Psoriasisin Oral Tedavilerinde Güncelleme (Metotreksat, Apremilast, Jak İnhibitörleri)

DOÇ.DR. TUĞBA ÖZKÖK AKBULUT

Metotrexat

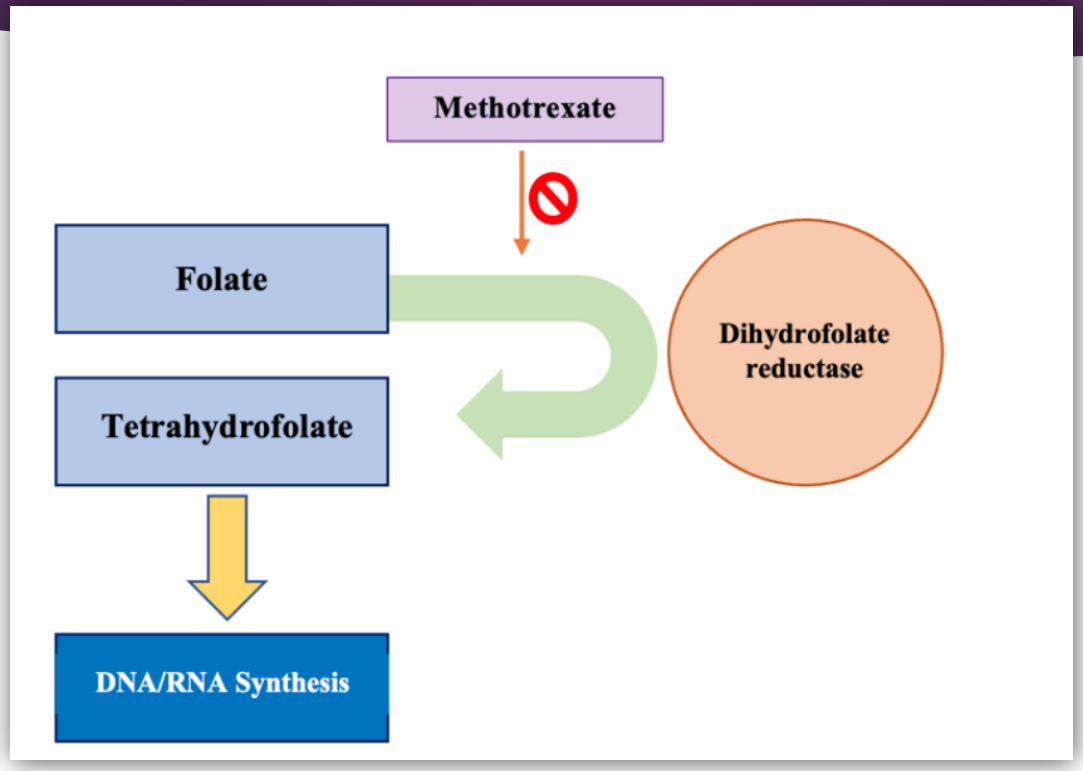
TABLE III.—*Overview on how long each treatment option has been in clinical use for psoriasis in Europe.*

Treatment	In clinical use for psoriasis since
Conventional systemic agent	
Acitretin	>25 years
Ciclosporin	>25 years
Fumaric acid esters	>25 years (in Germany)
Dimethylfumarate	2017 in Europe
Methotrexate	>25 years
TNF-α inhibitors	
Etanercept	2004
Infliximab	2005
Adalimumab	2007 Plaque Psoriasis
Certolizumab-pegol	Since 2018 (use in other indications notably earlier: 2009)
Anti-IL-12/23p40	
Ustekinumab	2009
Anti-IL-17	
Secukinumab	2015
Ixekizumab	2016
Brodalumab	2018
Anti-IL-23p19	
Guselkumab	2017
Tildrakizumab	2018
Risankizumab	2019
Small molecules	
Apremilast	2015

ITALIAN JOURNAL OF DERMATOLOGY AND VENEREOLOGY February 2022

İlk olarak 1949'da keşfedilmiş sentetik folik asit analoğudur.

1972'de şiddetli plak psoriasisde FDA onayı


Methotrexate
Folate
Tetrahydrofolate
Dihydrofolate reductase
DNA/RNA Synthesis

J Leukoc Biol. 2019;106:1063–1068.

DOI: 10.1002/JLB.5RU0519-145R

JLB JOURNAL OF LEUKOCYTE BIOLOGY

REVIEW

JAK inhibition by methotrexate (and csDMARDs) may explain clinical efficacy as monotherapy and combination therapy

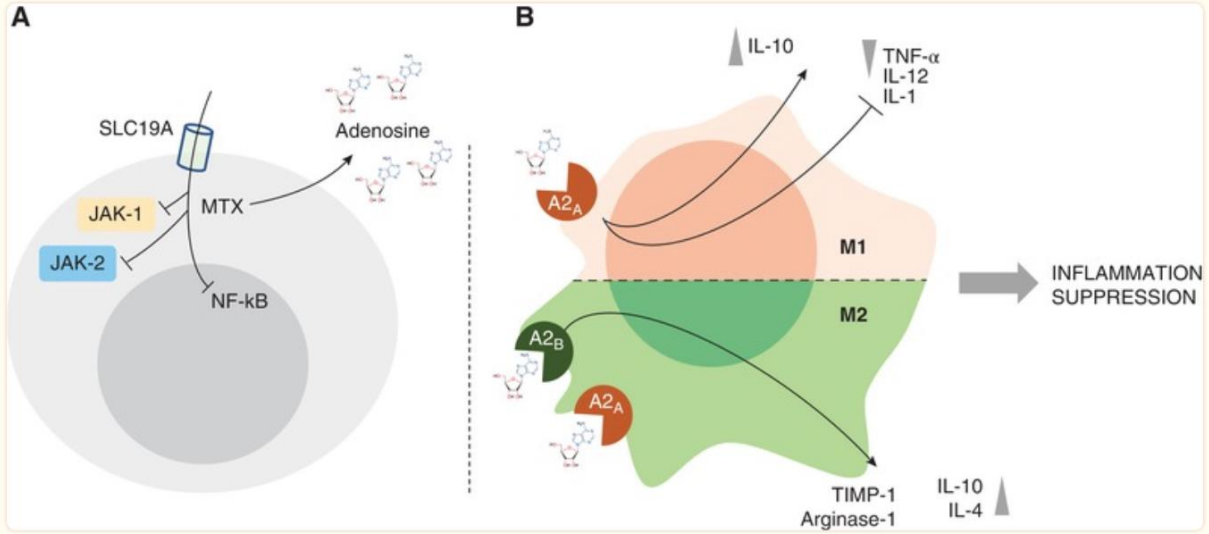


Figure 1

(**A, B**) MTX mechanisms of action and anti-inflammatory properties of adenosine on macrophages. (**A**) Intracellular uptake through SLC19A receptor, extracellular increase in Adenosine and repression of NF-kB activity. These effects and the inhibition of JAK-1/JAK-2 repress the autoimmune inflammation. (**B**) Schematic view of the anti-inflammatory activities of adenosine on M1 and M2 macrophages

Metotrexat- Etki mekanizması

- Dihidrofolat redüktazı inhibe eden folik asit antagonisti
- Nükleotid ve aminoasit sentezini inhibe ederek DNA sentezini azaltır, mitozu ve hızlı çoğalan hücrelerin proliferasyonunu önler.
- Lenfosit proliferasyonu ve sitokin üretimini baskılamak yoluyla da immünosüpresif etki gösterir.
- Metotreksat bu etkilerinin yanında T ve B hücrelerinden interlökin-1 (IL-1), tümör nekroz edici faktör-a gibi sitokinlerin üretimini de inhibe ederek immunmodulatuvar etki de gösterir.
- Sonuç olarak, metotreksatın psoriasis tedavisindeki etkinliği immün sistem üzerindeki etkisinin bir sonucudur

Metotrexat- Dermatolojik endikasyonları

- Plak psoriasis
- Generalize ya da lokal püstüler psoriasis
- Eritrodermik psoriasis
- Psoriatik artrit
- Erişkin, çocuk ve yaşlı olgularda da

- Oral, sc, im

Metotrexat- Kontrendikasyonları

Mutlak	Göreceli
- Şiddetli infeksiyonlar - Böbrek veya karaciğer fonksiyon bozuklukları - Aktif hepatit - Emzirme - Kronik alkol tüketimi - Kemik iliği fonksiyon bozukluğu/ hematolojik değişiklikler - İmmün yetmezlik - Akut peptik ülser - Akciğer fonksiyonunda belirgin azalma	- Böbrek veya karaciğer fonksiyon bozuklukları - Ülseratif kolit - Hepatit öyküsü - Uyum eksikliği - Çocuk sahibi olma isteğindeki doğurganlık çağındaki kadınlar ve erkekler - Gastrit - Diabetes Mellitus - Önceki maligniteler

TABLE XII.—*Recommended laboratory controls (MTX).*

Parameter [a]	Period in weeks/months			
	Pre-treatment	Within two weeks	During first two months, 1x every 4 weeks	Thereafter, every 3 months
Blood count	x	x	x	x
Liver enzymes [b]	x		x	x
Serum creatinine	x		x	x
Urine status	x			
Pregnancy test (urine or blood)	x			
HBV/HCV	x			
HIV	x			
Serum albumin [c]	x		x	x
PIIINP where available	x		Every 3 months [d]	

Not all tests may be necessary for all patients. Patient history, risk exposure and patient characteristics have to be taken into account. Further specific testing may be required according to clinical signs, risk, and exposure. The recommendations are based on clinical experience. No evidence is available.

[a] If blood leucocytes <3.0, neutrophils <1.0, thrombocytes <100, decrease the dose or discontinue the medication; [b] liver enzymes > 2-3x baseline values, initiate further diagnostics (including repeated testing/involve hepatologist) and consider decreasing the dose or discontinuing the medication; [c] in selected cases (e. g., in cases with suspected hypoalbuminemia or in patients using other drugs with high binding affinity for serum albumin); [d] in case of abnormal PIIINP during MTX treatment a hepatologist should be consulted.

Metotrexat

- Test dozu

FROM THE ACADEMY

Joint American Academy of Dermatology–National Psoriasis Foundation guidelines of care for the management of psoriasis with systemic nonbiologic therapies

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Dallas and San Antonio, Texas; Philadelphia and Pittsburgh, Pennsylvania; Birmingham, Alabama; Los Angeles, San Francisco, San Diego, and Irvine, California; Rochester, Minnesota; Milwaukee, Wisconsin; New York, New York; Portland, Oregon; Cleveland, Ohio; Boston, Massachusetts; St Louis, Missouri; Detroit and Ann Arbor, Michigan; Bethesda, Maryland; Chicago and Rosemont, Illinois; Sumter, South Carolina; Centennial, Colorado; Oklahoma City, Oklahoma; Atlanta, Georgia; and Cromwell and New Haven, Connecticut

Psoriasis is a chronic inflammatory disease involving multiple organ systems and affecting approximately 2% of the world's population. In this guideline, we focus the discussion on systemic, nonbiologic medications for the treatment of this disease. We provide detailed discussion of efficacy and safety for the most commonly used medications, including methotrexate, cyclosporine, and acitretin, and provide recommendations to assist prescribers in initiating and managing patients on these treatments. Additionally, we discuss newer therapies, including tofacitinib and apremilast, and briefly touch on a number of other medications, including fumaric acid esters (used outside the United States) and therapies that are no longer widely used for the treatment of psoriasis (ie, hydroxyurea, leflunomide, mycophenolate mofetil, thioguanine, and tacrolimus). (J Am Acad Dermatol 2020;82:1445-86.)

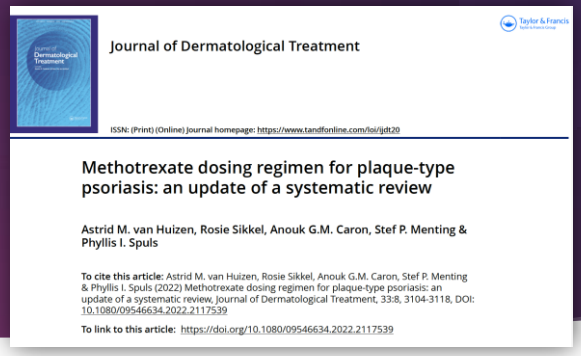
İki farklı yaklaşım

Test dozu tercih edenler: 2,5-5 mg test dozu

Güncel yaklaşımda test dozu gerekmeyebileceği vurgulanmakta

Yaşlı hastalarda ya da rölatif kontrendikasyonu olan hastalarda test dozu verilebilir

Metotrexat



Journal of Dermatological Treatment

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ijdt20

Methotrexate dosing regimen for plaque-type psoriasis: an update of a systematic review

Astrid M. van Huizen, Rosie Sikkel, Anouk G.M. Caron, Stef P. Menting & Phyllis I. Spuls

To cite this article: Astrid M. van Huizen, Rosie Sikkel, Anouk G.M. Caron, Stef P. Menting & Phyllis I. Spuls (2022) Methotrexate dosing regimen for plaque-type psoriasis: an update of a systematic review, Journal of Dermatological Treatment, 33:8, 3104-3118, DOI: 10.1080/09546634.2022.2117539

To link to this article: https://doi.org/10.1080/09546634.2022.2117539

- Başlama dozu

Based on the literature included in this SR we performed a previously published consensus project (91), resulting in the following recommendations for daily practice: a test dose may not be needed in adults, children and vulnerable patients (elderly, patients with renal insufficiency). The start dose of MTX could be 15 mg/week, 10 mg/m^2/week in children and 7.5–15 mg/week in vulnerable patients. MTX can be administered once a

Başlama dozu

Erişkinlerde 15 mg/hafta

Çocuklarda 10 mg/m2/hafta

Yaşlı hastalarda 7,5-15 mg/hafta

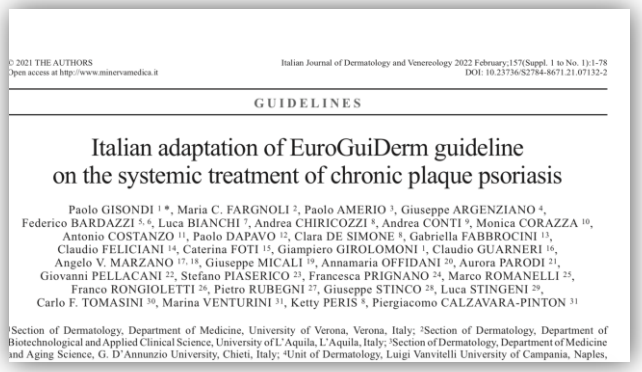
Yaşlılarda renal fonksiyonlarda azalma
miyelosupresyon riskinde artış

metotreksat tedavi dozu yetişkinlerden düşük olmalı

Ancak metotreksat tedavisinin kardiyovasküler komorbiditeler üzerinde olumlu etkisi □

Metotrexat- Etkinlik

- Yavaş etkili: Psoriasisli hastaların %75-80'inde metotreksata yanıt 4-8 haftada başlar
- Psoriasis Alan Şiddet İndeksi 75 (PAŞİ 75) yanıtına 16-24.haftada %36-42



Italian Journal of Dermatology and Venereology 2022 February;157(Suppl. 1 to No. 1):1-78
DOI: 10.23736/S2784-8671.21.07132-2

GUIDELINES

Italian adaptation of EuroGuiDerm guideline on the systemic treatment of chronic plaque psoriasis

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İdame dozu

15 mg/hafta öneriliyor

Cevap yetersizse doz 20 mg/hafta yükseltilebilir

25 mg/hafta sadece seçilmiş olgularda

www.thelancet.com Published online December 21, 2016 http://dx.doi.org/10.1016/S0140-6736(16)32127-4

Cabello Zurita, Camila et al. "Effectiveness and safety of Methotrexate in psoriasis: an eight-year experience with 218 patients." *The Journal of dermatological treatment* vol. 28,5 (2017): 401-405.

Br J Dermatol. 2023 Apr 20;188(5):618-627. doi: 10.1093/bjd/ljad004.

Effectiveness and persistence of acitretin, ciclosporin, fumaric acid esters and methotrexate for patients with moderate-to-severe psoriasis: a cohort study from BADBIR

Oras A Alabas [1], Kayleigh J Mason [2], Zenas Z N Yiu [1], Philip J Hampton [3], Nick J Reynolds [3], Caroline M Owen [4], Anthony Bewley [5], Philip M Laws [6], Richard B Warren [1], Mark Lunt [1], Catherine H Smith [7], Christopher E M Griffiths [1]; BADBIR Study Group

Collaborators, Affiliations + expand

PMID: 36763783 DOI: 10.1093/bjd/ljad004

Abstract

Background: Real-world data evaluating effectiveness and persistence of systemic therapies for patients with psoriasis are limited. Objectives To determine the effectiveness and persistence of acitretin, ciclosporin, fumaric acid esters (FAEs) and methotrexate in patients with moderate-to-severe psoriasis.

Methods: Data from the British Association of Dermatologists Biologics and Immunomodulators Register (BADBIR), a prospective, multicentre pharmacovigilance register of patients with moderate-to-severe psoriasis receiving biologic and/or conventional systemic therapies, were analysed. Eligible patients were ≥ 16 years of age receiving a first course of acitretin, ciclosporin, FAEs or methotrexate between 2007 and 2021 with ≥ 6 months' follow-up. Effectiveness was defined as achieving absolute Psoriasis Area and Severity Index (aPASI) ≤ 2 reported ≥ 4 weeks after treatment start date until date of cessation. To identify baseline clinical variables associated with treatment effectiveness, we used multivariable logistic regression models estimating the adjusted odds ratio (aOR) of achieving aPASI ≤ 2. To describe drug persistence associated with ineffectiveness, occurrence of adverse events or other reasons for discontinuation, survival estimates with 95% confidence intervals (CIs) were obtained using a flexible parametric model.

Results: In total, 5430 patients were included in the analysis. Overall, 1023 (19%) patients were receiving acitretin, 1401 (26%) patients were on ciclosporin, 347 (6%) patients were on FAEs, and 265

Tedavi etkisizliği için risk faktörleri

Önceki nonbiyolojik ajan maruziyeti
Erkek cinsiyet
Komorbidite varlığı
Alkol kullanımı

Conclusions: The real-world effectiveness and persistence of acitretin, ciclosporin, FAEs and methotrexate were generally low. Previous nonbiologic systemic therapies, male sex, comorbidities and alcohol consumption were risk factors associated with treatment ineffectiveness.

5430 hasta

2659 (%49) metotrexat

İlaçta kalım metotrexat grubunda daha yüksek

%46,1 (12 aylık ilaçta kalım)

Multicenter Study > Int J Dermatol. 2021 Sep;60(9):1140-1147. doi: 10.1111/ijd.15628.
Epub 2021 May 20.

Drug survival and predictor factors for discontinuation of methotrexate in psoriasis: a real life multicenter study

Tugba Ozkok Akbulut [1], Filiz Topaloglu Demir [2], Ilteris Oguz Topal [3], Asude Kara Polat [4], Ayse Serap Karadag [5], Melek Aslan Kayiran [5], Ezgi Ozkur [6], Ilknur Kıvanc Altunay [6]

Abstract

Background: Drug survival is useful to evaluate long-term drug performance in daily practice. The aim of this study was to evaluate drug survival for methotrexate (MTX) monotherapy in patients with plaque-type psoriasis.

Methods: We reviewed 3,512 follow-up charts of patients with psoriasis at five tertiary referral centers between January 2012 and January 2020. We analyzed baseline data and treatment outcomes of patients under MTX monotherapy. Drug survival was analyzed using Kaplan-Meier and Cox regression analyses.

Results: Patients with psoriasis who were treated with MTX monotherapy were enrolled (N = 649). The median duration of drug survival was 15 months (95% CI: 13.2-16.8). The overall drug survival rate was 54.7%, 17.4%, and 8% after 1, 3, and 5 years, respectively. The main reasons for discontinuation were adverse effects (n = 209, 32.2%) and inefficacy (n = 105, 15.6%). Based on multivariate Cox regression analysis, the presence of nausea/vomiting (HR: 2.01, 95% CI: 1.49-2.71; P < 0.001) was observed as a statistically significant risk factor for drug discontinuation. Age over 50 years (HR: 0.68, 95% CI: 0.48-0.97; P = 0.03) and using MTX dose ≥15 mg/weekly were positive predictors for drug survival (HR: 0.72, 95% CI: 0.54-0.95; P = 0.02).

Conclusions: The average drug survival of MTX was 15 months. MTX is still the first-line treatment of moderate-to-severe plaque psoriasis, as highlighted in guidelines. To prevent premature discontinuation, physicians need to look at the response time of at least 16-24 weeks, especially when a stepwise dose increment is used. The presence of nausea/vomiting seemed to be associated with an approximately twofold risk of discontinuation.

649 hasta

Bir yıllık ilaçta kalım %54,7

Metotrexat- Etkinlik

Randomized Controlled Trial > Clin Exp Dermatol. 2022 May;47(5):942-948.
doi: 10.1111/ced.15102. Epub 2022 Feb 9.

Comparison of the clinical efficacy of subcutaneous vs. oral administration of methotrexate in patients with psoriasis vulgaris: a randomized controlled trial

Charoen Choonhakarn [1], Suteeraporn Chaowattanapanit [1], Narachai Julanon [1], Panita Limpawattana [2]

Affiliations + expand

PMID: 35015903 DOI: 10.1111/ced.15102

Abstract

Background: Evidence demonstrates that parenteral administration of methotrexate (MTX) has a higher drug bioavailability than oral administration. This difference is even more pronounced for medium to high dosages.

Aim: To compare the efficacy, safety, and tolerability of oral and subcutaneous (SC) MTX for treatment of psoriasis.

Methods: A randomized, comparative, single-blind, 32-week study was conducted. The clinical response was evaluated using the Psoriasis Area Severity Index (PASI) and patient global satisfaction was assessed using a visual analogue scale (VAS).

Results: In total, 77 completed the study: 38 in the SC and 39 in the oral MTX group. No significant between-group differences were found in the number attaining PASI improvement of 75% (PASI75), 90% (PASI90) and 100% (PASI100) at Weeks 16 and 32: PASI75 (P = 0.14 and P = 0.21, respectively), PASI90 (P = 0.23 and P = 0.18) and PASI100 (P = 0.62 and P = 0.22). According to the mean VAS, no significant differences between the groups were found at any time points except at Week 32 that the mean VAS was significantly higher in the SC group (P = 0.03). Adverse events were comparable in both groups.

Conclusion: SC and oral administration of MTX had similar efficacies in improving the PASI score even at the highest tolerable dose; however, the SC MTX group had higher overall patient satisfaction than the oral MTX group. No difference in tolerability was found.

Oral ve sc uygulama ile benzer etkinlik

Metotrexat- Etkinlik

Randomized Controlled Trial > Dermatol Ther. 2022 Aug;35(8):e15656. doi: 10.1111/dth.15656. Epub 2022 Jul 5.

Comparison of overall efficacy and safety of oral versus subcutaneous methotrexate in severe psoriasis

Sunil Dogra [1], Namrata Singh [1], Sheetanshu Kumar [1], Tarun Narang [1], Sanjeev Handa [1]

Affiliations + expand

PMID: 35730664 DOI: 10.1111/dth.15656

Abstract

Subcutaneous (SC) methotrexate (MTX) is considered to be associated with a higher and predictable linear bioavailability as compared to oral MTX. Although various studies have reported SC MTX to be safe and effective in psoriasis, prospective head-to-head comparative trials on oral versus SC MTX are limited. To compare the efficacy and safety of SC versus oral MTX in severe psoriasis. It was a prospective, single-blinded, randomized controlled trial, in 100 eligible, adult patients of severe psoriasis randomized into two groups. Group-A (n = 50) patients were started on oral MTX at a full dose of 0.3 mg/kg/week (maximum 25 mg/week) given for 12 weeks or till achieving PASI90 [90% reduction in Psoriasis Area Severity Index (PASI) from baseline], whichever was earlier and group-B (n = 50) patients received SC MTX in the same dose and duration. MTX was then tapered gradually at 5 mg every 2 weeks and stopped. All patients were followed-up for 24 weeks post-treatment with monthly assessment of PASI and Dermatology Life Quality Index (DLQI) scores. Baseline demographic profiles of patients in both the groups were comparable. The mean ± SD baseline PASI scores were group-A: 15.1 ± 3.2 versus group-B:15.7 ± 3.3 (p = 0.35). The number of patients that achieved PASI90 at or before 12 weeks of treatment was numerically higher in group-B (39/50, 78%) versus group-A (31/50, 62%; p = 0.08) and the time to achieve PASI90 was significantly lesser (p < 0.001).Also, the percentage(%) decline in DLQI was significantly higher in group-B(p = 0.003). The overall side-effect profile was comparable between groups (p = 0.31), but the frequency of gastrointestinal side-effects was significantly less in group-B (p = 0.04). Among those patients who achieved a PASI90 response by week12, relapse rates were comparable during the subsequent 24 week follow-up period [group-A: 12/31 (39%), group-B: 11/39 (28%), and p-value = 0.33]. SC MTX results in a significantly faster achievement of PASI90 and greater reduction in DLQI as compared to oral MTX in patients who are candidates for systemic therapy with a comparable safety profile. CTRI/2018/01/011373, date of registration: 15 January, 2018; trial registered prospectively.

Sc uygulama ile daha hızlı PASİ
90 yanıtı
DLQI daha fazla iyileşme

Etkinlik- Folik acid eklenmesi

2022

ORIGINAL ARTICLE

Real-world Methotrexate Use in a Prospective Cohort of Paediatric Patients with Plaque Psoriasis: Effectiveness, Adverse Events and Folic Acid Regimen

Finola M. BRUINS[1], Maartje R. VAN ACHT[1], Inge M. G. J. BRONCKERS[1], Hans M. M. GROENEWOUD[2], Elke M. G. J. DE JONG[1] and Marieke M. B. SEYGER[1]
[1]Department of Dermatology, Radboud University Medical Centre, and [2]Department for Health Evidence, Radboud University, Nijmegen, The Netherlands

105 çocuk (ort yaş: 14,1)

2 yıllık takip

24. Haftada ve 48. haftada 1/3 hastada mutlak pası ≤2

Benzer GİS yan etki
Folik acid 5mg/hafta
1mg 6 gün/hafta

Abstract

In paediatric psoriasis, few studies have evaluated methotrexate effectiveness, adverse events and folic acid regimen. Therefore this study prospectively assessed methotrexate adverse events and effectiveness in paediatric patients with psoriasis in a real-world setting. Furthermore, gastrointestinal adverse events and methotrexate effectiveness were compared between folic acid regimens (5 mg once weekly vs 1 mg 6 times weekly). Data for paediatric patients with psoriasis treated with methotrexate from September 2008 to October 2020 were extracted from Child-CAPTURE, a prospective, daily clinical practice registry. Effectiveness was determined by Psoriasis Area and Severity Index (PASI). Comparison of persistent gastrointestinal adverse events between folic acid regimens were assessed through Kaplan-Meier analysis. A total of 105 paediatric patients with plaque psoriasis (41.0% male, mean age 14.1 years) were included. At week 24 and 48, an absolute PASI ≤ 2.0 was achieved by approximately one-third of all patients. During follow-up, 46.7% reported ≥ 1 persistent adverse events. After 1 and 2 years, approximately one-quarter of patients achieved a PASI ≤ 2.0 without persistent adverse events. Although non-significant, a possible trend towards lower occurrence of gastrointestinal adverse events was found for folic acid 1 mg 6 times weekly (p = 0.196), with similar effectiveness between folic acid regimens. These findings show that a subgroup of paediatric patients with psoriasis responded well to methotrexate treatment without considerable side-effects during a 2-year follow-up.

Acta Derm Venereol 2022

Metotrexat- Etkinlik

Randomized Controlled Trial > Clin Exp Dermatol. 2012 Oct;37(7):729-34.
doi: 10.1111/j.1365-2230.2012.04440.x. Epub 2012 Jul 25.

Efficacy and safety of systemic methotrexate in two fixed doses of 10 mg or 25 mg orally once weekly in adult patients with severe plaque-type psoriasis: a prospective, randomized, double-blind, dose-ranging study

S Dogra [1], V Krishna, A J Kanwar

Affiliations + expand

PMID: 22830389 DOI: 10.1111/j.1365-2230.2012.04440.x

Abstract

Background: Methotrexate (MTX) is the 'gold-standard' drug for the treatment of severe psoriasis. In the absence of any consensus on an optimum dose of MTX for psoriasis, there is wide variation in prescribing patterns between dermatologists, resulting in variable or delayed therapeutic effects.

Aim: To identify the most effective fixed single weekly dose of oral MTX with acceptable side-effects in the treatment of severe plaque-type psoriasis.

Methods: This was a prospective, randomized, double-blind, parallel-group, dose-ranging study, which enrolled 60 patients of both genders (aged 18-62 years) with severe chronic plaque-type psoriasis. Patients were randomly assigned to one of two groups: group A was treated with MTX 10 mg once weekly, and group B was treated with 25 mg MTX once weekly. The main outcome measure was change in Psoriasis Area and Severity Index (PASI) between the two groups from baseline to 12 weeks.

Results: Of the 60 patients, 51 (85%) completed the 12-week study. At the end of the study, 24 patients (92.3%) in the MTX 25 mg group had achieved a 75% reduction in PASI (PASI 75) from baseline, compared with 18 patients (72%) in the MTX 10 mg group (P>0.05). Mean time in weeks to achieve PASI 75 was significantly shorter in the MTX 25mg group (7.92±1.91) than in the MTX 10mg group (9.47±2.29) (P<0.05). In addition, 20 patients (69%) in the MTX 25mg group achieved 100% reduction in PASI compared with 9 patients (30%) in the MTX 10mg group within 12weeks of the study period (P<0.01). Adverse effects were generally mild, and were noted in 43.1% of the 51 patients who completed the study, with no significant difference in frequency between the two groups, although they were less severe in the 10mg group.

Conclusions: MTX 25mg is an effective dose as monotherapy for the treatment of severe psoriasis, whereas the 10mg dose is slow to act and less effective, but has a less severe side-effect profile.

25 mg metotrexat 10 mg'a kıyasla daha etkili

Yan etki riski artıyor!!!

Metotrexat Etkinlik

Clinical Trial > J Am Acad Dermatol. 2017 Dec;77(6):1030-1037.
doi: 10.1016/j.jaad.2017.08.017. Epub 2017 Oct 6.

Poor early response to methotrexate portends inadequate long-term outcomes in patients with moderate-to-severe psoriasis: Evidence from 2 phase 3 clinical trials

Kenneth B Gordon [1], Keith A Betts [2], Murali Sundaram [3], James E Signorovitch [4], Junlong Li [4], Meng Xie [4], Eric Q Wu [4], Martin M Okun [5]

Abstract

Background: Most methotrexate-treated psoriasis patients do not achieve a long-term PASI75 (75% reduction from baseline Psoriasis Area and Severity Index score) response. Indications of nonresponse can be apparent after only 4 weeks of treatment.

Objective: To develop a prediction rule to identify patients unlikely to respond adequately to methotrexate.

Methods: Patient-level data from CHAMPION (NCT00235820, N = 110) was used to construct a prediction model for week 16 PASI75 by using patient baseline characteristics and week 4 PASI25. A prediction rule was determined on the basis of the sensitivity and specificity and validated in terms of week 16 PASI75 response in an independent validation sample from trial M10-255 (NCT00679731, N = 163).

Results: PASI25 achievement at week 4 (odds ratio = 8.917) was highly predictive of response with methotrexate at week 16. Patients with a predicted response probability <30% were recommended to discontinue methotrexate. The rates of week 16 PASI75 response were 65.8% and 21.1% (P < .001) for patients recommended to continue and discontinue methotrexate, respectively.

Limitations: The CHAMPION trial excluded patients previously treated with biologics, and the M10-255 trial had no restrictions.

Conclusion: A prediction rule was developed and validated to identify patients unlikely to respond adequately to methotrexate. The rule indicates that 4 weeks of methotrexate might be sufficient to predict long-term response with limited safety risk.

4. Haftada PASI 25 yanıtı elde edilip edilmemesi 16. haftadaki PASI 75 yanıtı için prediktif

Yani 4. haftada PASI 25 yanıtı elde edilmiyorsa MTX ile uzun dönemde yanıt bekleme?

> Bull Exp Biol Med. 2022 Feb;172(4):460-463. doi: 10.1007/s10517-022-05413-6.
Epub 2022 Feb 17.

Genetic Markers of Therapeutic Efficacy of Methotrexate in Patients with Psoriasis

O E Voron'ko [1], K K Baskaev [1], V V Sobolev [2 3], E V Denisova [4], I M Korsunskaya [4]

Abstract

We studied the effect of C677T and A1298C polymorphisms of the MTHFR gene and 2R/3R polymorphisms of the TYMS gene on the sensitivity to methotrexate in patients with psoriasis (n=139). It was shown that genotype 3R/3R TYMS (OR 8.86, 95%CI 2.00-39.22) and complex genotypes MTHFR1298:A;TYMS:3R (OR 8.20, 95%CI 2.36-28.48) and MTHFR677:C;TYMS:3R (OR 5.40, 95%CI 1.95-14.94) were associated with sensitivity to methotrexate, while genotype 2R/2R TYMS (OR 8.20, 95%CI 2.36-28.48) and complex genotypes MTHFR1298:C;MTHFR677:T;TYMS:2R (OR 0.18, 95%CI 0.06-0.56) and MTHFR1298:C;MTHFR677:T (OR 0.23, 95%CI 0.09-0.59) were associated with resistance to methotrexate. The results can be used for preventive assessment of the effectiveness of methotrexate treatment in patients with psoriasis.

MTHFR Gene Polymorphism Association With Psoriatic Arthritis Risk and the Efficacy and Hepatotoxicity of Methotrexate in Psoriasis

Jie Zhu[1†], Zhicheng Wang[2†], Lu Tao[1], Ling Han[1], Qiong Huang[1], Xu Fang[1], Ke Yang[3], Guiqin Huang[1], Zhizhong Zheng[1], Nikhil Yawalkar[4], Zhenghua Zhang[1] and Kexiang Yan[1*]*

April 2022 | Volume 9 | Article 869912

MTHFR gen polimorfizmi
- ✓ PsA riski
- ✓ Etkinlik durumu
- ✓ Hepatotoksisite riski ilişkili

Aims: To assess whether *MTHFR* rs1801131 and rs1801133 SNPs are associated with concomitant psoriatic arthritis (PsA) and investigate the efficacy and hepatotoxicity of MTX in patients with psoriasis in the Han Chinese population.

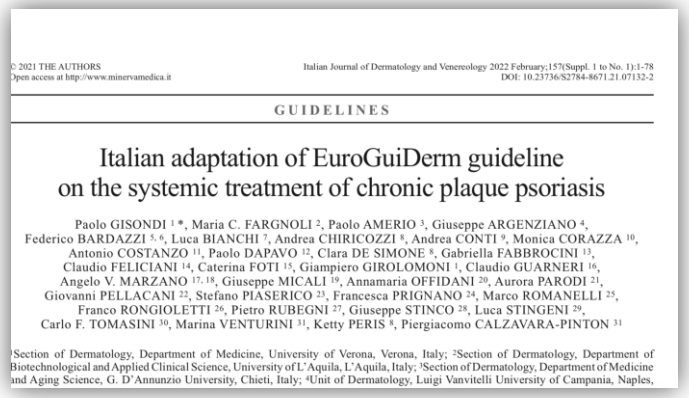
Methods: This prospective, single-arm, interventional study recruited a total of 309 patients with psoriasis, 163 with psoriatic arthritis and 146 without psoriatic arthritis, who completed a 12-week MTX treatment and 1,031 healthy controls. Patients' characteristics including age, gender, disease duration, height, weight, smoking status, alcohol consumption, medical history, disease severity and liver function test results were accessed and recorded. Single nucleotide polymorphism (SNP) genotyping of rs1801131 and rs1801133 in the *MTHFR* gene was performed.

Results: The rs1801133 CC genotype was more frequent in patients with PsA than those with PsO and healthy controls (42.3% vs. 28.8% vs. 33.1%, $p < 0.05$). The 90% reduction from baseline PASI score (PASI 90) response rates to MTX were significantly higher in patients with the rs1801133 TT genotype than those with the CT and CC genotype (33.96% vs. 19.31% vs. 14.41%, $OR = 2.76$, $p = 0.006$). The rs1801133 CT+TT genotype was more frequent in PsA patients with abnormal liver function than in those with normal liver function ($p < 0.05$). In addition, patients with the rs1801131 CT genotype had lower PASI 75 response rates to MTX ($OR = 0.49$, $p = 0.01$), and lower risk of ALT elevation ($OR = 0.46$, $p = 0.04$).

Conclusions: This study provided some evidence for *MTHFR* polymorphism association with the risk of PsA and the efficacy and hepatotoxicity of the low-dose MTX in the Chinese population. Given the relatively small sample size and potentially missed diagnosis of PsA, the results from this study warrant further investigation.

Metotrexat- Güvenlik

- Bulantı, Gis intolerans, halsizlik, saç dökülmesi sık yan etkilerden



Italian Journal of Dermatology and Venereology 2022 February;157(Suppl. 1 to No. 1):1-78
DOI: 10.23736/S2784-8671.21.07132-2

GUIDELINES

Italian adaptation of EuroGuiDerm guideline on the systemic treatment of chronic plaque psoriasis

Paolo GISONDI [1] *, Maria C. FARGNOLI [2], Paolo AMERIO [3], Giuseppe ARGENZIANO [4], Federico BARDAZZI [5, 6], Luca BIANCHI [7], Andrea CHIRICOZZI [8], Andrea CONTI [9], Monica CORAZZA [10], Antonio COSTANZO [11], Paolo DAPAVO [12], Clara DE SIMONE [8], Gabriella FABBROCINI [13], Claudio FELICIANI [14], Caterina FOTI [15], Giampiero GIROLOMONI [1], Claudio GUARNERI [16], Angelo V. MARZANO [17, 18], Giuseppe MICALI [19], Annamaria OFFIDANI [20], Aurora PARODI [21], Giovanni PELLACANI [22], Stefano PIASERICO [23], Francesca PRIGNANO [24], Marco ROMANELLI [25], Franco RONGIOLETTI [26], Pietro RUBEGNI [27], Giuseppe STINCO [28], Luca STINGENI [29], Carlo F. TOMASINI [30], Marina VENTURINI [31], Ketty PERIS [8], Piergiacomo CALZAVARA-PINTON [31]

[1]Section of Dermatology, Department of Medicine, University of Verona, Verona, Italy; [2]Section of Dermatology, Department of Biotechnological and Applied Clinical Science, University of L'Aquila, L'Aquila, Italy; [3]Section of Dermatology, Department of Medicine and Aging Science, G. D'Annunzio University, Chieti, Italy; [4]Unit of Dermatology, Luigi Vanvitelli University of Campania, Naples,

Special consideration during treatment

Please see SmPC and other sources for complete listing. The guideline subcommittee decided to comment on the following aspects.

In case of gastrointestinal complaints during MTX therapy drinking coffee and/or dark chocolate may be helpful in up to 30% of patients.[44]

Metotrexat- Güvenlik

- Hepatotoksisite riski ↑
  - Obezite
  - Lipid yüksekliği
  - diyabet varlığı

  } Nonalkolik yağlı karaciğer hastalığı daha sık

  - Alkol kullanımı
  - Hepatit B ve C inf
  - Kronik karaciğer hastalığı
  - Hepatotoksik ilaç kullanımı

Metotrexat- Güvenlik

- Miyelosüpresyon

- ✓ ileri yaş,
- ✓ renal yetmezlik
- ✓ yüksek doz veya sık aralıklarla metotreksat kullanımı

- ✓ folat desteğinin yokluğu
- ✓ ilaç etkileşimleri
- ✓ Hipoalbuminemi
- ✓ yüksek miktarda alkol tüketimi

- İlk dozda da görülebilir, ilerleyen dönemde de ortaya çıkabilir
- Özellikle risk faktörü olan olgularda doz arttırımı durumunda 6-8 hafta daha sıkı takip öneriliyor

J Am Acad Dermatol
Volume 82, Number 6

TABLE XIII.—*List of most important drugs with potential interactions (MTX).*

Drug	Type of interaction
Colchicines, CsA, NSAID, penicillin, probenecid, salicylates, sulfonamides	Decreased renal elimination of MTX
Chloramphenicol, co-trimoxazole, cytostatic agents, ethanol, NSAID, pyrimethamine, sulfonamides	Increased risk of bone marrow and gastrointestinal toxicity
Barbiturates, co-trimoxazole, phenytoin, probenecid, NSAID, sulfonamides	Interaction with plasma protein binding
Ethanol, leflunomide, retinoids, tetracyclines	Increased hepatotoxicity

Apremilast

Apremilast

- Ağızdan alınan selektif fosfodiesteraz-4 inh (PDE4)inh
- Antiinflamatuvar etki+ immünsupresif değil

Diğer sistemik tedavilere yanıt vermeyen veya kontrendikasyonları olan erişkin psoriasis ve/veya PsA hastaları için terapötik bir alternatif olarak karşımıza çıkmakta

FDA Approved Use

- Psoriatic arthritis
- Plaque psoriasis
- Oral ulcers associated with Behcet disease

Ülkemizde henüz geri ödeme kapsamında değil

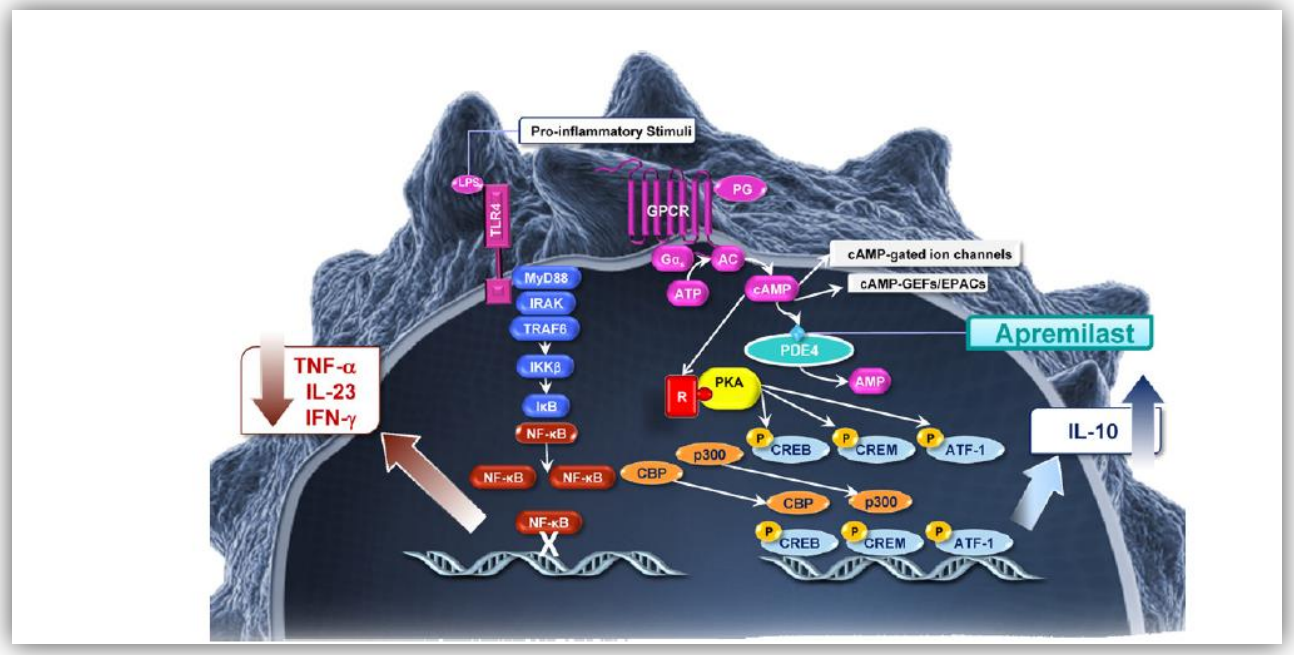
2014

2015

2022

Apremilast

- PDE4, bir hücre içi ikinci haberci olan siklik adenozin 3,5-monofosfatı (cAMP) parçalayarak inflamatuar yanıtı düzenler.
- PDE4'ün inhibisyonu cAMP seviyesini arttırır,
- Böylece proinflamatuar sitokin (IFN-γ,TNF-a, IL-12, IL-17 ve IL-23) üretiminin azalmasına
- antiinflamatuar mediatör olan IL-10 bir artışa neden olur



P. Schafer / Biochemical Pharmacology 83 (2012) 1583–1590

Apremilast

- Mutlak biyoyararlanımı %73
- Plazma maksimum konsantrasyonuna 2,5 saatte ulaşmakta
- Gıda alımı
- Apremilas
- rifampisin,
  birlikte kul
- Gebelik kat
- Emzirmede kontrendike

Hafif ve orta derecede böbrek yetmezliği
Orta ve şiddetli karaciğer yetmezliği
} Kullanılabilir

Bununla birlikte şiddetli böbrek yetmezliği olanlarda tavsiye edilmez.

Apremilast

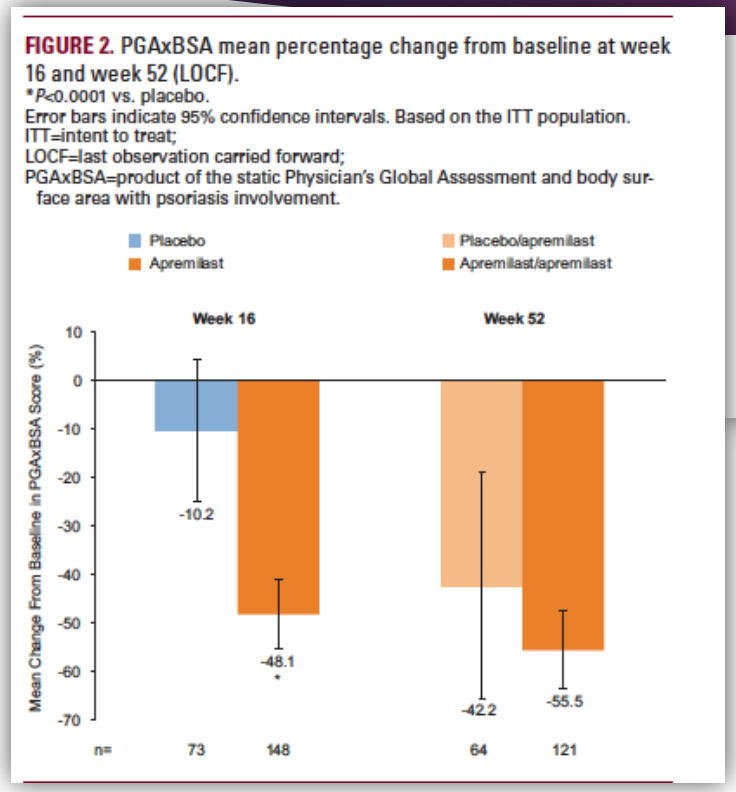
Dose for Psoriasis and PA				
	Psoriasis		Psoriasis Arthritis	
Day	Dosage		Dosage	
Day 1:	10mg		10mg	
Day 2:	10mg	10mg	10mg	10mg
Day 3:	10mg	20mg	10mg	20mg
Day 4:	20mg	20mg	20mg	20mg
Day 5:	20mg	30mg	20mg	30mg
Day 6 and after:	30mg	30mg	30mg	30mg

Başlangıç hastaları için
tedavi başlangıç paketi:

4 adet 10 mg
4 adet 20 mg
19 adet 30 mg'lık tablet

İdame tedavide
56 adet 30 mg'lık tablet

Apremilast



Efficacy and Safety of Apremilast in Systemic- and Biologic-Naive Patients With Moderate Plaque Psoriasis: 52-Week Results of UNVEIL

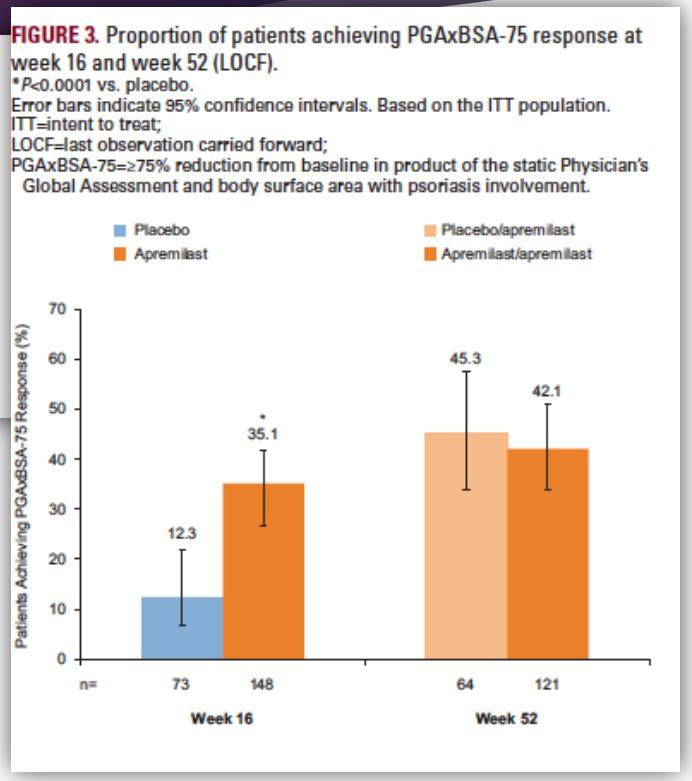
Linda Stein Gold MD,[a] Jerry Bagel MD,[b] Mark Lebwohl MD,[c] J. Mark Jackson MD,[d] Rongdean Chen PhD,[e] Joana Goncalves MD,[e] Eugenia Levi PharmD,[e] Kristina Callis Duffin MD MS[f]

[a]Henry Ford Health System, West Bloomfield, MI
[b]Psoriasis Treatment Center of Central New Jersey, East Windsor, NJ
[c]Icahn School of Medicine at Mount Sinai, New York, NY
[d]University of Louisville, Forefront Dermatology, Louisville, KY
[e]Celgene Corporation, Summit, NJ
[f]University of Utah, Salt Lake City, UT

221 Orta şiddetteki Psoriasis hasta (VYA 5-10)

Apremilast 30mg 2x1
Plasebo
2:1 oranında randomize

136 hasta çalışmayı tamamlıyor



Adv Ther (2023) 40:1787–1802
https://doi.org/10.1007/s12325-023-02468-3

ORIGINAL RESEARCH

Apremilast Use in Severe Psoriasis: Real-World Data from Central and Eastern Europe

Petra Cetkovská · Iva Dediol · Marija Šola · Martina Kojanová · Katarina Trčko · Antoanela Čarija · Romana Čeović · Daniela Ledić-Drvar · Marija Kaštelan · Andina Hrabar · Myriam Cordey Missoup · Khalid Mamun

Received: January 18, 2023 / Accepted: February 15, 2023 / Published online: March 2, 2023

Methods: APPRECIATE (NCT02740218) was an observational, retrospective, cross-sectional study assessing psoriasis patients 6 (± 1) months after apremilast treatment initiation. The study aimed to describe the characteristics of patients with psoriasis receiving apremilast, estimate treatment outcomes, including Psoriasis Area Severity Index (PASI), Body Surface Area (BSA), and Dermatology Life Quality Index (DLQI), and assess dermatologists' and patients'

Results: Fifty patients (Croatia: 25; Czech Republic: 20; Slovenia: 5) were enrolled. In patients continuing apremilast at 6 (± 1) months, mean (± SD) PASI score was reduced from 16.2 ± 8.7 points at treatment initiation to 3.1 ± 5.2 at 6 (± 1) months; BSA from 11.9% ± 10.3% to 0.8% ± 0.9%; DLQI from 13.7 ± 7.4 points to 1.6 ± 3.2. PASI 75 was reached by 81% of patients. Physicians reported that the overall treatment success fulfilled their expectations in more than two thirds of patients (68%). At least three-quarters of patients reported apremilast had a quite or very high benefit on the needs they identified as being most important. Apremilast was well tolerated; no serious or fatal adverse events were identified.

- 9 Avrupa ülkesi
- 50 psoriasis hastası
- PASI, VYA
- DLQI
- Tedavi memnuniyet anketi
- PBI (Hasta fayda indeksi)

Adv Ther (2023) 40:1787–1802
https://doi.org/10.1007/s12325-023-02468-3

ORIGINAL RESEARCH

Apremilast Use in Severe Psoriasis: Real-World Data from Central and Eastern Europe

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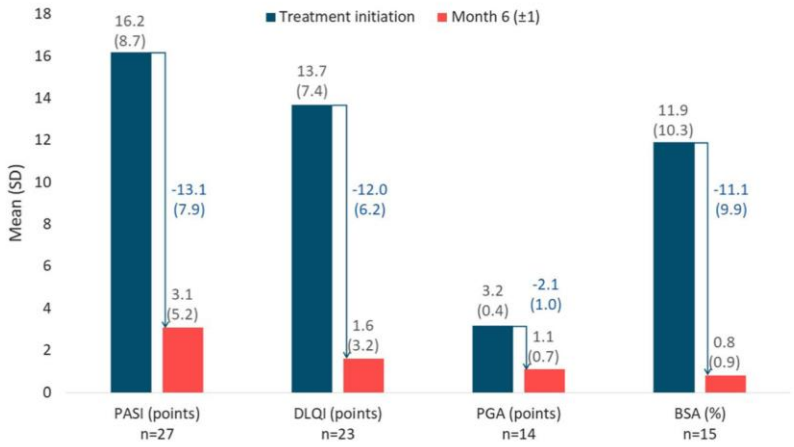
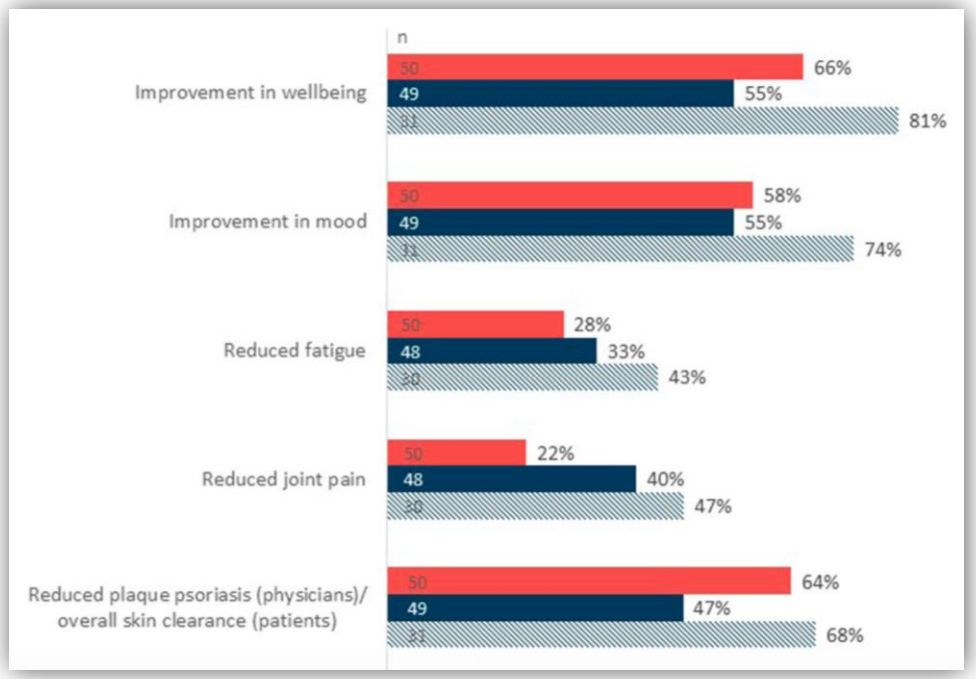
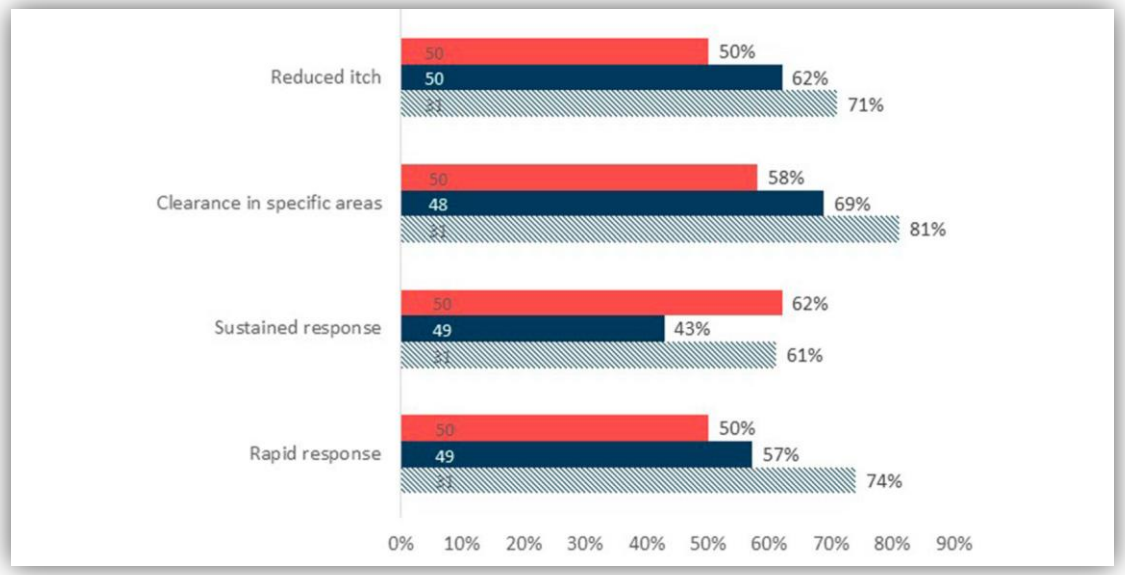
Received: January 18, 2023 / Accepted: February 15, 2023 / Published online: March 2, 2023







Physicians N=50 · All patients N=50 · Patients with ongoing therapy N=31

Adv Ther
https://doi.org/10.1007/s12325-023-02516-y

ORIGINAL RESEARCH

Real-World Apremilast Use for Treatment of Plaque Psoriasis in Italy: Patient Perspective, Characteristics, and Clinical Outcomes from the DARWIN Study

Claudia Giofrè · Gabriella Fabbrocini · Concetta Potenza · Rossana Tiberio · Paolo Gisondi · Claudio Marasca · Carmen M. A. Nuzzo · Emiliana Benincasa · Luca Bianchi on behalf of DARWIN study group

Received: February 14, 2023 / Accepted: April 4, 2023

ABSTRACT

Introduction: While several European studies have reported real-world apremilast use, patient-perceived benefits, and treatment satisfaction, local reimbursement criteria for apremilast vary and data from Italy are limited. ***Methods***: The cross-sectional DARWIN study enrolled consecutive patients who had initiated apremilast for plaque psoriasis 6 (± 1) months prior to enrolment at a single visit across 24 Italian dermatological sites. Disease severity was assessed using body surface area (BSA) and Physician Global Assessment (PGA). Patient-reported outcomes assessed 6 (± 1) months after apremilast initiation were Dermatology Life

Results: Of 184 patients enrolled between July 2019 and January 2021, 180 were included in the analysis. At apremilast initiation, median (25th–75th percentile) time since psoriasis diagnosis was 8.6 (3.2–22.2) years; median BSA, 10.0% (5.0–16.0); mean (standard seviation, SD) DLQI total score, 13.5 (8.0). Over half (54.9%) of patients with available data reported psoriasis had a very or extremely large effect on their quality of life (QoL); half reported itching (50.6%) and/or special areas involvement (50.0%). Most (73.9%) had comorbidities and were biologic-naïve (81.5%). The most common reasons for initiating apremilast were lack of efficacy of previous treatment (56.7%) and contraindications to other treatments (44.4%). At 6 (± 1) months, most patients were continuing apremilast and/or reported a Global PBI score ≥ 1 (minimum clinical benefit) (86.1% and 90.0%, respectively); approximately half achieved BSA ≤ 3% and/or DLQI total score ≤ 5 (47.1% and 48.5%); 18.8% achieved PGA = 0; mean (SD) TSQM-9 global treatment satisfaction score was 59.0 (24.8). Apremilast was well tolerated; no new safety signals were identified.

24 merkez

PBI (Hasta fayda indeksi) 6 ay sonunda 1'in üzerinde olan hasta oranı %86'larda

A1 The members of the DARWIN study group are listed in Acknowledgments.

A2 Prof. Fabbrocini prematurely passed away after the
A3 completion of this manuscript.

A4 **Supplementary Information** The online version
A5 contains supplementary material available at https://
A6 doi.org/10.1007/s12325-023-02516-y.

PBI – Patient Benefit Index

Importance of Treatment Goals

With the help of the following questions, we'd like to know how important the below mentioned goals are to you personally in the **current treatment** of your skin disease.

For each of the following statements, please mark **how important** this treatment goal is to you. If a statement does not apply to you, e.g. because you do not have pain, please mark "*does not apply to me*".

As a result of therapy, how important is it for you to...

		not at all					did not apply to me
1	...be free of pain	O					
2	...be free of itching	O					
3	...no longer have burning sensations on your skin	O					
4	...be healed of all skin defects	O					
5	...be able to sleep better	O					
6	...feel less depressed	O					
7	...experience a greater enjoyment of life	O					
8	...have no fear that the disease will become worse	O					
9	...be able to lead a normal everyday life	O					
10	...be more productive in everyday life	O					
11	...be less of a burden to relatives and friends	O					
12	...be able to engage in normal leisure activities	O					
13	...be able to lead a normal working life	O					
14	...be able to have more contact with other people	O					
15	...be comfortable showing yourself more in public	O					
16	...be less burdened in your partnership	O					
17	...be able to have a normal sex life	O					
18	...be less dependent on doctor and clinic visits	O					
19	...need less time for daily treatment	O					
20	...have fewer out-of-pocket treatment expenses	O					
21	...have fewer side effects	O					
22	...find a clear diagnosis and therapy	O					
23	...have confidence in the therapy	O	O	O	O	O	O
24	...get better skin quickly	O	O	O	O	O	O
25	...regain control of the disease	O	O	O	O	O	O

Please check once more if you have exactly marked each statement with an 'x'.

Our sincerest thanks for your cooperation!

8. Data analysis

- Part 1: Patient Needs Questionnaire (PNQ). The PNQ consists of the treatment goal items. It is analyzed descriptively. The analysis can include:
  a) means and standard deviations of all items („does not apply to me" is coded as 0 for this single-item analysis of the PNQ)
  b) for each item the percentage of the response „does not apply to me"
  c) for each item the percentage of responses with high agreement (quite or very)
  d) percentage of missing values
- Part 2: Patient Benefit Questionnaire (PBQ). The PBQ consists of the benefit items measuring the extent to which the treatment goals have been achieved. It is analyzed descriptively. The analysis can include:
  a) means and standard deviations of all items („did not apply to me" being treated as missing here!)
  b) for each item the percentage of the response „did not apply to me"
  c) for each item the percentage of responses with high agreement (quite or very)
  d) percentage of missing values
- The global score PBI is computed for each patient according to the following algorithm. Using this algorithm, the importance of each treatment goal is divided by the sum of all importance values of the respective patient and is multiplied with the goal attainment value. The resulting products are added up.

$$PBI = \sum_{i=1}^{k} \frac{PNQ_i}{\sum_{i=1}^{k} PNQ_i} PBQ_i$$

Algorithm for the computation of the PBI global benefit value with k preference items (PNQ) and benefit items (PBQ); possible range of item values and global score values: 0-4.

PBI – Patient Benefit Index

Treatment benefits

At the start of the treatment, you indicated in a questionnaire how important various goals were in the treatment of your skin disease.

Please mark each of the following statements according to the extent that these treatment goals **were achieved**, thereby indicating if the treatment has benefitted you. If a statement did not apply to you, e.g. because you had no pain, please mark "*did not apply to me*".

	...to...	not at all	somewhat	moderately	quite	very	did not apply to me
		O	O	O	O	O	O
		O	O	O	O	O	O
	...n my skin	O	O	O	O	O	O
		O	O	O	O	O	O
		O	O	O	O	O	O
		O	O	O	O	O	O
	...fe	O	O	O	O	O	O
	...come worse	O	O	O	O	O	O
	...e	O	O	O	O	O	O
		O	O	O	O	O	O
	...friends	O	O	O	O	O	O
	...activities	O	O	O	O	O	O
		O	O	O	O	O	O
	...her people	O	O	O	O	O	O
	...e in public	O	O	O	O	O	O
		O	O	O	O	O	O
		O	O	O	O	O	O
	...nic visits	O	O	O	O	O	O
		O	O	O	O	O	O
	...expenses	O	O	O	O	O	O
		O	O	O	O	O	O
		O	O	O	O	O	O
		O	O	O	O	O	O
24	...get better skin quickly	O	O	O	O	O	O
25	...regain control of the disease	O	O	O	O	O	O

Please check once more if you have exactly marked each statement with an 'x'.

Our sincerest thanks for your cooperation!

Dermatol Ther (Heidelb) (2023) 13:437–451
https://doi.org/10.1007/s13555-022-00877-w

Results: Seventeen original studies including five placebo-controlled randomized clinical trials (RCTs), one phase II clinical trial, two randomized methotrexate comparative trials, six cohort studies, and three case series were analyzed, totaling 1117 participants. Meta-analysis of four placebo-controlled RCTs investigating PP found apremilast treatment to be superior to placebo in achieving a PPPGA of 0/1 (baseline PPPGA of ≥ 3) at 16 weeks of treatment (n = 244; OR = 2.69 [1.62, 4.47]). Apremilast was superior to placebo in achieving PPPASI 50 at week 16 in the only

Clinical Trial > J Am Acad Dermatol. 2020 Jul;83(1):96-103. doi: 10.1016/j.jaad.2020.01.072.
Epub 2020 Feb 4.

Efficacy and safety of apremilast in patients with moderate to severe plaque psoriasis of the scalp: Results of a phase 3b, multicenter, randomized, placebo-controlled, double-blind study

Abby S Van Voorhees [1], Linda Stein Gold [2], Mark Lebwohl [3], Bruce Strober [4], Charles Lynde [5], Stephen Tyring [6], Ashley Cauthen [7], Howard Sofen [8], Zuoshun Zhang [9], Maria Paris [9], Yao Wang [9]

oriasis are bothered by symptoms in highly visible, pruritic

and safety of apremilast for moderate to severe scalp psoriasis.

ind, placebo-controlled study randomized adults with moderate adequate response/intolerance to at least 1 topical scalp he primary endpoint was the proportion of patients who sessment response, defined as score of 0 (clear) or 1 (almost ion, at week 16. Secondary endpoints included at least a 4- Whole Body Itch and Scalp Itch Numeric Rating Scales (NRSs) ogy Life Quality Index (DLQI) at week 16.

d patients (placebo: n = 102; apremilast: n = 201). With apremilast, significantly more patients achieved Scalp Physician Global Assessment (43.3% vs 13.7%), Scalp Itch NRS (47.1% vs 21.1%), and Whole Body Itch NRS (45.5% vs 22.5%) response, and significantly greater DLQI improvement was observed versus placebo (-6.7 vs -3.8; all P < .0001). Common adverse events with apremilast were diarrhea (30.5%), nausea (21.5%), headache (12.0%), and vomiting (5.5%).

Limitations: Patients with mild disease were not enrolled.

Conclusion: Apremilast showed efficacy for the treatment of moderate to severe scalp psoriasis.

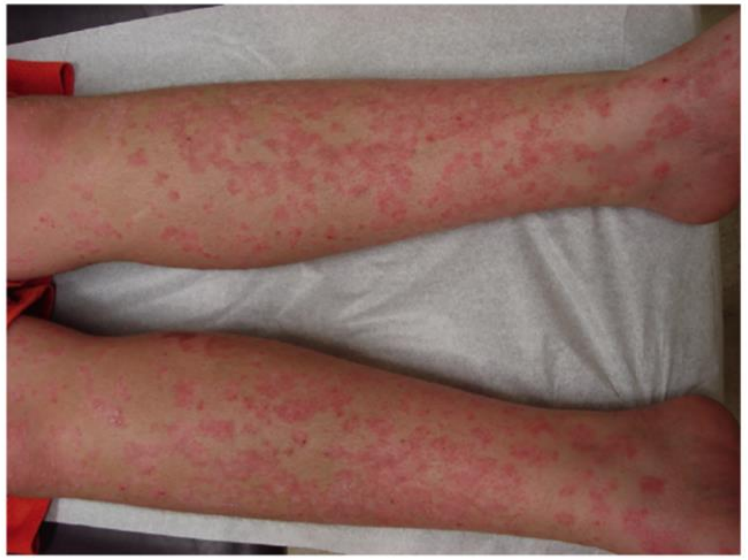


Fig 1. Severely pruritic plaque psoriasis on lower extremities before apremilast treatment.

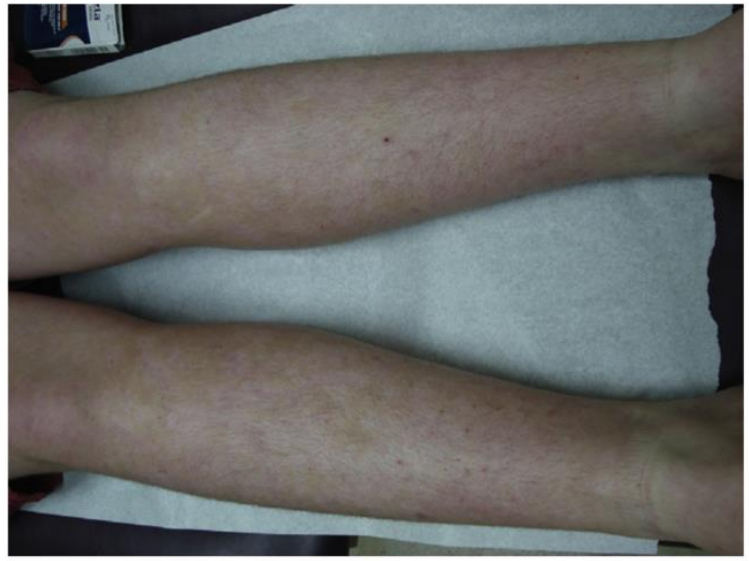


Fig 3. Plaques on lower extremities are beginning to clear after 2 months of apremilast treatment.

CASE REPORT

Pediatric psoriasis treated with apremilast

Rebecca L. Smith, MD
Fort Mill, South Carolina

- Etkinliğe yönelik olgu bildirimi var

Apremilast

- Diğer sistemik tedaviler ile kombine edilebilir
  - Hastaların tedaviye uyumunu artırır
  - Etkinlik açısından ek bir katkı sağlayıp sağlamadığı tartışmalı

Kishimoto M, Komine M, Kamiya K, Sugai J, Ohtsuki M. Drug survival of apremilast in a real-world setting. *J Dermatol*. 2019;46(7):615-617.

Apremilast- yan etki

- Diyare, bulantı, kusma, nazofarenjit, başağrısı
- İştah azalması, kilo kaybı
- Depresyon ve intihar eğiliminde artış
  - Plasebo %0,8
  - Apremilast %1,3 artmış depresif mood riski

- Apremilast tedavisi ile organa özgü veya kümülatif toksisite riski saptanmamış

Lee EB, Amin M, Egeberg A, Wu JJ. Adverse events associated with apremilast use and withdrawal for psoriasis in a real-world setting. J Eur Acad Dermatol Venereol. 2018;32:e393-4.

Jak İnhibitörleri

- Jak-Stat sinyal yolağı önemli hücresel süreçlerde bir odak noktası
- Disregüle olması enflamatuvar ve otoimmün hastalıklara yol açmakta

Table 1 JAK proteins and their cytokines

JAK protein	Cytokines
JAK1	IL-2, IL-4, IL-6, IL-7, IL-9, IL-10, IL-11, IL-15, IL-19, IL-20, IL-21, IL-22, IL-27, LIF, OSM, IFN-alpha, IFN-beta, IFN-gamma
JAK2	IL-3, IL-5, IL-6, IL-11, IL-12, IL-23, IL-27, GM-CSF, LIF, OSM, erythropoietin, thrombopoietin, leptin, growth hormone
JAK3	IL-2, IL-4, IL-7, IL-9, IL-15, IL-21
Tyk2	IL-6, IL-10, IL-11, IL-12, IL-19, IL-20, IL-21, IL-22, IL-23, IL-27, LIF, OSM, IFN-alpha, IFN-beta,

JAK Janus kinase, *IL* interleukin, *LIF* leukemia inhibitory factor, *OSM* oncostatin M *IFN* interferon, *EPO* erythropoietin, *G-CSF* granulocyte colony-stimulating factor, *GH* growth hormone, *GM-CSF* granulocyte–macrophage colony-stimulating factor, *TPO* thrombopoietin, *Tyk2* tyrosine kinase 2

Jak İnhibitörleri

- Küçük moleküllü tedaviler olan Jak inhibitörleri Th1, Th2, Th17, Th22 immün yollarında yer alan sitokinlerin üretimini baskılayarak antiinflamatuvar etkinlik gösterir

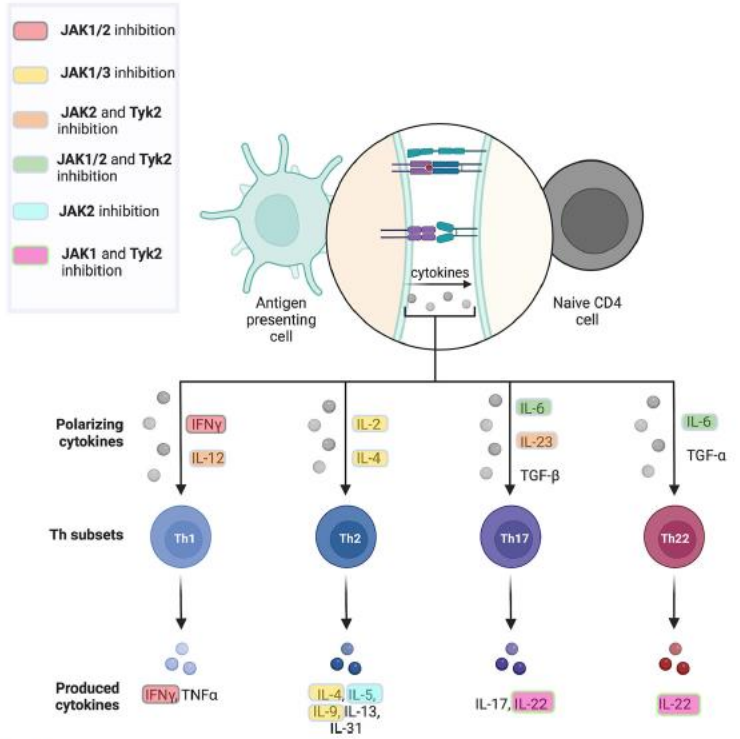
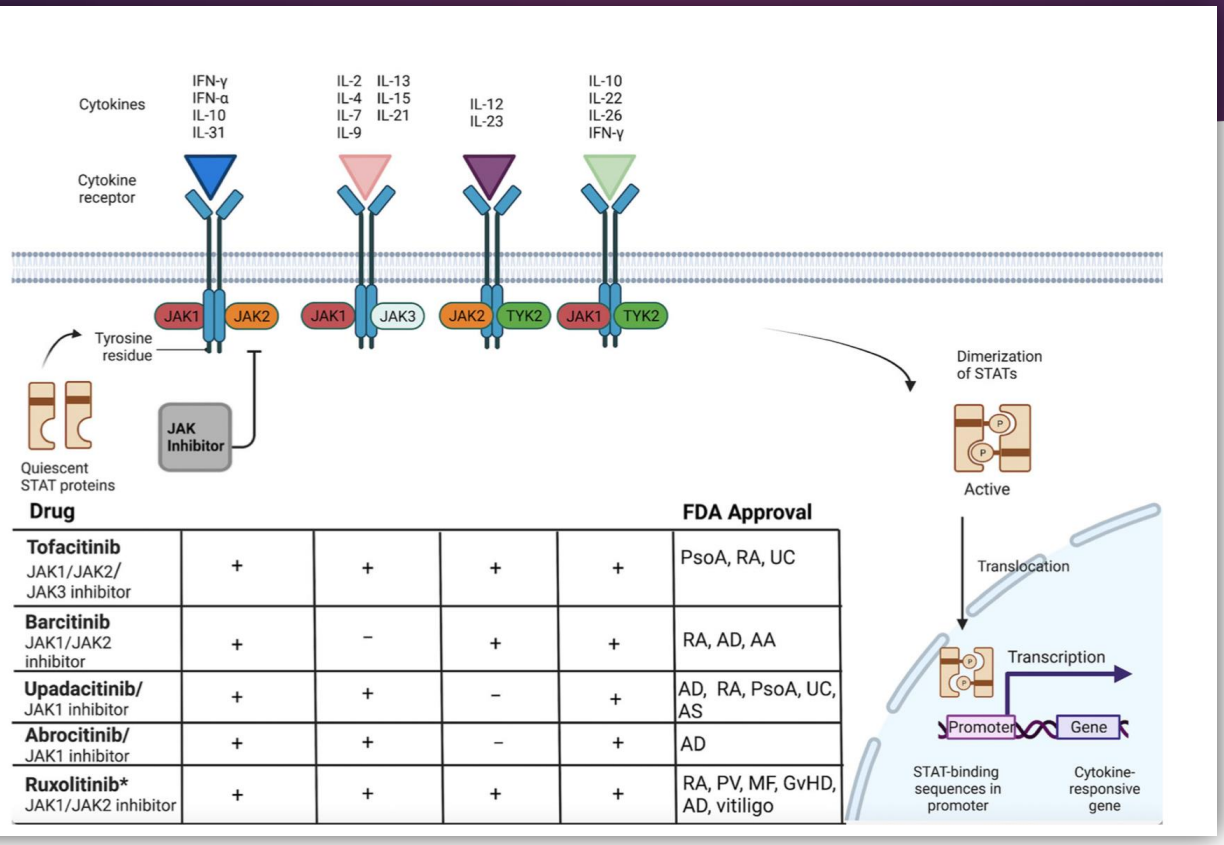


Fig. 2 JAK inhibitors targeting common immune pathways

Samuel C, Cornman H, Kambala A, Kwatra SG. A Review on the Safety of Using JAK Inhibitors in Dermatology: Clinical and Laboratory Monitoring. *Dermatol Ther (Heidelb)*. 2023;13(3):729-749.
Sarabia S, Ranjith B, Koppikar S, Wijeratne DT. Efficacy and safety of JAK inhibitors in the treatment of psoriasis and psoriatic arthritis: a systematic review and meta-analysis. *BMC Rheumatol*. 2022;6(1):71.
Papp K, Szepietowski JC, Kircik L, et al. Efficacy and safety of ruxolitinib cream for the treatment of atopic dermatitis: Results from 2 phase 3, randomized, double-blind studies. J Am Acad Dermatol. 2021;85(4):863–72.



Drug					FDA Approval
Tofacitinib JAK1/JAK2/ JAK3 inhibitor	+	+	+	+	PsoA, RA, UC
Barcitinib JAK1/JAK2 inhibitor	+	–	+	+	RA, AD, AA
Upadacitinib/ JAK1 inhibitor	+	+	–	+	AD, RA, PsoA, UC, AS
Abrocitinib/ JAK1 inhibitor	+	+	–	+	AD
Ruxolitinib* JAK1/JAK2 inhibitor	+	+	+	+	RA, PV, MF, GvHD, AD, vitiligo

Dermatol Ther (Heidelb) (2023) 13:729–749

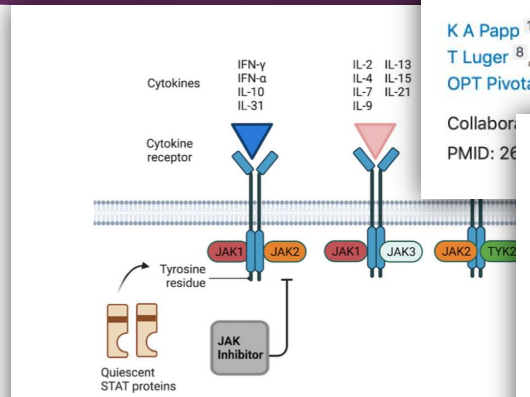
Jak İnhibitörleri

- **Tofacitinib**

FDA Approved Use

- Rheumatoid arthritis
- Psoriatic arthritis
- Ulcerative colitis
- Polyarticular course juvenile idiopathic arthritis

- Psoriasis deri yanıtı için çok daha yüksek dozlar gerekiyor, psoriasis vulgaris için FDA onayı yok



Drug			
Tofacitinib JAK1/JAK2/ JAK3 inhibitor	+	+	+
Barcitinib JAK1/JAK2 inhibitor	+	–	+
Upadacitinib/ JAK1 inhibitor	+	+	–
Abrocitinib/ JAK1 inhibitor	+	+	–
Ruxolitinib* JAK1/JAK2 inhibitor	+	+	+

Clinical Trial > Br J Dermatol. 2015 Oct;173(4):949-61. doi: 10.1111/bjd.14018.

Tofacitinib, an oral Janus kinase inhibitor, for the treatment of chronic plaque psoriasis: results from two randomized, placebo-controlled, phase III trials

K A Papp [1], M A Menter [2], M Abe [3], B Elewski [4], S R Feldman [5], A B Gottlieb [6], R Langley [7], T Luger [8], D Thaci [9], M Buonanno [10], P Gupta [10], J Proulx [10], S Lan [10], R Wolk [10]; OPT Pivotal 1 and OPT Pivotal 2 investigators

Collabor…

PMID: 26…

Abstract

Background: Tofacitinib is an oral Janus kinase inhibitor being investigated for psoriasis.

Objectives: To determine the 16-week efficacy and safety of two oral tofacitinib doses vs. placebo in patients with moderate-to-severe chronic plaque psoriasis.

Methods: Patients in two similarly designed phase III studies (OPT Pivotal 1, NCT01276639, n = 901; OPT Pivotal 2, NCT01309737, n = 960) were initially randomized 2 : 2 : 1 to tofacitinib 10 or 5 mg or placebo, twice daily. Coprimary efficacy end points (week 16) included the proportion of patients achieving Physician's Global Assessment (PGA) of 'clear' or 'almost clear' (PGA response) and the proportion achieving ≥ 75% reduction in Psoriasis Area and Severity Index (PASI 75).

Results: Across OPT Pivotal 1 and OPT Pivotal 2, 745 patients received tofacitinib 5 mg, 741 received tofacitinib 10 mg and 373 … greater proportion of patients achieved PGA respon… with tofacitinib 5 and 10 mg twice daily vs. placebo (… Pivotal 1, 41·9% and 59·2% vs. 9·…%; OPT Pivotal 2, 46·0% and 59·1% vs. 10·9%; all P < 0·001). High… PASI 75 rates were obse…ed with tofacitinib vs. placebo (OPT Pivotal 1, 39·9%, 59·2% and 6…%, respectively, for tofa…nib 5 and 10 mg twice daily and placebo; OPT Pivotal 2 …·0%, 59·6% and 11·4%; all P < 0·001 vs. placebo). … event (AE) rates … generally similar across groups; rates of serious AEs, infections, malignancies and discontinuations due to AEs were low. Twelve patients reported herpes zoster across the tofacitinib treatment groups in both studies vs. none in the respective placebo groups. The most common AE across groups was nasopharyngitis.

Conclusions: Oral tofacitinib demonstrated significant efficacy vs. placebo during the initial 16 weeks of treatment in patients with moderate-to-severe psoriasis. Safety findings were consistent with prior studies.

Samuel C, Cornman H, Kambala A, Kwatra SG. A Review on the Safety of Using JAK Inhibitors in Dermatology: Clinical and Laboratory Monitoring. *Dermatol Ther (Heidelb)*. 2023;13(3):729-749.

Europe PMC Funders Group
Author Manuscript
Sci Transl Med. Author manuscript; available in PMC 2017 December 20.

Published in final edited form as:
Sci Transl Med. 2016 November 02; 8(363): 363ra149. doi:10.1126/scitranslmed.aag1974.

Resolving *TYK2* locus genotype-to-phenotype differences in autoimmunity

Calliope A. Dendrou[1], Adrian Cortes[1,2], Lydia Shipman[1], Hayley G. Evans[1], Kathrine E. Attfield[3], Luke Jostins[2], Thomas Barber[1], Gurman Kaur[3], Subita Balaram Kuttikkatte[3], Oliver A. Leach[1], Christiane Desel[1], Soren L. Faergeman[1,4], Jane Cheeseman[5], Matt J. Neville[5,6], Stephen Sawcer[7], Alastair Compston[7], Adam R. Johnson[8], Christine Everett[8], John I. Bell[9], Fredrik Karpe[5,6], Mark Ultsch[8], Charles Eigenbrot[8], Gil McVean[2], and Lars

Abstract

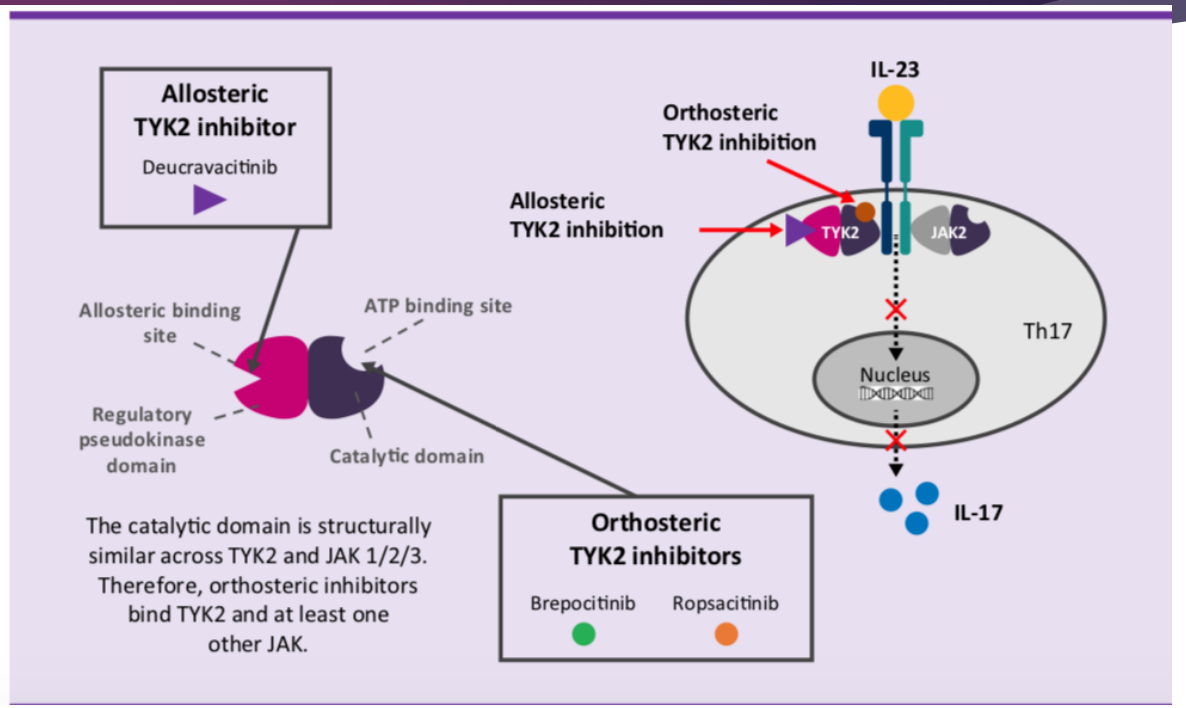
Thousands of genetic variants have been identified that contribute to the development of complex diseases, but determining how to fully elucidate their biological consequences for translation into clinical benefit is challenging. Conflicting evidence regarding the functional impact of genetic variants in the tyrosine kinase 2 (*TYK2*) gene, which is differentially associated with common autoimmune diseases, currently obscures the potential of TYK2 as a therapeutic target. We aimed to resolve this conflict by performing genetic meta-analysis across disorders, subsequent molecular, cellular, *in vivo* and structural functional follow-up and epidemiological studies. Our data revealed a protective homozygous effect that defined a signaling optimum between autoimmunity and immunodeficiency and identified TYK2 as a potential drug target for multiple autoimmune disorders.

Genetik çalışmalar, TYK2'nin reseptör aracılı aktivasyonunu önleyen bir TYK2 kodlama varyantının

PsO da dahil olmak üzere birçok otoimmün hastalığa karşı koruma sağladığını göstermiştir.

Jak İnhibitörleri

- **Deucrovacitinib**
- TYK2 inhibisyonu,
- IL-23 ve IL-17 arasındaki kritik sinyal bağlantısını hedeflemekte



Samuel C, Cornman H, Kambala A, Kwatra SG. A Review on the Safety of Using JAK Inhibitors in Dermatology: Clinical and Laboratory Monitoring. *Dermatol Ther (Heidelb)*. 2023;13(3):729-749.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 2 Trial of Selective Tyrosine Kinase 2 Inhibition in Psoriasis

Kim Papp, M.D., Ph.D., Kenneth Gordon, M.D., Diamant Thaçi, M.D., Ph.D.
Akimichi Morita, M.D., Ph.D., Melinda Gooderham, M.D., Peter Foley, M.D.
Ihab G. Girgis, Ph.D., Sudeep Kundu, Ph.D., and Subhashis Banerjee, M.D.

- 12. Haftada PASI 75
- 3 mg 2x1 %69
- 6 mg 2x1 %67
- 12 mg 1x1 %75

systemic therapy or phototherapy [12]. In a phase 2 trial (NCT02931838) of deucravacitinib in patients with moderate-to-severe PsO, the proportion of patients who achieved a 75% or greater improvement from baseline in Psoriasis Area and Severity Index (PASI 75) at week 12 (primary endpoint) was significantly higher, with deucravacitinib 3 mg twice daily (BID; 69%), 6 mg BID (67%), and 12 mg daily (QD; 75%) compared with placebo (7%; $P < 0.001$) [27].

Psoriasis: Targets and Therapy 2023:13

Psoriasis: Targets and Therapy

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REVIEW

Effectiveness and Safety of Deucravacitinib for the Management of Psoriasis: A Review of the Current Literature

Luca Potestio*, Angelo Ruggiero*, Gabriella Fabbrocini, Fabrizio Martora, Matteo Megna

Table 1 Effectiveness of Deucravacitinib for Psoriasis Management in Clinical Trials

Author	Study Phase/ Period	Patients	Study Group	Efficacy			
				PASI75 n (%)	PASI90 n (%)	PASI100 n (%)	sPGA 0/1 n (%)
Papp et al[22]	Phase2 12w	267	Placebo: 45 Deucravacitinib: 3mg QAD: 44 3mg QD: 44 3mg BID: 45 6mg BID: 45 12mg QD: 44	Placebo: 3 (6.7) Deucravacitinib: 3mg QAD: 4 (9.1) 3mg QD: 17 (38.6) 3mg BID: 31 (68.9) 6mg BID: 30 (66.7) 12mg QD: 33 (75.0)	Placebo: 1 (2.2) Deucravacitinib: 3mg QAD: 3 (6.8) 3mg QD: 7 (15.9) 3mg BID: 20 (44.4) 6mg BID: 20 (44.4) 12mg QD: 19 (43.2)	Placebo: 0 Deucravacitinib: 3mg QAD: 1 (2.3) 3mg QD: 0 3mg BID: 4 (8.9) 6mg BID: 8 (17.8) 12mg QD: 11 (25.0)	Placebo: 3 (6.7) Deucravacitinib: 3mg QAD: 9 (20.5) 3mg QD: 17 (38.6) 3mg BID: 34 (75.6) 6mg BID: 29 (64.4) 12mg QD: 33 (75.0)
Armstrong et al[24]*	Phase3 52w*	666	Placebo: 166 Deucravacitinib 6mg QD: 332 Apremilast 30mg BID: 168	Placebo: 21 (12.7) Deucravacitinib: 194 (58.4) Apremilast: 59 (35.1)	Placebo: 7 (4.2) Deucravacitinib: 118 (35.5) Apremilast: 33 (19.6)	Placebo: 1 (0.6) Deucravacitinib: 47 (14.2) Apremilast: 5 (3.0)	Placebo: 12 (7.2) Deucravacitinib: 178 (53.6) Apremilast: 54 (32.1)
Strober et al[25]*	Phase3 52w*	1020	Placebo: 255 Deucravacitinib 6mg QD: 511 Apremilast 30mg BID: 254	Placebo: 24 (9.4) Deucravacitinib: 271 (53.0) Apremilast: 101 (39.8)	Placebo: 7 (2.7) Deucravacitinib: 138 (27.0) Apremilast: 46 (18.1)	Placebo: 3 (1.2) Deucravacitinib: 52 (10.2) Apremilast: 11 (4.3)	Placebo: 22 (8.6) Deucravacitinib: 253 (49.5) Apremilast: 86 (33.9)

Note: *Results at week 16 before rerandomization or treatment cross over.

Abbreviations: W, week; QAD, every other day; QD, once a day; BID, two times a day; PASI, Psoriasis Area Severity Index; PASI75, PASI reduction of at least 75%; PASI90, PASI reduction of at least 90%; PASI100, PASI reduction of 100; sPGA 0/1, static Physician's Global Assessment 0/1.

Deucrovacitinib

- Erişkin orta şiddetli plak psoriasisde sistemik tedaviler ve fototerapiye yanıtsız hastalarda FDA onayı almıştır

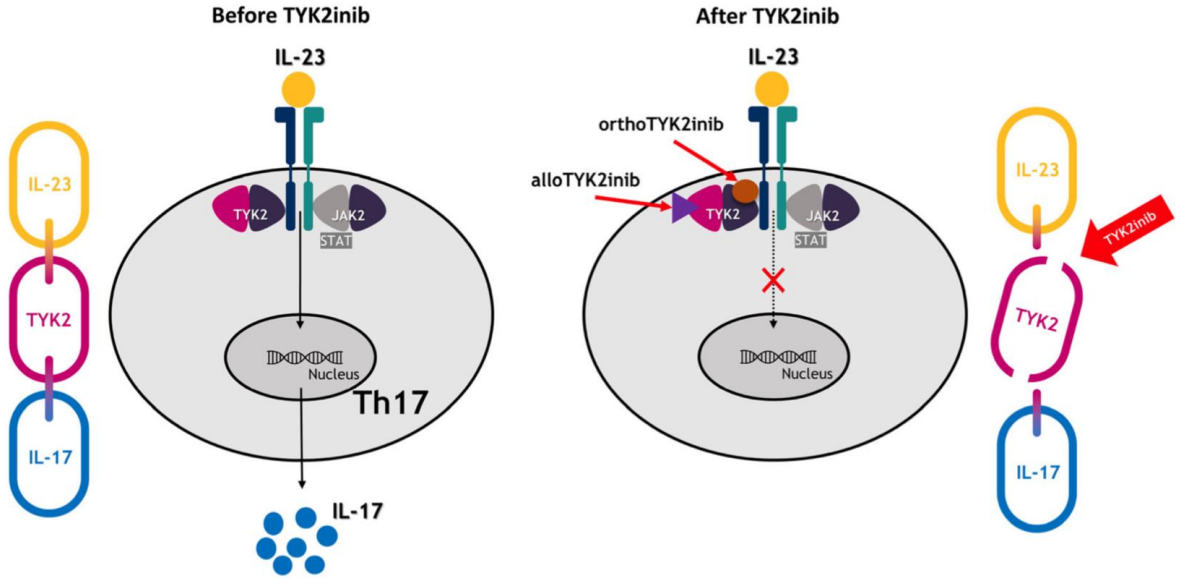


Fig. 3 TYK2 connects IL-23 and IL-17 [3, 51]. TYK2 is the critical intracellular transduction link between interleukin (IL)-23 and the production of IL-17. Inhibition of TYK2 signaling by allosteric (alloTYK2inib) or orthosteric (orthoTYK2inib) inhibitors breaks the link between IL-23 and IL-17 production. *JAK* Janus kinase, *STAT* signal transducer and activator of transcription, *Th17* T-helper cell type 17, *TYK2* tyrosine kinase 2, *TYK2inib* tyrosine kinase 2 inhibitor

Deucravacitinib, an oral, selective, allosteric tyrosine kinase 2 inhibitor, in scalp, nail, and palmoplantar psoriasis: subgroup analyses of the phase 3 POETYK PSO-1 and PSO-2 trials

Andrew Blauvelt,[1] Phoebe Rich,[2] Howard Sofen,[3] Jo Lambert,[4] Joseph F Merola,[5] Mark Lebwohl,[6] Thomas Scharnitz,[7] Kim Hoyt,[7] Renata M Kisa,[7] Subhashis Banerjee[7]

[1]Oregon Medical Research Center, Portland, OR, USA; [2]Oregon Dermatology and Research Center, Portland, OR, USA; [3]UCLA School of Medicine, Los Angeles, CA, USA; [4]Ghent University, Ghent, Belgium; [5]Brigham and Women's Hospital, Brigham Dermatology Associates, and Harvard Medical School, Boston, MA, USA; [6]Icahn School of Medicine at Mount Sinai, New York, NY, USA; [7]Bristol Myers Squibb, Princeton, NJ, USA

Introduction

- Deucravacitinib, an oral, selective, allosteric tyrosine kinase 2 (TYK2) inhibitor, is approved by the US Food and Drug Administration for the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy[1]
  - Uniquely binds to the regulatory domain instead of the catalytic domain of TYK2[2]
    - ≥100-fold greater selectivity for TYK2 vs Janus kinase (JAK) 1/3 and ≥2000-fold greater selectivity for TYK2 vs JAK 2 in cells[2,3]
  - Inhibits TYK2-mediated cytokine signaling involved in psoriasis pathogenesis (eg, interleukin-23, Type I interferons)[2]
- Two 52-week, phase 3 psoriasis trials (POETYK PSO-1 and POETYK PSO-2) previously demonstrated that deucravacitinib was superior to placebo and apremilast at Week 16 based on the coprimary endpoints[4,5]:
  - ≥75% reduction from baseline in Psoriasis Area and Severity Index (PASI 75)
  - Static Physician's Global Assessment score of 0 (clear) or 1 (almost clear) with a ≥2-point improvement from baseline (sPGA 0/1)
- Clinical efficacy and overall safety and tolerability were maintained for up to 2 years[4]

Objective

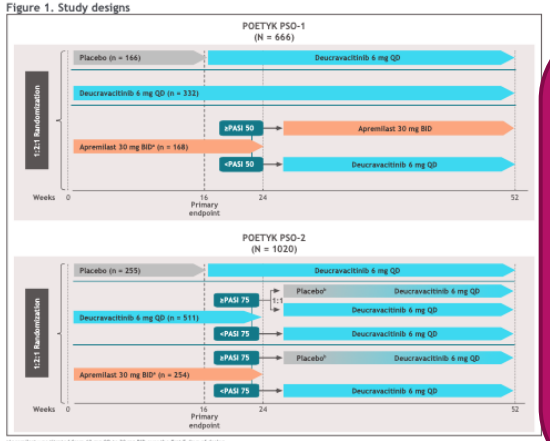
- Evaluate the efficacy of deucravacitinib treatment in patients with moderate to severe scalp, fingernail, and palmoplantar psoriasis

Methods

Study designs

- POETYK PSO-1 (NCT03624127) and PSO-2 (NCT03611751) enrolled adults with moderate to severe plaque psoriasis (PASI ≥12, sPGA ≥3, body surface area involvement ≥10%) (**Figure 1**)

Figure 1. Study designs



[a]Apremilast was titrated from 10 mg QD to 30 mg BID over the first 5 days of dosing.
[b]Upon relapse (≥50% loss of Week 24 PASI percentage improvement from baseline), patients were to be switched to deucravacitinib 6 mg QD.
BID, twice daily; PASI, Psoriasis Area and Severity Index; PASI 50, ≥50% reduction from baseline in PASI; PASI 75, ≥75% reduction from baseline in PASI; QD, once daily.

Outcomes

- This analysis looked at scalp-, fingernail-, and palmoplantar-specific outcomes in pooled patients from POETYK PSO-1 and PSO-2, including:
  - Scalp-specific PGA score of 0 or 1 (ss-PGA 0/1) and ≥90% reduction from baseline in Psoriasis Scalp Severity Index (PSSI 90) in patients with moderate to severe scalp psoriasis (ss-PGA ≥3) at baseline
  - PGA-Fingernails score of 0 or 1 (PGA-F 0/1) in patients with moderate to severe fingernail psoriasis (PGA-F ≥3) at baseline
  - Palmoplantar PGA score of 0 or 1 (pp-PGA 0/1) and palmoplantar PASI (pp-PASI) response in patients with moderate to severe palmoplantar psoriasis (pp-PGA ≥3) at baseline
- Outcomes in patients randomized to deucravacitinib vs placebo are reported through Week 16, and efficacy in deucravacitinib-treated patients is reported through Week 24
- Outcomes in patients who crossed over from placebo to deucravacitinib at Week 16 are reported from Weeks 16–52

Statistical analysis

- None of the statistical comparisons of deucravacitinib vs placebo were multiplicity controlled

Results

Baseline patient demographics and disease characteristics

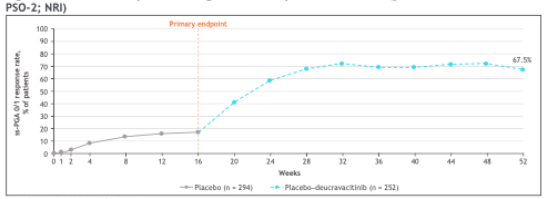
- In the pooled POETYK PSO-1 and PSO-2 population (N = 1264; **Table 1**):
  - 63.9% (n = 808) had moderate to severe scalp psoriasis
  - 14.6% (n = 184) had moderate to severe fingernail psoriasis
  - 6.5% (n = 82) had moderate to severe palmoplantar psoriasis
- Presence of moderate to severe disease in these special areas was balanced overall in the deucravacitinib group vs the placebo group

Table 1. Baseline patient demographics and disease characteristics

Parameter	POETYK PSO-1 and PSO-2	
	Placebo (n = 421)	Deucravacitinib (n = 843)
Age, mean (SD), y	47.5 (13.7)	46.5 (13.5)
Weight, mean (SD), kg	90.6 (21.1)	90.6 (21.9)
Female, n (%)	127 (30.2)	277 (32.9)
Race, n (%)		
White	360 (85.5)	741 (87.9)
Asian	42 (10.0)	83 (9.8)
Other	19 (4.5)	19 (2.3)
Disease duration, mean (SD), y	18.9 (12.9)	18.6 (12.7)
Prior systemic treatment use, n (%)		
Yes	248 (58.9)	474 (56.2)
Nonbiologic (± biologic)	183 (43.5)	326 (38.7)
Biologic	146 (34.7)	295 (35.0)
No	173 (41.1)	369 (43.8)
sPGA, n (%)		
3 = moderate	345 (81.9)	665 (78.9)
4 = severe	75 (17.8)	178 (21.1)
PASI, mean (SD)	20.9 (8.6)	21.1 (8.0)
BSA, mean (SD), %	25.3 (16.1)	26.4 (15.8)
ss-PGA ≥3, n (%)	294 (69.8)	514 (61.0)
PGA-F ≥3, n (%)	72 (17.1)	112 (13.3)
pp-PGA ≥3, n (%)		

- In patients who crossed over from placebo to deucravacitinib at Week 16, 67.5% achieved ss-PGA 0/1 at Week 52 (**Figure 4**) and 62.3% achieved PSSI 90 at Week 52
  - These rates were comparable to Week 24 findings in patients who received continuous deucravacitinib from Day 1

Figure 4. ss-PGA 0/1[a] responses through Week 52 in placebo crossovers (pooled POETYK PSO-1 and PSO-2; NRI)

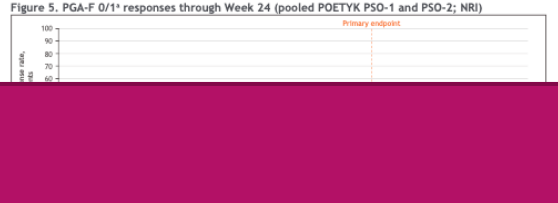


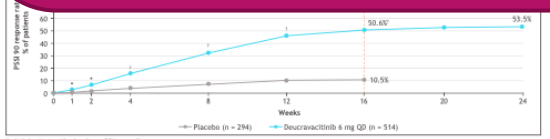
[a]Included patients with a baseline ss-PGA score ≥3.
Missing data were imputed with NRI.
NRI, nonresponder imputation; ss-PGA 0/1, scalp-specific Physician's Global Assessment score of 0 or 1.

Fingernail psoriasis

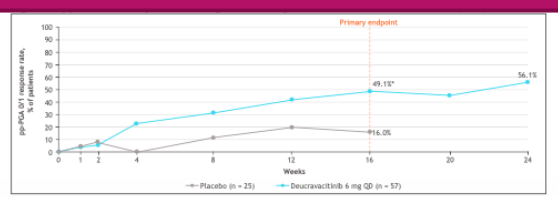
- Significantly more patients receiving deucravacitinib vs placebo achieved PGA-F 0/1 at Week 16 (**Figure 5**)
  - PGA-F 0/1 responses at Week 16 increased through Week 24 in deucravacitinib-treated patients
- In patients who crossed over from placebo to deucravacitinib at Week 16, 51.6% achieved PGA-F 0/1 at Week 52 (**Figure 6**)

Figure 5. PGA-F 0/1[a] responses through Week 24 (pooled POETYK PSO-1 and PSO-2; NRI)





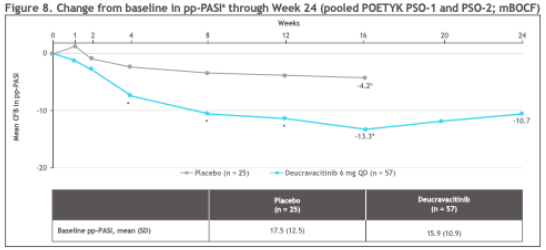
[a]Included patients with a baseline ss-PGA score ≥3.
*P < 0.05 vs placebo. †P < 0.0001 vs placebo. Missing data were imputed with NRI.
NRI, nonresponder imputation; PSSI 90, ≥90% reduction from baseline in Psoriasis Scalp Severity Index; QD, once daily; ss-PGA, scalp-specific Physician's Global Assessment.



[a]Included patients with a baseline pp-PGA score ≥3.
*P < 0.0052 vs placebo. Missing data were imputed with NRI.
NRI, nonresponder imputation; QD, once daily; pp-PGA 0/1, palmoplantar Physician's Global Assessment score of 0 or 1.

- Mean change from baseline in pp-PASI, adjusted for baseline covariates, was significantly greater with deucravacitinib vs placebo at Week 16 (**Figure 8**)
  - Greater efficacy with deucravacitinib vs placebo was observed as early as Week 4
  - pp-PASI responses at Week 16 were maintained through Week 24 in deucravacitinib-treated patients

Figure 8. Change from baseline in pp-PASI[a] through Week 24 (pooled POETYK PSO-1 and PSO-2; mBOCF)



	Placebo (n = 25)	Deucravacitinib (n = 57)
Baseline pp-PASI, mean (SD)	17.5 (12.5)	15.9 (10.9)

[a]Included patients with a baseline pp-PGA score ≥3.
[b]Data in placebo crossover patients through Week 52 are currently unavailable.
*P ≤ 0.0097 vs placebo. Missing data were imputed with the mBOCF method.
CFB, change from baseline; mBOCF, modified baseline observation carried forward; pp-PASI, palmoplantar Psoriasis Area and Severity Index; pp-PGA, palmoplantar Physician's Global Assessment; QD, once daily.

Conclusions

scalp, fingernail, or palmoplantar psoriasis at
n placebo in improving disease burden in these
ovements observed in deucravacitinib-treated

k 16 achieved comparable responses at
ed continuous deucravacitinib treatment

e, allosteric TYK2 inhibitor, in patients with

Saçlı deri, tırnak ve palmoplantar tutulumda

16. Haftada Plasebo ve apremilasta kıyasla üstün etkinlik

quibb Company; September 2022.

016/j.jaad.2022.07.002. Online ahead of print.
j.jaad.2022.08.061. Online ahead of print.
ology (EADV) Spring Symposium; 12–14 May 2022;

antage, LLC, an OPEN Health company, Parsippany, NJ,

Pfizer, Regeneron, Sanofi, and UCB; Scientific adviser AnaptysBio, Arcutis, Arena, Asian, Athenex, Bluefin ermavant, EcoR1, Eli Lilly, Escient, Evelo, Evommune, Forte os, Leo Pharma, Merck, Novartis, Pfizer, Rapt, Regeneron, rialSpark, UCB, Vibliome, and Xencor; Clinical study olytrin, Almirall, Amgen, Arcutis, Athenex, Boehringer Ingelheim, Bristol Myers Squibb, Concert, Dermavant, Eli Lilly, Evelo, Evommune, Galderma, Incyte, Janssen, Leo Pharma, Merck, Novartis, Pfizer, Regeneron, Sun Pharma, and UCB

- **PR:** Research (principal Investigator on pharmaceutical trials): AbbVie, Arcutis, Bristol Myers Squibb, Dermavant, Eli Lilly, Janssen, Novartis, Sun Pharma, and UCB
- **HS:** Clinical Investigator: AbbVie, Amgen, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, Janssen, Leo Pharma, Novartis, and Sun Pharma
- **JL:** Unrestricted grants: AbbVie, Almirall, Celgene, Eli Lilly, Janssen-Cilag, Leo Pharma, Novartis, and UCB; Speaker: AbbVie, Almirall, Bristol Myers Squibb, Janssen-Cilag, Pfizer, and UCB; Consultant: AbbVie, BMS, Celgene, Eli Lilly, Janssen-Cilag, Leo Pharma, Novartis, and UCB
- **JFM:** Consultant and/or Investigator: Amgen, AbbVie, Biogen, Bristol Myers Squibb, Dermavant, Eli Lilly, Janssen, Leo Pharma, Novartis, Pfizer, Regeneron, Sanofi, Sun Pharma, and UCB
- **ML:** Research funds on behalf of Mount Sinai: AbbVie, Amgen, Arcutis, Avotres, Boehringer Ingelheim, Dermavant, Eli Lilly, Incyte, Janssen, Ortho Dermatologics, Regeneron, and UCB; Consultant: Aditum Bio, Almirall, AltruBio AnaptysBio, Arcutis, Arena, Aristea, Arrive Technologies, Avotres, BiomX, Boehringer Ingelheim, Brickell Biotech, Bristol Myers Squibb, Cara, Castle Biosciences, CorEvitas' (Corrona) Psoriasis Registry, Dermavant, Dr Reddy's Laboratories, Evelo Biosciences, Evommune, Forte Biosciences, Helsinn Therapeutics, Hexima, Leo Pharma, Meiji Seika Pharma, Mindera, Pfizer, Seanergy, and Verrica
- **TS, RMK, and SB:** Employees and shareholders: Bristol Myers Squibb
- **KH:** Contractor: Bristol Myers Squibb via Syneos Health

Presented at the 2022 Fall Clinical Dermatology Conference; October 20–23, 2022; Las Vegas, NV

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Table 1 continued

Agent	PsO and PsA approval status	Mechanism of action	Downstream signaling	AEs/off-target impact
Deucravacitinib [27, 65, 72, 74]	PsO (approved by FDA in USA and by PDMA in Japan; submitted to EMA) PsO in pediatric population (phase 2/3) PsA (phase 3)	Selective TYK2 inhibitor via allosteric mechanism by binding to the regulatory (pseudokinase) domain of TYK2	IL-12, IL-23, IFN-α, IFN-β	URTI, blood CPK increased, herpes simplex, mouth ulcers, folliculitis, and acne

Brepocitinib (PF-06700841) [29–31]	PsO (oral, phase 2 completed; further development pursued only as a topical formulation, phase 2) PsA (oral, phase 2)	Dual TYK2/JAK1 inhibitor via binding to the active site in the catalytic domain of TYK2	IL-12, IL-23, IL-15, IL-21, IL-10, IL-27, IFN-α, IFN-β	Hematologic abnormalities, nasopharyngitis, URTI, and headache
Ropsacitinib (PF-06826647) [32, 33, 69]	PsO (phase 2) PsA (development not pursued)	Dual TYK2/JAK2 inhibitor via binding to the active site in the catalytic domain of TYK2	IL-12, IL-23, IFN-α, IFN-β	Changes in hematologic and chemistry parameters and increases in triglycerides. Most common AEs are nasopharyngitis, URTI, and increased blood pressure

Brepocitinib

ORIGINAL ARTICLE

Journal of Investigative Dermatology (2020) **140,** 1546–1555; doi:10.1016/j.jid.2019.11.027

Molecular and Cellular Responses to the TYK2/JAK1 Inhibitor PF-06700841 Reveal Reduction of Skin Inflammation in Plaque Psoriasis

Karen M. Page[1], Mayte Suarez-Farinas[2], Maria Suprun[2], Weidong Zhang[1], Sandra Garcet[3], Judilyn Fuentes-Duculan[3], Xuan Li[3], Matthew Scaramozza[1], Elizabeth Kieras[1], Christopher Banfield[1], James D. Clark[1], Andrew Fensome[1], James G. Krueger[3] and Elena Peeva[1]

- TYK2/Jak1 inh
- Brepocitinib tedavisinin psoriasis lezyonlarında enflamatuar gen ekspresyonunu lezyonsuz deride gözlenen seviyelere indirdiği biyomarker çalışmalarında gösterilmiş
- inflamatuar gen ifadesindeki azalmalar, histolojik ve klinik sonuçlardaki gelişmelerle ilişkili

TYK2/JAK1 Inhibitor PF-06700841 in Patients with Plaque Psoriasis: Phase IIa, Randomized, Double-Blind, Placebo-Controlled Trial

Seth B. Forman[1], David M. Pariser[2], Yves Poulin[3,4], Michael S. Vincent[5], Steven A. Gilbert[5], Elizabeth M. Kieras[5], Ruolun Qiu[5], Dahong Yu[5], Jocelyne Papacharalambous[5], Christopher Tehlirian[5] and Elena Peeva[5]

12. Haftada

30 mg/gün ile

PASI 75 %86,2

PASI 90 %51,7

plaseboya göre üstün

($P < 0.05$)

- Teşekkür ederim