhibitor therapy for rheumatoid arthritis .”

Fleischmann ja kollegat (2021 Kokotekstinä)

Rheumatology key messages

- This report includes >1600 patient-years' follow-up of sarilumab in RA patients refractory to TNFis.
- Sarilumab's tolerability over 5 years was consistent with phase III studies; no new safety concerns arose.
- Efficacy was unaffected by >1 TNFi failure/dose reduction from 200 to 150 mg in most patients.

Tutkijoiden johtopäätökset:
“In conclusion, in patients with RA refractory to TNFi, the long-term safety profile of sarilumab in the open-label extension was consistent with that of the randomized controlled trial and the expected profile of IL-6 blockade over >1600 years of cumulative observation. Efficacy was sustained over 5 years’ follow-up. Sarilumab was an effective treatment option for patients in this population.”
“In patients with RA refractory to TNFi, sarilumab’s long-term term safety profile was consistent with previous clinical studies and post-marketing reports. Efficacy was sustained over 5 years.”

Tanaka ja kollegat (2022 Kokotekstinä) selvittivät sarilumabin vasta-aineiden esiintymistä sarilumabihoidon aikana.

Tutkijoiden johtopäätös:
“In conclusion, when sarilumab was administered as monotherapy or in combination with methotrexate or non-methotrexate conventional synthetic disease-modifying anti-rheumatic drugs (= csDMARDs) in Japanese patients with rheumatoid arthritis, treatment- emergent antidrug antibodies occurred infrequently at a low titre and did not alter the safety or efficacy of sarilumab 150mg or 200mg q2w. These results support the use of sarilumab at the recommended dose of 200 mg q2w as monotherapy or in combination with conventional synthetic disease-modifying anti-rheumatic drugs in Japanese patients with rheumatoid arthritis .”

Tony ja kollegat (2022 Kokotekstinä)

Key messages

- Sarilumab effectively attenuates disease activity of RA patients with inadequate response to janus kinase inhibitors or tocilizumab.
- Safety in patients pretreated with janus kinase inhibitors or tocilizumab was consistent with the anticipated profile of sarilumab.

Tutkijoiden johtopäätös:
“Sarilumab treatment was effective in patients with inaduquate response to JAKi and tocilizumab, with an expectable safety profile and drug retention over 6 months. Confirmation of these promising results should encourage further studies on this treatment sequence, which is of high practical relevance.”

Tanaka ja kollegat (2023 Kokotekstinä) tutkivat jälkikäteen sarilumabin vaikutusta nivelreumaan liittyvässä anemiassa.
Tulokset:

Sarilumabi paransi anemiaa verrattuna lumelääkitykseen.

Tanaka ja kollegat (2024)
Tutkijoiden johtopäätös:
“In conclusion, the proportion of patients with unacceptable pain and uncontrolled inflammation decreased in patients treated with sarilumab, either as monotherapy or in combination with non- methotrexate conventional synthetic disease-modifying antirheumatic drugs. These results extend findings from previous studies to patients in alternative clinically relevant situations in Japan.”

Tanaka ja kollegat (2024 Kokotekstinä) vertasivat sarilumabin tehoa ja turvallisuutta alle 65 vuotiailla ja yli 65 vuotiailla nivelreumapotilailla.
Tulos: Ei tullut eroa ryhmien välillä

Tutkijoiden johtopäätös:

“In conclusion, this study revealed no clear difference in the efficacy and safety of sarilumab between patients aged ≥65 and <65 years. These results support the use of sarilumab in older Japanese patients with moderately to severely active RA.”

Kivitz ja kollegat (2024 Kokotekstinä)

Key Summary Points
Why carry out this study?
Sarilumab is approved for the treatment of adult patients with rheumatoid arthritis (RA). However, there is a need for longitudinal real-world observational studies that can confirm the information provided by randomized controlled trials.
The PROspective sarilumab (preFILled syringe/pen) multinational observational (PROFILE) study evaluated the real-world effectiveness and safety of sarilumab as monotherapy or in combination with csD-MARDs in patients with moderate-to-severe RA in routine clinical practice.
What was learned from the study?
This observational study confirmed the safety and effectiveness of sarilumab in adult patients with RA in routine clinical practice.
Improvements in clinical outcomes were observed through week 52 for patients on either sarilumab mono- or combination therapy.
The safety profile of sarilumab was consistent with that observed in randomized clinical trials, and no new safety signals emerged.

Tutkijoiden johtopäätökset:

“In this 1-year, observational, real-world study, sarilumab therapy resulted in improved clinical outcomes. Little difference was observed between the outcomes of patients treated with sarilumab as monotherapy and combination therapy. The safety profile observed in this routine clinical practice setting is consistent with that in sarilumab randomized clinical trials, and no new safety signals emerged.”

Kameda ja kollegat (2024 Kokotekstinä)

Tutkijoiden johtopäätökset:
“This interim analysis shows that sarilumab therapy was well tolerated by Japanese patients with rheumatoid arthritis in the real-world setting, regardless of age and no new safety signals were detected. Alongside data from previous clinical trials, no relationship seems to be established between the incidence of neutropenia during rheumatoid arthritis and the development of serious infections.”

Sarilumabi nivelreumaan liittyvän interstitiaalisen keuhkokuumeen hoidossa

Interstitiaalinen keuhkokuume (= välikudospenumonia, keuhkojen välikudostulehdus, interstitiaalinen pneumonia) on keuhkorakkuloiden ja kapillaarien välikudoksen tulehdus.

Suzuki ja kollegat (2024 Kokotekstinä)

Tutkijoiden johtopäätös:
“*In our study, SAR exhibited encouraging efficacy in stabilising RA-ILD in most cases.*”

Sarilumabi nivelreumaan liittyvän keuhkopussitulehduksen (pleuriitti) hoidossa

Sunaga ja Inoue (2024 Kokotekstinä) esittivät tapausselostuksen, missä 68-vuotiaalle miehelle tuli moniniveltulehdus (polyartriitti) ja nesteen kertymistä (effuusio) vasempaan keuhkopussiin.

Tutkimuksia:

- Lasko 24 mm/tunti
- CRP 6.2 mg/l
- RF 435 IU/ml
- Sitrulliinipeptidivasta-aineen (cyclic citrullinated peptide antibody = CCPAb) 2760 U/ml

Hoito:
Aluksi hän sai sulfasalatsiinia (1 gramma/vrk) + prednisoloni 20 mg/vrk. Lääkitys tehosi.
Kun prednisolonin annos pieneni, paheni pleuriitti ja niveltulehdukset pahenivat.
Hänelle aloitettiin sarilumabi, jolloin artriitti parani ja pleuriitti parani. Katso alapuolella olevat kuvat.

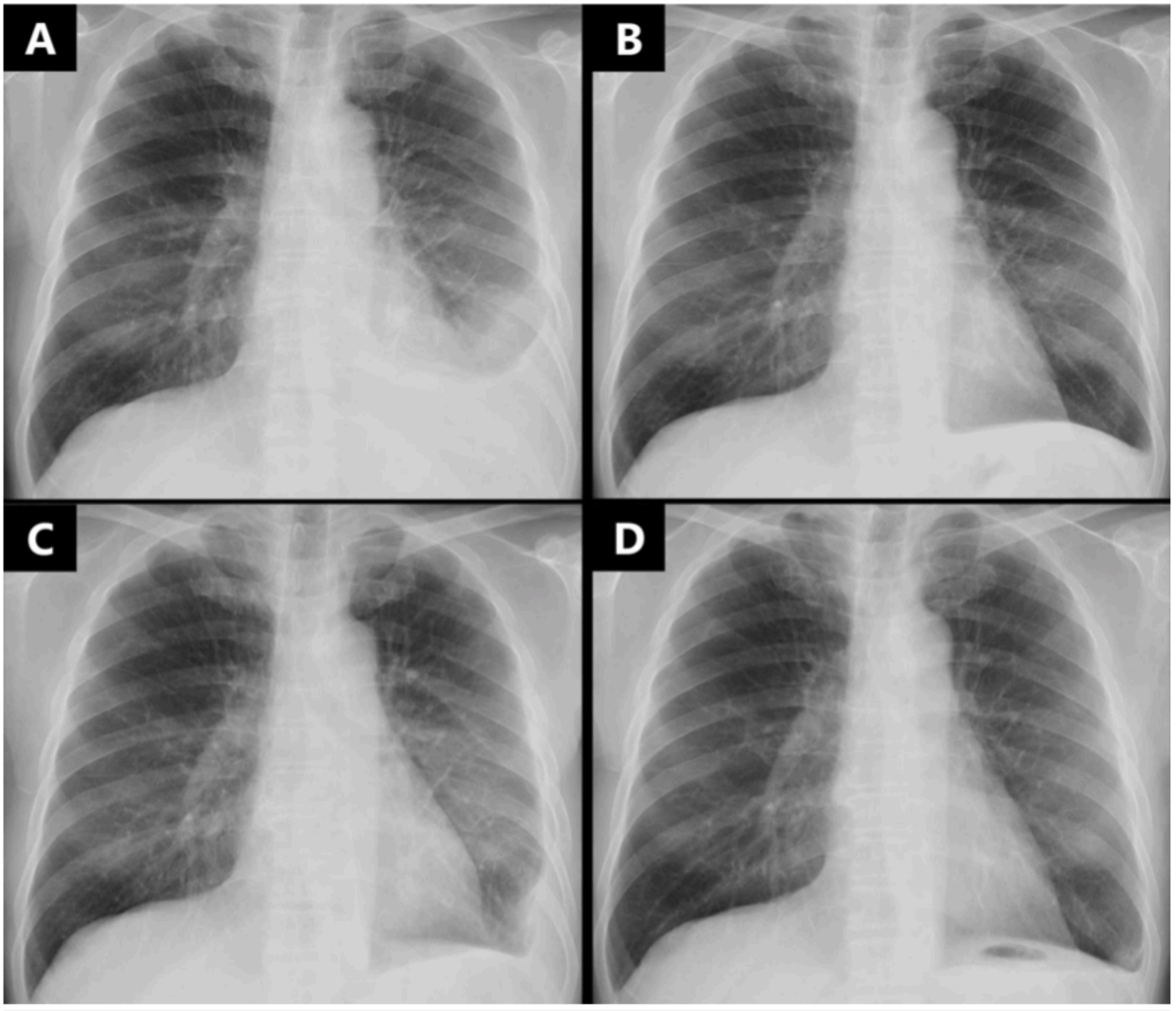


FIGURE 1: Changes in rheumatoid pleural effusion (RPE) observed via chest X-ray.

(A) Left-sided RPE at initial presentation. (B) Improvement in RPE at week 7 after prednisolone initiation. (C) Relapse of RPE at week 35 after prednisolone tapering. (D) Decrease in RPE at week 6 after sarilumab initiation.

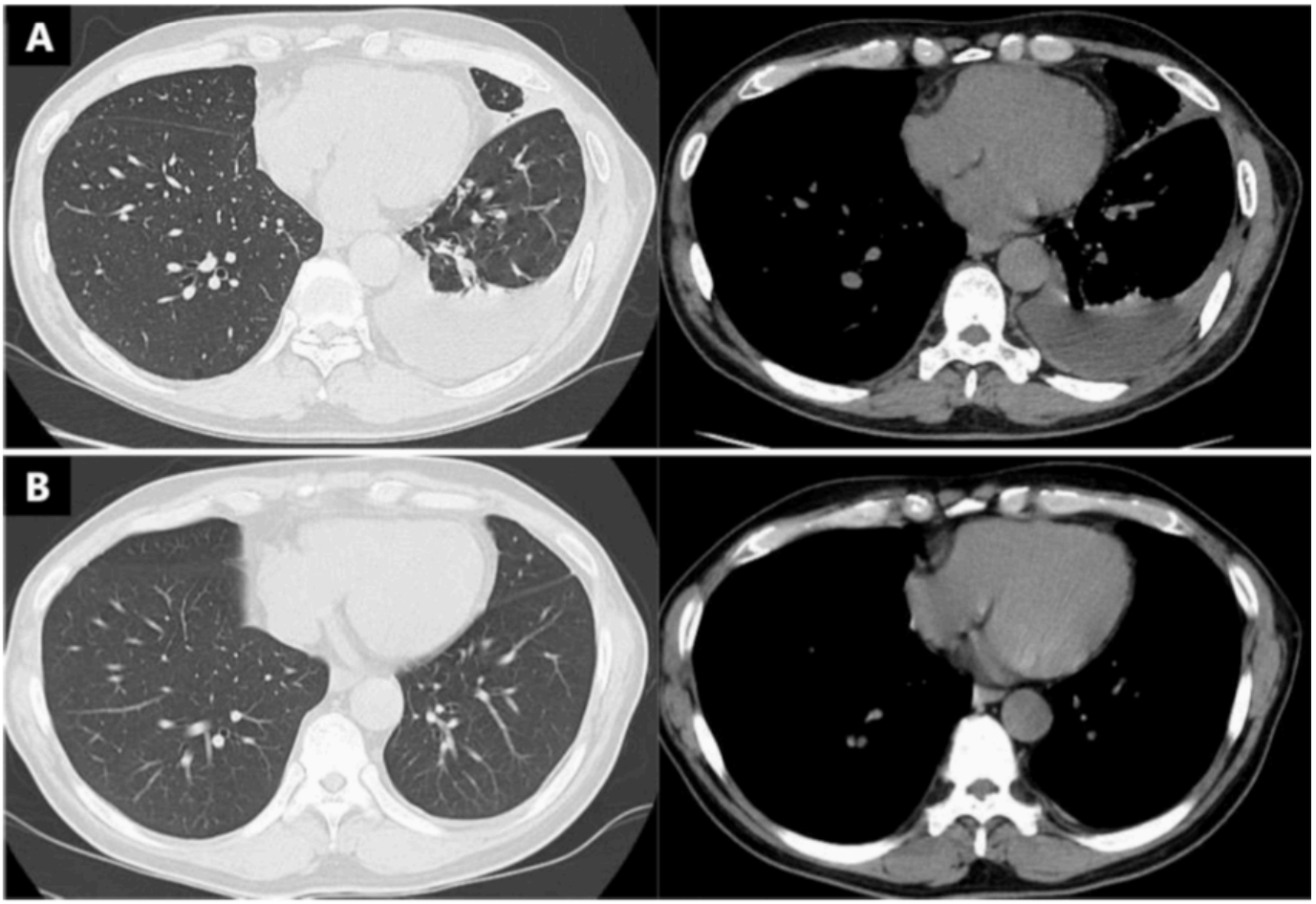


FIGURE 2: Changes in RPE observed via chest computed tomography (CT).

(A) Left-sided RPE at initial presentation. (B) Resolution of RPE three months after sarilumab initiation.

RPE, rheumatoid pleural effusion

Tutkijoiden johtopäätös:

“Rheumatoid pleural effusion is a rare complication of rheumatoid arthritis with no effective treatment. Moreover, studies on the use of biological disease modifying anti-rheumatic drugs for rheumatoid pleural effusion treatment are scarce. Previous studies have suggested similarities in the inflammatory processes of

pleuritis and synovitis in rheumatoid arthritis. This case suggests that IL-6 inhibitors effectively induce the remission of refractory rheumatoid pleural effusion , even without glucocorticoids. Furthermore, our findings highlight sarilumab as an effective fast-acting therapeutic for both rheumatoid pleural effusion and arthritis.”

Sarilumabin vasta-aineet

Wells ja kollegat (2019 Kokotekstinä)
antoivat yhteensä 132 nivelreumapotilaalle ihonalaisesti sekukinumabia joko 150 mg tai 200 mg kahden viikon välein. Tutkimus kesti kuusi kuukautta.
Tulokset:

- Sarilimumabin annoksella 150 mg kahden viikon välein kehittyi vasta-aineita sarilimumabia kohtaan 11 prosentilla potilaista.
  Neutraloivia vasta-aineita tuli 11 prosentille potilaista.

- Sarilimumabin annoksella 200 mg kahden viikon välein kehittyi vasta-aineita 6 prosentilla potilaista ja 3 prosentilla tutkituista tuli neutraloivia vasta-aineita.

Tutkijoiden johtopäätös:
Antidrug antibodies titers were low and persistent antidrug antibodies and neutralizing antibodies occurred relatively infrequently in both sarilumab dose groups. Antidrug antibodies did not meaningfully impact the safety or efficacy of either dose of sarilumab over 24 weeks.

Kontrolloidut tutkimukset

Huizinga ja kollegat (2014 Kokotekstinä)

Tutkijoiden johtopäätökset:
“The MOBILITY Part A study demonstrated that four subcutaneous sarilumab doses (150 mg q2w, 100 mg

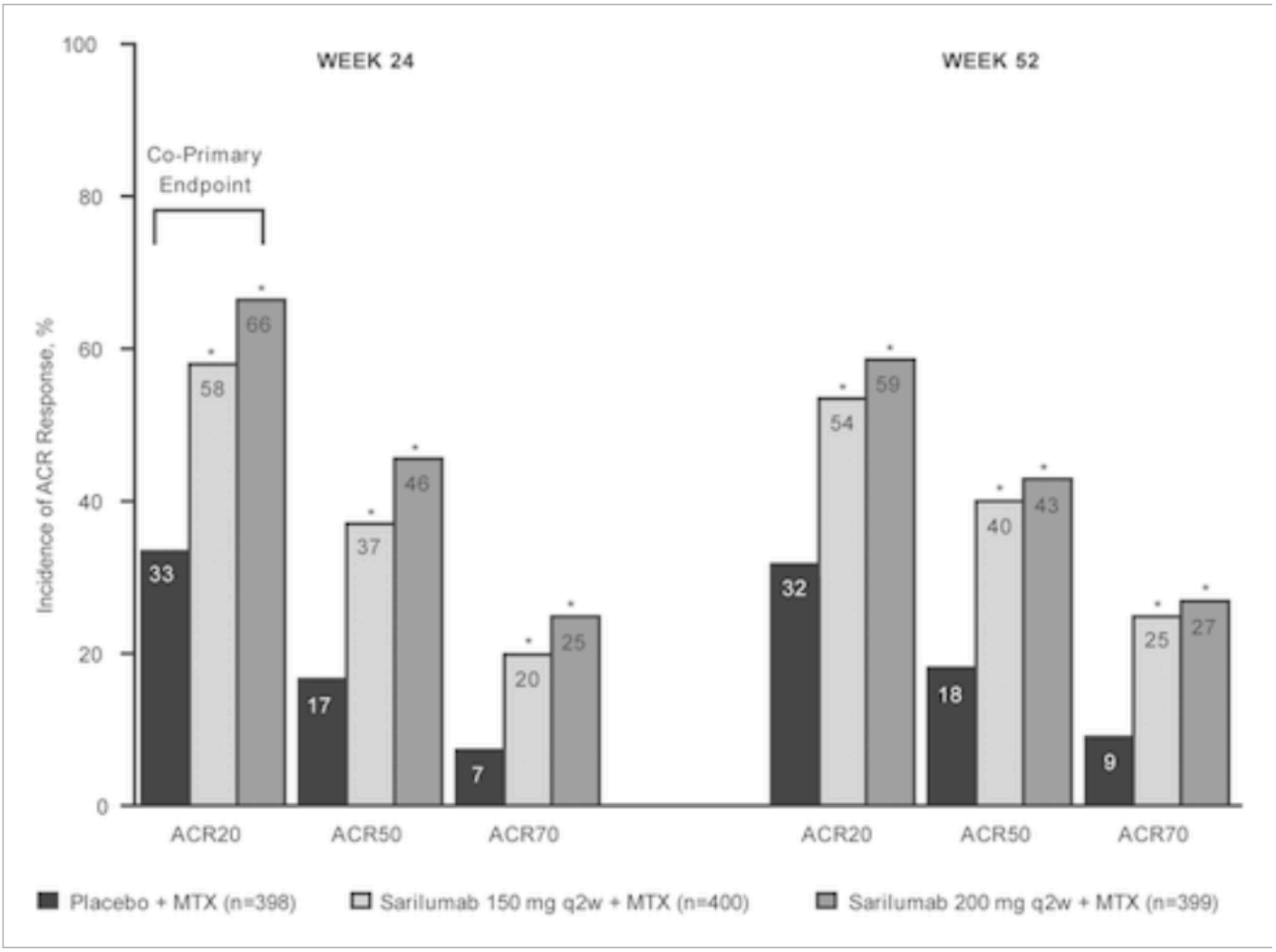
qw, 200 mg q2w, 150mg qw) administered in combination with methotrexate over 12 weeks were effective in reducing the signs and symptoms of moderate-to-severe rheumatoid arthritis in patients with an inadequate response to methotrexate . Among these doses, the efficacy findings, as well as the pharmacokinetic and pharmacodynamic parameters, showed that the every other week dosing regimens (150 mg and 200 mg q2w) were as effective as the weekly dosing regimens (100 mg and 150 mg qw). Sarilumab was generally well tolerated, with changes in neutrophil counts and trends for other safety lab parameters favouring q2w dosing. In light of the above and the convenience of every other week dosing, the 150mg and 200mg q2w doses are being assessed in multiple Phase III studies in patients with rheumatoid arthritis .”

“Sarilumab improved signs and symptoms of rheumatoid arthritis over 12 weeks in patients with moderate-to-severe rheumatoid arthritis with a safety profile similar to reports with other IL-6 inhibitors. Sarilumab 150 mg and sarilumab 200 mg q2w had the most favourable efficacy, safety and dosing convenience and are being further evaluated in Phase III.”

Genovese ja kollegat (2015 Kokotekstinä) antoivat satunnaistetussa lumekontrolloidussa tutkimuksessa sarilumabia nivelreumapotilaille, joilla ei oltu saatu riittävää hoitovastetta metotreksaatilla. Potilaita oli yhteensä 1369 ja heidät jaettiin seuraaviin ryhmiin:

- metotreksaatti + sarilumabi 150 mg kahden viikon välein
- metotreksaatti + sarilumabi 200 mg kahden viikon välein
- metotreksaatti + lumelääke kahden viikon välein

Tulokset: Katso alapuolella oleva taulukko.
Vuoden kuluttua (52 viikkoa) saavutettiin 40 prosentilla potilaista ACR50 hoitovaste sarilumabin annoksella 150 mg/2 viikkoa + metotreksaatti. Vastaava tulos saavutettiin 43 prosentilla potilaista sarilumabin annoksella 200 mg/2 viikkoa.



Proportion of patients in the placebo plus methotrexate (MTX), sarilumab 150 mg every 2 weeks (q2w) plus MTX, and sarilumab 200 mg every 2 weeks plus MTX groups who achieved American College of Rheumatology 20% (ACR20), ACR50, and ACR70 improvement responses at week 24 and week 52. Values in bars indicate the response rates. * = $P < 0.0001$ versus placebo plus MTX (results based on nonresponder imputation).

Sivuvaikutukset:

	Sarilumabi	Sarilumabi	Lumelääke

	150 mg	200 mg	
Vakava infektio	3 %	4 %	2 %
ALAT nousu 3 kertaa yli viitealueen	10 %	8 %	2 %
Korkea kokonais-kolesteroli	37 %	43 %	18 %
Neutroliifien lasku välille 500-1000/yl	5 %	8 %	0
Neutroliifien lasku alle 500/yl	0.9 %	0.7 %	0

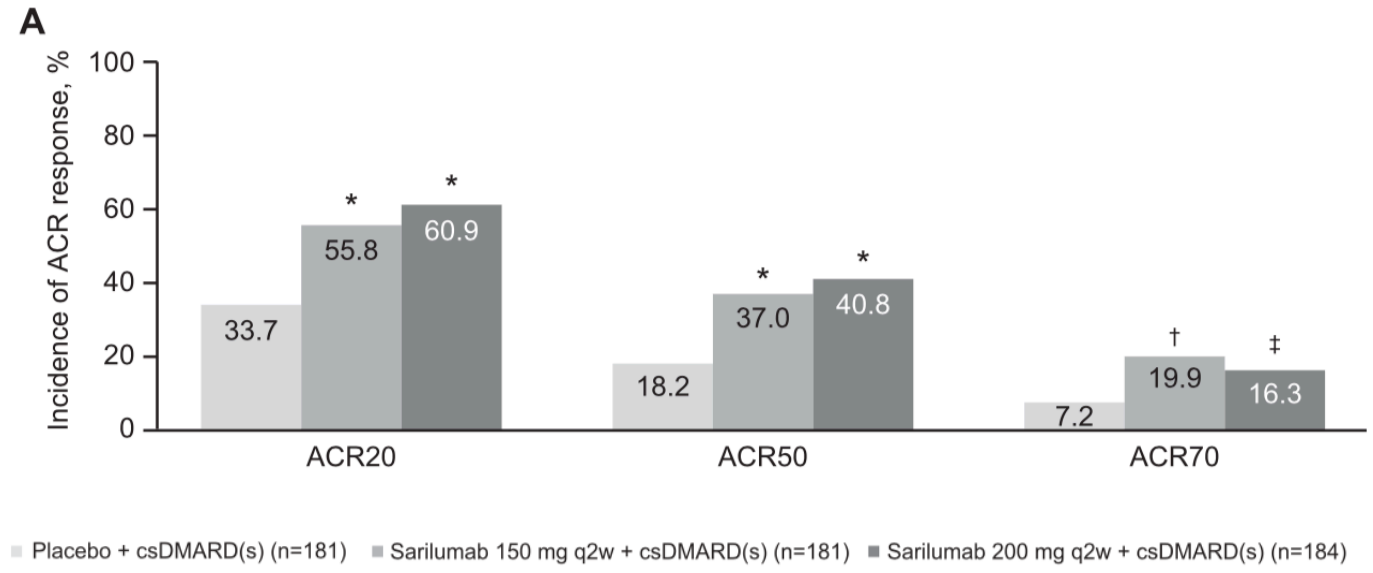
Tutkijoiden johtopäätös:
“In rheumatoid arthritis patients treated with sarilumab (150 mg or 200 mg every 2 weeks) in combination with methotrexate , both doses provided sustained clinical efficacy, as shown by significant improvements in symptomatic, functional, and radiographic outcomes. Sarilumab was generally well tolerated. The adverse events observed in this study were consistent with the effects of interleukin-6 signaling blockade.”

Fleischmann ja kollegat (2017 Kokotekstinä) vertasivat yhteensä 546 nivelreumapotilaalla satunnaistetussa, kaksoissokkotutkimuksessa sarilumabia lumelääkkeeseen seuraavasti:

- Sarilumabia 150 mg kahden viikon välein + tavanomainen reumalääkitys
- Sarilumabia 200 mg kahden viikon välein + tavanomainen reumalääkitys
- Lumelääke kahden viikon välein + tavanomainen reumalääkitys

Kuuden kuukauden (24 viikkoa) mitattiin potilaiden ACR20 hoitovaste.

- Sarilumabi 150 mg/2 viikkoa sai aikaan 56 %:lla potilaista ACR20 hoitovasteen.
- Sarilumabi 200 mg/2 viikkoa sai aikaan 61 %:lla potilaista ACR20 hoitovasteen.
- Lumelääkkeellä saatiin 34 %:lla potilaista ACR20 hoitovasteen.



Sarilimumabin sivuvaikutukset

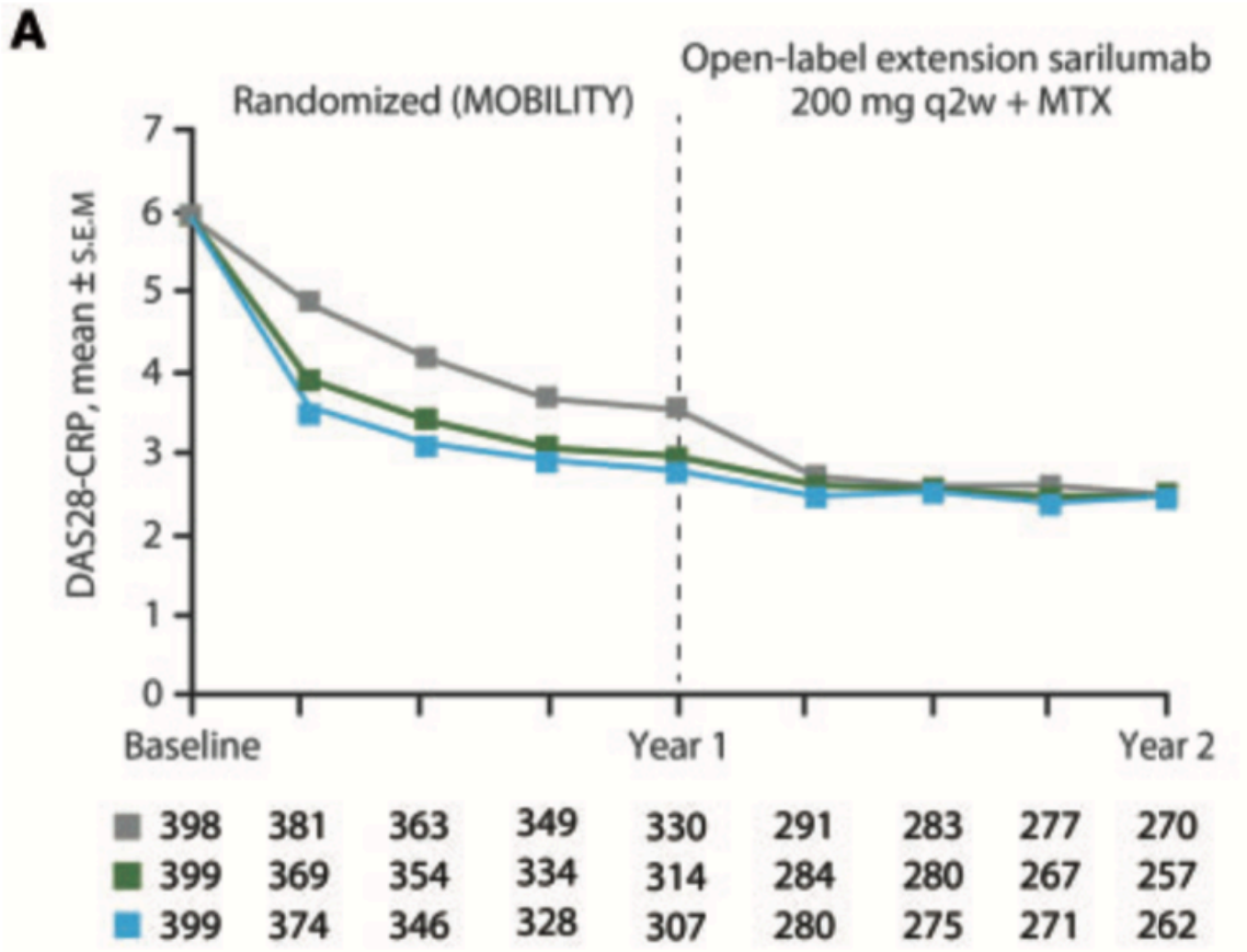
	Lumelääke + tavanomainen lääkitys	Sarilumab 150 mg/2 viikkoa + tavanomainen lääkitys	Sarilumab 200 mg/2 viikkoa + tavanomainen lääkitys	
Vakava sivuvaikutus	3 %	3 %	5 %	
Infektio	27 %	22 %	30 %	
Nenän ja nielun infektio	5 %	6 %	4 %	
Neutropenia	11 %	13 %	13 %	
ALAT nousu	1 %	3 %	5 %	

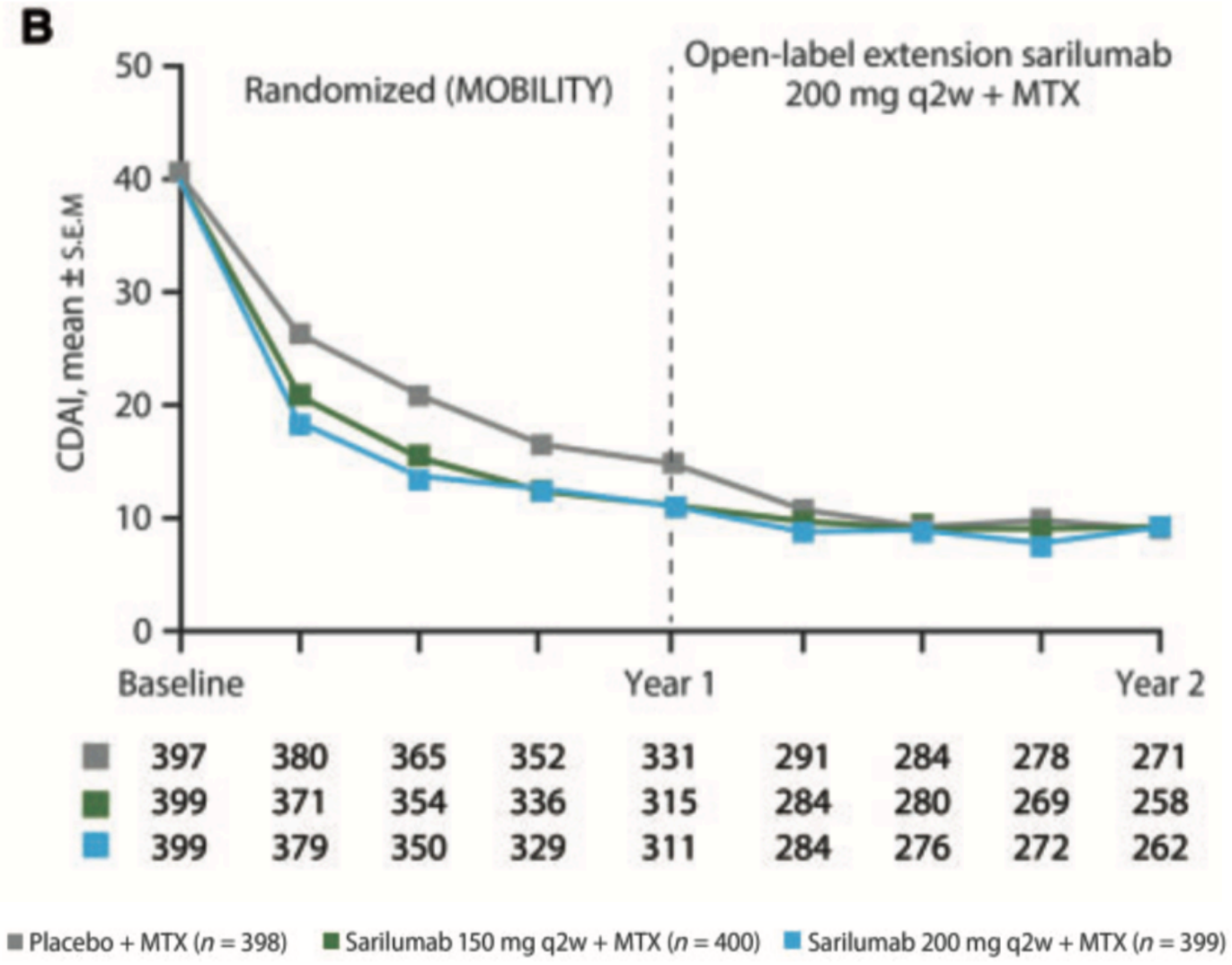
LDL nousu	9 % tutkituista	28 % tutkituista	25 % tutkituista	

Tutkijoiden johtopäätös:

“Sarilumab 150 mg and sarilumab 200 mg every 2 weeks plus conventional synthetic DMARDs (disease modifying antirheumatic drugs) improved the signs and symptoms of rheumatoid arthritis and physical function in patients with an inadequate response or intol- erance to anti-TNF agents. Safety data were consistent with interleukin-6 receptor blockade and the known safety profile of sarilumab.”

Genovese ja kollegat (2018 Kokotekstinä) vertasivat MOBILITY tutkimuksessa 1197 nivelreumapotilaalla sarilimumabia (150 mg tai 200 mg kahden viikon välein) lumelääkkeeseen vuoden ajan. Näillä potilailla ei oltu saatu metotreksaatilla riittävää tehoa.
Avoimessa jatkotutkimuksessa selvitettiin sarilimumabin tehoa ja sivuvaikutuksia yhteensä kahden vuoden seurannan aikana.
Tulokset:
Clinical efficacy for patients completing 1 year of open-label extension, by original randomization


A
Randomized (MOBILITY)
Open-label extension sarilumab
200 mg q2w + MTX
DAS28-CRP, mean ± S.E.M
7
6
5
4
3
2
1
0
Baseline
Year 1
Year 2
398 381 363 349 330 291 283 277 270
399 369 354 334 314 284 280 267 257
399 374 346 328 307 280 275 271 262



Rheumatology key messages

- The 2-year, safety/efficacy profile of sarilumab is consistent with prior findings and IL-6R inhibition.
- Sarilumab dose reductions successfully managed laboratory abnormalities while retaining treatment efficacy.
- Patients initiated on sarilumab 200 mg q2w had best radiographic and physical function outcomes.

Tutkijoiden johtopäätös:
“In conclusion, 2-year treatment of active, moderate-to-severe rheumatoid arthritis with sarilumab, along with dose reduction in the event of laboratory abnormalities, resulted in durable efficacy outcomes and a safety

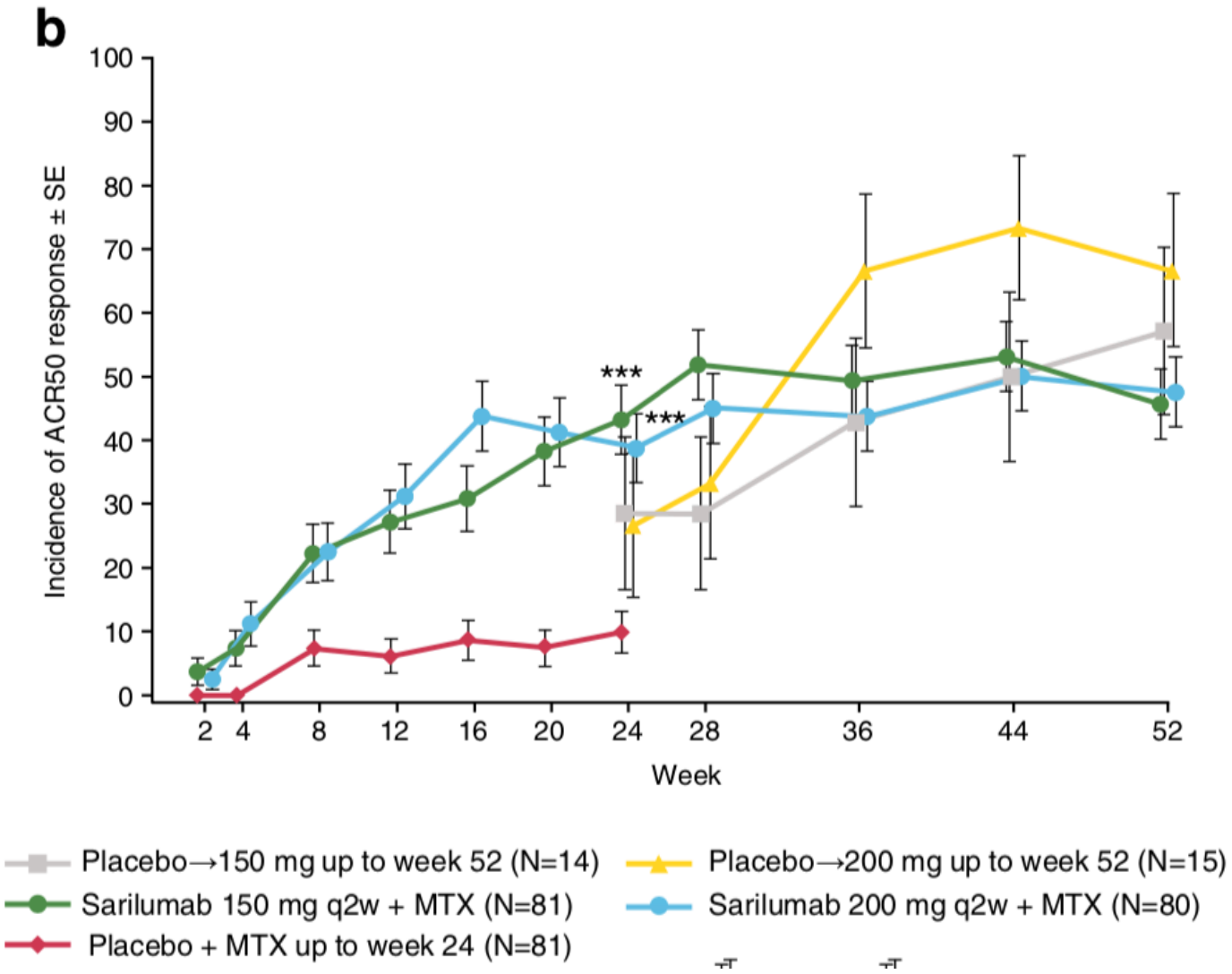
profile consistent with previous reports and IL-6R blockade.”

Tanaka ja kollegat (2019 Kokotekstinä) antoivat satunnaistetussa lumekontrolloidussa kaksoissokkotutkimuksessa 243 nivelreumapotilaalle sarulimumabia seuraavasti:

- Sarilimumabia 150 mg ihonalaisesti kahden viikon välein + metotreksaatti
- Sarilimumabia 200 mg ihonalaisesti kahden viikon välein + metotreksaatti
- Lumelääke + metotreksaatti 24 viikon ajan. Sen jälkeen jatkettiin sarilimumabi 150 mg kahden viikon välein + metotreksaatti yhteensä 52 viikon ajan.
- Lumelääke + metotreksaatti 24 viikon ajan. Sen jälkeen jatkettiin sarilimumabi 200 mg kahden viikon välein + metotreksaatti yhteensä 52 viikon ajan.

Tulokset: Katso alapuolella oleva kuva.

- Lumelääke + metotreksaatti hoidossa saavutettiin 24 viikon kohdalla alle 10 prosentilla potilaista ACR50 hoitovaste (punainen käyrä). Kun lumelääkkeen tilalle aloitettiin sarilumabi, saavutettiin sarilumabin + metotreksaatin yhdistelmähoidolla viikolla 52 yli 50 prosentilla potilaista ACR50 hoitovaste.
- Metotreksaatin annos oli välillä 6-16 mg kerran viikossa.



Kommenttini: Pelkällä metotreksaatilla saavutettiin odotettua huonompi hoitovaste viikolla 24 (Alle 10 prosentilla potilaista saatiin ACR50 hoitovaste). Tähän vaikutti varmaan se, että tutkimukseen oli valittu potilaita, joilla metotreksaatilla ei oltu saatu riittävää hoitovastetta.

Sivuvaikutukset:

	Lumelääke + metotreksaatti	Sarilimumabi 150 mg + metotreksaatti	Sarilimumabi 200 mg + metotreksaatti		
Lääkityksen lopetus sivuvaikutuksen vuoksi	4 %	7 %	9 %		
Lääkkeen aiheuttama kuolema	0 %	0 %	0 %		

Nenän ja nielun infektio	15 %	20 %	15 %		
Matalat neutrofiilit	0 %	9 %	14 %		
Suutuleh-dus	4 %	6 %	10 %		
Maksan toiminta-häiriö	5 %	11 %	14 %		
ALAT koholla	5 %	6 %	4 %		
Ihottuma	1 %	5 %	4 %		

Tutkijoiden johtopäätös:
“In Japanese inadequate response to methotrexate patients treated with sarilumab (150 and 200 mg q 2 week) in combination with methotrexate, sustained clinical efficacy was shown by significant improvement in signs, symptoms, and physical function; bridging between this and a previous global study was achieved. At week 52, the safety profiles of both doses of

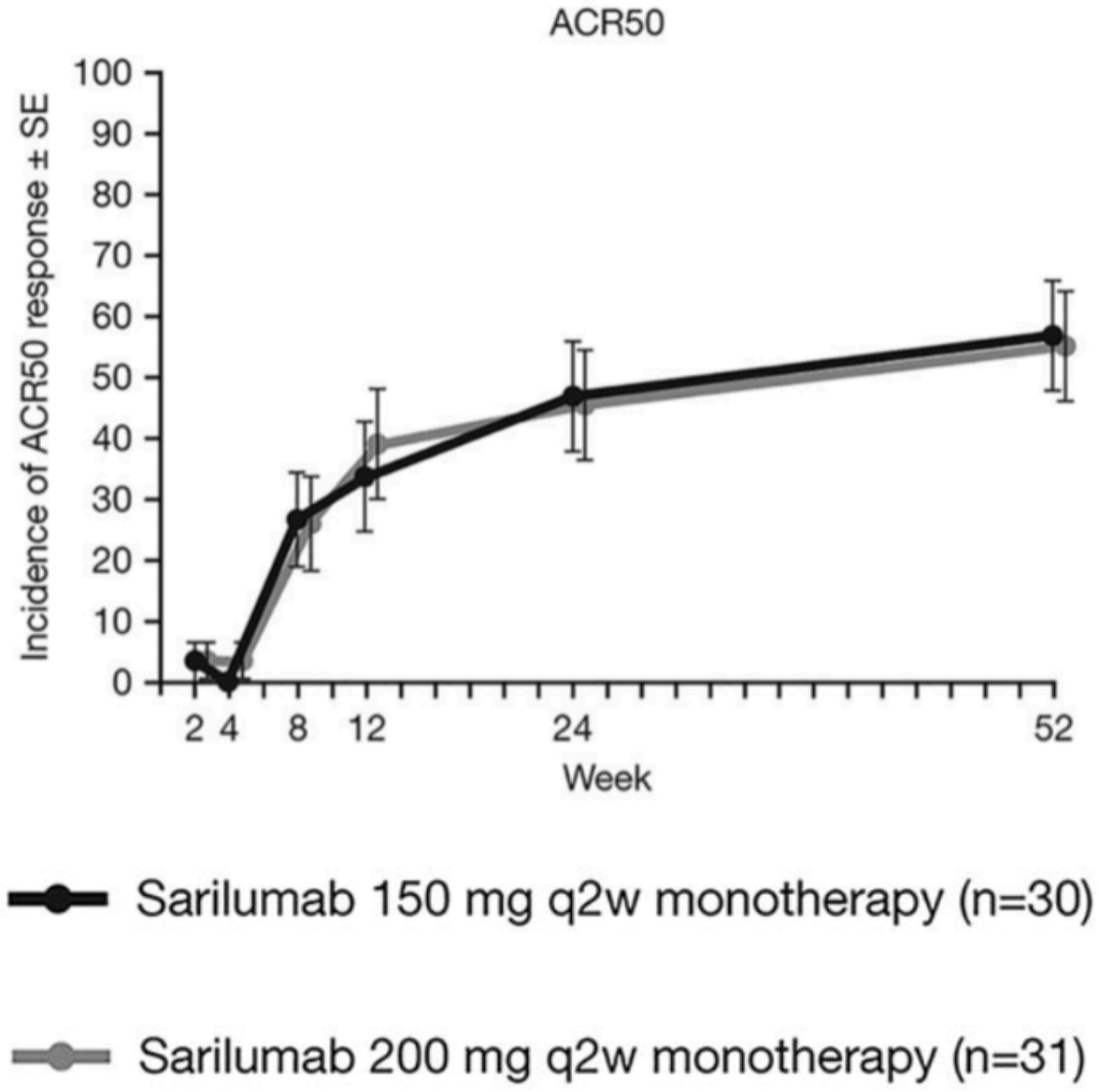
sarilumab were generally similar, as previously observed and as expected based on IL-6 class. “

Kameda ja kollegat (2020 Kokotekstinä) antoivat yhteensä 91 nivelreumapotilaalle satunnaistetussa kaksoissokkotutkimuksessa sarilimumabia seuraavasti:

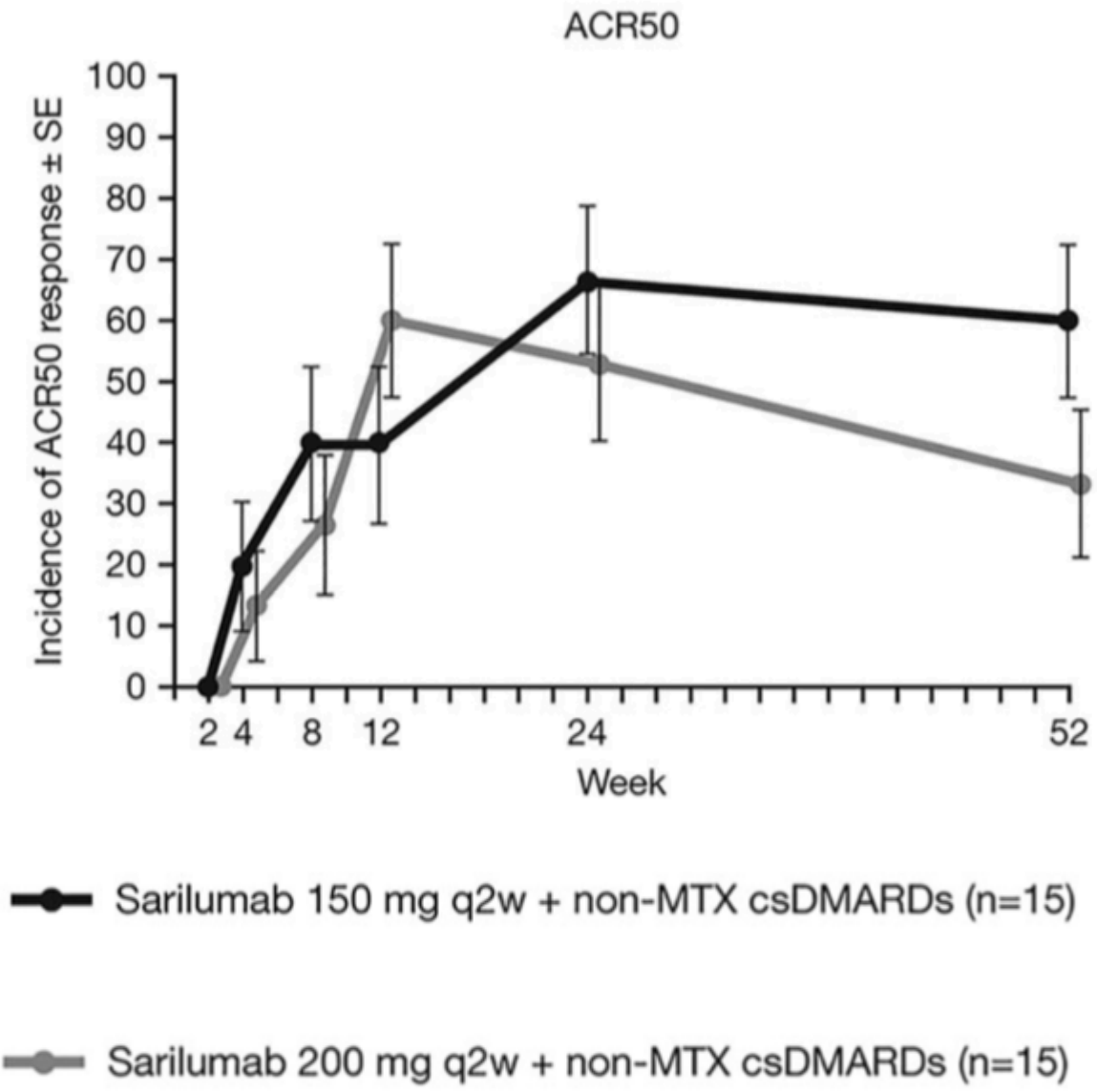
- sarilimumabi 150 mg kahden viikon välein yksilääkehoitona
- sarilimumabi 200 mg kahden viikon välein yksilääkehoitona
- sarilimumabi 150 mg kahden viikon välein + tavanomainen reumalääkitys ilman metotreksaattia
- sarilimumabi 200 mg kahden viikon välein + tavanomainen reumalääkitys ilman metotreksaattia

Tutkimus kesti 52 viikkoa.

Tulokset:



Sarilimumabin yksilääkehoidolla saavutettiin vuodessa ACR50 hoitovaste noin puolella potilaista. Ei ollut eroa annosten 150 mg ja 200 mg välillä. Katso yläpuolella oleva kuva.



Monilääkehoidossa yllättäen sarilimumabilla 200 mg annoksella saatiin huonompi ACR50 hoitovaste kuin 150 mg annoksella. Katso yläpuolella oleva kuva.

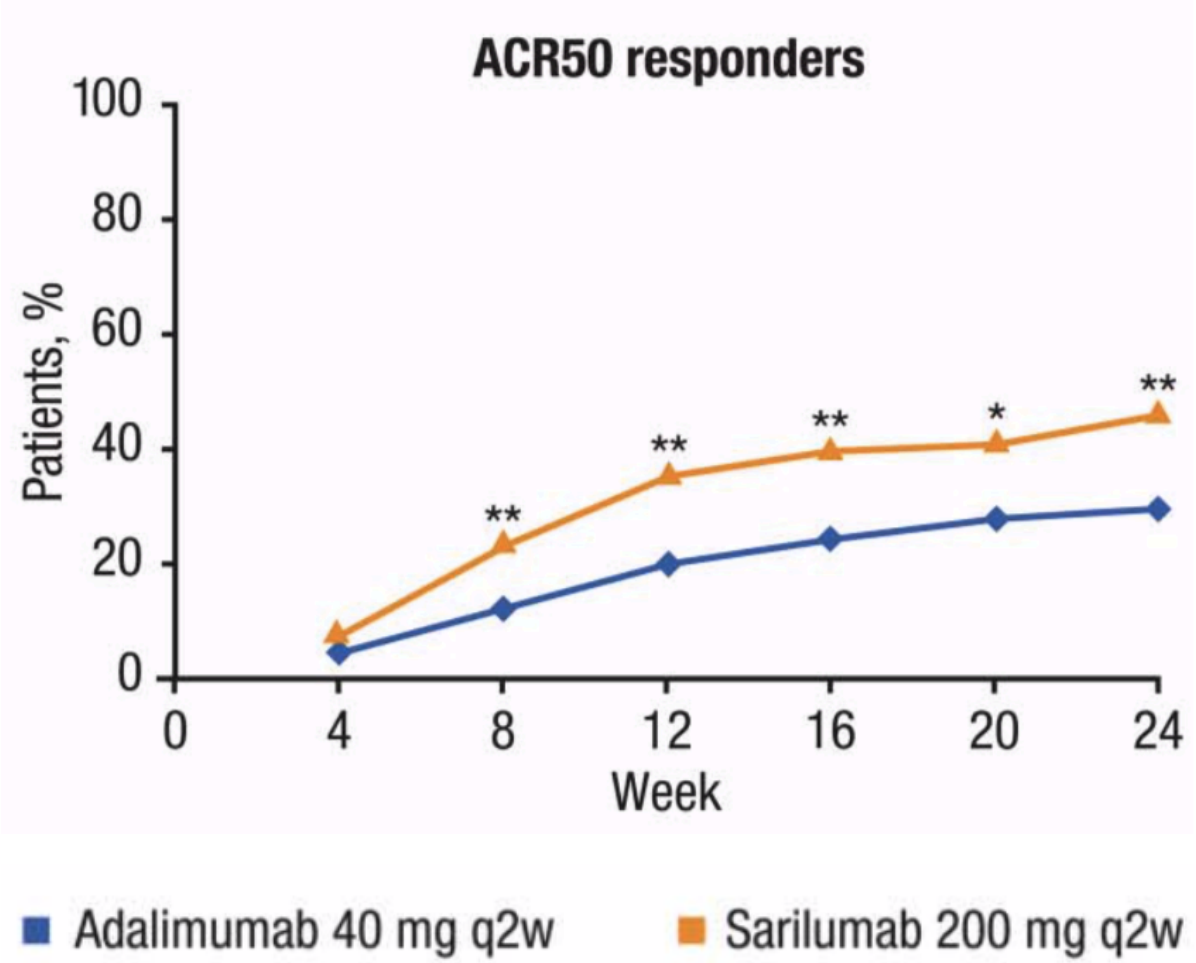
Tutkijoiden johtopäätös:
“The safety profile of sarilumab was consistent with known class effects of interleukin-6 signaling blockade therapeutics. Sarilumab as mono- or combination therapy improved clinical signs/ symptoms and physical function in Japanese rheumatoid arthritis patients.”

Ishii ja kollegat (2023 Kokotekstinä)

Tutkijoiden johtopäätös
“In conclusion, the pharmacokinetics, pharmcodynamics, and safety observations in the present studies were consistent with the anticipated effects of sarilumab when administrated subcutaneous with or without concomitant methotrexate in Japanese RA patients. Our findings add further support to the use of sarilumab subcutaneous mono- or combination-therapy for the treatment of rheumatoid arthritis in this patient group.”

Sarilumimabin vertailu adalimumabiin nivelreuman hoidossa

Burmester ja kollegat (2017 Kokotekstinä) aloittivat satunnaistetussa kaksoisokkotutkimuksessa yhteensä 369 nivelreumapotilalle joko sarilumabin (200 mg kahden viikon välein) tai adalimumabin (40 mg kahden viikon välein). Tutkimukseen valittiin potilaat, joille metotreksaatti ei ollut tehonnut tai oli aiheuttanut sivuvaikutuksia.
Tulokset:
Kuuden kuukauden kuluttua ACR50 hoitovaste 46 prosentilla sarilimumabia saaneista ja 30 prosentilla adalimumabia saaneista. Katso alapuolella oleva kuva.



Sivuvaikutuksia oli molemmissa ryhmissä yhtä paljon (64 %).
Sarilimumabilla yleisin sivuvaikutus oli neutrofiilien lasku ja injektiokohdan reaktio. Adalimumabilla suurin sivuvaikutus oli pääkipu sekä nivelreuman paheneminen.
Salimumabia saaneista oli infektio 29 prosentilla ja adalimumabia saaneista 28 prosentilla.
Vaikea infektio esiintyi yhdellä prosentilla molemmissa ryhmissä.

Tutkijoiden johtopäätös:

“Sarilumab monotherapy demonstrated superiority to adalimumab monotherapy by improving the signs and symptoms and physical functions in patients with rheumatoid arthritis who were unable to continue methotrexate treatment. The safety profiles of both therapies were consistent with anticipated class effects.”

Burmester ja kollegat (2019 Kokotekstinä)

Key messages

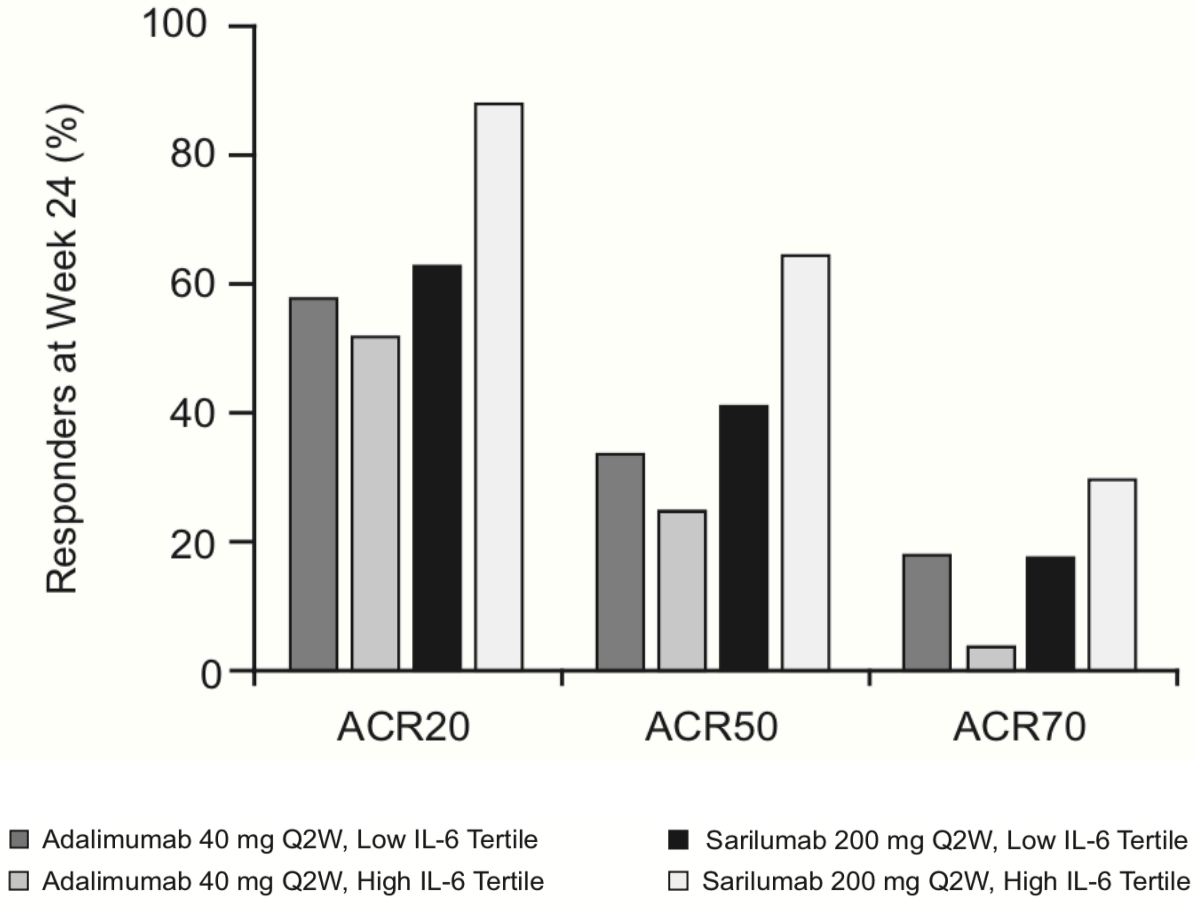
What is already known about this subject?

- In the 24-week phase III MONARCH study (NCT02332590), both sarilumab 200 mg every 2 weeks and adalimumab 40 mg every 2 weeks were associated with a meaningful improvement in disease activity in adult patients with rheumatoid arthritis (RA) who were intolerant of, or inadequate responders to, methotrexate (MTX) or who were deemed inappropriate for MTX treatment. Sarilumab monotherapy demonstrated superiority to adalimumab monotherapy for improving RA signs and symptoms and physical function.

What does this study add?

- Findings from this open-label extension (OLE) study support the long-term safety and efficacy of sarilumab in patients who continued sarilumab from double-blind through OLE for a total of 72 weeks. Safety profile and incidence of treatment-emergent adverse events were similar for patients who switched from adalimumab to sarilumab on entry into the OLE versus patients who continued on sarilumab.
- Patients switching from adalimumab to sarilumab achieved additional clinically meaningful improvements in disease activity and in patient-reported outcomes in the OLE, primarily within 12 weeks of switching. These improvements approached levels of improvement observed in patients who continued sarilumab after completing the double-blind phase.

Boyapati ja kollegat (2020 Kokotekstinä) mittasivat nivelreumapotilailta IL-6 pitoisuuden plasmasta ennen ja jälkeen sarilimuabin aloituksen jälkeen. Kontrolliryhmä sai adalimumabia. Katso alapuolella oleva kuva. Tulokset: Potilaat, joilla plasman IL-6 pitoisuus oli korkea, saatiin sarilimumabilla parempi hoitotulos (vaalea korkea pylväs).



Tutkijoiden johtopäätös:

IL-6 may be a prognostic marker of disease progression and severity, and patients with high IL-6 levels may be likely to benefit from sarilumab compared to adalimumab or MTX.

Gabay ja kollegat (2020 Kokotekstinä)

Tutkijoiden johtopäätökset:
“In this analysis, sarilumab treatment was associated with decreases in circulating biomarkers of the acute-phase response, bone resorption, synovial inflammation and CV risk compared with adalimumab. Several biomarkers, including MMP-3, SAA and CRP, were associated with clinical efficacy and individually predicted response to sarilumab treatment. Further studies evaluating the predictive value of changes in these biomarkers are necessary to confirm these findings and identify patients more likely to respond to sarilumab administration.”

“Sarilumab was associated with greater positive effects on bone remodelling and decreases in biomarkers of the acute-phase response, synovial inflammation and cardiovascular risk vs. adalimumab. High baseline

concentrations of SAA, CRP and MMP-3 are predictive of clinical and patient-reported outcome responses to sarilumab treatment and prospective validation is warranted to confirm these results.”

Sarilumabin yksilääkehoidon vertailu sarilumabin ja metotreksaatin yhdistelmähoitoon

Burmester ja kollegat (2021 Kokotekstinä)

Rheumatology key messages

- Sarilumab, monotherapy or in combination with methotrexate, demonstrated clinical improvements in patients with rheumatoid arthritis.
- The efficacy of sarilumab monotherapy was similar to its combination with methotrexate.
- Sarilumab monotherapy may be a valuable treatment strategy in patients with a contraindication/intolerance to methotrexate.

Tutkijoiden johtopäätös:
“This post hoc analysis in patients with RA, based on the aggregate data from two clinical studies, demonstrated similar efficacy of sarilumab when administered as either monotherapy or in combination with methotrexate. These data suggest that sarilumab monotherapy may be considered as a potential treatment alternative for patients in whom combination therapy with methotrexate is not appropriate.”

“This analysis demonstrated that the efficacy of sarilumab monotherapy was similar to that of sarilu- mab and MTX combination therapy.”

Sarilumabin ja otilimabin vertailu nivelreuman hoidossa

Taylor ja kollegat (2023 Kokotekstinä) totesivat lumekontrolloidussa tutkimuksessa, että anti-granuloscyte-makropfage kolony-stimulating factor antibody (= Anti-GM-CSF) ei tehonnut nivelreuman hoidossa kolmen kuukauden seurannan aikana. Sarilumabilla saatiin tehoa. Sarilimumabin ACR20 olli tasolla 50 %.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Despite recent advances in rheumatoid arthritis (RA) therapy, there are patients who are refractory and remain symptomatic despite having been treated with all currently available treatment options.

⇒ It has been reported multiple times that response to therapy decreases, with subsequent lines of therapy; therefore, patients with multiple advanced therapeutic failures represent a current unmet need in RA treatment.

⇒ The granulocyte-macrophage colony-stimulating factor antibody (GM-CSF) pathway has been identified as a promising target for the treatment of RA and has been postulated to play a role in pain responses.

⇒ While preclinical studies have demonstrated that GM-CSF inhibition improved inflammatory arthritis and pain, clinical efficacy trials of monoclonal antibodies targeting GM-CSF or the GM-CSF receptor in patients with RA has generated mixed results.

WHAT THIS STUDY ADDS

⇒ This phase III randomised controlled trial investigated the safety and efficacy of otilimab, a high-affinity anti-GM-CSF monoclonal antibody, in patients with a previous inadequate response to conventional synthetic and biologic disease-modifying antirheumatic drugs and/or Janus kinase inhibitors.

⇒ Otilimab failed to demonstrate a difference in American College of Rheumatology ≥20% response compared with placebo, did not improve secondary end points and failed to demonstrate non-inferiority to sarilumab in this RA population.

⇒ This trial corroborates previous sarilumab studies and provides robust clinical efficacy, safety and pharmacokinetic/pharmacodynamic data for an anti-GM-CSF monoclonal antibody in a geographically diverse population of patients with RA who have had multiple therapeutic failures.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ For many years, GM-CSF has been considered an attractive target in the treatment of RA, and a novel mechanism of action might have the potential to be effective in patients who fail to respond to currently approved therapies.

⇒ Although previous phase I and phase II randomised controlled trials (RCTs) have reported the benefit of targeting the GM-CSF pathway, to date, only otilimab has progressed to phase III.

⇒ While negative, results from this RCT may help to inform clinical trial design and therapeutic target selection in future approaches to novel pharmacotherapy in this RA patient population.

Tutkijoiden johtopäätös:
“In this treatment refractory patient population, otilimab failed to meet the primary end point of ACR20 response versus placebo at week 12 and most of the predefined secondary end points were not reached. As otilimab was demonstrated to be no different to placebo and less effective than sarilumab in this trial, and less effective than tofacitinib in contRAst 1 and contRAst 2, otilimab is unlikely to be a valuable addition to the current therapeutic armamentarium for rheumatoid arthritis.”

Sarilimumabin ja upadasitinibin vertailu nivelreuman hoidossa

Huizinga ja kollegat (2023 Kokotekstinä) vertasivat kolmen erillisen tutkimuksen perusteella sarilimumabin ja upadasititinibin (JAK-1 estäjä) tehoja keskenään nivelreuman hoidossa.
Tulos: Valmisteiden teho oli yhtä hyvä.

Key Summary Points

Why carry out this study?

The interleukin (IL)-6 receptor inhibitor, sarilumab, and the Janus kinase (JAK)-1 inhibitor, upadacitinib, are approved for treatment of patients with moderately to severely active rheumatoid arthritis (RA), but head-to-head comparisons in clinical trials have not been performed to date.

In the absence of head-to-head comparisons, and where there are only one or two trials for a treatment, approaches for the indirect comparisons of different treatments include the matching-adjusted indirect comparison (MAIC) and the simulated treatment comparison (STC).

What did the study ask? What was the hypothesis of the study?

We used the MAIC and STC analyses to estimate the relative efficacy of sarilumab and upadacitinib in patients with RA who had an inadequate response to previous biologic disease-modifying antirheumatic drugs (bDMARDs) using data from the TARGET (sarilumab) and SELECT-BEYOND (upadacitinib) trials.

What was learned from the study? What were the study outcomes/conclusions?

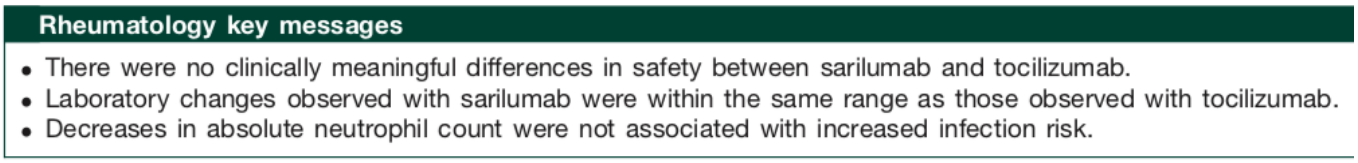
Our results, obtained using the two population-adjusted indirect comparisons (MAIC and STC), suggest a similar effect of sarilumab and upadacitinib when given in combination with conventional synthetic DMARDs.

What has been learned from the study?
To the best of our knowledge, this analysis was the first indirect comparison of sarilumab and upadacitinib, and one of the first studies in RA to utilize the STC methodology.
Indirect comparisons have become increasingly common in assessing comparative efficacy; their use should be encouraged but critically evaluated.

Tutkijoiden johtopäätös:
“Our results, obtained using two population-adjusted indirect comparisons, suggest a similar effect of sarilumab and upadacitinib when given in combination with stable conventional synthetic DMARDs. Indirect comparisons have become increasingly common in assessing comparative efficacy; their use should be encouraged but critically evaluated.”

Sarilimumabin ja tosilitsumabin vertailu

Emery ja kollegat (2019 Kokotekstinä)



Tutkijoiden johtopäätökset:
“Overall, no clinically meaningful differences were observed with regard to safety between sarilumab and tocilizumab in either study, including the incidence and types of treatment-emergent adverse events. Laboratory changes (e.g. decrease in ANC and increase in ALT) noted in the sarilumab groups were within the same range as those noted in the tocilizumab groups. Although numeric differences in incidence of absolute neutrophil count <1.0 giga/l between the sarilumab and tocilizumab groups were observed in ASCERTAIN, considering the results of Study 1309, this most likely reflects differences in pharmacokinetics (related to route of administration; s.c. for sarilumab and i.v. for tocilizumab) and dosing interval (q2w for sarilumab versus q4w for tocilizumab) in relation to the sampling schedule (q2w). Decreased absolute neutrophil count was not associated with an increased incidence of infection.”

Tony ja kollegat (2022 Kokotekstinä)

Key messages

- Sarilumab effectively attenuates disease activity of RA patients with inadequate response to janus kinase inhibitors or tocilizumab.
- Safety in patients pretreated with janus kinase inhibitors or tocilizumab was consistent with the anticipated profile of sarilumab.

Tutkijoiden johtopäätös:
“Sarilumab treatment was effective in patients with inadequate response to janus kinase inhibitor and tocilizumab, with an expectable safety profile and drug retention over 6 months. Confirmation of these promising results should encourage further studies on this treatment sequence, which is of high practical relevance.”
“In summary, this analysis suggests that sarilumab might represent an effective treatment option with an expectable safety profile for patients with inadequate to JAKi or tocilizumab.”

Den Broeder ja kollegat (2023 Kokotekstinä)

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Tocilizumab and sarilumab are both IL-6-receptor antagonists used in the treatment of rheumatoid arthritis (RA) with similar efficacy and safety. One previous study reported maintained efficacy after switching from tocilizumab to sarilumab, but this switch coincided with a switch in administration route from intravenous tocilizumab to subcutaneous sarilumab and a change from blinded to open-label treatment, hence the effects of switching in case of shortages or for other non-medical reasons (costs and injection frequency) are unclear.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ This study investigates whether it is possible to switch from tocilizumab to sarilumab in patients with RA doing well on tocilizumab.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ This study suggests that tocilizumab and sarilumab are not interchangeable at the individual patient level, as switching resulted in an increase in disease activity and suboptimal sarilumab persistence.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ Despite their similar pharmacology, our results suggest that tocilizumab and sarilumab are not interchangeable and discourage non-medical switching between the two.

Tutkijoiden johtopäätös:
“In summary, this study fails to show that non-medical switching from tocilizumab to sarilumab is non-inferior, in fact, the switch appears to result in an increase in disease activity and suboptimal sarilumab persistence. Despite the mechanistic similarity of both drugs, they therefore do not appear to be interchangeable at the individual patient level.”

Sarilimumabi muiden sairauksien hoidossa

Sarilimumabi aikuistyypin Stillin taudin hoidossa

Avoimet tutkimukset

Njonnou ja kollegat (2019 Kokotekstinä) totesivat 25-vuotiaalla miehellä aikuistyypin Stillin taudin. Hänellä olivat seuraavat löydökset:

- Yli kaksi viikkoa jatkunut korkea kuume
- Vasemman polven kipu
- Veren valkosolut koholla (21000 kpl/yl)
- Kurkkukipua
- ALAT koholla 111 U/l (normaalisti alle 45)
- Reumatekijä negatiivinen ja tumavasta-aineet negatiiviset.
- Seerumin ferritiini korkea 2619 yg/l (normaalisti alle 350)

Hoito: Metyyliprednisoloni alkaen annoksella 0.5 mg/kg. Kun metyyliprednisolonin annos laski tasolle 2 mg/vrk, uusiutui kuume, valkosolujen nousu ja CRP nousi (100 mg/l). Ferritiini oli 3806 yg/l.
Hoito: Metyyliprednisolonilla (0.5 mg/kg) ei saatu sairautta rauhoittumaan.
Hän sai kaksi annosta tosilitsumabia. Sen jälkeen hän sai sarilimumabia 200 mg kahden viikon välein kolmen kuukauden ajan. Sarilimumabilla saavutettiin paraneminen. Sen jälkeen jatkettiin tosilitsumabilla, koska tässä vaiheessa hänen vakuutusyhtiönsä suostui korvaamaan tosilitsumabihoidon.

Rheumatology key message

- Sarilumab is effective as a corticoid-sparing agent in corticodependent adult onset Still's disease.

Sarilumabi selkärankareuman hoidossa

Kontrolloitu tutkimus

Sieper ja kollegat (2015 Kokotekstinä) antoivat satunnaistetussa,

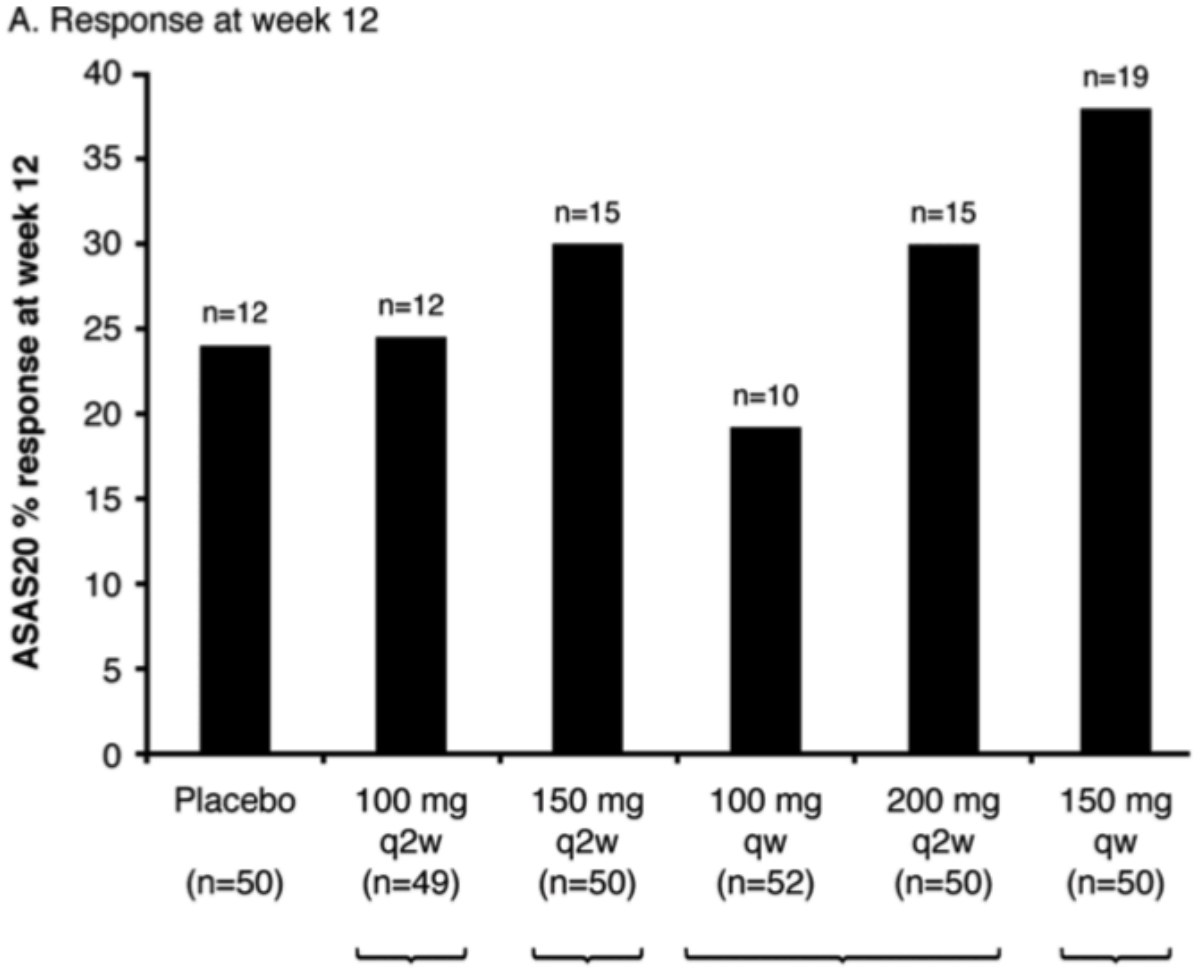
lumekontrolloidussa

kaksoissokkotutkimuksessa 301

selkärankareumapotilaalle sarilimumabia seuraavasti:

- lumelääke kahden viikon välein 12 viikkoa
- sarilimumbi 100 mg kahden viikon välein
- sarilimumbi 150 mg kahden viikon välein
- sarilimumbi 200 mg kahden viikon välein
- sarilimumabi 100 mg kerran viikossa 12 viikon ajan
- sarilimumabi 150 mg kerran viikossa 12 viikon ajan

Tulokset:
Tutkimuksessa ei saanut tilastollista eroa lumelääkkeen ja sarilimumabin välillä. Katso alapuolella oleva kuva.



Tutkijoiden johtopäätös:
“The ALIGN study shows that IL-6Rα blockade with sarilumab was not an effective treatment for ankylosing spondylitis. Sarilumab was generally well tolerated with a manageable safety profile.”

Sarilimumabi uveitis posteriorin hoidossa

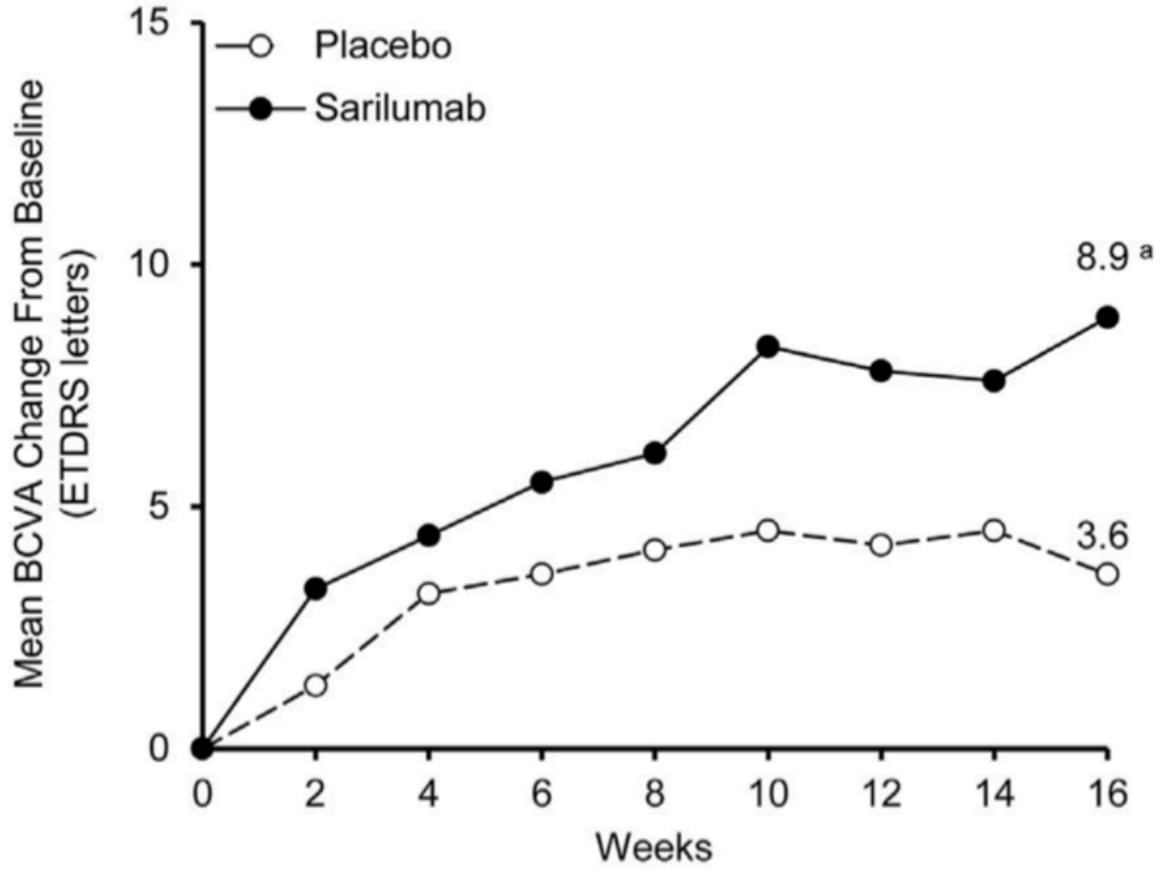
Uveitis posterior = suonikalvon tulehdus
Uveitis anterior = värikalvon ja sädekehän tulehdus

Avoin tutkimus

Heissigerova ja kollegat (2018 Kokotekstinä) antoivat satunnaistetussa kaksoissokkotutkimuksessa 58 uveiittia sairastavalle joko sarilimumabia 200 mg kahden

viikon välein tai lumelääkettä. Tutkimus kesti neljä kuukautta.

Tulokset: Sarilimumabi paransi uveiitin aiheuttamia tulehdusmuutoksia paremmin kuin lumelääke.



Visual outcomes of study eyes. A, Mean changes in best-corrected visual acuity (BCVA) from baseline through week 16 in overall population.

Tutkijoiden johtopäätös:

“In conclusion, the SATURN study has provided data suggesting that inhibition of IL-6 signaling with SC sarilumab given every 2 weeks for 16 weeks could provide clinical benefits in the management of NIU of the posterior segment by improving VH, macular edema, and vision. This may be of particular importance in patients with uveitis presenting with signs of more active ocular inflammation, reduced vision, and macular edema despite ongoing treatment with systemic corticosteroids or immunomodulatory therapy.”

Sarilumabi makulan rakkulaisen turvotuksen hoidossa

Verkkokalvon makula on tarkkaan näkemiseen ja värien näkemiseen liittyvä verkkokalvon keskiosa.

Sarilumabi polymyalgia rheumatican hoidossa

Kawka ja kollegat (2024 Kokotekstinä)

Tässä heidän tekstiään sarilimumabista

IL-6 signaling inhibition. **Sarilumab**, an IL6R inhibitor, is the only bDMARD currently marketed for PMR. **Tocilizumab**, another IL6R inhibitor, is considered under development because of the lack of marketing authorization for PMR, while the only study that was

examining **sirukumab**, a IL6 inhibitor, has been withdrawn.

Sarilumab was evaluated in the SAPHYR study, published in 2023 . This phase III, randomized, double-blind, placebo-controlled trial involved 118 patients who were either treated with sarilumab 200 mg every two weeks for 52 weeks in addition to glucocorticoids for the first 14 weeks, or given a placebo plus glucocorticoids for 52 weeks. Significantly more patients receiving sarilumab completed a sustained remission at 52 weeks in the sarilumab group compared to the patients in the placebo group (28% vs 10%, p = 0.02). Furthermore, the cumulative glucocorticoids dose was significantly lower in the sarilumab group than in the placebo group (777 mg vs 2044 mg, $p < 0.001$).

Sarilumabi jättisoluarteriitin hoidossa

Kawka ja kollegat (2024 Kokotekstinä)

“Tocilizumab has been examined across 3 phase II studies , 1 phase II/III study , and 1 phase III study. All these studies reported positive outcomes. Notably, the SEMAPHORE study, a phase III double-blind, parallel-group, placebo-controlled randomized trial, enrolled 101 patients with glucocorticoid-dependent PMR who continued to show disease activity despite being on glucocorticoid therapy with a dose of 10 mg/day or higher . Participants were treated with either intravenous tocilizumab at a dosage of 8 mg/kg or a placebo, in addition to a tapering course of glucocorticoids. Low disease activity (PMR-AS<10) with glucocorticoid independence (≤5 mg absolute value or decrease ≥10 mg from week 0 to week 24 [prednisone equivalent]) at week 24 was significantly more frequently in the tocilizumab group than in the placebo group (67.3% vs 31.4%, $p < 0.001$).”

Kontrolloidut tutkimukset

Sarilimumabi SARS-CoV-2 keuhkokuumeen hoidossa

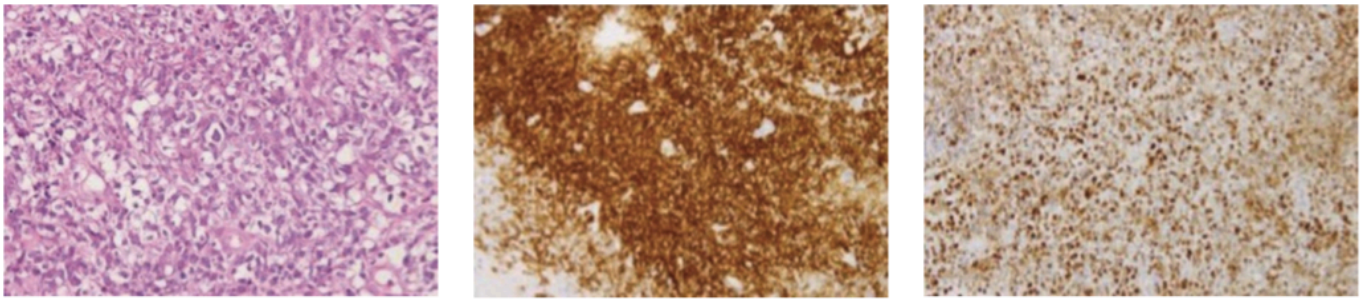
Sarilimumabi ja lymfoproliferatiivinen sairaus

Lymfoproliferatiivinen sairaus (lymphoproliferative disorder) on jonkin mononukleaarisen solutyypin pahanlaatuinen kasvain (Esimerkiksi B- tai T-solulymfooma ja Hodgkinin lymfooman kaltainen tila).
Wikipedia: Lymphoproliferative disorders

Tada ja kollegat (2023 Kokotekstinä) julkaisivat kaksi tapausselostusta.

Tapaus 1
84-vuotias nainen oli saanut nivelreuman hoidoksi metotreksaattia kuuden vuoden ajan.
Hänellä todettiin tuumori kielen alla.

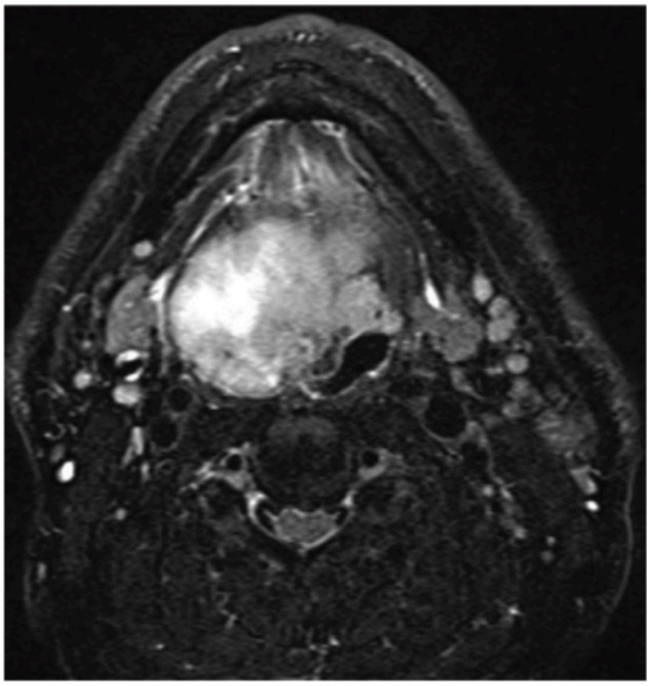
Tietokonekerroskuvauksessa näkyi imusolmukkeiden suurentumista molemmin puolin keuhkoportissa (hilum pulmonis) ja keuhkojen vällikarsinassa (mediastinum). Imusolmukkeen koepalassa CD20 positiivisia ja EBV positiivisia soluja.



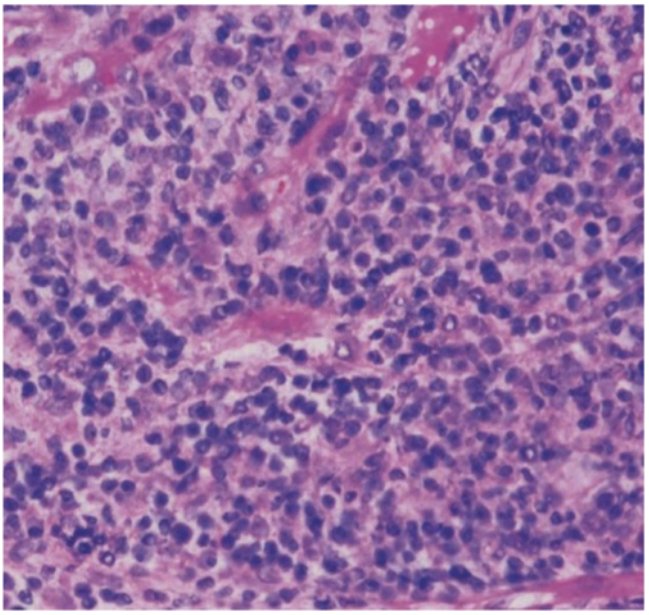
Lymphoproliferative disorders in patient 1. (a) Pathology of the mass shows medium-to-large lymphoid cells with pale cytoplasm and polymorphic nuclei (H&E stain ×200). (b) Immunohistochemical staining shows that the lymphoid cells are positive for CD20. (c) Lymphoid cells are positive for EBV-encoded small RNA in *in situ* hybridization. H&E: hematoxylin and eosin; EBV: Epstein–Barr virus.

Päädyttiin diagnoosiin DLBCL (= Diffuse large B-cell lymphoma).
Kun metotreksaatti keskeytettiin, pienenivät suurentuneet imusolmukkeet.
Tämän jälkeen nivelreuma paheni ja aloitettiin sarilimumabi 300 mg ihonalaisesti kahden viikon välein. Saatiin hyvä hoitotulos ja sarilimumabi on jatkunut viiden vuoden ajan.

Tapaus 2
76-vuotias mies oli saanut nivelreuman hoidoksi metotreksaattia viiden vuoden ajan. Hänelle tuli kurkkukipua ja nielusta löytyi tuumori.



(b)



(c)

(b) Gadolinium-enhanced magnetic resonance imaging shows a mass (47 × 37 × 52 mm) in the midpharynx.

(c) Histopathology of the mass shows an accumulation of atypical lymphoid cells (H&E stain ×200).

A diagnosis of DLBCL is made.

Päädyttiin diagnoosiin DLBCL = (= Diffuse large B-cell lymphoma)

Hoito: Metotreksaatti lopetettiin, jonka jälkeen nielun tuumori pieneni kolmessa viikossa.
Kun nivelreuma aktivoitui aloitettiin aluksi tosilitsumabi ja kaksi vuotta myöhemmin sarilumabi, joka paransi nivelreuman (remissio).

Sarilimumabi ja luusto

Klinder ja kollegat (2022 Kokotekstinä)
Tutkijoiden johtopäätökset:
“In conclusion, it was shown that, while effects of IL-6/IL-6R supplementation were mild, the highest tested concentrations of IL-6 and sIL-6R can significantly induce pro- osteogenic markers such as alkaline phosphatase (ALP) activity after a stimulation period of 72 h. IL-6 receptor blockade for 72 h led to a reduction in regulatory proteins of important intracellular signaling pathways as well as mediators required for bone matrix maintenance including matrix gla protein (MGP) and SPP1 which encode matrix Gla protein and osteopontin, two proteins that are of particular importance in the regulation of skeletal mineralization . While reductions in

those proteins might indicate that the administration of sarilumab exerts later effects on bone mineralization, there were no differences among control, stimulation, and inhibition of IL-6 signaling concerning the mineralization capacity after longer observation intervals of up to 14 days. Thus, the long-term mineralization experiments suggest that sarilumab might not exert a detrimental effect on bone formation.

The extent to which these effects may significantly influence bone formation or bone resorption in the highly inflammatory context of rheumatoid arthritis patients cannot be derived from our study, as we used only one proinflammatory cytokine in our rather static environment with IL-6 and sIL-6R. Therefore, further studies, e.g., in a highly inflammatory milieu with additional proinflammatory mediators, are required to investigate the interplay between IL-6R inhibition by sarilumab and the extent of its effects on crucial intracellular signaling pathways involved in bone homeostasis. For this purpose, the investigation of the effects in specific co-cultures with relevant cells may generate meaningful results, as intercellular communication is a major factor in the induction of intracellular signaling pathways. Further investigations with osteoblasts from rheumatoid arthritis patients must be performed to specifically demonstrate the clinical significance of IL-6R inhibition on bone-remodeling

processes in the context of rheumatoid arthritis patients.”

Sarilimumabi ja aikuistyypin diabetes

Lurati ja kollegat (2021 Kokotekstinä)

Key Messages

1. Diabetes mellitus and rheumatoid arthritis increase cardiovascular risk.

2. High levels of pro-inflammatory cytokines, as in uncontrolled rheumatoid arthritis, are correlated with poorer glucose balance in diabetes.

3. Better control of arthritis leads to better control of concomitant diabetes.

Tutkijoiden johtopäätökset:

“In our study, the use of anti-IL6 drugs (tocilizumab and sarilumab) has been shown to lead to a further improvement in glycated hemoglobin values compared

to the use of other classes of biological disease modifying antirheumatic drug (= bDMARD). However, the small size of the sample in question prevents us from reaching definitive conclusions (p=0.047). Further study with longitudinal IL-6 measurement is needed in order to determine if IL-6 is in the causal pathway leading from obesity to diabetes. It therefore remains unknown whether blocking IL-6 might prevent the onset of diabetes mellitus in the general population and in patients with rheumatoid arthritis . In conclusion, our study, although with evident limitations (observational design, low number of patients, lack of a control group), provides preliminary evidence of a potential insulin-sensitizing effect of biological disease modifying antirheumatic drugs resulting from an anti-inflammatory effect, demonstrated by the significant reduction in the values of acute phase reactants. Obviously, our data need to be confirmed by more rigorous studies, including a control group, and at least direct measurements of insulin sensitivity. Our finding, if confirmed, could improve the management of comorbidity in rheumatoid arthritis patients. Cardiometabolic risk management, according to the EULAR recommendations, should be one of the biggest focuses for clinicians dealing with rheumatoid arthritis patients because greater disease activity in rheumatoid arthritis is associated with a greater risk of diabetes.”

++++++++++

Sarilimumabin sivuvaikutukset

Fleischmann ja kollegat (2020 Kokotekstinä) seurasivat keskimäärin 2.8 vuoden ajan 2887 nivelreumapotilasta, jotka saivat sarlumabia yhdistelmähoitona perinteisten reumalääkkeiden kanssa. Lisäksi he seurasivat 471 nivelreumapotilasta keskimäärin 1.7 vuoden ajan. Nämä saivat sarilumabia yksilääkehoitona (=monoterapia). Tutkimuksessa seurattiin sivuvaikutusten esiintymistä. Tulokset:

Fleischmann ja kollegat (2020 Kokotekstinä)

Sivuvaikutus	Yhdistelmä-hoito		Yksilääke-hoito	
Vakava sivuvaikutus	24 %		11 %	
Lääkityksen lopetus	24 %		11 %	

sivuvaikutuksen vuoksi				
Sivuvaikutuksen aiheuttama kuolema	1.1 %		1.1 %	
Neutropenia	19 %		18 %	
Ylempien hengtystei-den infektio	13 %		8 %	
Virtsatie-infektio	11 %		7 %	
ALAT koholla	11 %		6 %	
Keuhkokuume	2 %		0.2 %	
Hoidon keskeytyminen sivuvaikutuksen vuoksi				
• Neutropenia	3 %		2 %	
• ALAT nousu	2 %		0.6 %	
• Vyö-ruusu	1 %		0.6 %	
• Keuh-kokuume	0.8 %		0.2 %	
• Pistos paikan punoi-tus	0.5 %		1.3 %	

Fleischmann ja kollegat (2020 Kokotekstinä)

Sivuvaikutus	Yhdistelmähoito		Yksilääkehoito
Vakava infektio	8 %		1.5 %
Tuberkuloosi	0.1 %		0.2 %
Vyöruusu	2 %		1 %
Leukopenia	21 %		20 %
Maksavaurio	16 %		8 %
Mahahaava	0.1 %		0
Sydänkohtaus tai aivovaurio	1 %		0.4 %
Kolesterolin nousu	12 %		4 %
Lääkeyliherk-kyys	11 %		8 %
Pistoskohdan reaktio	12 %		10 %
Demyelisoiva sairaus	0 %		0.2 %
Tromboembolia	2 %		0.6 %

Rheumatology key messages

- This analysis represents the most comprehensive long-term safety report of sarilumab in RA to date.
- Sarilumab's long-term safety profile was consistent with phase III studies, with no new safety concerns.
- Neutropenia was not associated with increased risk of infection or serious infection.

Infektiot

Bakteeri

- Staphylococcus aureus

- Streptococcus

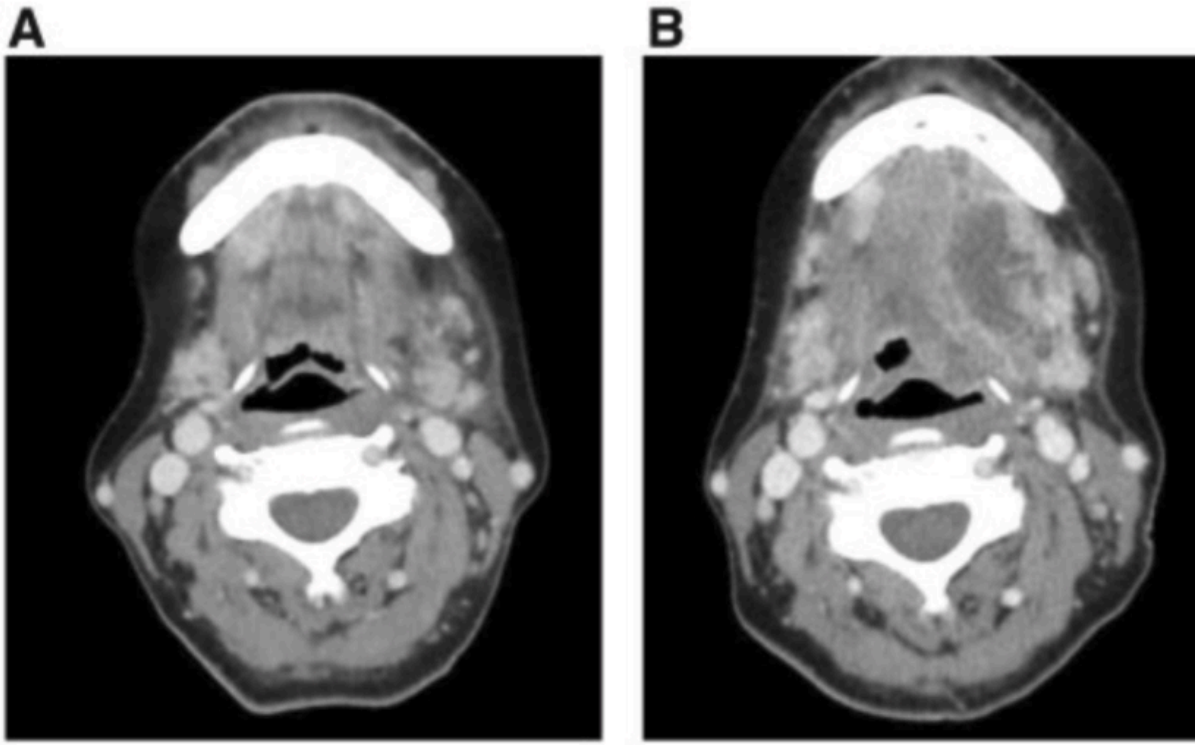
Streptococcus (ketjukokki) ovat ketjuina esiintyviä kokkibakteereja, joista monet kuuluvat ihmisen suun ja nielun normaalikasvustoon ja joista monet ovat tärkeitä

taudinaiheuttajina. Streptokokit jaetaan hemolyysikykynsä mukaan ryhmiin alfa, beeta ja gamma, joista betahemolyyttiset streptokokit jaetaan soluseinämän antigeenien mukaan edelleen ryhmiin A-U.

Streptococcus pyogenes aiheuttaa mm. nielurisatulehdusta, tulirokkoa, märkärupea, ruusua (erysipelas), haavainfektioita ja sepsistä.
Se on betahemolyyttinen streptokokki.

Shiota ja kollegat (2020 Kokotekstinä) aloittivat 49-vuotiaalle naiselle sarilumabin (200 mg ihonalaisesti kahden viikon välein).
Kymmenen kuukautta myöhemmin hänelle tuli vasemman puolen niskakipua.
Löydöksiä:

- Lämpö 37.0 C
- Vasemman leuan seudussa oli hiukan turvotusta ja kipua.
- Hän ei kyennyt avaamaan suutaan kunnolla.
- Veren valkosolut 6020 kpl/yl.
- Hb 142 g/l
- CRP < 0.8 mg/l
- Tietokonekerroskuvauksessa kehittyi kuudessa päivässä märkäpesäke (abskessi) vasemman leukaluun seutuun. Katso alapuolella oleva kuva.



(A) On admission, soft tissue of the left jaw was slightly swollen, but there was no abscess. (B) On day 6, an abscess can be seen at the left submandibular region.

- Märkäpesäkkeessä kasvoi ryhmän A Streptococcus pyogenes

Hoito: Keftriaksoni, joka tehosi

Tutkijoiden johtopäätös:

“We should keep in mind that a normal CRP level cannot exclude the possibility of serious infections in

patients treated with sarilumab. Gaensbauer et al. reported a case of staphylococcal scalded-skin syndrome in a patient receiving tocilizumab. The case had a normal CRP, but serum procalcitonin was markedly elevated. They suggested that serum procalcitonin can be a diagnostic marker of bacterial infections in patients receiving tocilizumab. Other inflammatory markers may be useful for the detection of infections in patients treated with sarilumab. When patients treated with sarilumab present with new symptoms, physicians must be aware of the possibility of infection, even if the CRP level is normal."

Rheumatology key message

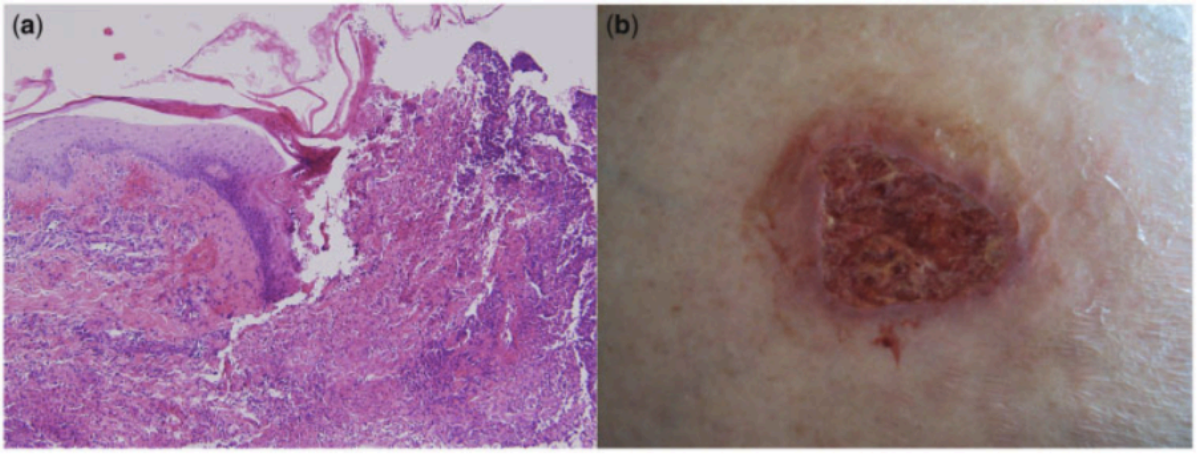
- Severe abscesses can be masked by treatment with sarilumab.

Mycobacterium chelonae

Wikipedia: Mycobacterium chelonae

Dos Santos Sobrin ja kollegat (2020 Kokotekstinä) antoivat 62 vuotiaalle nivelreumaa airastavalle naiselle sarilumabia viiden vuoden ajan.

Fig. 1 Ulcer formed at the site of injection of sarilumab



(a) Histology of the skin biopsy of the ulcer, with loss of continuity of the epidermis and chronic and acute inflammatory infiltrate without granulomatous findings. (b) Peri-umbilical cutaneous infection at the injection site.

Sarilumabi ja raskaus

Nana ja kollegat (2024 Kokotekstinä)

Tutkijoiden johtopäätös:
“In conclusion, we add further data for the use of anti-IL-6 in the third trimester of pregnancy. To our knowledge, we are the first to report neonatal haematological parameters and CRP response to infection after anti-IL-6 exposure in pregnancy. Although we have described transient neonatal cytopenias, they were not associated with adverse neonatal outcomes. Future studies of the administration of anti-IL-6 throughout pregnancy should be completed in women with rheumatological disease, in whom the risk of prematurity is smaller than in those with severe COVID-19, and thus studies in this population might be

better able to delineate the effect of anti-IL-6 on transient neonatal cytopenias.”