BIOLOOGILISED RAVIMID NAHAHAIGUSTE RAVIS

PILLE KONNO

DERMATOVENEROLOOG

KONVERENTS BIOLOOGILINE RAVI 14.02.2019, Tallinn

Eesti Reumatoloogia Selts
Estonian Society for Rheumatology

Meditsiini UUDISED

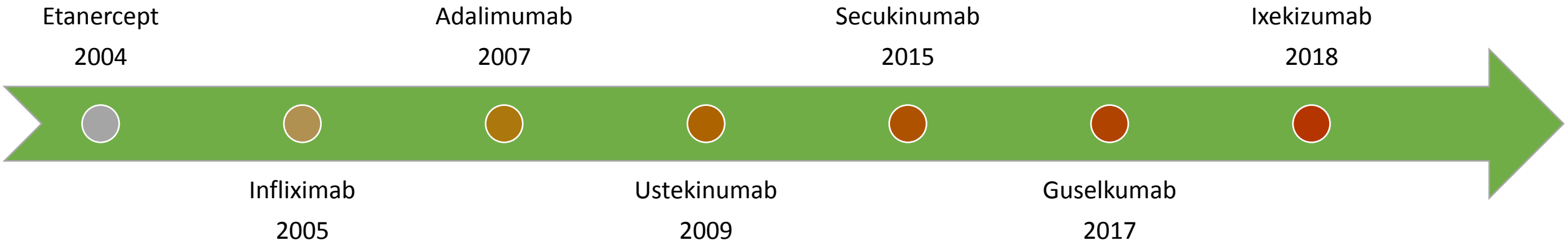
TAUST

2000	2010	2010	2011	2013
Dermato-veneroloog	CAIN457 2. faas	I bioloogilise ravi patsient	I HK bioloogilise ravi patsient	I Publikatsioon
AS ITK	Secukinumab	Adalimumab	Adalimumab	Secukinumab

[Efficacy and safety of secukinumab in the treatment of moderate-to-severe plaque psoriasis: a randomized, double-blind, placebo-controlled phase II dose-ranging study.]

Papp KA, Langley RG, Sigurgeirsson B, Abe M, Baker DR, Konno P, Haemmerle S, Thurston HJ, Papavassilis C, Richards HB. Br J Dermatol. 2013 Feb;168(2):412-21. doi: 10.1111/bjd.12110. Epub 2013 Jan 18. PMID: 23106107

PSORIAASI BIOLOOGILISTE RAVIMITE AJATELG



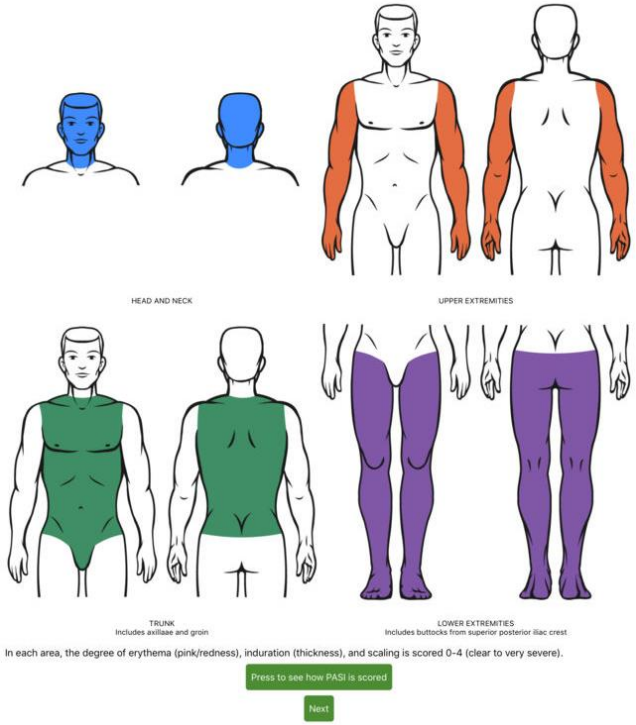
https://www.ema.europa.eu/
https://www.xcenda.com/insights/htaq-fall-2016-psoriasis-and-psoriatic-arthritis-targeted-therapies

PSORIAASI BIOLOOGILISED RAVIMID

2011	2015	2017	2019
Infliximab Adalimumab Ustekinumab Etanercept	Secukinumab	Guselkumab	Ixekizumab
Kood 344R	Kood 392R (biosimilar)	Kood 223R (1. valik)- 716,88 EUR 226R (2. valik) – 1200,09 EUR	

1. PSORIASIS VULGARIS – L40.0

PSORIAASI RASKUSASTME HINDAMINE



1. **PASI Score** (*Psoriasis Area and Severity Index*) ***0- 72,0***

2. **BSA** (*Body Surface Area*) ***0-100%***

3. **DLQI** (*Dermatology Life Quality Index*) ***0-30***

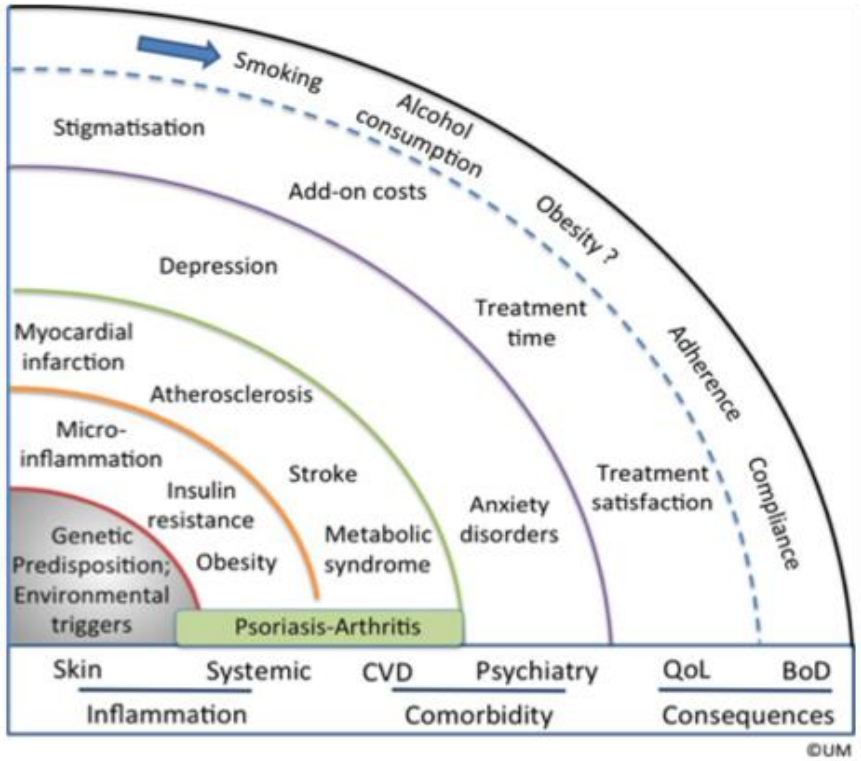
https://www.dermnetnz.org/topics/pasi-score/
http://pasi.corti.li/

Table 1: Calculation of the Psoriasis Area and Severity Index

Severity of psoriatic lesions (0 = none, 1 = slight, 2 = moderate, 3 = severe, 4 = very severe)				
	Head	Trunk	Upper limbs	Lower limbs
Erythema	0-4	0-4	0-4	0-4
Induration	0-4	0-4	0-4	0-4
Scaling	0-4	0-4	0-4	0-4
Total score = TS	Sum of the above	Sum of the above	Sum of the above	Sum of the above
Area of psoriatic involvement 0 = none, 1 = <10%, 2 = 10-30%, 3 = 30-50%, 4 = 50-70%, 5 = 70-90%, 6 = 90-100%				
Degree of involvement = DI	0-6	0-6	0-6	0-6
Multiply TS × DI	TS × DI	TS × DI	TS × DI	TS × DI
Correction factor for area of involvement = CF	0.10	0.30	0.20	0.40
TS × DI × CF	A	B	C	D
A + B + C + D = total PASI				

Adapted from table 8.2, Calculation of the Psoriasis Area and Severity Index (PASI), from Bolognia JL[13]

PSORIAASI ASPEKTID



Mrowietz U et al, 2014

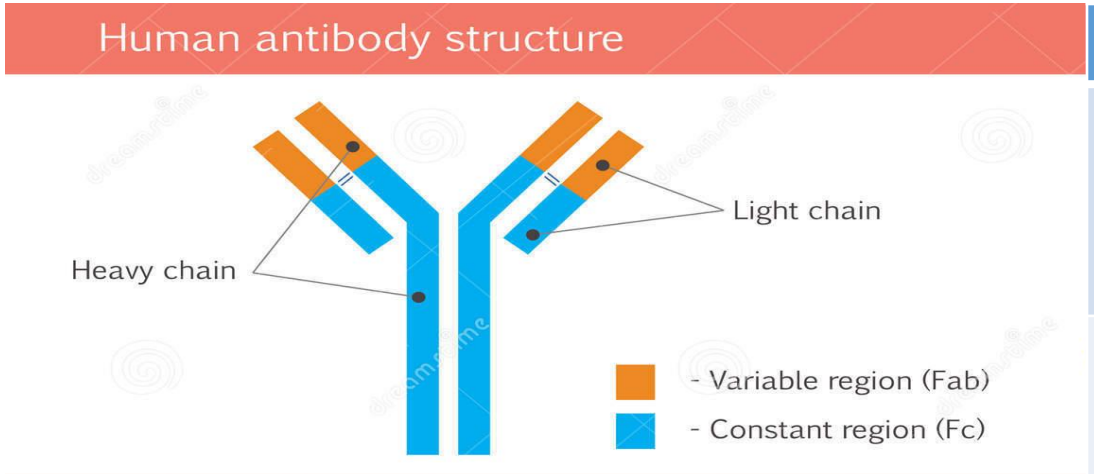
Mõju tööle	
• Töölt puudumine haiguse tõttu	39%
• Töö kaotus	21%
• Raskusi uue töökoha leidmisega	20%
• Takistused edutamisel	16%
Stigmatisatsioon	
• Häbitunne nahalööbe tõttu	81%
• Välimusega rahulolematus	75%
Depressioon	
• Depressiivsed meeleolud	54%
Suitsiidirisk	
• Soov surra	10%
• Suitsiidimõtted	6%
(Journal der Deutchen Dermatologischen Gesellschaft, Vol.7, Oct.2009)	

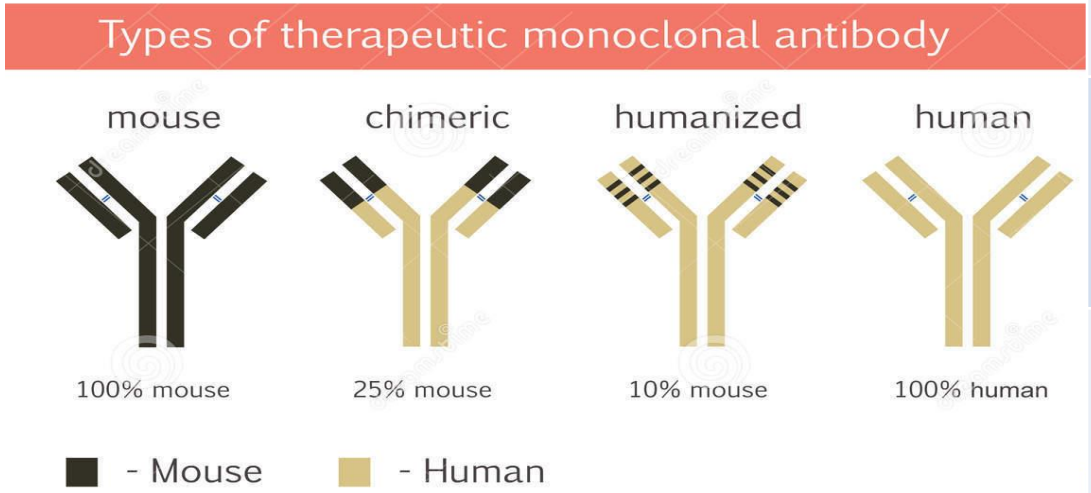
EESMÄRGID DERMATOLOOGIAS

EESMÄRK	PASI 50	PASI 75	PASI 90	PASI 100
AASTA	ENNE 2004	2004	2011	2014
RAVI	MTX	TNF INHIBIITORID	IL12/IL23 INHIBIITORID	IL-17 INHIBIITORID

https://www.clinicaltrialsregister.eu/about.html

MIS ON MIS? MONOKLONAALSED ANTIKEHAD

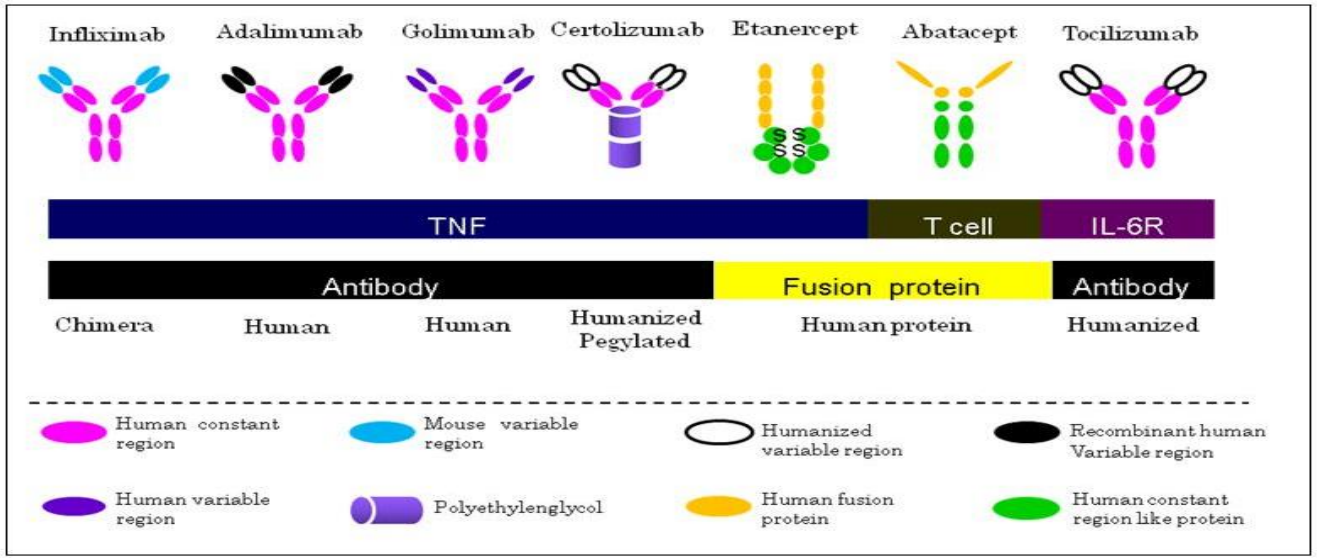




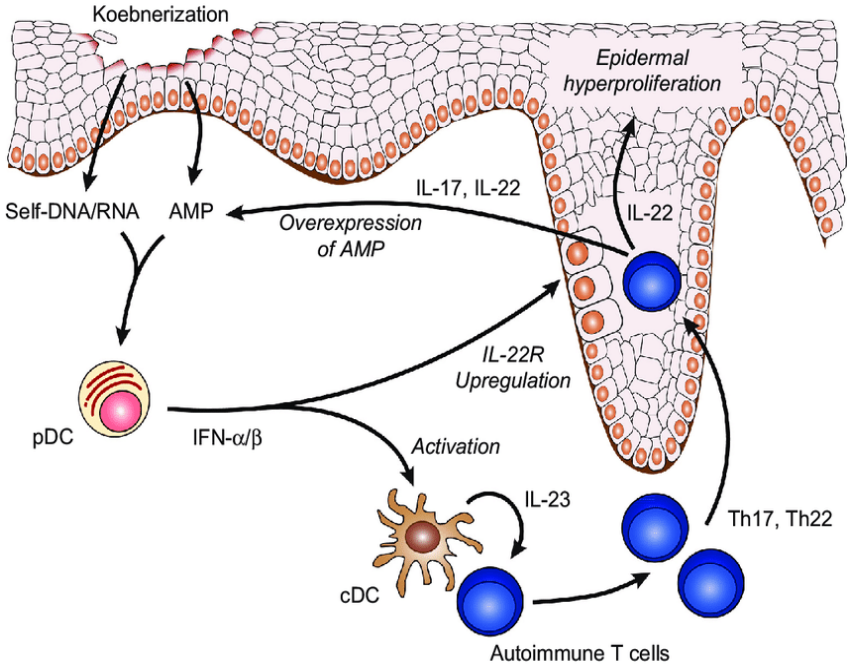
-cept	Retseptor ravim	Etanercept, abatacept, rilonacept
-ximab	Chimeric, monoklonaalne AK	Infliximab, rituximab
-zumab	Humanized, monoklonaalne AK	Certilizumab, tocilizumab, eculizumab
-mumab	Fully human, monoklonaalne AK	Adalimumab, golimumab, belimumab

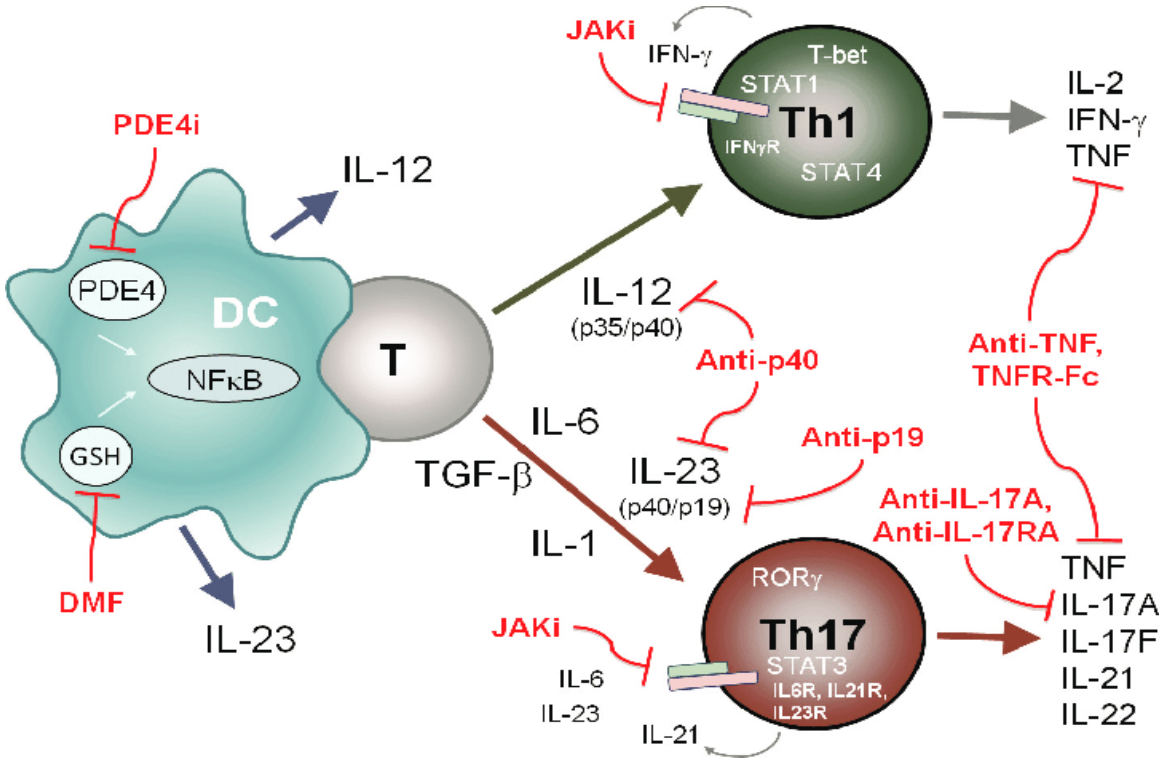
Prefix		Target
Varia	-o(s)-	luu
	-vi(r)-	viral
	-ba(e)-	bacterial
Ada-	-li(m)-	immune
	-le(s)-	infectious
	-ci(r)-	cardiovascular
	-mu(l)-	musculoskeletal
Secu- Uste-	-ki(n)-	interleukin
	-co(l)-	colonic tumor
	-me(l)-	melanoma
	-ma(r)-	mammary tumor
	-go(t)-	testicular tumor
	-go(v).	ovarian tumor
	-pr(o)-	prostate tumor
	-neu(r)-	nervous system
	-tox(a)-	toxin as target

	Source	Suffix
-u	**human**	-mab
-o-	**mouse**	
-a-	**rat**	
-e-	**hamster**	
-i-	**primate**	
-xi-	**chimeric**	
-zu-	**humanized**	
-axo-	**Rat/murine hybrid**	

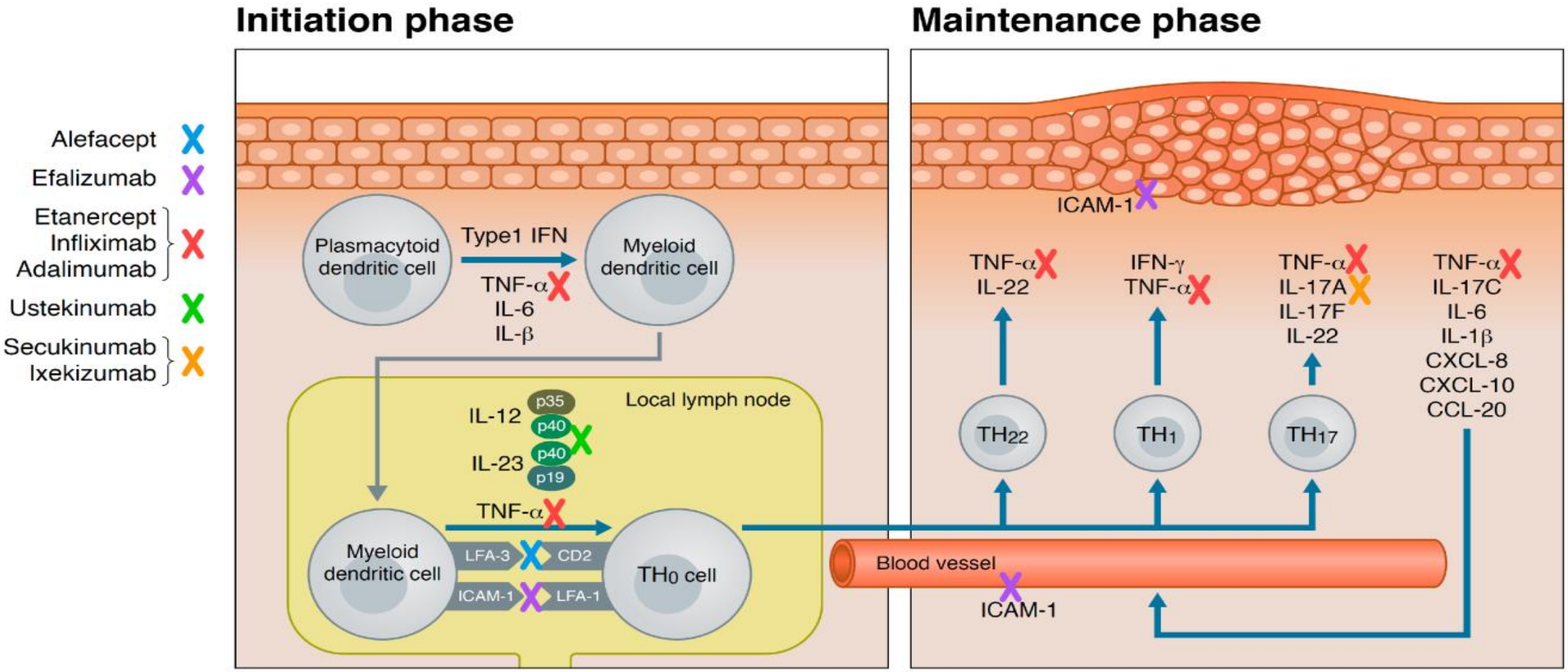


PSORIAASI PATOGENEES





BIOLOOGILISE RAVIMI TOIME



PSORIAASI BIOLOOGILINE RAVI EESTIS

	Adalimumab	Etanercept	Infliximab	Ustekinumab	Secukinumab	Guselkumab	Ixekizumab
	TNF	TNF	TNF	IL-12/23	IL-17	IL-23	IL-17A
Manustamine	s/c	s/c	i/v	s/c	s/c	s/c	s/c
Induktsiooni doos	JAH 80mg	EI	JAH 2W, 4W	JAH	JAH 0,1,2,3,4W	JAH 0,4W	JAH 2W (12W)
Doos	40 mg 2W	25/50 mg 1-2x W	5mg/kg (400mg) 8W	45/90 mg 12W	150/300mg 4W	100mg 8W	80mg 4W
Ise manustatav	JAH	JAH	EI	JAH	JAH	JAH	JAH
Kaalust sõltuv doos	EI	EI	JAH	JAH	EI	EI	EI

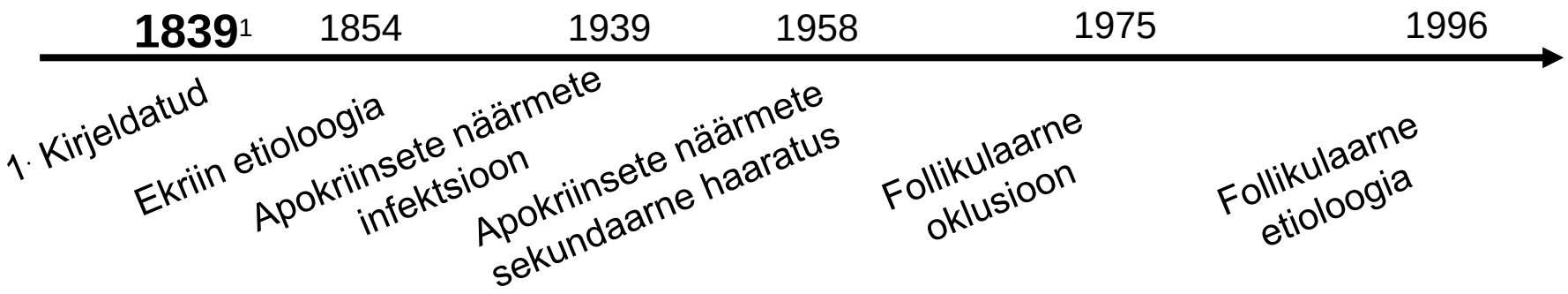
KONVENTSIONAALNE RAVI VÕRRELDES BIOLOOGILISE RAVIGA

	ACT	MTX	CYA	APR	Anti TNF	UST	Anti IL-17
Nahk	(+)	+	++	+	++	++	+++
Pea	(+)	+	++	+	++	++	++
Küüned	+	+	+	+	++	++	++
PPP	+	+	+	+/++	-	+	+
PsA	-	+	+	+/++	++	+/++	++
Dactylitis/ Enthesitis	-	-	+	+	++	++	++
Ohutus	+	+	+/-	+	+/++	++	+/++

Reich, K, 2018 - Expert clinical opinion

2. HIDRADENITIS SUPPURATIVA (HS) MÄDANE HIGINÄÄRMEPÕLETIK (L73.2)

HS TEADUSLIK ARENG



Sünonüümid:
Acne Inversa
Verneuil's Disease
Ectopic Acne
Pyoderma Fistulans Significa
Fox-Den Disease

Erinevad teooriad:

- Follikulaarne versus apokriinne
- Inflammatoorne vs. infektsioosne
- Geneetiline vs. keskkonna mõjudest tingitud

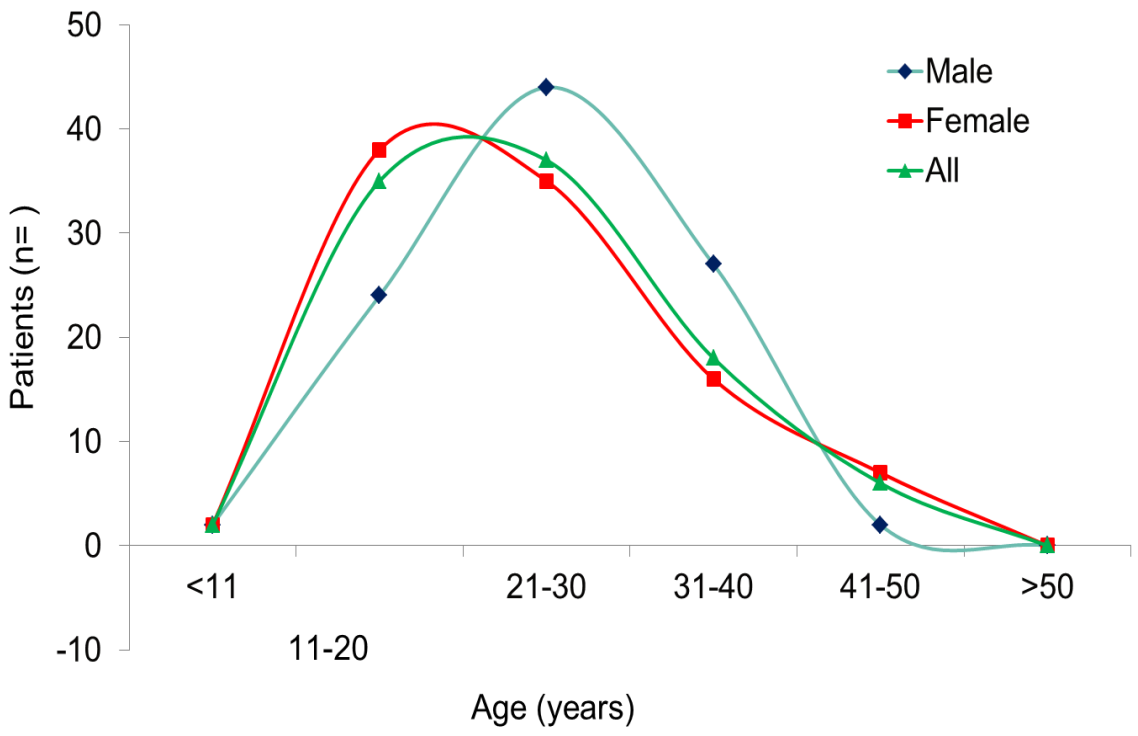
HS on krooniline, väga valulik, retsidiveeruv apokriinsete higinäärmete põletik

Alikhan. JAAD 2009;60:539. Brunsting. Arch Dermatol Syph 1952;65:303. van der Zee HH, Laman JD, Prens EP. Experimental Dermatology, 2012, 21, 735–739. Jemec GBE. N Engl J Med 2012;366:158-64

HS ESINEMINE

- Supuratiivne hidradeniit (HS) on krooniline, retsidiveeruv higinäärmeid haarav põletikuline nahahaigus, mis lokaliseerub keha erinevates piirkondades (Fimmel S, Zouboulis CC, Kurzen H, Kurokawa I, Jemec GB 2008)

- Haigust põeb ligikaudu 1% elanikkonnast
- Sagedamini haigestuvad naised, vanuses 20-40 eluaastat (Jemec GB, Revuz JE, Canoui-Poitrine F, Wolkenstein P, et al. Prevalence and factors associated with hidradenitis suppurativa: results from two case-control studies. J Am Acad Dermatol 2008)



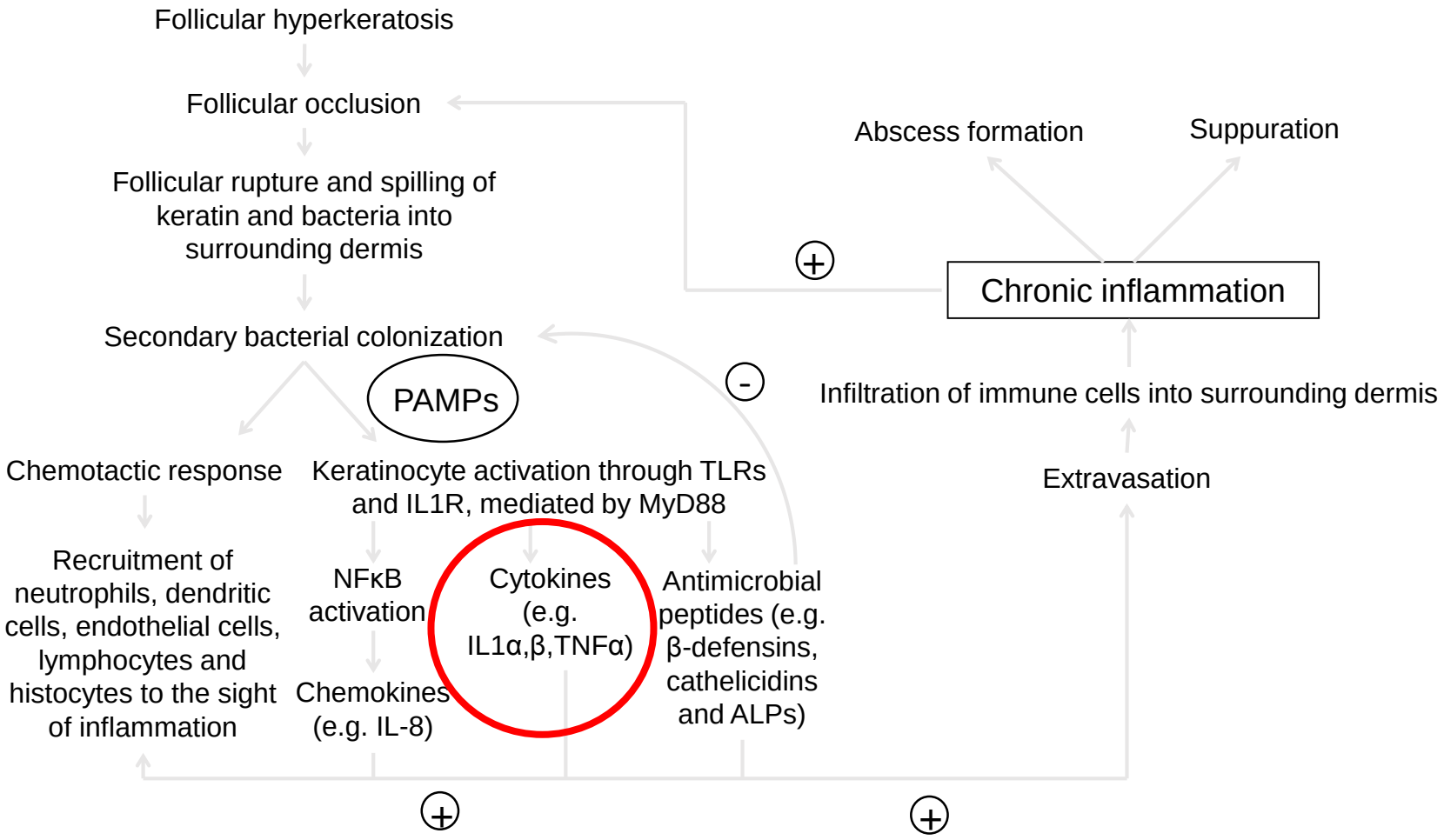
Sundaram M, et al. EADV 2012: P012. von der Werth. JEADV 2000;14:389. Cosmatos et al. JAAD. 2013 Mar;68(3):412-9. Jemec GB. N Engl J Med. 2012;366(2):158-164. Palmer R, Keefe M. Clin Dermatol. 2001;26:501–503

HS RISKIFAKTORID

Vanus	Sagedamini 21-23a
Sugu	Naistel esineb 2-5 korda sagedamini kui meestel
Geneetika/perekonna anamnees	Autosoom-dominantne pärilikkus, kandidaatgeenid 6. ja 9. kromosoomis
Suitsetamine	HS patsientide hulgas on suitsetajaid 12 korda sagedamini. Suitsetamine korreleerub HS raskusastmega
Adipoossus	4.42 korda kõrgem HS patsientide hulgas, võib samuti mõjutada haiguse raskusastet
Hormoonid	Limiteeritud tõendid HS ja hüperandrogenismi, polütsüstilise munasarjade sündroomi vahel

Jemec GB. N Engl J Med. 2012;366(2):158-164. Revuz JE, et al. J Am Acad Dermatol. 2008;59(4):596-601. Alikhan A, et al. J Am Acad Dermatol. 2009;60(4):539-561. Yazdanyar S, et al. Curr Opin Infect Dis 2011;24(2):118-123

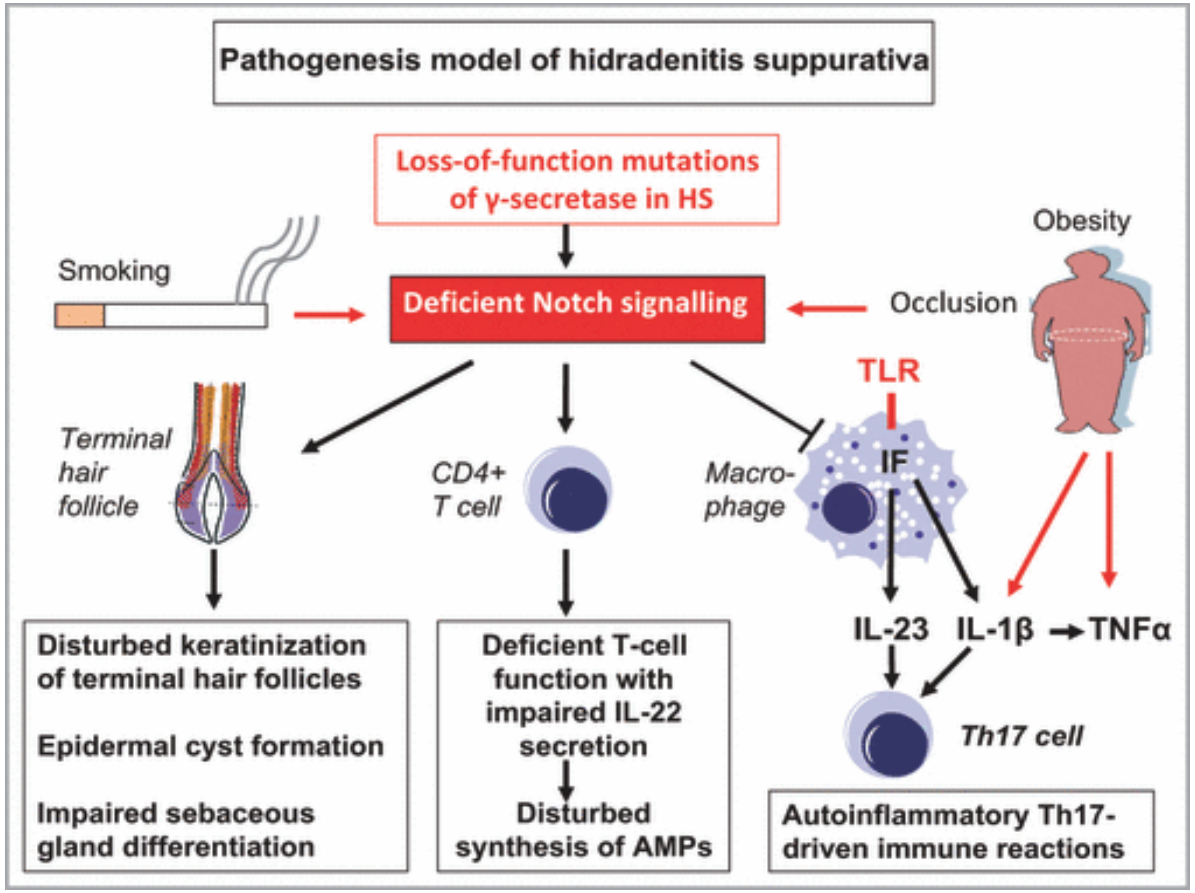
HS PATOGENEES



PAMPs,pathogen-associated molecular pathogens
TLRs, toll-like receptors

Nazary M et al. Eur J Pharm 2011;672:1 – 8

HS PATOGENEES

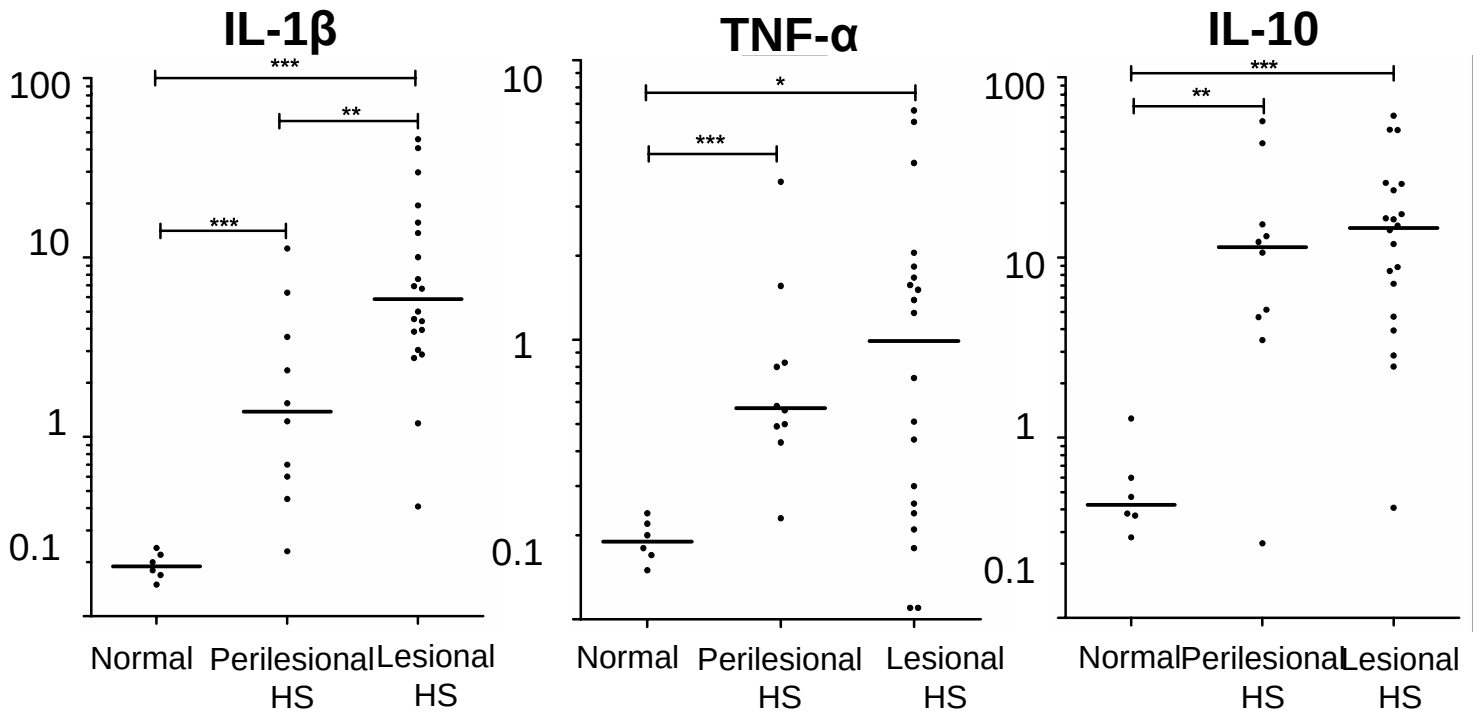


Melnik BC, et al, Br J Dermatology, 2013

HS patogenees ekspertide arvates
Anti mikroobsete peptiidide (AMP) ekskretsioon
Folliiklite biomehhaniline olukord
Tsütokiinide vabanemine
TNF-a vabanemine
On erinevad HS fenotüübid
Suitsetamisega seotud

HS TSÜTOKIINIDE TASE

- Tsütokiinide tase korreleerub HS raskusastmega

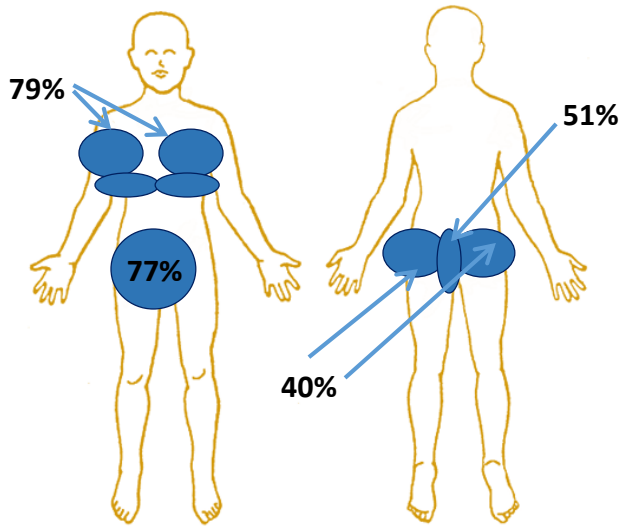


Fold ↑ in Lesion		
	PsO	HS
IL-1β	4	31
TNFα	1	5
IL-10	2	34

van der Zee. Br J Dermatol 2011;164:1292.

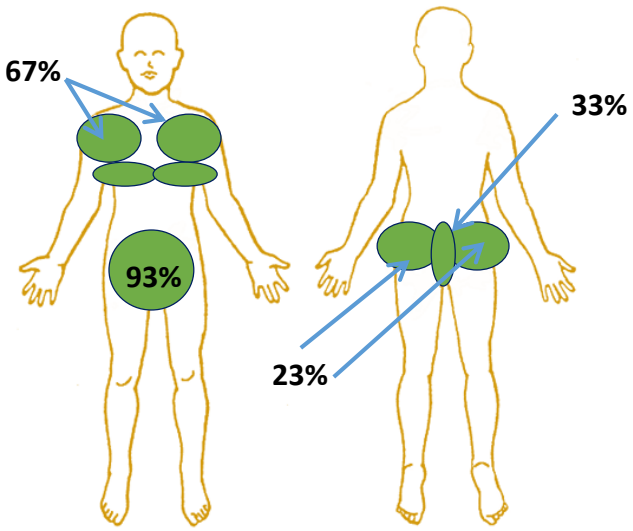
KLIINILISE PILDI ERINEVUS MEESTEL JA NAISTEL

Mehed



Kaenlaalused*	*P*=.06
Tuharad*	*P*=.006
Perianaalselt ja gluteaalselt*	*P*=.05

Naised



Kubeme piirkond*	*P*<.001
Rindade all*	*P*<.001

*The P value is comparing the statistical differences between men and women (n=302)

Poli F, et al. Clinical Presentation in HS. Jemec et al, eds. Springer, Heidelberg, 2006;11–24.

HS RASKUSASTMED

- Hurley staadium
- Sartorius skoor
- HS Physician’s Global Assessment Score (PGA)
- HS Severity Index (SI)
- Hidradenitis Suppurativa Clinical Response (HiSCR)

HS RAVI VÕIMALUSED

Ravi	Näiteks	Märkused
Süsteemsed/lokaalsed AB	Clindamycin	Ravib põletikku, kuid mitte haigust
Retinoid	Isotretinoin	Aitab konglobaat acne puhul, mitte HS puhul, kuna rasueritus väheneb
Antiandrogeen	Spironolactone	Parem tulemus kui AB
Intralesionaalsed kortikosteroidid	Triamcinolone	Sobib üksiku lesiooni puhul
Süsteemsed GKK	Prednisolone	Ägeda haigsetumise puhul võib olla effektiivne, reboundi oht
Süsteemsed Immunosupressandid	Cyclosporine	Ei ole parem tulemus kui GKK
Osalised immunosuppressandid	Dapsone	Mehhanism ebaselge, esineb mõningane efektiivsus
Kirurgia	Ekstsisioon/laser	Valu suhtes kontroll hea, kuid retsidiveerumise risk
TNF Antagonistid	Humira	Oluline efektiivsus võrreldes platseebo grupiga

Yazdanyar S et al. 2010;5(3):335-343. Gill L, et al. F1000 Prime Rep. 2014;6:112.

HS BIOLOOGILINE RAVI

- Kui konventsionaalsed ravimid on osutunud ebaefektiivseteks, siis on näidustatud **bioloogiline ravi**. HS Euroopa S1 ravijuhises on bioloogilistest ravimitest **adalimumab** toodud ära ühe valikuna **infliksimabi** kõrval.
- Ravi osutatakse mõõduka ja raske HS patsiendile (Hurley II ja III st), kellel haigus on olnud resistentne senistele konventsionaalsetele ravimeetoditele.
- **Adalimumab** on TNFα vastane monoklonaalne inimese IgG1 antikeha, mis on oma efektiivsust ja ohutust tõestanud erinevate krooniliste immuunpõletikuliste haiguste ravis (nt reumatoidartriit, psoriaas, psoriaatiline artriit). Adalimumabi efektiivsus HS ravis on tõestatud randomiseeritud II ja III faasi kliinilistes ravimuuringutes. Adalimumab on Euroopa Liidus ainus HS näidustusel registreeritud bioloogiline ravim.

HS kriteeriumid:

1) Esmased positiivsed diagnoosikriteeriumid:
   - ✓ anamneesis korduvalt (vähemalt 2-3 korda 6 kuu jooksul) esinevad valulikud ja/või supuratiivsed haiguskolded;
   - ✓ kliinilises pildis sõlmede, abstsesside, fistlite ja armide esinemine nahavoltides, eelislokalisatsiooniga kaenlaalustes, kubemevoltides ja anogenitaalpiirkonnas, kuid haaratud võivad olla kõik teised nahavoldid, sh ka rinnavoldid, tuharad ja kukal.
2) Teisesed positiivsed diagnoosi kriteeriumid:

✓ perekonnas HS esinemine;

✓haiguskoldest võetud bakterioloogiline külv on negatiivne, esineb normaalne mikrofloora

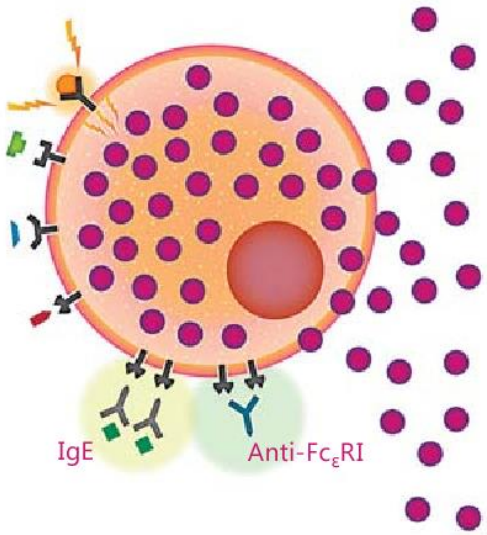
3. KROONILINE URTIKAARIA (CSU) – L50.8

CSU PATOGENEES

Mast cell activation:
Omalizumab*
Plasmapheresis
IVIG
Anti-CD20

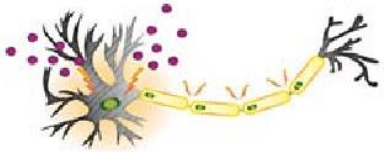
Mast cell degranulation:
Antihistamines*
Corticosteroids
Cyclosporine*
Tacrolimus
Phototherapy
Metothrexate

Receptors on target organs:
Antihistamines*
Antileukotrienes
Dapsone
Colchicine
Mycophenolate mofetil
Anti-IL-1/anti-TNF

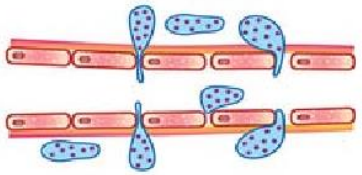


IL-1
IL-2
IL-4
IL-5
IL-6
IL-8
IL-13
TNF-α
GM-CSF
VPF/VEGF
PGD_2
LTC_4
LTD_4
PAF
Histamine
Serotonin
Heparine
Chondroitin sulfate
Tryptase

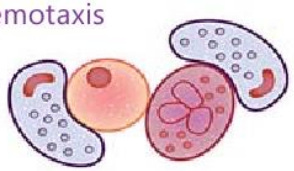
▶ Pruritus

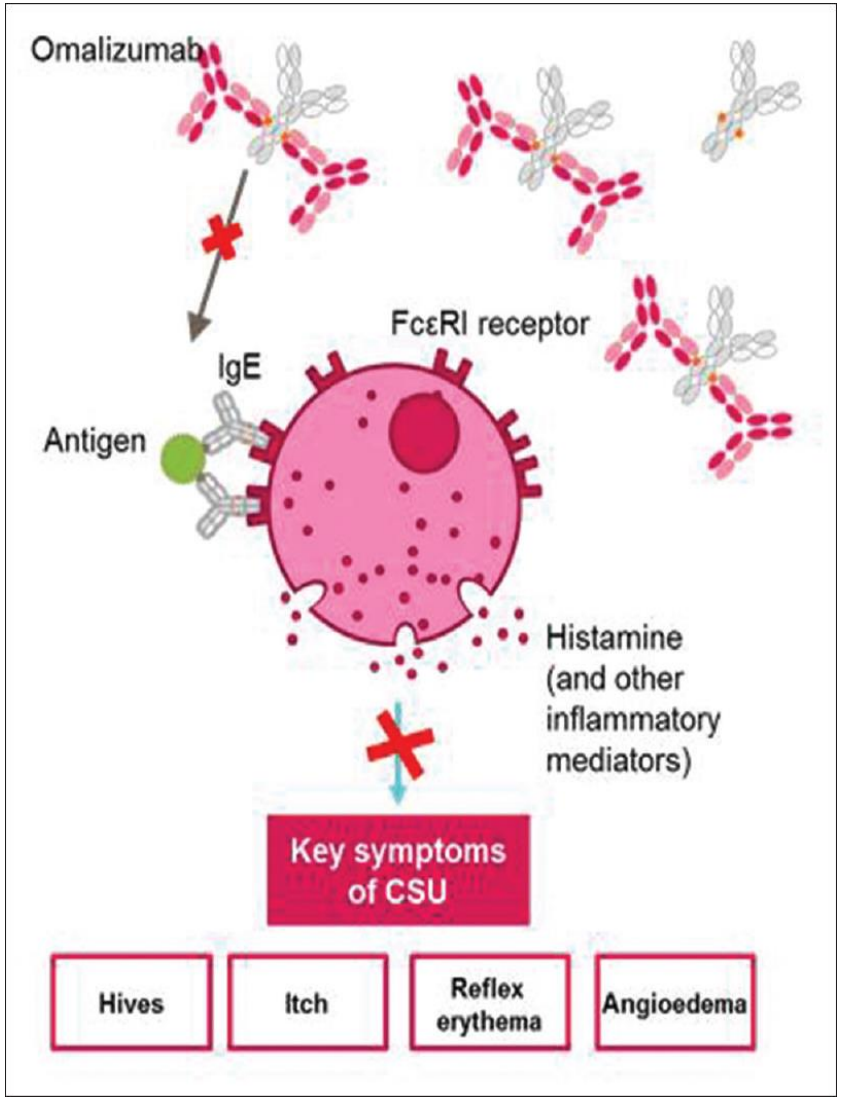


▶ Vasodilatation and extravasation



▶ Chemotaxis





CSU BIOLOOGILINE RAVI

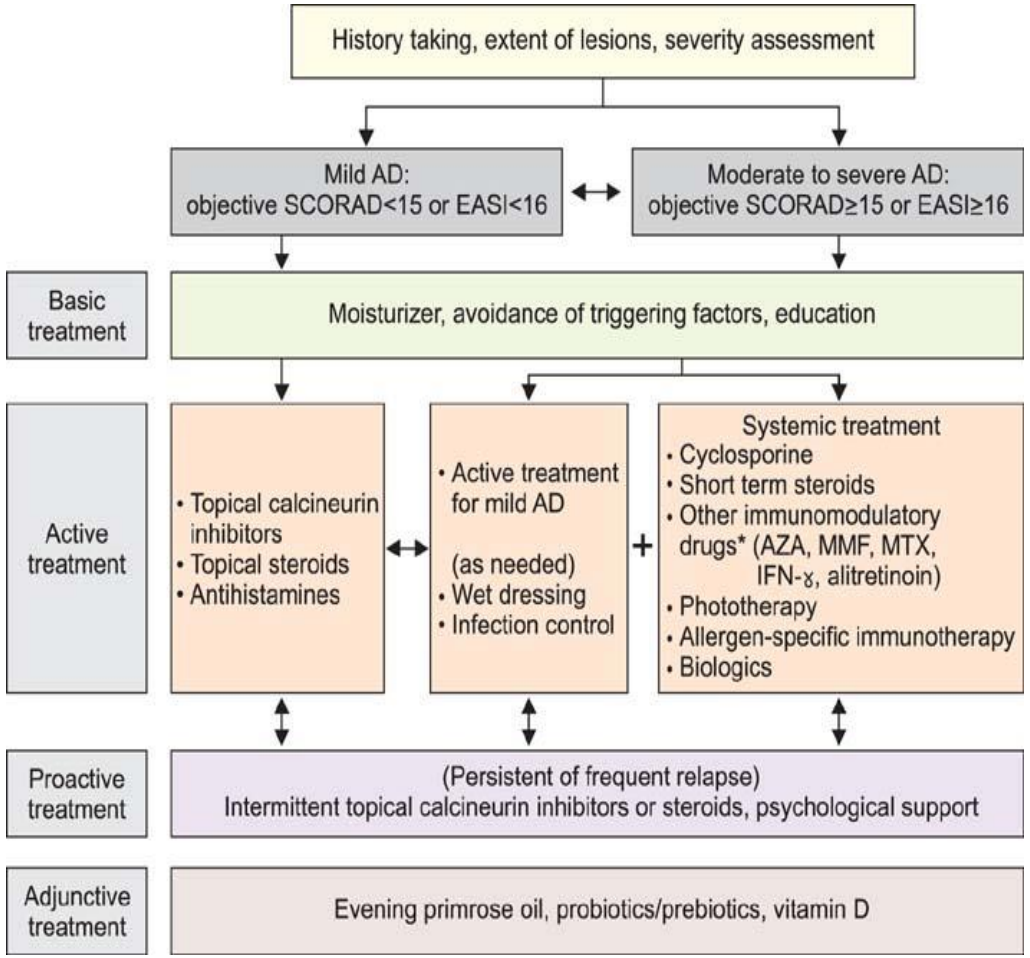
- Omalizumab (Xolair)
- Üks viaal sisaldab 75 või 150 mg omalizumabi.
- Omalizumab on humaniseeritud monoklonaalne antikeha, toodetud rekombinantse DNA tehnoloogia abil hiina hamstri munasarja (Chinese hamster ovary, CHO) imetaja rakuliinis.
- Pärast lahustamist sisaldab viaal 125 mg/ml omalizumabi (75 mg 0,6 ml-s).
- 150-300mg s/c 4w

BIOLOGICS FOR CHRONIC URTICARIA.

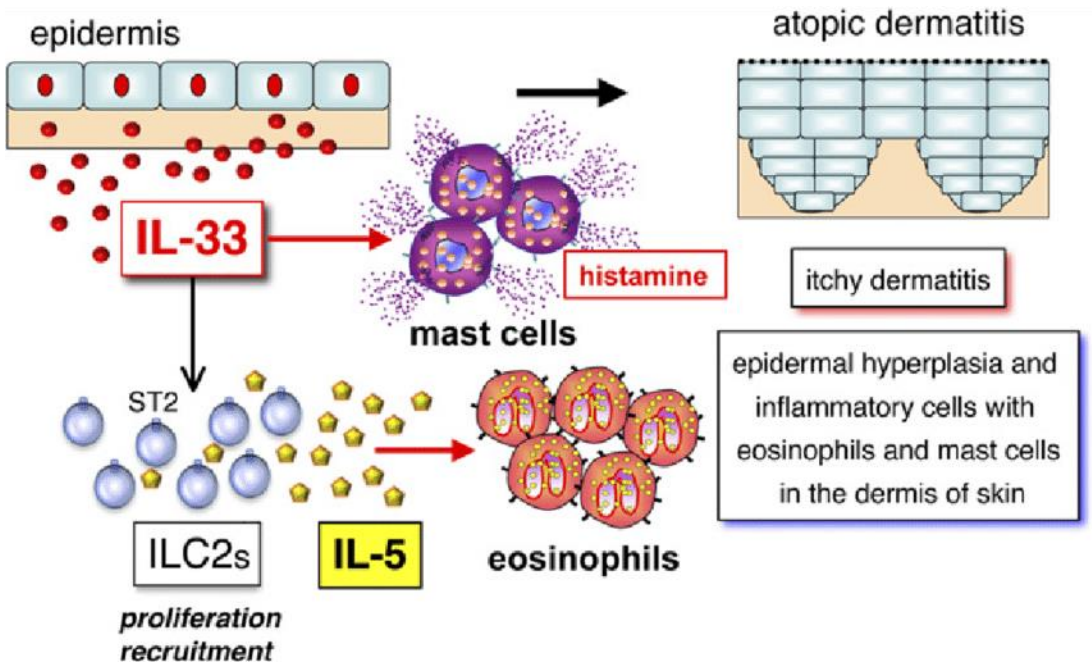
Biologic	Target	Diseases Studied
Omalizumab	IgE	CSU (FDA approved) Physical urticarias Urticarial vasculitis
Quilizumab	IgE	CSU
Etanercept Adalimumab Infliximab	TNF-alpha	CSU Physical urticarias Urticarial vasculitis
Rituximab	CD20	CSU Physical urticarias Urticarial vasculitis
Anakinra Canakinumab Rilonacept	IL-1	CAPS Schnitzler syndrome CSU Urticarial vasculitis

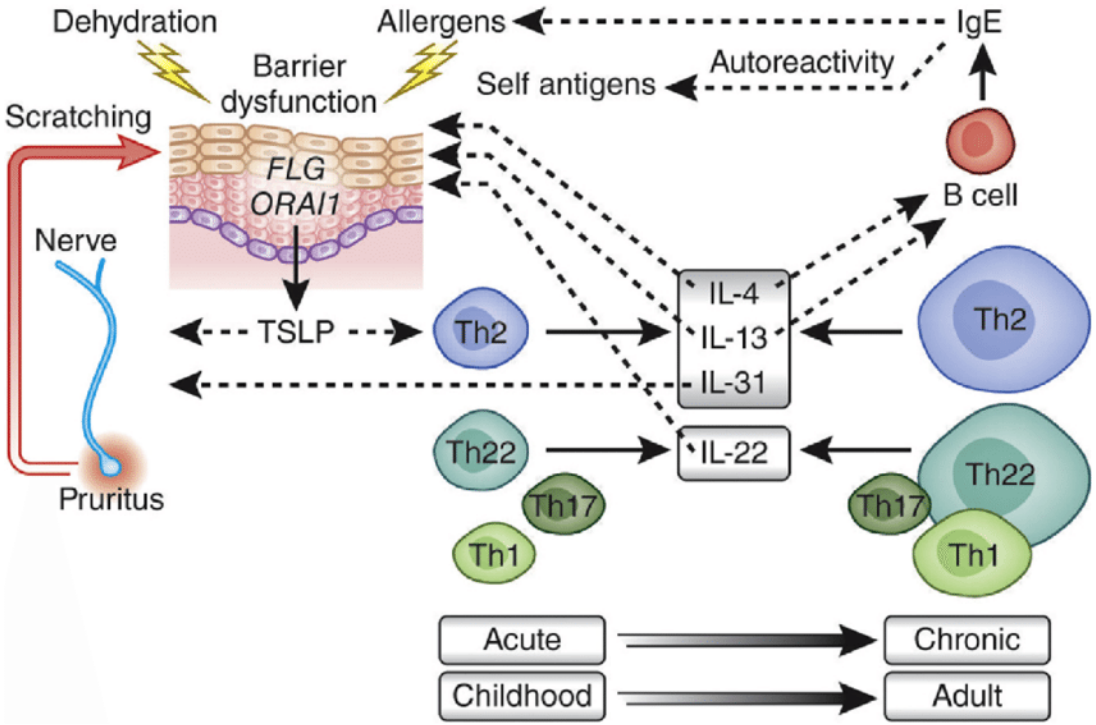
CSU: chronic spontaneous urticaria.

4. ATOOPILINE DERMATIIT (AD) – L20.8

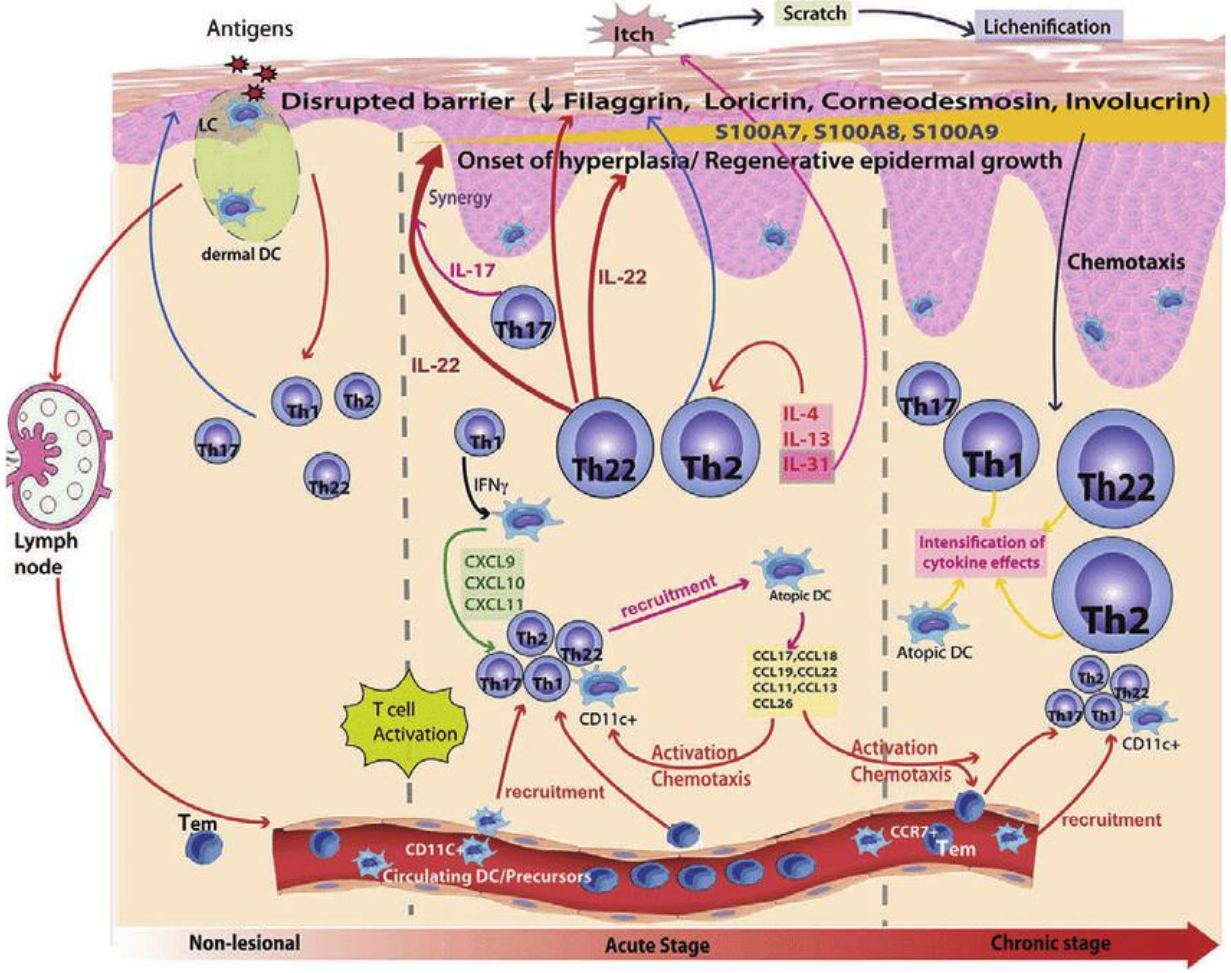


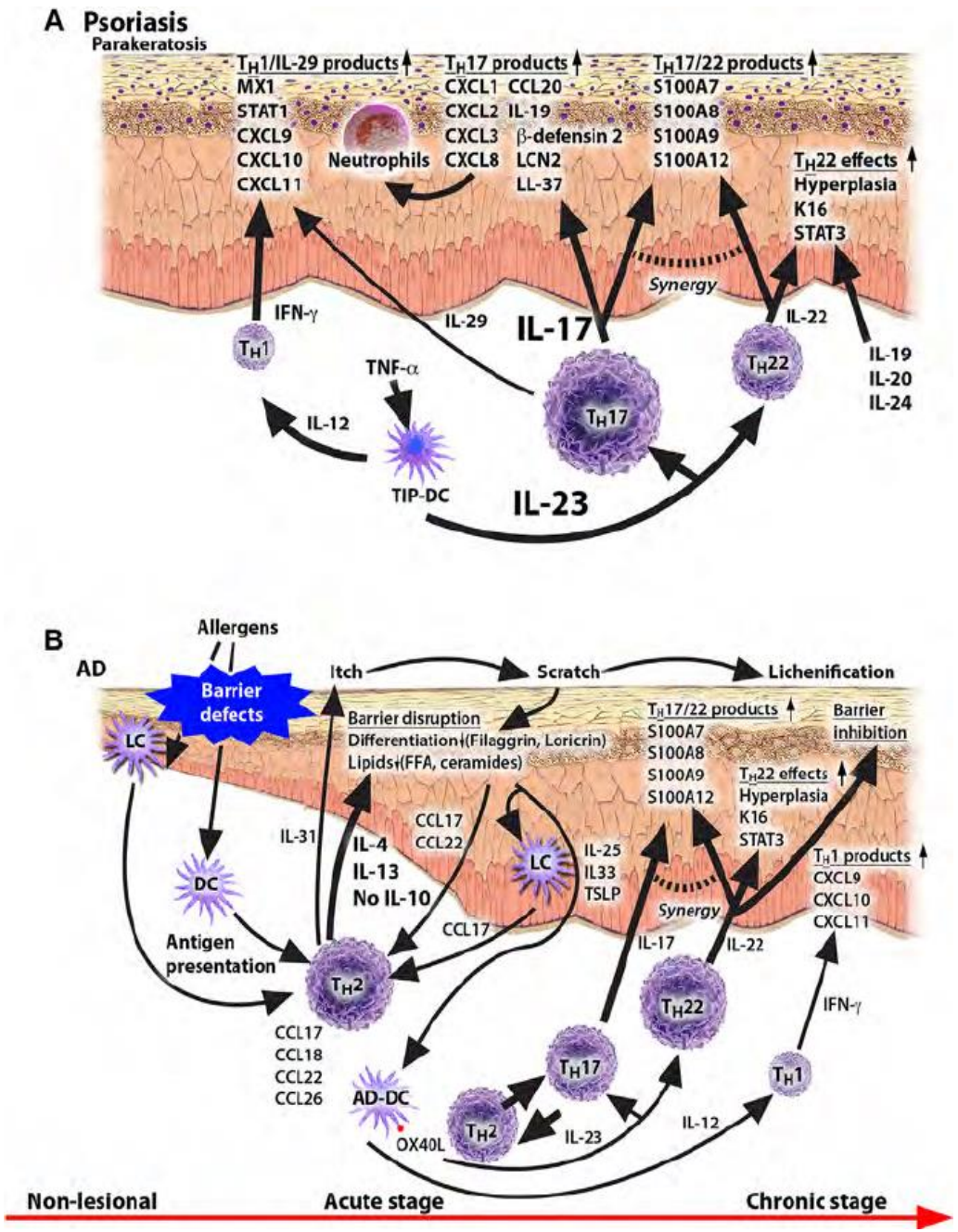
AD PATOGENEES





PSORIAASI JA AD VÕRDLUS





AD BIOLOOGILINE RAVI -Dupilumab

- Dupilumab (Dupixient) 300mg s/c
- Atoopilise dermatiidiga patsientide organismis tekib palju valke interleukiin 4 (IL-4) ja interleukiin 13 (IL-13), mis osalevad haigust põhjustavates protsessides.
- Monoklonaalne antikeha, mis blokeerib IL-4 ja IL-13 retseptoreid.
- Retseptorite blokeerimisega takistab dupilumaab IL-4 ja IL-13 toimimist ja leevendab haiguse sümptomeid.
- Induktsioon doos 2x 300mg, edasi 2w.

UUED BIOLOOGILISE RAVI NÄIDUSTUSED:

PEMFIGUS

- Rituximab

ALOPECIA AREATA

- Ruxolitinib
- Bariticinib

VITILIGO

- Tofacitininb

PYODERMA GANGRENOSUM

GRANULOMA ANNULARE

PITYRIASIS RUBRA PILARIS