PRACTOPICS 25 november 2022

Reumatologie

De Knop Kathleen	[Sint-Augustinus, Sint-Jozef]
Vos Ine	[Sint-Augustinus, Sint-Jozef]
Vanden Bulcke Michaël	[Sint-Augustinus, Sint-Vincentius]
De Bock Wouter	[Sint-Augustinus]
De Clercq Luc	[Sint-Augustinus]
Hoffman Ilse	[Sint-Augustinus, Sint-Vincentius]

JAK-inhibitoren

The new kids on the block

De Knop Kathleen
Vos Ine
Vanden Bulcke Michaël

Overzicht

A. Inleiding
   1. De januskinasen
   2. De januskinase-inhibitoren

B. JAK inhibitoren in de reumatologie
   1. Welke Pathologie, combinaties, plaats in guidelines
   2. Welke effecten
   3. Screening bij opstart
   4. Monitoring

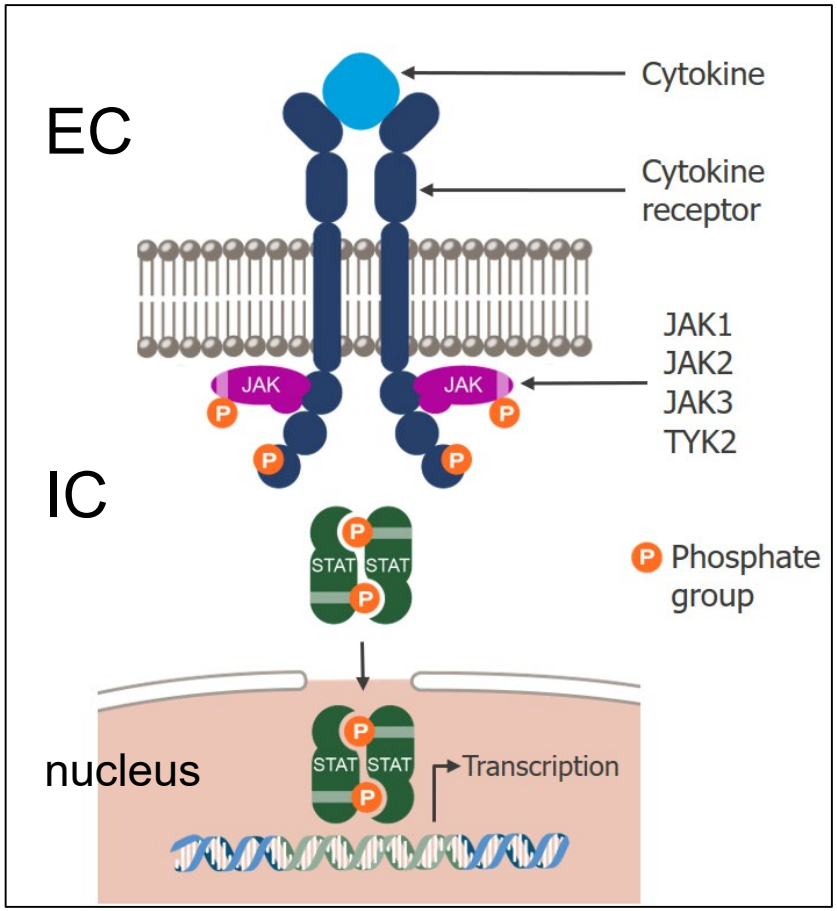
C. Veiligheid bij JAK-inhibitoren
   1. Infectieus
   2. Veneus Trombo-emboligeen Event (VTE)
   3. Major Adverse Cardiovascular Event (MACE)
   4. Oncologisch
   5. Zwangerschap & borstvoeding

D. Toekomst van JAK-inhibitore

E. Take home messages

A. Inleiding

1. De Januskinasen



A. Inleiding

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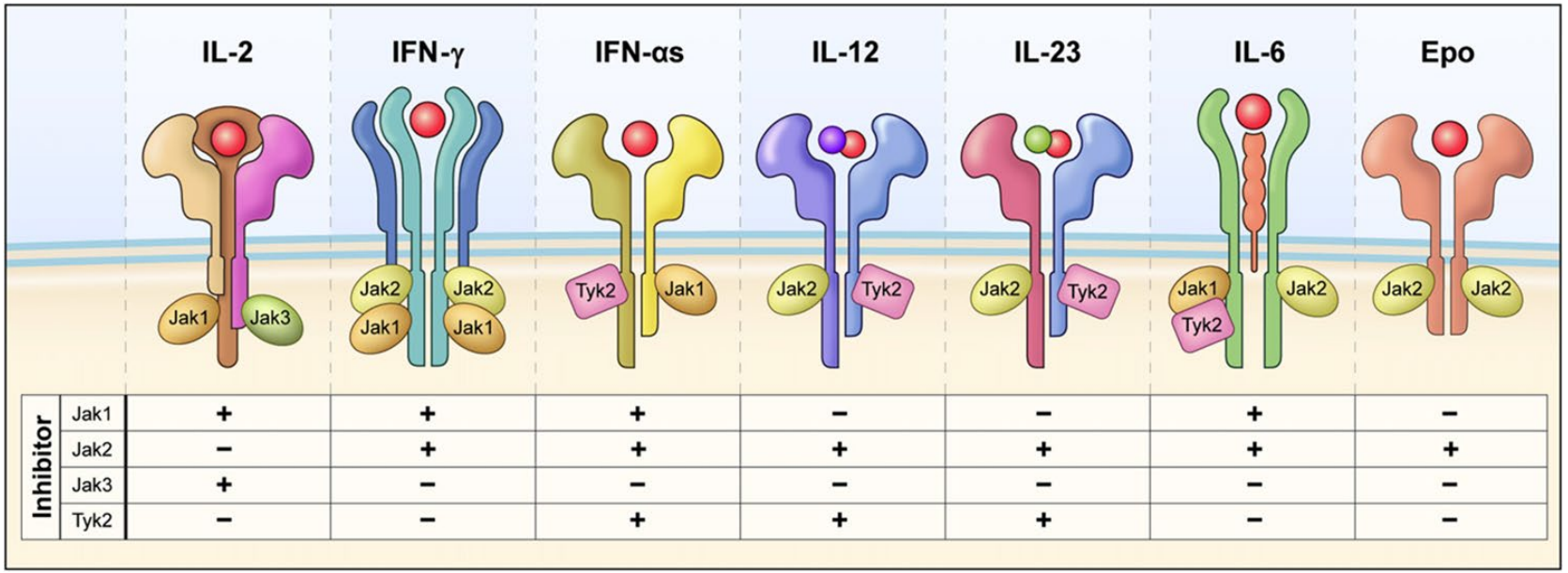
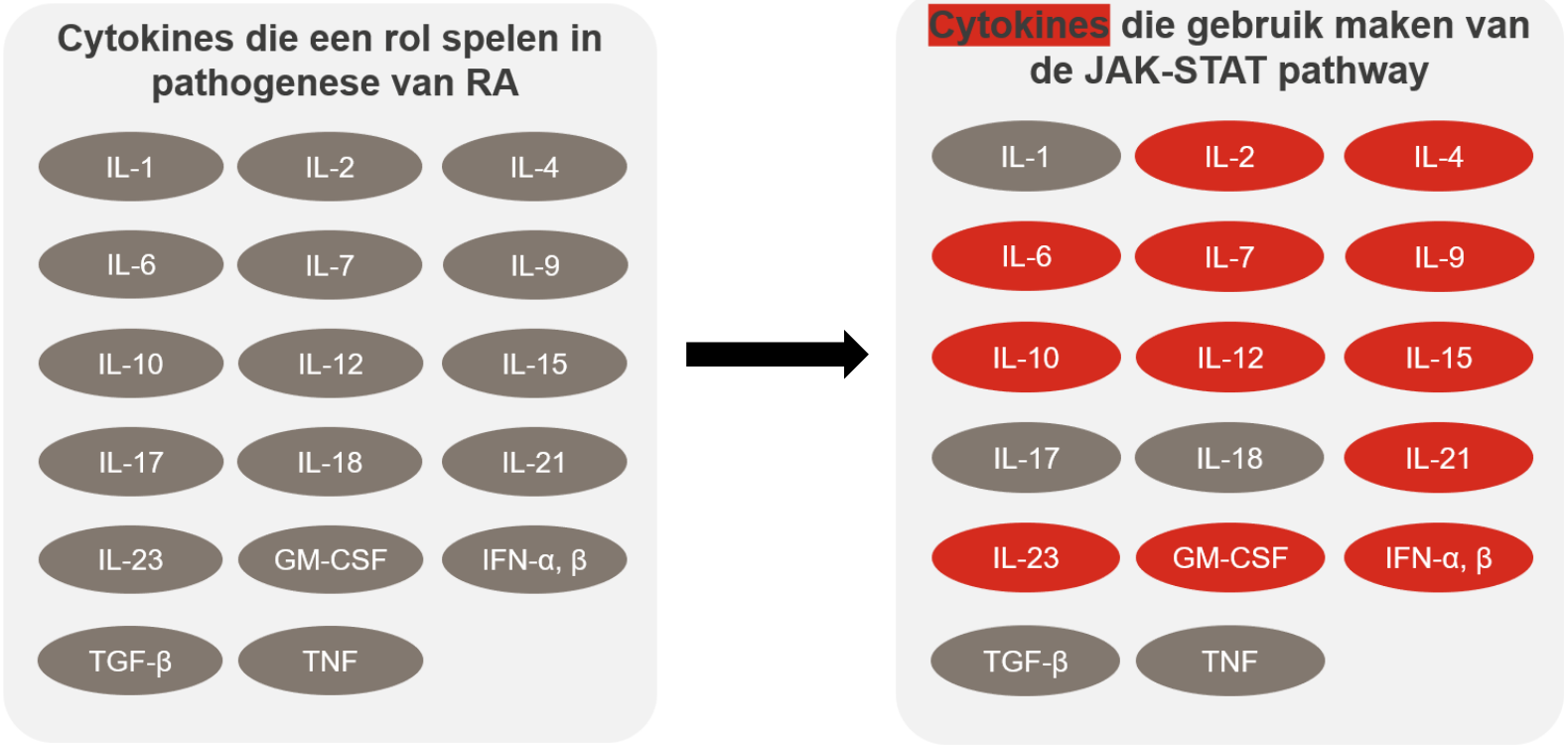


Inhibitor	IL-2	IFN-γ	IFN-αs	IL-12	IL-23	IL-6	Epo
Jak1	+	+	+	−	−	+	−
Jak2	−	+	+	+	+	+	+
Jak3	+	−	−	−	−	−	−
Tyk2	−	−	+	+	+	−	−

A. Inleiding

1. De Januskinasen



A. Inleiding

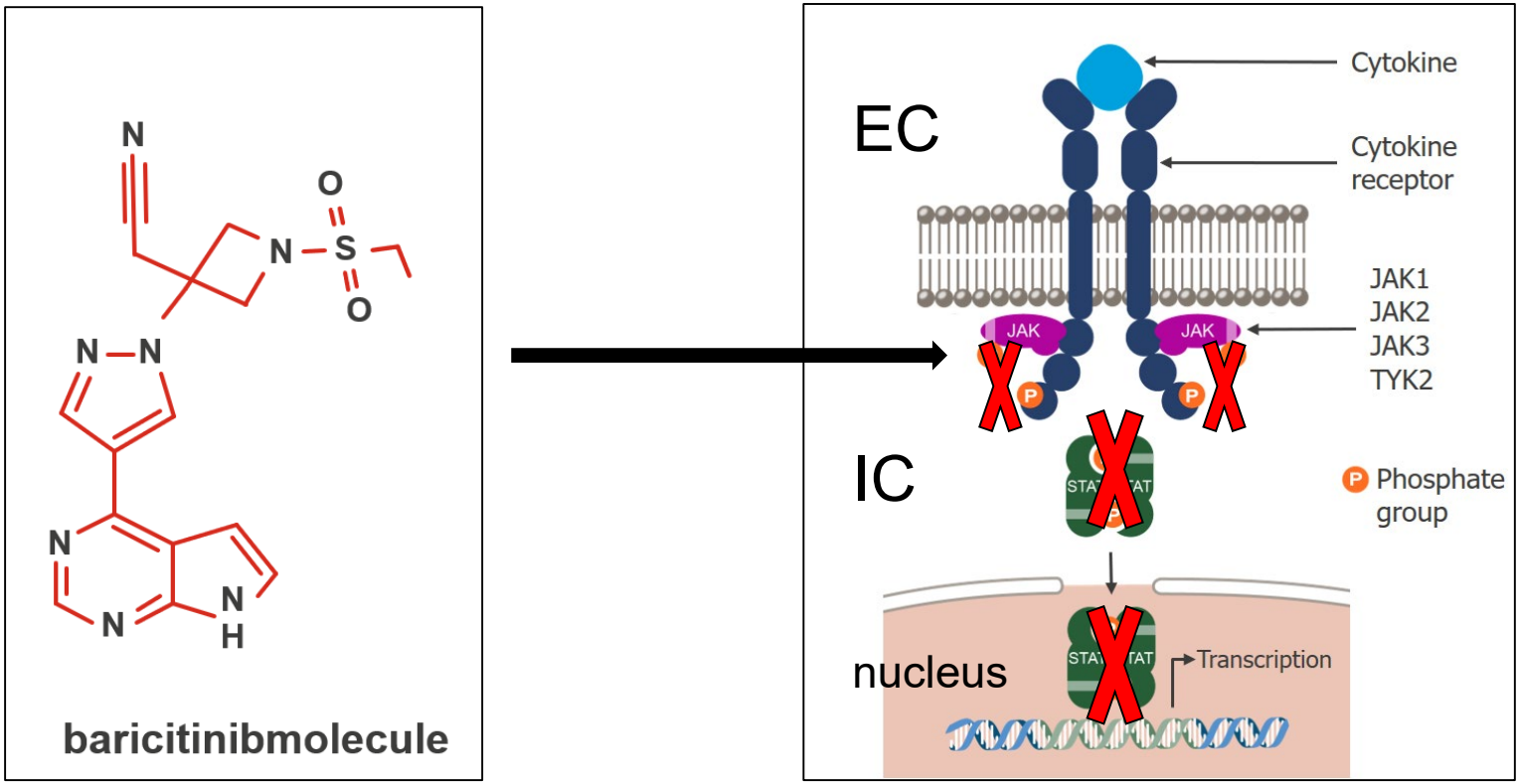
2. De Januskinase-inhibitoren

*Table 2. Nomenclature of disease-modifying antirheumatic drugs, proposed by Smolen et al., and adopted by the EULAR Task Force in the 2013 recommendations (Smolen et al. 2014, *Smolen et al. 2014).*

Disease Modifying Antirheumatic Drugs (DMARDs)			
Synthetic DMARDs (sDMARDs)		Biological DMARDs (bDMARDs)	
Conventional synthetic DMARDs (csDMARDs)	Targeted synthetic DMARDs (tsDMARDs)	Biological originator (boDMARDs)	Biosimilar (bsDMARDs)
Methotrexate (MTX) *Leflunomide (LEF)* *Sulfasalazine (SSZ)* *Hydroxychloroquine**	*Tofacitinib*	TNF blockers - *Adalimumab* (HUMIRA) - *Certolizumab* (CIMZIA) - *Etanercept* (ENBREL) - *Golimumab* (SIMPONI) - *Infliximab* (REMICADE) Anti-IL6R -*Tocilizumab* (ROACTEMRA) LcT co-stimulation blocker -*Abatacept* (ORENCIA) Anti-CD20 (LcB targeting) -*Rituximab* (MABTHERA) IL-1Ra -*Anakinra* (KINERET)†	TNF blockers -*Etanercept* (BENEPALI) - *Infliximab* (REMSIMA, INFLECTRA)

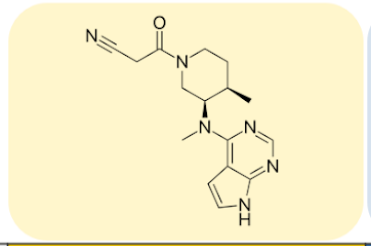
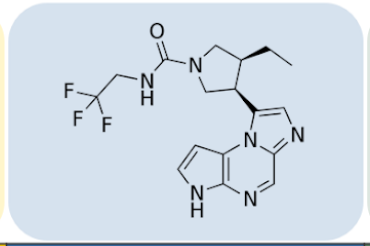
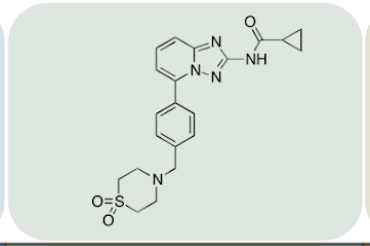
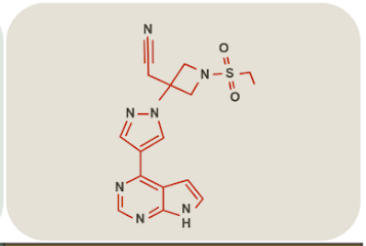
A. Inleiding

2. De Januskinase-inhibitoren



A. Inleiding

2. De Januskinase-inhibitoren

				
	Tofacitinib	**Upadacitinib**	**Filgotinib**	**Baricitinib**
Dose	5 mg BID (5 mg QD[a]) 11 mg XR QD	15 mg XR QD	200 mg QD (100 mg QD[a])	4 mg QD (2 mg QD[a])
JAK selectivity (*in vitro*), IC_{50}	JAK3: 1.6, JAK1: 3.2, JAK2: 4.1, TYK2: 34	JAK1: 47, JAK2: 120, JAK3: 2304, TYK2: 4690	JAK1: 10, JAK2: 28, TYK2: 116, JAK3: 810	JAK1: 5.9, JAK2: 5.7, JAK3: >400, TYK2: 53
Half-life	~3 hours	8-14 hours	19 hours	12 hours
Excretion	Unchanged parent: 70% hepatic, 30% renal	Parent and metabolites: 43% urine, 53% feces	Parent and metabolites: 87% urine, 15% feces	Parent and metabolites: ~69% urine, 15% feces
Drug-drug interactions	Strong CYP3A4 inhibitors or inducers, moderate CYP3A4 inhibitors with strong CYP2C19 inhibitors, immunosuppressants	Strong CYP3A4 inhibitors or inducers	CES2 inhibitors, CYP1A2 or P-gp or BCRP substrates	OAT3 inhibitors with a strong inhibition potential, such as probenecid

B. JAK-inhibitoren in de reumatologie

1. Welke pathologie, combinaties, plaats in guidelines

Reumatoïde artritis

Bij onvoldoende effect/ intolerantie van 2 csDMARDS o.a. MTX

Monotherapie/ combinatie met MTX of andere csDMARDs

Tofacitinib, Upadacitinib, Baricitinib, Filgotinib

B. JAK-inhibitoren in de reumatologie

1. Welke pathologie, combinaties, plaats in guidelines

Artritis psoriatica

Bij onvoldoende effect op tenminste één csDMARD én ten minste één bDMARD

EMA/FDA goedkeuring voor

- Tofacitinib
- Upadacitinib

Filgotinib: resultaten van fase III trial nog niet gepubliceerd (EQUATOR)

B. JAK-inhibitoren in de reumatologie

1. Welke pathologie, combinaties, plaats in guidelines

Axiale spondyloartritis

Actieve, niet-radiografische axiale spondyloartritis met objectieve tekenen van ontsteking (CRP stijging en/of MRI criteria), die onvoldoende reageren op NSAID's

➔ Upadacitinib

Actieve spondylitis ankylopoetica bij volwassenen die onvoldoende reageren op conventionele behandeling.

➔Tofacitinib + Upadacitinib

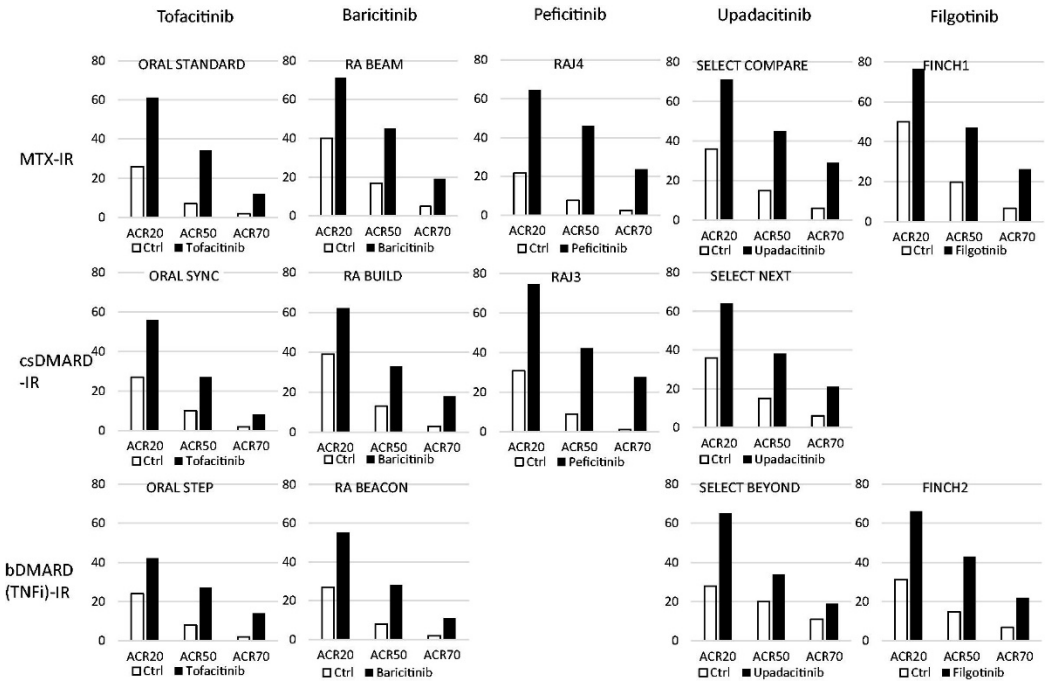
B. JAK-inhibitoren in de reumatologie

1. Welke pathologie, combinaties, plaats in guidelines

Name	Mechanism	Dose	Indicatie	
Tofacitinib (Xeljanz®)	JAK1 & JAK3 inhibition (JAK2)	2x 5mg/d p.o.	RA PsA SA JIA juveniele PsA	Colitis ulcerosa
Baricitinib (Olumiant®)	JAK1 & JAK2 inhibition	4 mg/d p.o. 2mg/d p.o.	RA	Alopecia areata Atopische dermatitis
Upadacitinib (Rinvoq®)	JAK1 & JAK2 inhibition	15 mg/d p.o.	RA PsA nr-ax SpA + SA	Colitis ulcerosa Atopische dermatitis
Filgotinib (Jyseleca®)	JAK1 inhibition	100 mg of 200 mg/d p.o.	RA	Colitis ulcerosa

B. JAK-inhibitoren in de reumatologie

2. Welke effecten



B. JAK-inhibitoren in de reumatologie

2. Welke effecten

Snelle respons (< 2 weken)

Opvallende verbetering op pijnklachten

JAK-STAT pathway belangrijke rol in perifere en centrale pijnmechanismen

Downregulatie van centrale pijn verwerkende pathways

B. JAK-inhibitoren in de reumatologie

3. Welke screening bij opstart

TBC (Mantoux / IGRA en RX thorax)

HBV / HCV/ HIV

Bloedbeeld, leverfunctie, nierfunctie, lipidenprofiel

Vaccinatie status

Navraag zwangerschapswens

B. JAK-inhibitoren in de reumatologie

4. Monitoring

Perifeer bloedonderzoek, leverset en nierfunctie 3-maandelijks

Lipidenprofiel 3 maanden na start

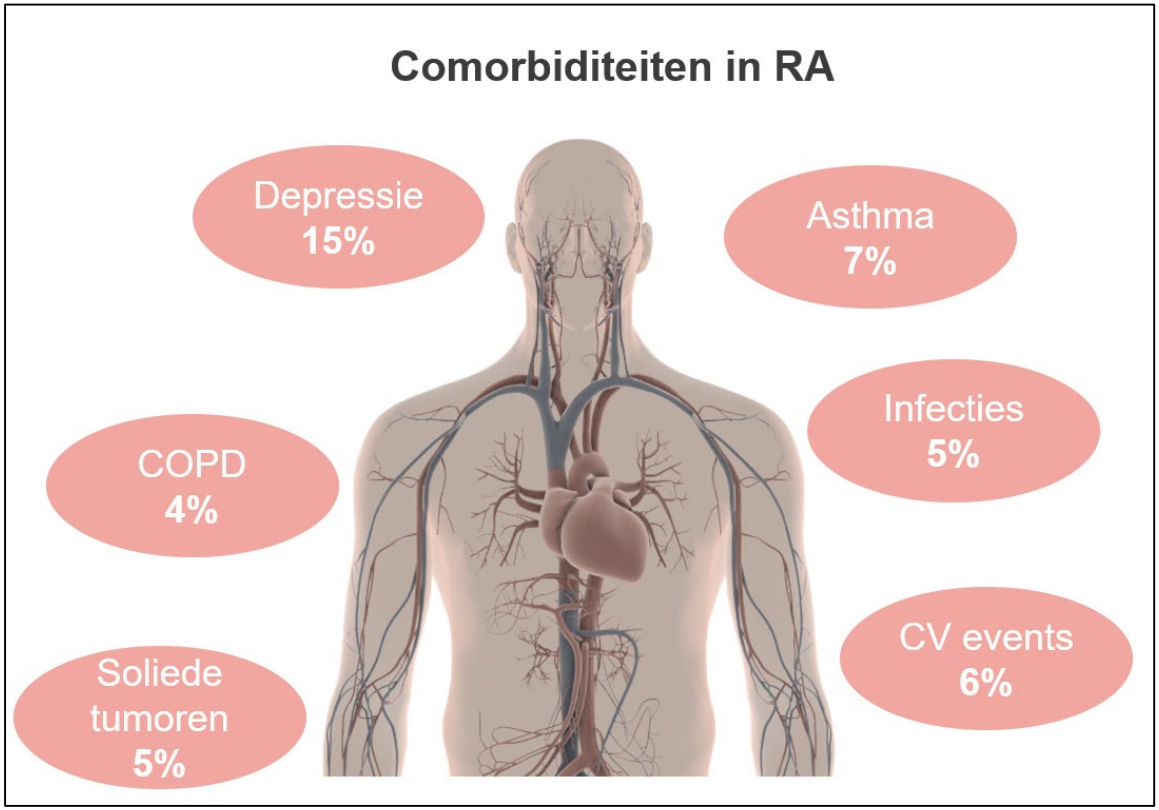
Onderbreken bij ernstige infecties, in geval van koorts en bij electieve hoog risico (tand)heelkundige ingrepen.

Jaarlijks huidonderzoek

Optimalisatie vaccinatieschema:

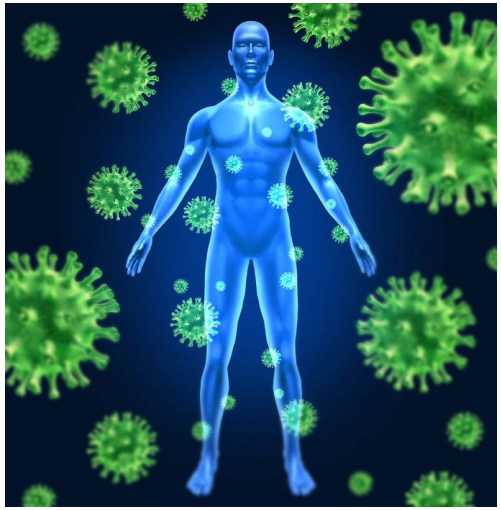
- Contra-indicatie voor elk levend verzwakt vaccin (o.a. mazelen, rubella, bof en gele koorts).
- Influenza- en Pneumococcenvaccinatie
- Covid-19 vaccinatie

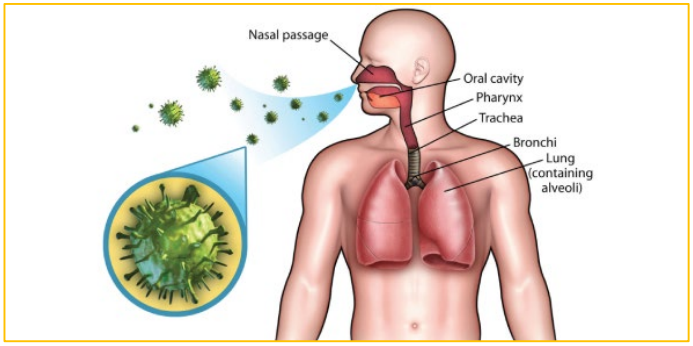
C. Veiligheid bij JAK-inhibitoren

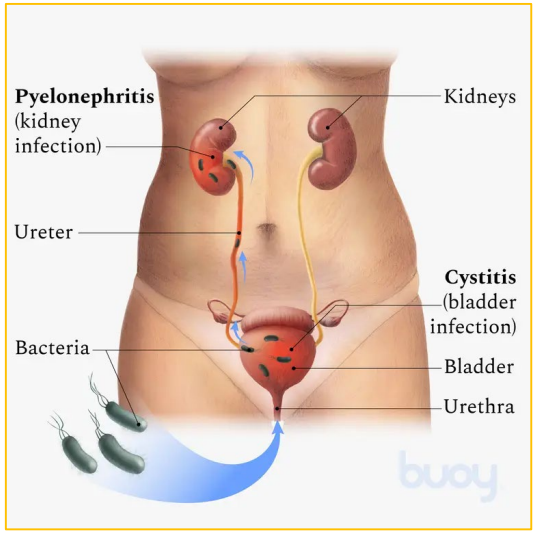


C. Veiligheid bij JAK-inhibitoren

1. Infecties







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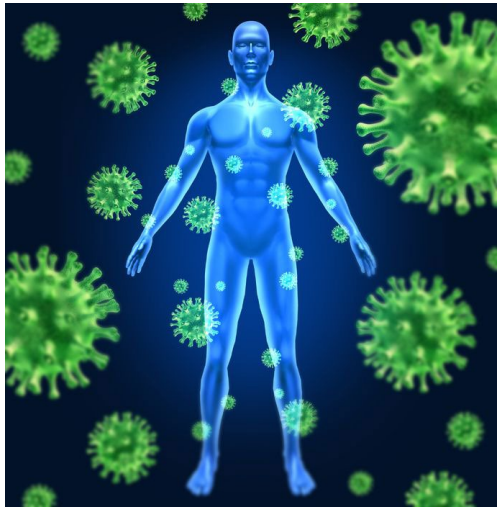


JAKi RCT's

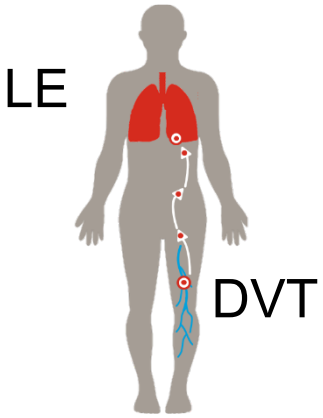
SI **1.7-3.2**

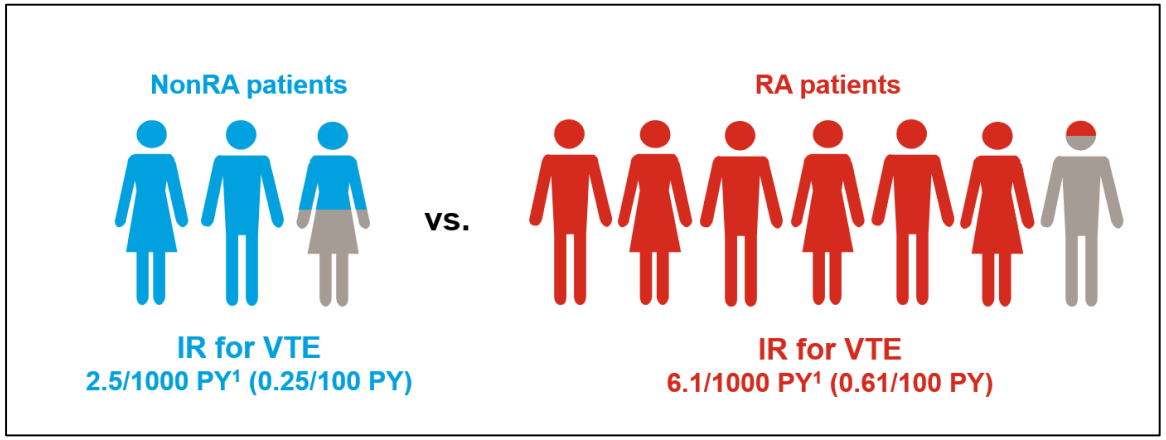
HZ **1.7-3.5**

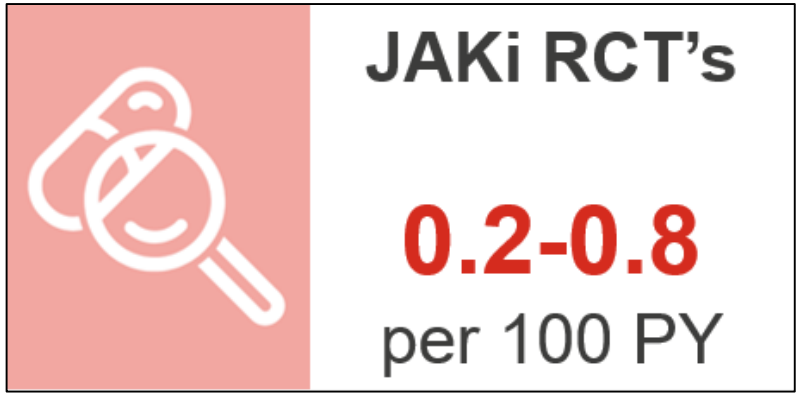
per 100 PY

C. Veiligheid bij JAK-inhibitoren

2. Veneus Trombo-emboligeen Event (VTE)







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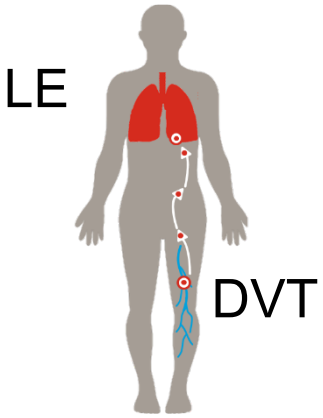


Study	JAKi Events	JAKi PEY	Placebo Events	Placebo PEY	Risk Ratio (95% CI)	% Weight
Sandborn 2012	0	5.1	1	7.4	0.67 (0.05, 8.70)	6.27
Sandhorn 2014	0	2.6	0	2.6	1.00 (0.05, 20.22)	4.58
Van Vollenhoven 2012 (ORAL-Standard)	1	471.3	0	41.75	0.19 (0.01, 2.51)	6.27
Mease 2017 (OPAL Broaden)	1	291.8	0	24.2	0.18 (0.01, 2.35)	6.27
Papp 2012	0	11.3	0	11.5	1.02 (0.05, 20.57)	4.58
Fleischmann 2012 (ORAL-Solo)	0	274.6	2	28.3	0.03 (0.00, 0.35)	7.05
Tanaka 2011	0	12.23	0	6.5	0.53 (0.03, 10.74)	4.58
Tanaka 2016	1	11	0	11.3	2.24 (0.17, 29.16)	6.27
Dougados 2017 (RA-Build)	2	223.1	0	95.2	1.43 (0.13, 16.13)	7.05
Genovese 2018 (SELECT-Beyond)	5	95.8	0	39	2.80 (0.29, 27.26)	7.99
Burmester 2018 (SELECT-Next)	0	51	0	51	1.00 (0.05, 20.22)	4.58
van der Heijde 2019 (SELECT-Axis 1)	0	25	0	25.3	1.01 (0.05, 20.46)	4.58
Fleischmann 2019	1	289.6	1	250.3	0.86 (0.05, 13.82)	5.38
Kremer 2016	0	2.1	0	.7	0.33 (0.02, 6.74)	4.58
Kameda 2020 (SELECT-Sunrise)	0	11.3	0	11.3	1.00 (0.05, 20.22)	4.58
Genovese 2019 (FINCH-2)	0	138.9	0	68.3	0.49 (0.02, 9.94)	4.58
Mease 2018 (EQUATOR)	0	20	0	20.3	1.01 (0.05, 20.52)	4.58
van der Heijde 2018 (TORTUGA)	1	13.4	0	13.4	2.18 (0.17, 28.39)	6.27
Overall (I-squared = 0.0%)					0.68 (0.36, 1.29)	100.00

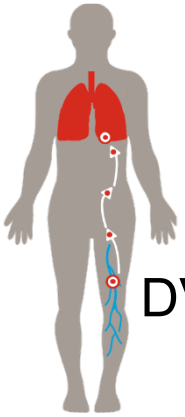
Figure 2. Forest plot of overall venous thromboembolism events. JAKi = JAK inhibitors; PEY = patient exposure years; 95% CI = 95% confidence interval. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/art.41580/abstract.

Yates M, Mootoo A, Adas M, et al. Venous thromboembolism risk with JAK inhibitors: A meta-analysis. Arthritis Rheumatol. 2021

C. Veiligheid bij JAK-inhibitoren

2. Veneus Trombo-emboligeen Event (VTE)

LE



DVT

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA confirms measures to minimise risk of serious side effects with Janus kinase inhibitors for chronic inflammatory disorders

- > 65 jaar
- Verhoogd risico op cardiovasculaire events
- Rokers met een equivalent van ≥10 pakjaren
- Verhoogd risico op kanker
- Verhoogd risico op veneus-tromboemboligene events

+

Indien toch geopteerd wordt voor JAKi, dosis reduceren

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2. Veneus Trombo-emboligeen Event (VTE)

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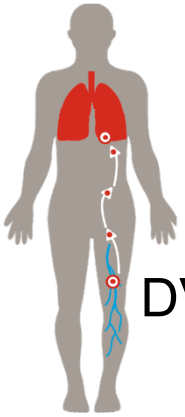


DVT

ORIGINAL ARTICLE

Cardiovascular and Cancer Risk with Tofacitinib in Rheumatoid Arthritis

Steven R. Ytterberg, M.D., Deepak L. Bhatt, M.D., M.P.H., Ted R. Mikuls, M.D., M.S.P.H., Gary G. Koch, Ph.D., Roy Fleischmann, M.D., Jose L. Rivas, M.D., Rebecca Germino, Ph.D., Sujatha Menon, Ph.D., Yanhui Sun, Ph.D., Cunshan Wang, Ph.D., Andrea B. Shapiro, M.D., Keith S. Kanik, M.D., et al., for the ORAL Surveillance Investigators*

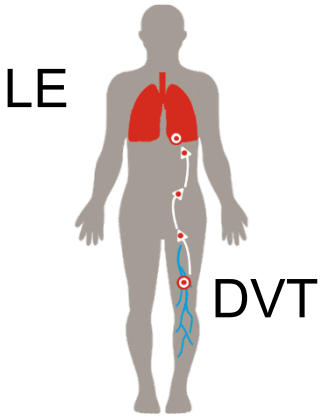
ClinicalTrials.gov

Home > Search Results > Study Record Detail

A Study of Baricitinib in Participants With Rheumatoid Arthritis (RA-BRANCH)

C. Veiligheid bij JAK-inhibitoren

2. Veneus Trombo-emboligeen Event (VTE)

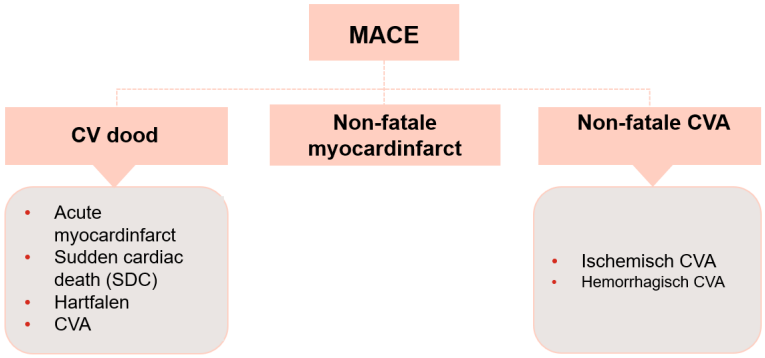


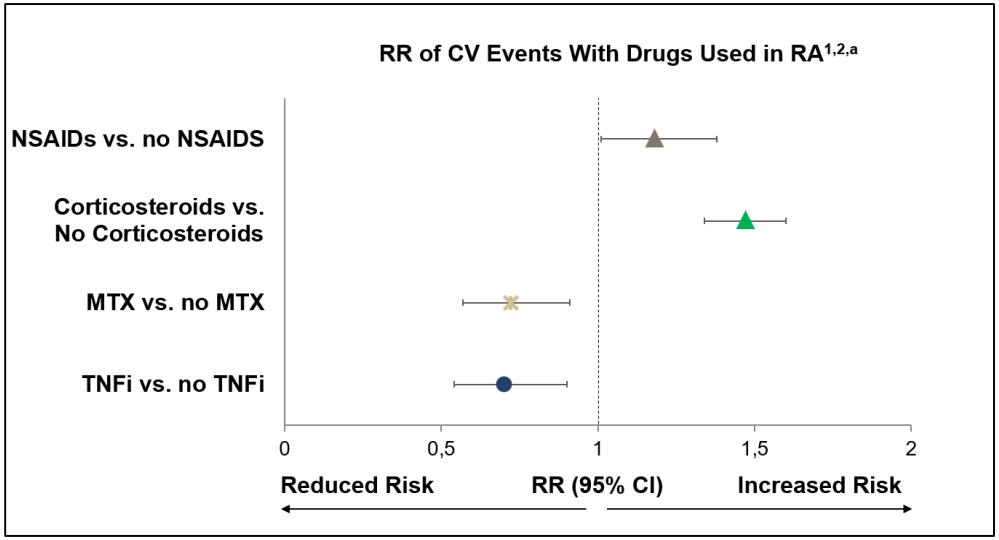
ORAL Surveillance

TOFA 5 mg BID	TNFi
PE: **0.2**	PE: **0.1**
DVT: **0.2**	DVT: **0.1**
per 100 PY	per 100 PY

C. Veiligheid bij JAK-inhibitoren

3. Major Adverse Cardiovascular Event (MACE)





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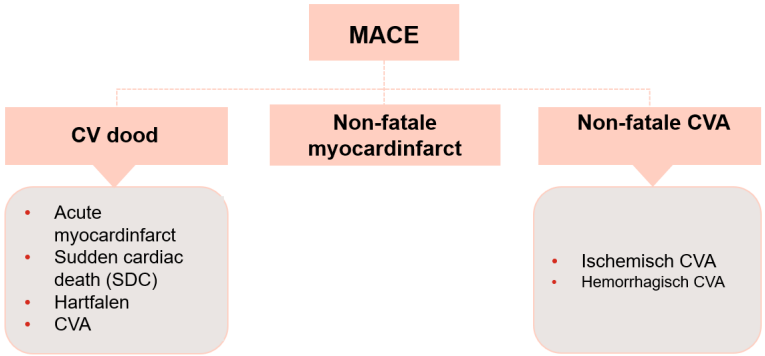

Rheumatoid arthritis

Impact of Janus kinase inhibitors on risk of cardiovascular events in patients with rheumatoid arthritis: systematic review and meta-analysis of randomised controlled trials

Wenhui Xie [1], Yanrong Huang [1], Shiyu Xiao [2], Xiaoying Sun [1], Yong Fan [1], Zhuoli Zhang [1]

Correspondence to Professor Zhuoli Zhang, Department of Rheumatology and Clinical Immunology, Peking University First Hospital, Beijing 100006, China; zhuoli.zhang@126.com

C. Veiligheid bij JAK-inhibitoren

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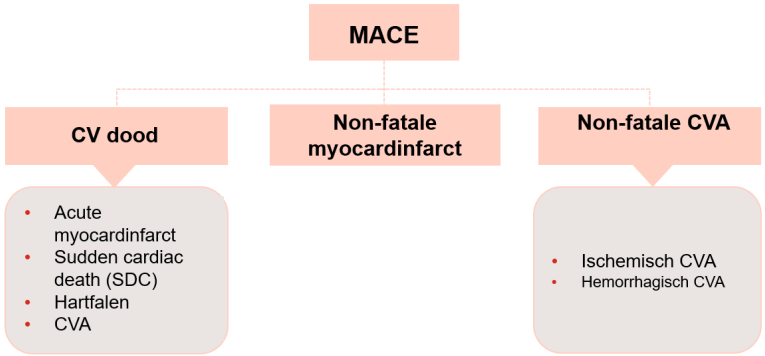

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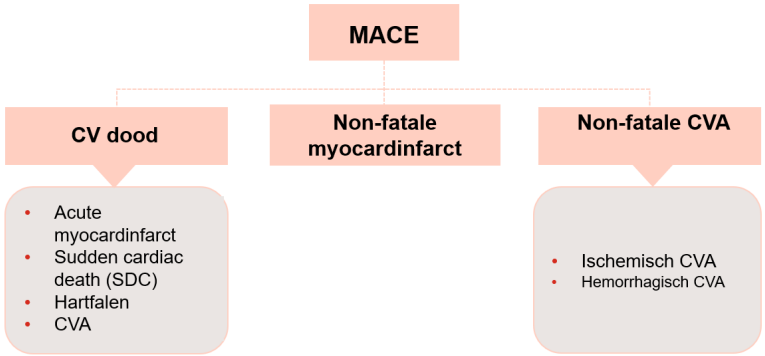
3. Major Adverse Cardiovascular Event (MACE)



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ORAL Surveillance

TOFA 5 mg BID	TNFi
0.9	**0.7**
per 100 PY	per 100 PY

Number Needed to Harm (NNH) = 567 patiëntenjaren
= 113 patiënten 5 jaar behandelen om één MACE event meer te veroorzaken

C. Veiligheid bij JAK-inhibitoren

4. Oncologisch

Patients with RA have a 1.1-times increased risk of malignancy vs. the general population[1]

Incidence rates of malignancy events in RA

RWE[a,2]	JAKi RCTs[b, 3-6]	ORAL Surveillance[c,7]	
		TOFA 5 mg BID	TNFi
0.8-2.3 per 100 PY	**0.5-0.9** per 100 PY	**1.1** per 100 PY	**0.8** per 100 PY

[a]In patients treated with biologic disease-modifying antirheumatic drugs; [b]Range includes a mix of incidence and exposure-adjusted incidence rates, excluding NMSC; [c]CV-risk factor enriched trial population, figures not including NMSC.
BID: twice daily; CV: cardiovascular; JAKi: Janus kinase inhibitor; NMSC: nonmelanoma skin cancer; PY: patient years; RA: rheumatoid arthritis; RCT: randomized controlled trial; RWE: real-world evidence; TNFi: tumor necrosis factor inhibitor; TOFA: tofacitinib.
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C. Veiligheid bij JAK-inhibitoren

4. Oncologisch

ORIGINAL ARTICLE

Cardiovascular and Cancer Risk with Tofacitinib in Rheumatoid Arthritis

Steven R. Ytterberg, M.D., Deepak L. Bhatt, M.D., M.P.H., Ted R. Mikuls, M.D., M.S.P.H., Gary G. Koch, Ph.D., Roy Fleischmann, M.D., Jose L. Rivas, M.D., Rebecca Germino, Ph.D., Sujatha Menon, Ph.D., Yanhui Sun, Ph.D., Cunshan Wang, Ph.D., Andrea B. Shapiro, M.D., Keith S. Kanik, M.D., et al., for the ORAL Surveillance Investigators*

Hoger risico op maligniteiten bij tofacitinib dan bij TNF inhibitors.

IR tofacitinib (4.2%; 122 patiënten) en TNF inhibitor (2.9%; 42 patiënten)

Number Needed to Harm (NNH) = 276 patiëntenjaren
= 55 patiënten 5 jaar behandelen om één event meer te veroorzaken

C. Veiligheid bij JAK-inhibitoren

5. Zwangerschap en borstvoeding

De JAK-inhibitoren zijn **gecontra-indiceerd** tijdens de zwangerschap en borstvoeding

Anticonceptie is vereist tijdens de behandeling én

- tot 1 week na de behandeling voor baricitinib en filgotinib
- tot 4 weken na de behandeling voor tofacitinib en upadacitinib.

D. Toekomst van JAK-inhibitoren

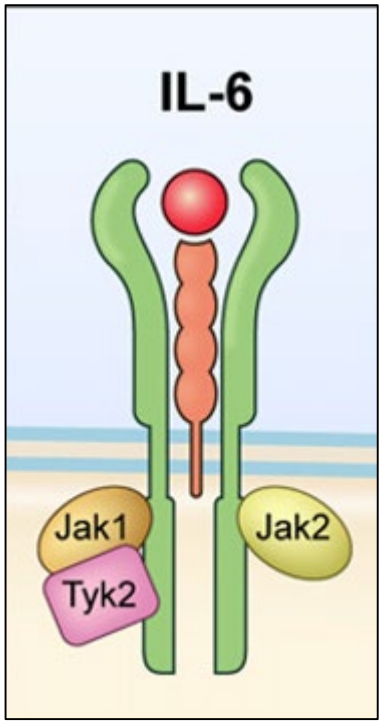
Fase 1 en 2 klinisch studies op komst voor

- SLE, SSc, Sjögren syndroom en dermatomyositis

- Interferonopathieën

- Alopecia areata, atopische dermatitis, ziekte van Crohn, vitiligo, hemophagocytair syndroom, niet-infectieuze uveitis, cutane lupus erythematosus.

D. Toekomst van JAK-inhibitoren



E. Take home messages

- Janus Kinasen zijn betrokken bij talloze pathways (zowel inflammatoire als non-inflammatoire)

- JAK inhibitoren hebben een plaats bij de behandeling van verschillende reumatische aandoeningen (o.a. RA, PsoA en AxSpa).

- Ongecontroleerde reumatische ziekteactiviteit verhoogd risico op comorbiditeiten zoals infecties, VTE, MACE en tumoren.

- Bijwerkingen JAK inhibitoren op deze vlakken (infecties, VTE, MACE, tumoren) wordt volop onderzocht. Advies om rekening te houden met risicoprofiel van patiënt.

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Dank u voor uw aandacht.

Zijn er nog vragen?