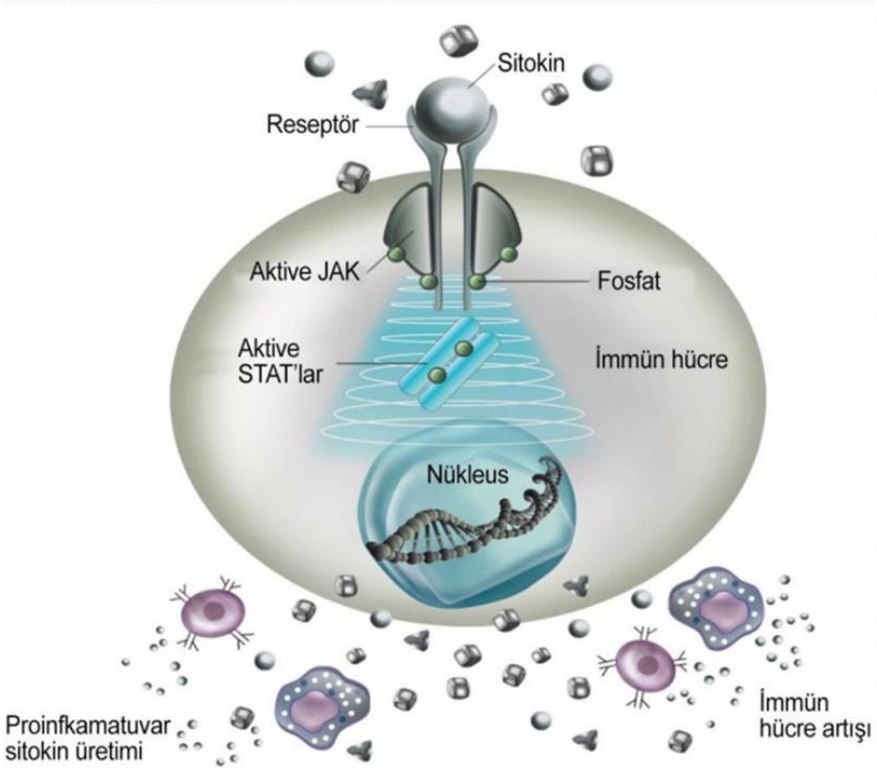
HEDEFE YÖNELİK SENTETİK DMARD'LAR

Dr. Pınar Talu Erten
Medicana İnternational İzmir Hastanesi

JAK Kinaz Ailesi

- JAK kinaz ailesi, 4 tirosin kinazından oluşur: JAK1, 2, 3 ve TYK2
- JAK'lar hücre yüzeyinden nükleusa sinyallerin aktarılmasını sağlarlar.
- Birçok sitokin hücre yüzeyindeki reseptörlere bağlanarak JAK sinyal yolağını aktive eder ve böylece bir çok farklı immün ve hücresel fonksiyonu regüle ederler.



O'Shea JJ et al. *Annu Rev Med.* 2015;16:311-28

JAK'ların Görevleri

JAK'lar

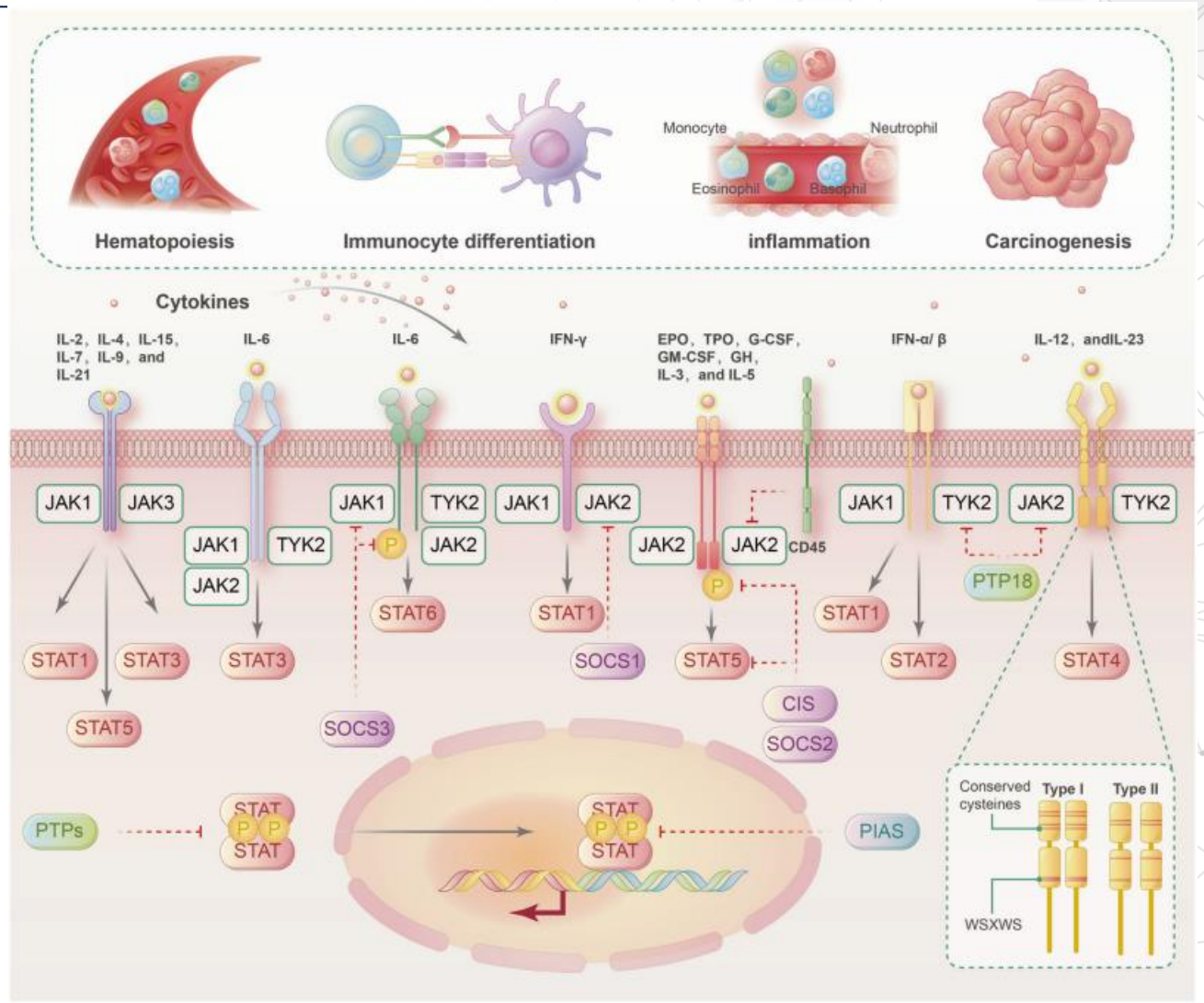
- Hücre proliferasyonu ve diferansiyasyonu[1,2]
- Hücre migrasyonu ve apoptoz[3]
- Anti- ve pro-inflamatuar etkiler[4]
- Hematopoez[5]
- Doğal ve adaptif immünite[6]

1. O'Shea JJ, et al. *Annu Rev Med*. 2015;16:311–28; 2. Kiu H, Nicholson SE, *Growth Factors*. 2012;30:88–106; 3. Rawlings JS, et al. *J Cell Sci.* 2004;117:1281–3; 4. Walker JG, Smith MD, *J Rheumatol*. 2005;32:1650–53; 5. Ward AC, et al. *Blood.* 2000;95:19–29; 6. Cutolo M, *Ther Adv Musculoskelet Dis*. 2013;5:3–11

JAK-STAT Yolağı

- Sitokinlerden ve büyüme faktörlerinden sinyal yolağının aşağıya iletilmesi için gereklidirler.
- Genelde ikili kombinasyonlar oluştururlar
- Her bir kombinasyon farklı moleküllerin sinyalizasyonunda görev alır.

- Antiinflamatuvar etkiler: **JAK1** inhibisyonu
- **JAK2** eritropoez ve tromboemboli
- **JAK3** lenfosit proliferasyonu ve immün homeostaz
- **TYK2** antiviral yanıt ile ilişkili



[a]IL-10/IL-22 may have pro- or anti-inflammatory activities depending on the cellular environment and/or disease state. [b]Type II cytokine receptors such as those for gp130 subunit sharing receptors for IL-6 and IL-11 as well as IL-10, IL-19, IL-20, and IL-22, mainly signal through JAK1, but also associate with JAK2 and TYK2

Cohen S. Int J Clin Rheumatol 2012;7:413–23; O'Shea JJ, et al. Annu Rev Med 2015;66:311–28; Levy D, Darnell Jr JE. Nat Rev Mol Cell Biol 2002;3:651–62; Schwartz DM, et al. Nat Rev Rheumatol 2016;12:25–36; Ghoreschi K, et al. Immunol Rev 2009;228:273–87; Sanjabi S, et al. Curr Opin Pharmacol 2009;9:447–53; Winthrop KL. Nat Rev Rheumatol 2017;13:234–43; Firestein GS and McInnes IB. Immunity 2017;46:183-196

Selektivite, Etkililik ve Yan Etki Dengesi

JAK1 inhibisyonu:

IL-6, interferon vb kilit sitokin yolaklarının blokajı[1,2]

İnflamasyonu azaltır ve eklemleri korur

JAK2 inhibisyonu:

Eritropoetin vb büyüme faktörü sinyalinin blokajı[2-3]

GM-CSF'nin blokajı[4]

Kronik hastalıklarda anemiyi arttırabilir GM-CSF inhibisyonu yoluyla inflamasyonu azaltır

JAK3 inhibisyonu:

IL-2, IL-4, IL-15 vb g-zincir sinyal yolaklarının sitokinlerinin blokajı[1,2]

NK hücrelerini azaltır—enfeksiyon ve maligniteye karşı daha düşük koruma

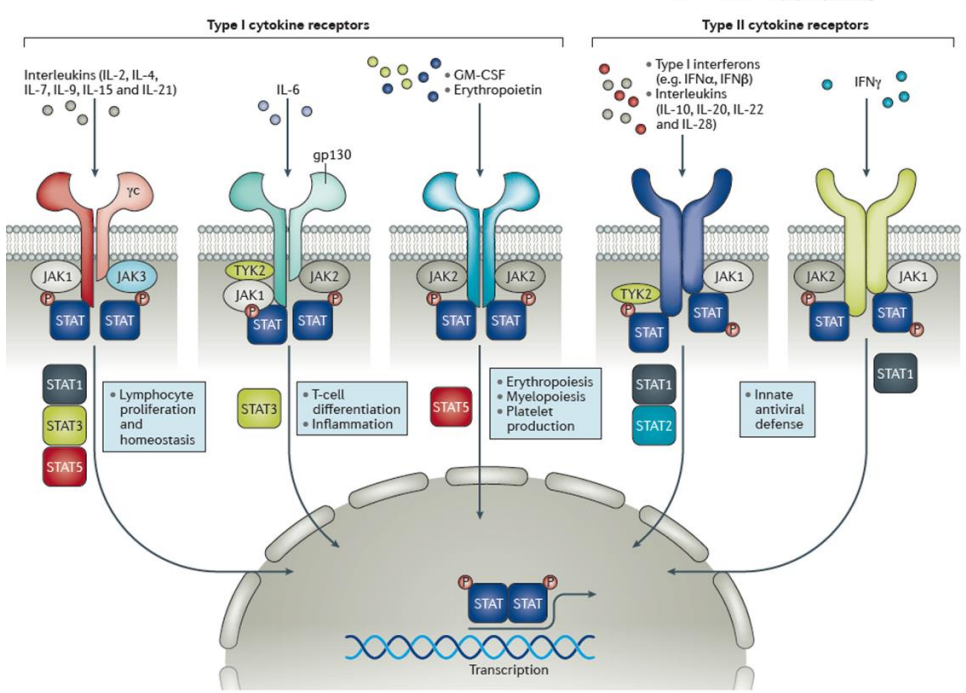
1. O'Shea JJ, et al. Ann Rheum Dis 2013; 2. Kiu H, Nicholson SE. Growth Factors 2012;30:88–106; 3. Kremer JM, et al. Arthritis Rheumatol 2009;60:1895–905: 4. Brizzi et al J. Bio Chem 1996;271:3566-67

Seçiciliklerine göre JAK inhibitörleri birinci kuşak ve ikinci kuşak olarak gruplandırılmıştır

- Birinci kuşak JAK inh: non-selektif inhibitörler
  - Tofacitinib: JAK1, JAK2, JAK3 ve daha az TYK2 inh
  - Baricitinib: JAK1-JAK2 inh

- İkinci kuşak JAK inh: Daha selektif JAK inhibisyonu
  - Upadacitinib: JAK1
  - Filgotinib: JAK1
  - Peficitinib: JAK 1, JAK3

Decernotinib
İtacitinib



Romatoid artrit

Tofacitinib

Baricitinib

Upadacitinib

Filgotinib

Ankilozan Spondilit

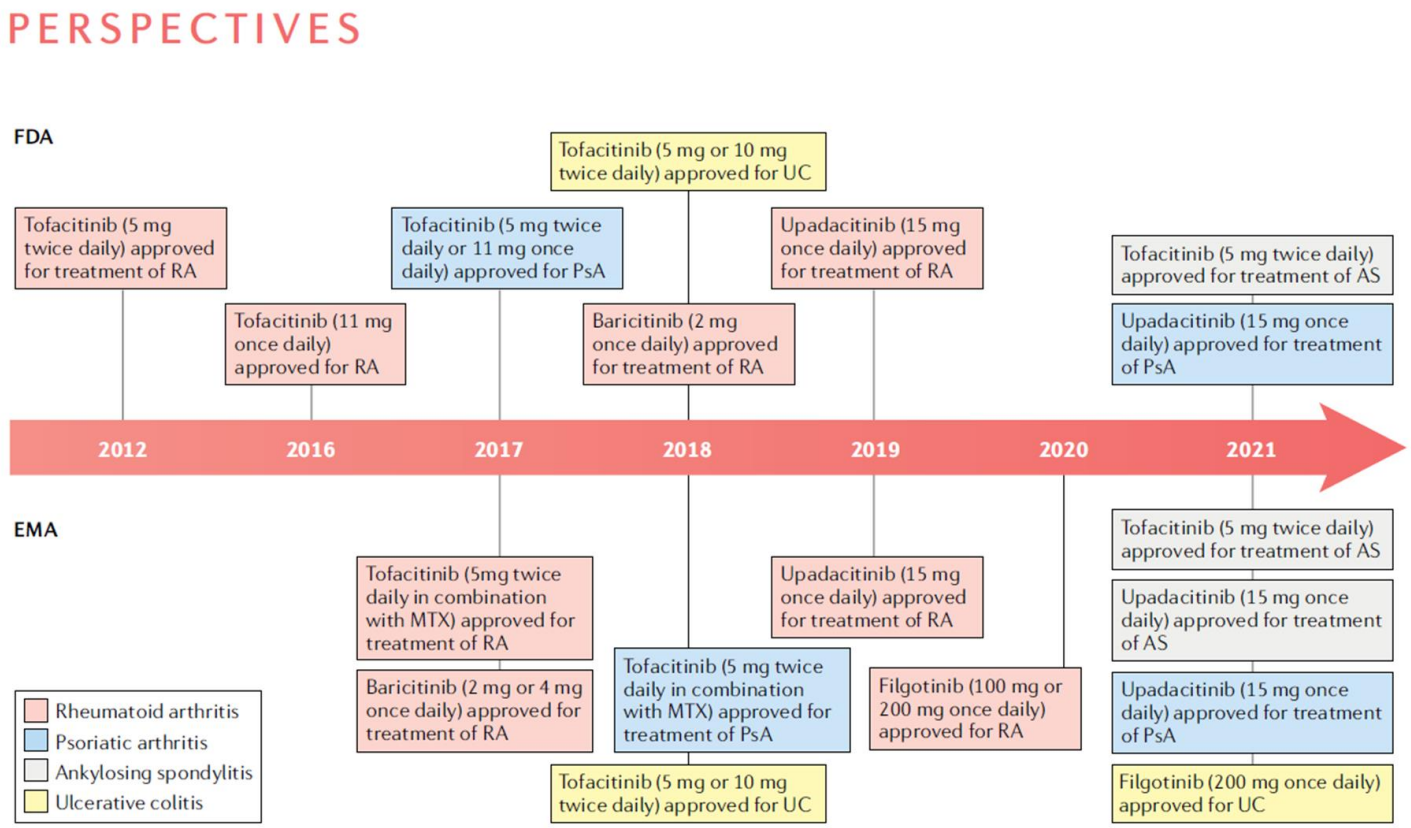
Tofacitinib

Upadacitinib

Psoriatik artrit

Tofacitinib

Upadacitinib



TOFASİTİNİB

- Non selektif birinci kuşak JAK inh.
- (JAK1, JAK2, JAK3 > TYK2 inh)
- Dozu: 2x5 mg/gün oral
- Endikasyonları :RA, AS, PsA, UC
- MTX ve diğer csDMARD'lar ile kombine edilebilir
- Monoterapi olarak kullanılabilir

Table 4. Tofacitinib phase III clinical trials in moderate to severe rheumatoid arthritis.

Trial	ORAL Start MTX-naïve (n = 958)	ORAL Solo c/bDMARD-IR (n = 611)	ORAL Sync c/bDMARD-IR (n = 795)	ORAL Scan MTX-IR (n = 797)	ORAL Standard MTX-IR (n = 717)	ORAL Strategy MTX-IR (n = 1146)	ORAL Step TNF-IR (n = 399)
Participants	MTX-naïve patients with active RA	Active RA patients with inadequate response to ≥ 1 c/bDMARD receiving stable doses of antimalarial	Active RA patients with inadequate response to ≥ 1 c/bDMARD	Active RA patients receiving background MTX	Active RA patients receiving stable doses of MTX	Active RA patients receiving stable doses of MTX	Moderate to severe RA patients with inadequate response to anti-TNF drugs
Type of therapy	Monotherapy	Monotherapy	Combination therapy	Combination therapy	Combination therapy	Monotherapy	Combination therapy
Active Comparator	MTX	/	/	/	ADA	ADA + MTX non-inferiority	/
Background treatment	None	None	cDMARD	MTX	MTX	None	MTX
Arms	(1) TOFA 5 mg bid (2) TOFA 10 mg bid (3) MTX	(1) TOFA 5 mg bid (2) TOFA 10 mg bid (3) PBO advanced at 3 months to TOFA 5 mg bid or 10 mg bid	(1) TOFA 5 mg bid (2) TOFA 10 mg bid (3) PBO advanced to TOFA 5 mg bid or 10 mg bid at 6 months (3 months for non-responders)	(1) TOFA 5 mg bid (2) TOFA 10 mg bid (3) PBO advanced to TOFA 5 mg bid or 10 mg bid at 6 months (3 months for non-responders)	(1) TOFA 5 mg bid (2) TOFA 10 mg bid (3) PBO advanced to TOFA 5 mg bid or 10 mg bid at 6 months (3 months for non-responders) (4) ADA	(1) TOFA 5 mg bid (2) TOFA 10 mg bid (3) ADA + MTX	(1) TOFA 5 mg bid (2) TOFA 10 mg bid (3) PBO advanced to TOFA 5 mg bid or 10 mg bid at 3 months
Duration (months)	24	6	12	24	12	12	6
Features	X-Rays			X-Rays			
Coprimary endpoints	ΔmTSS ACR70 (month 6)	ACR20 HAQ-DI DAS28-ESR < 2.6 (month 3)	ACR20 DAS28-ESR < 2.6 (month 6) HAQ-DI (month 3)	ACR20 ΔmTSS DAS28-ESR < 2.6 (month 6) HAQ-DI (month 3)	ACR20 DAS28-(ESR) < 2.6 (month 6) HAQ-DI (month 3)	ACR50 (month 6)	ACR20 HAQ-DI DAS28-ESR < 2.6 (month 3)

TOFASİTİNİB-YAN ETKİLER

- Yan etkiler:
  - Nazofarenjit
  - ASYE
  - HZV enfeksiyonu
  - Üriner sistem enfeksiyonu
  - Bulantı
  - BFT/KCFT yüksekliği (mtx ile beraber kullanımı kcft yüksekliği riskini artırır)
  - Dislipidemi (Orta düzeyde ve geri dönüşümlü LDL ve HDL yüksekliği)
  - Nötropeni/anemi (genellikle orta-hafif)
  - Ödem
  - Baş ağrısı
  - Dispne

  - Enfeksiyon
  - Maligniteler
  - Nadir olmasına rağmen az sayıda RA hastasında GIS perforasyonu bildirilmiştir

Curtis, J.R.; Lee, E.B.; Kaplan, I.V.; Kwok, K.; Geier, J.; Benda, B.; Soma, K.; Wang, L.; Riese, R. Tofacitinib, an oral Janus kinase inhibitor: Analysis of malignancies across the rheumatoid arthritis clinical development programme. Ann. Rheum. Dis. 2015, 75, 831–841

FDA requires warnings about increased risk of serious heart-related events, cancer, blood clots, and death for JAK inhibitors that treat certain chronic inflammatory conditions

Approved uses also being limited to certain patients

The NEW ENGLAND JOURNAL of MEDICINE

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., and Carol A. Connell, R.N., Ph.D., for the ORAL Surveillance Investigators*

- 2021'de FDA uyarılarına kadar JAK inhibitörlerinin kısa ve uzun dönem güvenilirlikleri bDMARDlar ile benzer olarak kabul edilmekteydi.
- Ekim 2021'de FDA tarafından JAK inhibitörlerinde TNF inhibitörlerine göre
  - Artmış ölüm,
  - Majör kardiyovasküler yan etki (MACE),
  - Malignite
  - Tromboz riski olduğu belirtilmiştir.
- JAK inhibitörlerinin tüm onaylanmış kullanımları, ancak bir ya da daha fazla sayıda TNF inhibitörüne dirençli olgularda kullanımı ile sınırlandırılmıştır.
- Yine FDA tarafından bu yan etkilerin 'sınıf yan etkisi' olabileceği nedeniyle onaylanmış diğer iki JAK inhibitörü olan baricitinib ve upadacitinib için de uyarılar genişletilmiştir

ORAL Surveillance (A3921133) sonuçları

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cardiovascular and Cancer Risk with Tofacitinib in Rheumatoid Arthritis

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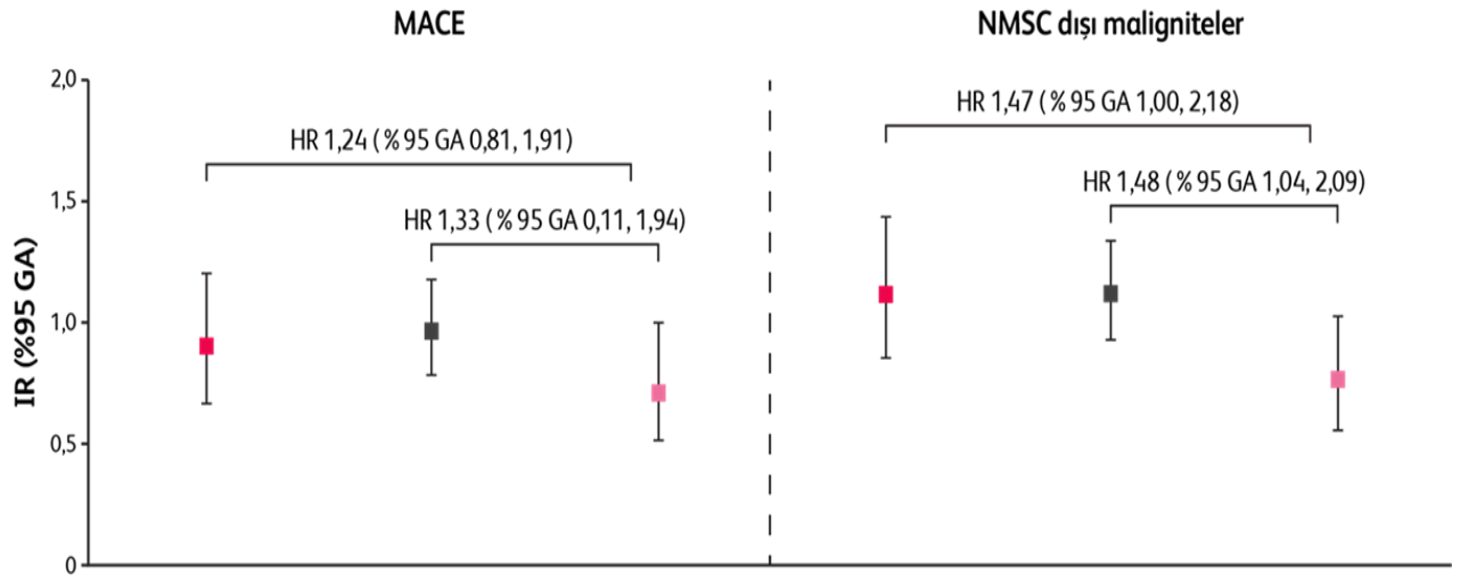

	Tofasitinib 5 mg BID	Tüm Tofasitinib	TNFi	Tofasitinib 5 mg BID	Tüm Tofasitinib	TNFi
n/N	47/1.455	98/2.911	37/1.451	62/1.455	122/2.911	42/1.451
PY	5.166,32	10.038,28	5.045,27	5.491,48	10.803,19	5.482,30
IR (%95 GA)	0,91 (0,67, 1,21)	0,98 (0,79, 1,19)	0,73 (0,52, 1,01)	1,13 (0,87, 1,45)	113 (0,94, 1,35)	0,77 (0,55, 1,04)
NNH vs TNFi	567	412	--	276	275	--

Ann Rheum Dis. 2022 June ; 81(6): 798–804. doi:10.1136/annrheumdis-2021-221915.

Tofacitinib and risk of cardiovascular outcomes: results from the Safety of TofAcitinib in Routine care patients with Rheumatoid Arthritis (STAR-RA) study

Farzin Khosrow-Khavar[1], **Seoyoung C. Kim**[1,2], **Hemin Lee**[1], **Su Been Lee**[1], **Rishi J. Desai**[1]

[1]Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital & Harvard Medical School, Boston, MA, USA.

[2]Division of Rheumatology, Inflammation, and Immunity, Brigham and Women's Hospital & Harvard Medical School, Boston, MA, USA.

- We did not find evidence for an increased risk of cardiovascular outcomes with tofacitinib in RA patients treated in the real-world setting; however, tofacitinib was associated with an increased risk of cardiovascular outcomes, albeit statistically non-significant, in RA patients with cardiovascular risk factors.
- Gerçek yaşam verilerinde tedavi edilen RA hastalarında tofasitinib ile kardiyovasküler sonuç riskinin arttığına dair kanıt bulamadık; ancak tofasitinib, kardiyovasküler risk faktörleri olan RA hastalarında istatistiksel olarak anlamlı olmasa da artmış kardiyovasküler sonuç riski ile ilişkilendirilmiştir

Arthritis Rheumatol. 2022 October ; 74(10): 1648–1659. doi:10.1002/art.42250.

Tofacitinib and risk of malignancy: results from the Safety of TofAcitinib in Routine care patients with Rheumatoid Arthritis (STAR-RA) Study

Farzin Khosrow-Khavar, PhD[1], Rishi J. Desai, PhD[1], Hemin Lee, MD, MPH[1], Su Been Lee, BA[1], Seoyoung C. Kim, MD, ScD[1,2]

[1]Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital & Harvard Medical School, Boston, MA, USA.

[2]Division of Rheumatology, Inflammation, and Immunity, Brigham and Women's Hospital & Harvard Medical School, Boston, MA, USA.

- We did not find evidence for an increased risk of malignancy with tofacitinib, in comparison with TNFI, in RA patients treated in the real-world setting. However, our results cannot rule out a possibility of an increase in risk that may accrue with a longer treatment duration.
- Gerçek dünya ortamında tedavi edilen RA hastalarında TNFI ile karşılaştırıldığında tofasitinib ile malignite riskinin arttığına dair kanıt bulamadık. Bununla birlikte, sonuçlarımız daha uzun bir tedavi ile ortaya çıkabilecek bir risk artışı olasılığını göz ardı edemez

BARİSİTİNİB

- Non selektif birinci kuşak JAK inh.
- (JAK1, JAK2>JAK3, TYK2 inh)
- Dozu: 2-4 mg/gün oral
- Endikasyonları :RA!!!
- MTX ve diğer csDMARD'lar ile kombine edilebilir
- Monoterapi olarak kullanılabilir

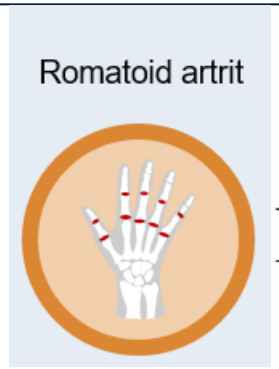

Table 2. Baricitinib phase III trials in moderate to severe rheumatoid arthritis.

Study	RA-BEGIN MTX-Naïve (n = 588)	RA-BEAM MTX-IR (n = 1308)	RA-BUILD cDMARD-IR (n = 684)	RA-BEACON bDMARD-IR (n = 527)	RA-BEYOND OLE Study (n = 3073)
Inclusion criteria	- RA - Patients who received no prior cDMARD therapy (up to 3 weekly MTX doses permitted)	- Active RA - Patients with inadequate response to MTX, who received therapy for ≥12 weeks before trial entry, including ≥8 weeks at stable doses	- Active RA and inadequate response or intolerance to ≥ 1 cDMARD - Use of up to 2 concomitant cDMARDs was permitted at entry; these must have been used for at least 12 preceding weeks with stable doses for at least 8 preceding weeks	- Moderately to severe active RA - Patients must have previously received ≥ 1 TNFi and discontinued the treatment because of an inadequate response or unacceptable side effects - bDMARDs must have been discontinued at least 4 weeks before randomization (≥6 months for rituximab) - Use of ≥1 concomitant cDMARD at entry; these must have been used for at least 12 preceding weeks with stable doses for at least 8 preceding weeks	- Patients who completed a BARI phase II or phase III trial
Type of therapy	Monotherapy + combination therapy	Combination therapy	Combination therapy	Combination therapy	Monotherapy—patients who completed previous BARI RA studies
Background treatment	None/MTX	MTX	cDMARDs	cDMARDs	cDMARDs
Active comparator	MTX	ADA + MTX			
Arms	(1) BARI 4 mg sid (2) BARI 4 mg sid + MTX (3) MTX 10 mg/week	(1) PBO (2) BARI 4 mg sid (3) ADA 40 mg/sc q2wk	(1) BARI 2 mg sid (2) BARI 4 mg sid (3) PBO	(1) BARI 2 mg sid (2) BARI 4 mg sid (3) PBO	(1) BARI 2 mg sid (2) BARI 4 mg sid
Duration (weeks)	52	52	24	24	Ongoing (completion estimated in 2024)
Primary endpoint	ACR20 (Week 24)	ACR20 (Week 12)	ACR20 (Week 12)	ACR20 (Week 12)	Long term Safety
Key secondary endpoint	Week 24: DAS28-CRP HAQ-DI mTSS SDAI remission	Week 12: DAS28-CRP HAQ-DI mTSS (Week 24) SDAI remission Morning Joint stiffness	Week 12: DAS28-CRP HAQ-DI SDAI remission Morning Joint stiffness	Week 12: DAS28-CRP HAQ-DI SDAI remission	Long term Efficacy
Main results (ACR20):	(Week 24) BARI 4 mg vs. MTX: 77% vs. 62% ($p \leq 0.01$); BARI 4 mg vs. BARI 4 mg + MTX: 77% vs. 78% (Week 52) BARI 4 mg vs. MTX: 73% vs. 56% ($p \leq 0.05$); BARI 4 mg vs. BARI 4 mg + MTX: 73% vs. 73%	(Week 12) BARI vs. PBO: 70% vs. 40% ($p < 0.001$); BARI vs. ADA: 70% vs. 61% ($p = 0.014$) (week 24) BARI vs. PBO: 74% vs. 37% ($p < 0.001$); BARI vs. ADA: 74% vs. 66% ($p \leq 0.05$)	(Week 12) BARI 2 mg vs. PBO: 66% vs. 39% ($p \leq 0.001$); BARI 4 mg vs. PBO: 62% vs. 39% ($p \leq 0.001$)	(Week 12) BARI 2 mg vs. PBO: 49% vs. 27% ($p < 0.001$); BARI 4 mg vs. PBO: 55% vs. 27% ($p < 0.001$) (Week 24) BARI 2 mg vs. PBO: 45% vs. 27% ($p \leq 0.001$); BARI 4 mg vs. PBO: 46% vs. 27% ($p \leq 0.001$)	Currently recruiting

BARİSİTİNİB-YAN ETKİLER

Pnömoni

HZV enfeksiyonu (Japonlarda HZV enfeksiyonu riski genel popülasyona göre artmıştır)

Gastroenterit

Üriner sistem enfeksiyonları

Sellülit

Hiperkollesterolemi (doz bağımlı)

Ciddi hepatik yetmezlikli hastalarda kullanımı kontrendikedir. Özellikle MTX ile kombinasyonunda 16. haftadan itibaren transaminaz yüksekliği görülebilir.

Anemi: Özellikle tedavinin ilk 2 haftasında trombosit değerleri yükselebilmekte ve sonrasında stabilize olmaktadır. Hb değerleri başlangıçta düşebilir ve zamanla yükselir

Renal yetmezlikte doz ayarı önerilmekte ve GFR<30 ml/dk düzeyinde kullanımı önerilmemektedir

TOFA VE DİĞER BİYOLOJİKLERİN GÜVENİLİRLİK FARKLARI?

ACR Open Rheumatology
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American College of Rheumatology
Empowering Rheumatology Professionals

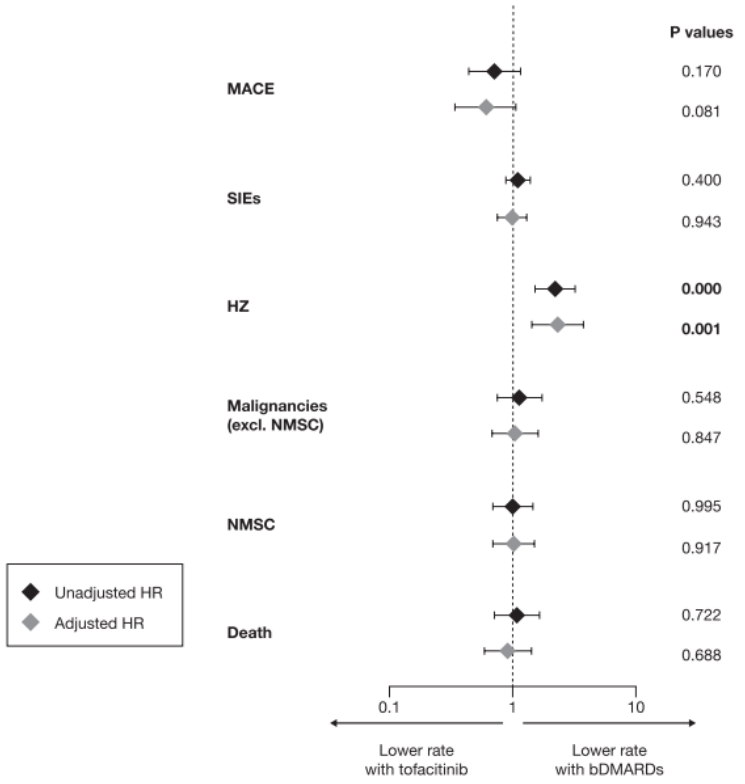
Postapproval Comparative Safety Study of Tofacitinib and Biological Disease-Modifying Antirheumatic Drugs: 5-Year Results from a United States–Based Rheumatoid Arthritis Registry

Joel M. Kremer,[1] Clifton O. BinghamIII,[2] Laura C. Cappelli,[2] Jeffrey D. Greenberg,[3] Ann M. Madsen,[4] Jamie Geier,[4] Jose L. Rivas,[5] Alina M. Onofrei,[6] Christine J. Barr,[6] Dimitrios A. Pappas,[7] Heather J. Litman,[6] Kimberly J. Dandreo,[6] Andrea B. Shapiro,[8] Carol A. Connell,[9] and Arthur Kavanaugh[10]

US Corrona RA registry results

Bu kayıt analizinde, her iki kohort da benzer MACE, SIE, malignite, ölüm ve VTE oranlarına sahipti;

HZV oranları tofacitinib kullananlar için bDMARD kullananlara göre daha yüksekti.



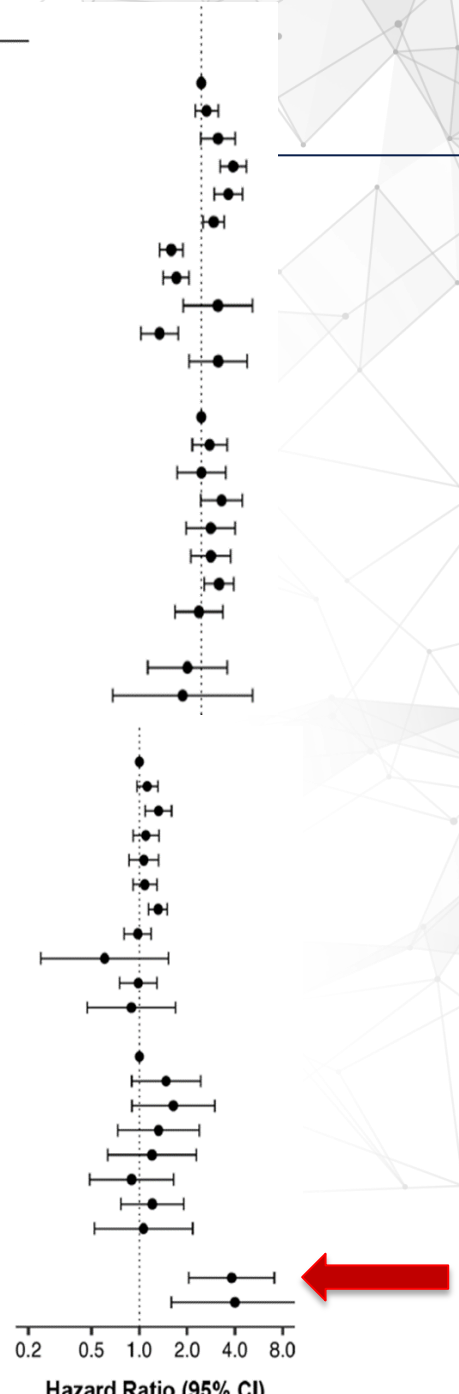
TOFA-BARİ VE DİĞER BİYOLOJİKLERİN GÜVENİLİRLİK FARKLARI?

- Anti-Rheumatic Therapies in Sweden (ARTIS)
- 2010 -2020 arası b/tsDMARD ile başlanan hastalar
- Haziran 2021'e kadar takip edilen
- N=20 117 kayıtlı tüm RA'lı hastaları içeren ülke İsveç kohort çalışması.

Frisell T, *et al*. *Ann Rheum Dis* 2023;**82**:601–610. doi:10.1136/ard-2022-223762

- Advers olaylara bağlı olarak tedavinin kesilmesinde farklılıklar var
- Ne kardiyovasküler olaylar ne de genel ciddi enfeksiyonlar, bDMARD'lara kıyasla barisitinib veya tofasitinib ile daha sık görülmedi
- JAKi ile daha yüksek herpes zoster oranları

Outcome	Events	Crude IR	wIR	wHR (95% CI)
Stop for adverse events				
Etanercept	446	18.0	29.8	1.0 (Ref.)
Adalimumab	348	27.9	34.1	1.07 (0.92–1.25)
Infliximab	99	12.5	38.9	1.25 (0.99–1.58)
Certolizumab	203	33.9	43.6	1.53 (1.28–1.82)
Golimumab	191	32.7	40.8	1.44 (1.19–1.73)
Abatacept	459	55.2	36.8	1.18 (1.03–1.36)
Rituximab	328	21.8	18.3	0.67 (0.57–0.78)
Tocilizumab	241	31.1	20.5	0.72 (0.60–0.85)
Sarilumab	30	94.7	57.4	1.25 (0.79–1.98)
Baricitinib	114	39.0	23.0	0.57 (0.45–0.73)
Tofacitinib	56	97.6	50.1	1.25 (0.85–1.84)
Major adverse cardiovascular event				
Etanercept	240	10.1	12.3	1.0 (Ref.)
Adalimumab	145	12.2	13.6	1.12 (0.89–1.41)
Infliximab	86	11.3	12.2	1.00 (0.72–1.39)
Certolizumab	76	13.2	16.0	1.31 (0.99–1.73)
Golimumab	60	10.7	13.9	1.14 (0.82–1.58)
Abatacept	125	16.1	13.9	1.14 (0.87–1.48)
Rituximab	290	21.0	15.7	1.27 (1.04–1.55)
Tocilizumab	84	11.4	11.9	0.97 (0.70–1.33)
Sarilumab	4	13.1	15.8	
Baricitinib	30	10.7	9.9	0.83 (0.49–1.42)
Tofacitinib	7	12.9	9.2	0.78 (0.31–1.99)
Serious Infection				
Etanercept	571	24.8	30.8	1.0 (Ref.)
Adalimumab	343	29.6	35.3	1.12 (0.96–1.31)
Infliximab	265	36.0	41.1	1.32 (1.09–1.60)
Certolizumab	167	30.4	33.3	1.10 (0.91–1.33)
Golimumab	134	24.9	32.3	1.07 (0.86–1.32)
Abatacept	278	38.6	33.8	1.08 (0.91–1.29)
Rituximab	609	47.5	39.3	1.31 (1.15–1.50)
Tocilizumab	235	33.5	29.6	0.98 (0.80–1.19)
Sarilumab	7	23.3	21.8	0.61 (0.24–1.53)
Baricitinib	105	39.5	33.6	0.98 (0.75–1.29)
Tofacitinib	25	47.3	30.5	0.89 (0.47–1.69)
Diagnosed herpes zoster				
Etanercept	50	2.0	2.5	1.0 (Ref.)
Adalimumab	38	3.1	3.7	1.48 (0.90–2.43)
Infliximab	27	3.4	4.0	1.64 (0.90–2.99)
Certolizumab	18	3.0	3.2	1.32 (0.73–2.38)
Golimumab	15	2.6	3.0	1.20 (0.63–2.28)
Abatacept	23	2.8	2.2	0.89 (0.49–1.64)
Rituximab	55	3.7	3.0	1.21 (0.77–1.91)
Tocilizumab	14	1.8	2.6	1.06 (0.52–2.17)
Sarilumab	1	3.2	0.9	
Baricitinib	29	10.0	9.8	3.82 (2.05–7.09)
Tofacitinib	8	14.1	10.2	4.00 (1.59–10.06)



Frisell T, *et al*. *Ann Rheum Dis* 2023;**82**:601–610. doi:10.1136/ard-2022-223762

TOFA-BARİ VE DİĞER BİYOLOJİKLERİN ETKİNLİK VE GÜVENİLİRLİK FARKLARI?

-17 522, TNFi, 2775 ABA, 3863 IL-6i, 7686 JAKi

-JAKi ve IL-6i'nin düzeltilmiş ilaç kesilme ve 1 yıllık CDAI yanıt oranları, TNFi ile benzer

-TNFi ile karşılaştırıldığında JAKi'nin advers olaylar nedeniyle daha sık olarak kesilmiş

-Tedaviyi bırakmanın ana tek nedeni etkisizlik

EPIDEMIOLOGICAL SCIENCE

Effectiveness of TNF-inhibitors, abatacept, IL6-inhibitors and JAK-inhibitors in 31 846 patients with rheumatoid arthritis in 19 registers from the 'JAK-pot' collaboration

Lauper K, *et al*. *Ann Rheum Dis* 2022;**81**:1358–1366. doi:10.1136/annrheumdis-2022-222586

TOFA-BARİ VE DİĞER BİYOLOJİKLERİN GÜVENİLİRLİK FARKLARI?

1) Klinik uygulamada kullanılan JAKi için %50-%100 oranında artmış VTE riskini doğrulamakta
2) JAKi ile VTE oranının TNFi'den, diğer biyolojik hastalık modifiye edici antiromatizmal ilaçlardan ve arka plandaki romatoid artrit popülasyonundan daha yüksek olduğunu göstermekte
3) Artmış VTE oranının derin ven trombozundan ziyade artmış pulmoner emboli oranı ile açıklandığını ortaya koymaktadır.

Rheumatoid arthritis

OPEN ACCESS

EPIDEMIOLOGICAL SCIENCE

Venous thromboembolism with JAK inhibitors and other immune-modulatory drugs: a Swedish comparative safety study among patients with rheumatoid arthritis

Rheumatoid arthritis

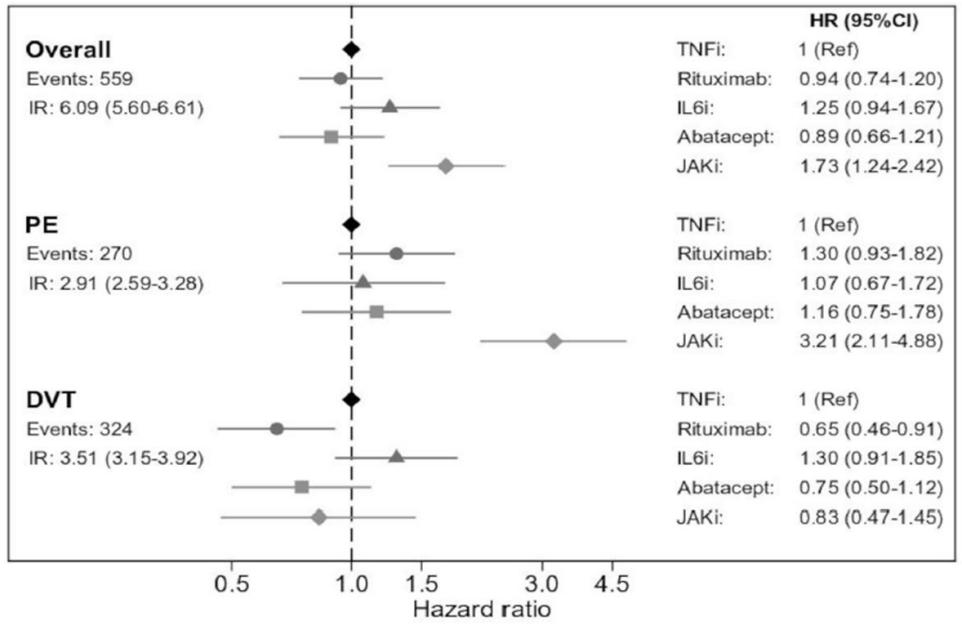
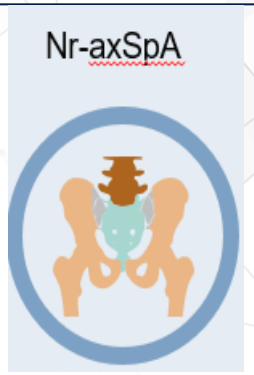


Figure 2 Events, incidence rates per 1000 person-years and HRs for VTE by treatment cohort (TNFi as reference), overall and by VTE subtype, in Swedish patients with RA between 2010 and 2021. b/tsDMARD, biologic/targeted synthetic disease-modifying antirheumatic drug; DVT, deep vein thrombosis; IR, incidence rate; JAKi, Janus kinase inhibitor; PE, pulmonary embolism; RA, rheumatoid arthritis; VTE, venous thromboembolism.

Molander V, *et al*. *Ann Rheum Dis* 2023;**82**:189–197. doi:10.1136/ard-2022-223050

UPADASİTİNİB

- İkinci kuşak JAK inhibitörüdür
- JAK1 selektif inh
- Dozu:15mg/gün
- Endikasyonları: RA, PsA, AS, Nr-axSpA, UC
- Araştırma halinde: Crohn,DHA



Study Name	Population	Primary Endpoints	UPA 15 mg	UPA 30 mg	PBO	MTX	ADA	ABA	Conclusion
NEXT [21]	csDMARD-IR	ACR20 at wk 12	64% ‡	66% ‡	36%	-	-		Both doses of UPA QD were superior to placebo.
		DAS28-CRP ≤ 3.2 at wk 12	48% ‡	48% ‡	17%	-	-		
BEYOND [22]	bDMARD-IR	ACR20 at wk 12	65% ‡	56% ‡	28%	-	-		Both doses of UPA QD were superior to placebo.
		DAS28-CRP ≤ 3.2 at wk 12	43% ‡	42% ‡	14%	-	-		
COMPARE [23]	Methotrexate -IR	ACR20 at wk 12	71% †,‖	-	36%	-	63%		UPA 15 mg QD was superior to adalimumab
		DAS28-CRP < 2.6 at wk 12	29% †,¶	-	6%	-	18%		
CHOICE [24]	bDMARD-IR	Change from baseline in the DAS28-CRP (non-inf.)	−2.52 points ‖					−2.00 points	UPA 15 mg QD was superior vs. abatacept
MONOTHERAPY [25]	Methotrexate -IR	ACR20 at wk 14	68% ¶¶	71% ¶¶	-	41%	-		Both doses of UPA QD were superior to continuing MTX
		DAS28-CRP ≤ 3.2 at wk 14	45% ¶¶	53% ¶¶	-	19%	-		
EARLY [26]	Naïve or limited exposure to methotrexate	ACR50 at wk 12	52% ¶	56% ¶		28%			Both doses of UPA QD were superior to MTX
		DAS28-CRP < 2.6 at wk 24	48% ¶	50% ¶		19%			

Türkiye'deki endikasyonları:

Erişkinlerde orta veya şiddetli aktif **romatoid artrit**te bir veya daha fazla TNF blokeri kullanımına yetersiz cevap olması veya intolerans olması durumunda endikedir

Erişkinlerde aktif **psöriatik artrit** tedavisinde bir veya daha fazla TNF blokeri kullanımına yetersiz cevap olması veya intolerans olması durumunda endikedir.

Bir veya daha fazla TNF blokeri kullanımına yeterli cevap alınamayan veya intoleransı olan, objektif enflamasyon bulgularına sahip erişkin hastalarda aktif **radyografik olmayan aksiyal spondiloartrit**in tedavisinde endikedir.

Bir veya daha fazla TNF blokeri kullanımına yeterli cevap alınamayan veya intoleransı olan aktif **ankilozan spondilit**li erişkin hastaların tedavisinde endikedir

Upadacitinib for Patients with Rheumatoid Arthritis: A Comprehensive Review J. Clin. Med. 2023, 12, 1734

UPA GÜVENLİK

15 RKÇ

Ortalama yaşı 51

N=10.656 hasta

12-52 haftalık bir takip süresi

LDL-C, HDL-C,MACE üzerine etkisi incelenmiş.

LDL-K/HDL-K oranı değişmemiştir. Hem LDL-K hem de HDL-K düzeylerini artırmaktadır

≤52 haftalık takip süresince kardiyovasküler hastalık riski üzerindeki etkisi saptanmamıştır.

Journal of *Clinical Medicine*

MDPI

Systematic Review

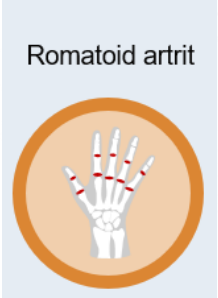
The Effect of Upadacitinib on Lipid Profile and Cardiovascular Events: A Meta-Analysis of Randomized Controlled Trials

Anastasios Makris [1], Fotios Barkas [2], Petros P. Sfikakis [3], Evangelos Liberopoulos [3] and Aris P. Agouridis [1,4,*]

J. Clin. Med. 2022, 11, 6894.

DİĞER JAKi

-Peficitinib :ikinci kuşak ancak Pan-JAK inh.JAK3 >>JAK2 selektivitesi



Kan hücreleri üzerine etkilerini azaltarak, güvenlik profilini güçlendirir

-Filgotinib: ikinci kuşak JAK 1 selektif inh.

EPO, CSF ve trombopoietin yolağı üzerine etkisi yoktur. Anemi, trombositopeni riskini artırmaz

-Decernotinib: selektif JAK3 inh. Çalışmaları devam.

-Itacitinib: Selektif JAK1 inh. GVHD için onaylı !!!!!!!!!!!!! RA çalışmaları var

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA'nın kronik enflamatuvar hastalıklarda Janus kinaz inhibitörleri kullanımı ile ciddi yan etki riskini en aza indirmek için önlemler önerileri son olarak Ocak 2023'de yayınlandı. Komite, bu ilaçların aşağıdaki hastalarda sadece uygun tedavi alternatiflerinin olmadığı durumlarda kullanılmasını tavsiye etmiştir:

65 yaş ve üstü olan hastalar

Kardiyovasküler sorun riski yüksek olan hastalar (kalp krizi veya inme gibi)

Sigara içenler veya geçmişte uzun içmiş olan hastalar

Kanser riski yüksek olan hastalar

VTE riski olan hastalar

EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update

Table 1. Updates in the 2022 EULAR recommendations on the management of rheumatoid arthritis

	Updated recommendations in 2022 (Numbering based on 2019 recommendations)	Evidence for the update
8	If the treatment target is not achieved with the first csDMARD strategy, when poor prognostic factors are present, a bDMARD should be added; **JAK-inhibitors may be considered, but pertinent risk factors must be taken into account.**	• The ORAL Surveillance study showed that tofacitinib was associated with increased risk of MACE and malignancy,[2] prompting the recommendation to include risk assessment when prescribing JAK inhibitors. • However, the Corrona RA registry showed comparable risk for MACE and malignancy between tofacitinib and bDMARDs.[6]
9	bDMARDs and tsDMARDs should be combined with a csDMARD; in patients who cannot use csDMARDs as comedication, IL-6 inhibitors and tsDMARDs* may have some advantages compared with other bDMARDs.	
10	If a bDMARD or tsDMARD has failed, treatment with another bDMARD or a tsDMARD* should be considered; if one TNF-inhibitor **or IL-6 receptor inhibitor** therapy has failed, patients may receive an agent with another mode of action or a second TNF-α/**IL-6 receptor** inhibitor.	• Clinical data show that patients continue to benefit after switching to a second IL-6 inhibitor. • Risk assessment is recommended for those switching to a JAK inhibitor.

Recommendation

EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update

8.	If the treatment target is not achieved with the first csDMARD strategy, when poor prognostic factors are present, a bDMARD should be added; JAK-inhibitors may be considered, but pertinent risk factors* must be taken into account.
9.	bDMARDs and tsDMARDs* should be combined with a csDMARD; in patients who cannot use csDMARDs as comedication, IL-6 pathway inhibitors and tsDMARDs* may have some advantages compared with other bDMARDs.
10.	If a bDMARD or tsDMARD* has failed, treatment with another bDMARD or a tsDMARD*$^{+}$ should be considered; if one TNF or IL-6 receptor inhibitor therapy has failed, patients may receive an agent with another mode of action or a second TNF-/ IL-6R-inhibitor^{++}.
11.	After glucocorticoids have been discontinued and a patient is in sustained remission, dose reduction of DMARDs (bDMARDs/tsDMARDs* and/or csDMARDs) may be considered.

Bir JAK inhibitörü reçete edilirken kardiyovasküler olaylar ve maligniteler için aşağıdaki risk faktörleri göz önünde bulundurulmalıdır:

65 yaş üstü,

Sigara içme öyküsü,

Kardiyovasküler diğer risk faktörleri (diyabet, obezite, hipertansiyon gibi),

Malignite için diğer risk faktörleri (başarılı bir şekilde tedavi edilmiş melanom dışı cilt kanseri dışında mevcut veya önceki malignite öyküsü),

Tromboembolik olaylar için risk faktörler (miyokard enfarktüsü veya kalp yetmezliği öyküsü, kanser, kalıtsal kan pıhtılaşma bozuklukları veya tromboz öyküsü ve ayrıca kombine hormonal kontraseptifler veya hormon replasman tedavisi alan, büyük cerrahi geçiren veya hareketsiz hastalar).

ABSTRACT NUMBER: 0542

ASAS-EULAR Recommendations for the Management of Axial Spondyloarthritis: 2022 Update

conventional synthetic DMARDs for pure axial involvement. Recommendation 9 describes the indication for biological DMARDs (bDMARDs i.e. TNFi, IL-17i) and this was expanded to targeted synthetic DMARDs (tsDMARDs i.e. JAKi). b/tsDMARDs are indicated for patients with elevated CRP, MRI inflammation of SI joints or radiographic sacroiliitis who have high disease activity (ASDAS≥2.1) and failed ≥2 NSAIDs (Figure). BASDAI is no longer recommended to assess treatment start. Current practice is to start a TNFi or IL-17i as there is more accumulated evidence, particularly on safety, and experience with these drug classes. The continuation of a b/tsDMARD should be considered if an

hing principles (unchanged compared to the previous version of the ecommendations were formulated (Table). All recommendations sion were kept: eight unchanged (#2,3,6,7,8,13,14,15); three with minor ıre (#1,4,5) and two with relevant updates (#9,12), while two newly ns (#10,11) were added. The first 5 recommendations focus on personalised medicine, including treatment target and monitoring, non-pharmacological management and non-steroidal anti-inflammatory drugs (NSAIDs) as first choice pharmacological treatment. Recommendations 6-8 deal with analgesics and discourage long-term glucocorticoids and conventional synthetic DMARDs for pure axial involvement. Recommendation 9 describes the indication for biological DMARDs (bDMARDs i.e. TNFi, IL-17i) and this was expanded to targeted synthetic DMARDs (tsDMARDs i.e. JAKi). b/tsDMARDs are indicated for patients with elevated CRP, MRI inflammation of SI joints or radiographic sacroiliitis who have high disease activity (ASDAS≥2.1) and failed ≥2 NSAIDs (Figure). BASDAI is no longer recommended to assess treatment start. Current practice is to start a TNFi or IL-17i as there is more accumulated evidence, particularly on safety, and experience with these drug classes. The continuation of a b/tsDMARD should be considered if an improvement of ASDAS≥1.1 has been achieved after ≥12 weeks. The new recommendation 10 addresses extra-musculoskeletal manifestations, with TNF monoclonal antibodies preferred for recurrent uveitis or inflammatory bowel disease, and IL-17i for significant psoriasis. In light of overdiagnosis and overtreatment, treatment failure should trigger re-evaluation of the diagnosis and consideration of the presence of comorbidities (#11 – new). If active axSpA is confirmed after failing a b/tsDMARD, switching to another b/tsDMARD is recommended (#12). Tapering, but not immediate discontinuation of a bDMARD, can be considered in patients in sustained remission (#13). The unchanged recommendations #14 and #15 deal with surgery and spinal fractures.

Conclusion: The 2022 ASAS-EULAR recommendations provide up-to-date guidance on the management of patients with axSpA.

SLE- JAKi

- MRL/lpr lupus eğilimli fareler- Tofacitinib tedavisi SLE'de hastalık aktivitesini azaltmıştır. (nefrit, mukokutanöz prezentasyon ve otoantikor sentezi).
- Interferonlar ve proinflamatuar sitokinlerin ekspresyonunu azaltır. Endotel hasarını ve işlev bozukluğunu onarabilir.
- Vaka raporları ve küçük gözlemsel çalışmalar tofasitinibin hastalık aktivitesini azalttığını göstermekte.
- SLE-tofasitinib :plasebo kontrollü çalışmada hastalık aktivitesindeki azalmada istatistiksel olarak anlamlı bir değişiklik olmamıştır.

- SLE-barisitinib: Çift kör plasebo kontrollü 314 lupus, hastaların %70'i (24. haftada) SLEDAI artriti ve döküntüsü düzelmiştir
- Dorner ve ark. IFN I ilgili sitokinlerin inh. anti-dsDNA azalması. SLEDAI 2000 ölçeğinde iyileşme ve hassas-şiş eklemlerde azalma

- Kutanöz lupus eritematozus hastalarında filgotinib (sadece JAK-1 inh olduğu için?) başarısız
- UPA ile ilgili SLE etkinliği az

JAK inhibitors and autoimmune rheumatic diseases, Autoimmun Rev.2023 Apr

SKLERODERMA- JAKi

Literatürün sistematik incelemesini içeren bir yayında : 59 hasta (ort. yaş 47 ± 15 yıl). Ort. tedavi süresi 12ay (6-12)

- 35 hastada (%59), ilk basamak tedavi olarak reçete edilmiştir.
- JAKi (47 hastada tofacitinib ve 12 hastada baricitinib)

-52/59 hastada (%88) anlamlı kutanöz yanıt (mRSS'de azalma – mod.Rodnan cilt skoru - >5 puan ve başlangıçtan itibaren %25).

-31 interstisyel akciğer hastalığı (İAH) olan hastaların 28/29'unda takip süresi boyunca İAH ilerlemesi görülmemiştir (2 hastada eksik veri).

-Sadece iki hasta tedaviler sırasında hastalık progresyonu yaşadı.

JAK inhibitors and autoimmune rheumatic diseases, Autoimmun Rev.2023 Apr

Article

Evolution of Rheumatoid-Arthritis-Associated Interstitial Lung Disease in Patients Treated with JAK Inhibitors: A Retrospective Exploratory Study

Vincenzo Venerito [1,†], Andreina Manfredi [2,†], Antonio Carletto [3], Stefano Gentileschi [4], Fabiola Atzeni [5], Serena Guiducci [6], Marlea Lavista [1], Laura La Corte [5], Elisa Pedrollo [3], Arnaldo Scardapane [7], Caterina Tomassini [2], Bruno Frediani [4], Carlo Salvarani [2,8], Florenzo Iannone [1] and Marco Sebastiani [2,*]

- Nisan 2018'den Haziran 2022'ye kadar 6 üçüncü basamak İtalyan merkezde JAKi uygulanan 43 RA-ILD'li hastalar

Table 2. HRCT evolution in different JAKi groups.

Outcome n (Column%; Row%)	Baricitinib (n.28)	Tofacitinib (n.9)	Filgotinib (n.3)	Upadacitinib (n.3)	Total (n.43)
Improved	2 (7.14; 100)	0	0	0	2 (4.65; 100)
Stable	23 (82.14; 62.16)	8 (88.89; 21.62)	3 (100; 8.11)	3 (100; 8.11)	37 (86.05; 100)
Worsened	2 (10.71; 75)	1 (11.11; 25)	0	0	4 (9.30; 100)
Total	28 (100; 68.12)	9 (100; 20.93)	3 (100; 6.98)	3 (100; 6.98)	43 (100; 100)

p for Fisher's exact test = 1.0; No differences were recorded according to the duration of follow-up or the previous therapies

- FVC 22/28 (78.57%) hastada, DLCO 18/25 (72%) hastada stabil (19.1 ay)

J. Clin. Med. **2023**, *12*, 957. https://doi.org/10.3390/jcm12030957

Otoimmun hastalıklar-JAK

Sjögren'de JAK

- 11 hastalık bir çalışmada, barisitinib, aktif SS'lu hastada artrit, döküntü ve İAH üzerine etkin ve iyi tolere edilebilir bulunmuştur.

Dermatomiyozit'te JAK

- MDA5-positive amiyopatik dermatomiyozit ilişkili İAH (tek merkezli, açık etiketli bir klinik çalışma)

  Tofasitinib ile FVC, DLCO, HRCT ve sağkalım düzelmiş (6. ayda)

- Barisitinib ile refrakter juvenil DM deri ve kas bulguları düzelmiş.

JAK inhibitors and autoimmune rheumatic diseases, Autoimmun Rev.2023 Apr

VASKÜLİT-JAKi

- Nükseden Dev Hücreli Arterit hastalarında, baricitinib'in faz 2 çalışması ve upadacitinib'in bir faz 3 çalışması umut verici ön sonuçlarla devam etmektedir.

- Baricitinib: (faz II) PMR için [NCT04027101] ve DHA [NCT03026504].

- Başka çok merkezli, randomize kontrollü faz 3 çalışması dev hücreli arteriti [NCT03725202]upadacitinib'in güvenlilik ve etkinliğini değerlendirmek için halen devam etmektedir.

JAK inhibitors and autoimmune rheumatic diseases, Autoimmun Rev.2023 Apr

Jaki ve onaylı endikasyonlar

JAKi	USA	Europe	Japan
Ruxolitinib	Myelofibrosis Polycythemia vera Acute and chronic graft-versus-host disease Atopic dermatitis		
Abrocitinib	Atopic dermatitis		
Tofacitinib	Rheumatoid arthritis Psoriatic arthritis Ulcerative colitis Juvenile idiopathic arthritis Ankylosing spondylitis	Rheumatoid arthritis Psoriatic arthritis	
Baricitinib	Rheumatoid arthritis Severe* COVID-19	Rheumatoid arthritis Atopic dermatitis Alopecia areata	
Upadacitinib	Rheumatoid arthritis Psoriatic arthritis Ulcerative colitis Ankylosing spondylitis Non-radiographic axial spondyloarthritis (nr-axSpA) Atopic dermatitis	Rheumatoid arthritis Psoriatic arthritis Axial spondyloarthritis Ulcerative colitis Atopic dermatitis	
Delgocitinib (topical#)			Atopic dermatitis
Fedratinib	Myelofibrosis**		
Filgotinib		Rheumatoid arthritis	Rheumatoid arthritis
Pacritinib	Myelofibrosis		
Peficitinib			Rheumatoid arthritis
Deucravacitinib	Psoriasis		

The Emerging Safety Profile of JAK Inhibitors in Rheumatic Diseases. BioDrugs 2023, Sep37(5)

Key Points

Janus kinase inhibitor (JAKi) use is associated with serious infection risk similar to tumor necrosis factor inhibitor (TNFi) biologics, but a higher tofacitinib dose is associated with higher risk of serious infections compared with TNFi biologics.
JAKi use increases the risk of herpes zoster, which increases with higher JAKi doses, and this is numerically higher with baricitinib compared with other JAKi drugs.
This risk of herpes zoster with tofacitinib is higher than that with TNFi biologics; concomitant glucocorticoid use increases the risk of herpes zoster and vaccination is protective.
JAKi use for 1 year or longer is associated with an increased risk of venous thromboembolism (VTE) compared with active comparators (an approved biologic).

The Emerging Safety Profile of JAK Inhibitors in Rheumatic Diseases. BioDrugs 2023, Sep37(5)

Teşekkürler…