VİTİLİGODA GÜNCEL TEDAVİLER

«Akıllı İlaçlarla Dermatolojide Güncellemeler»

Prof. Dr. Cemal BİLAÇ

Manisa CBÜ Tıp Fakültesi, Dermatoloji AD

MANİSA
CELAL BAYAR
ÜNİVERSİTESİ
Tıp Fakültesi

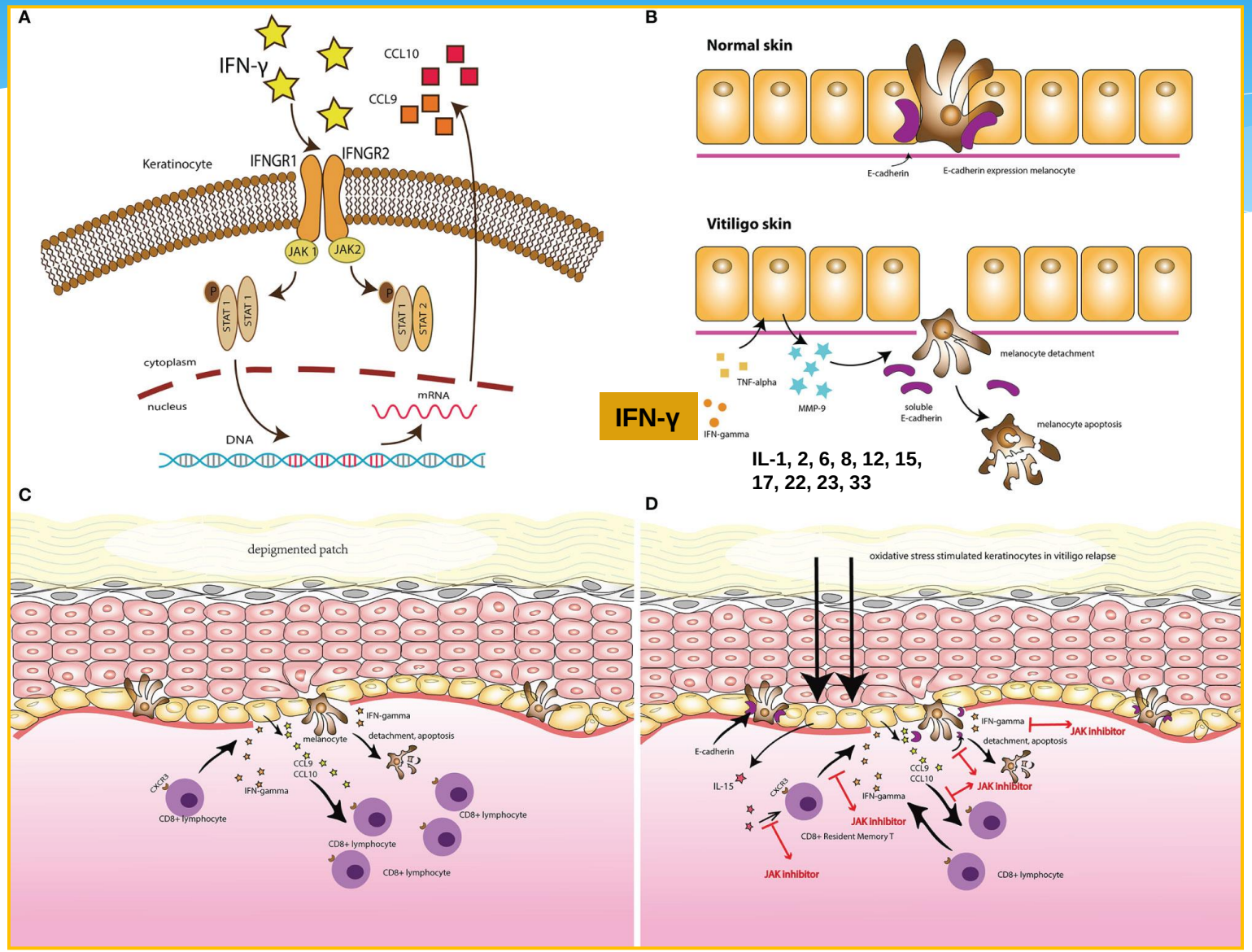
VİTİLİGO

* Melanositlerin kaybına bağlı depigmente maküller/yamalar
* Kronik inflamatuar pigmentasyon bozukluğu
* Prevalans %0,5-2
* Damgalanma, sosyal izolasyon, mental sağlık ve yaşam kalitesinde olumsuz etkilenme

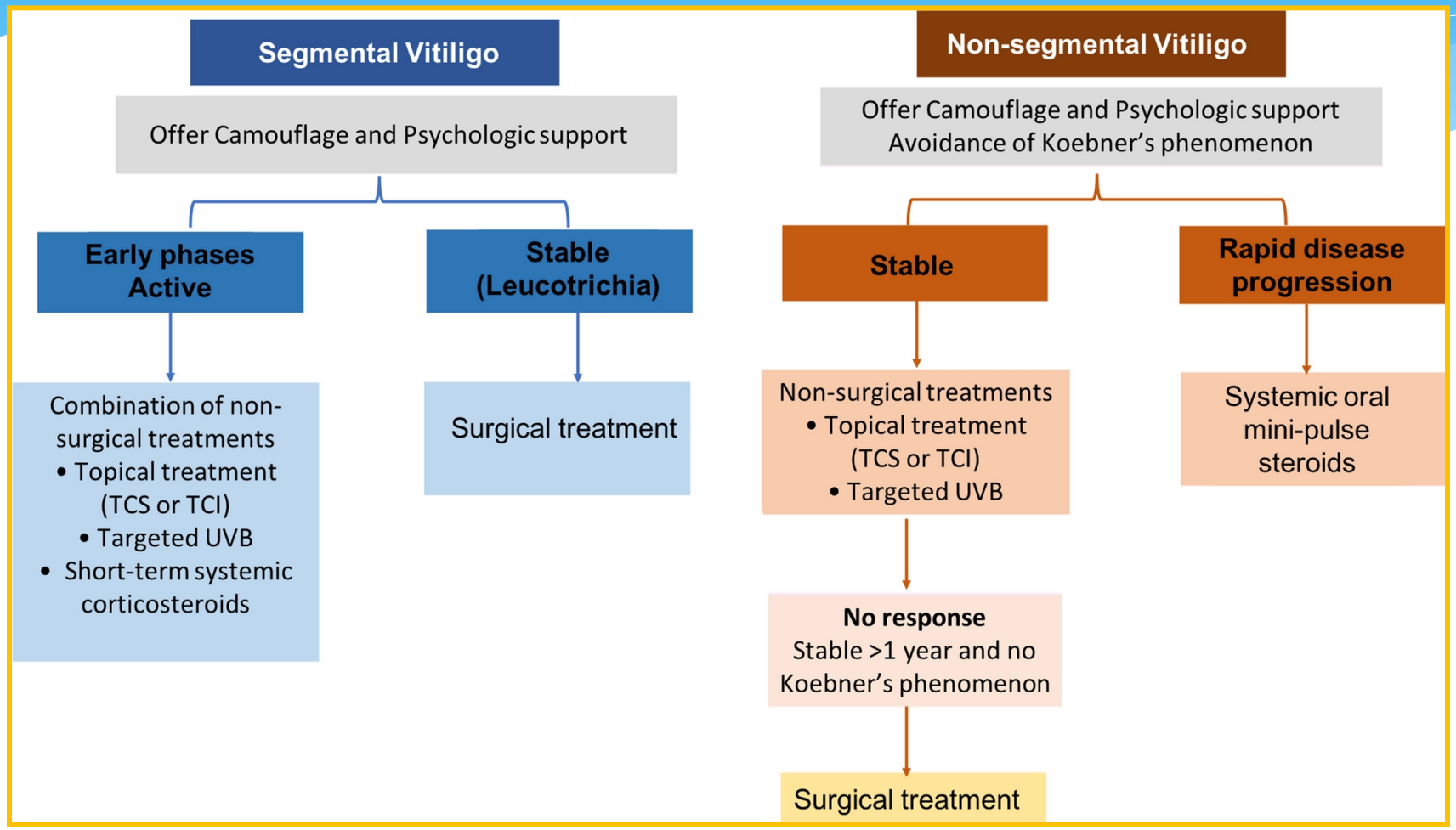
VİTİLİGO PATOGENEZ

Hipotez	
Genetik	non-Mendelian, multifaktöriyel, poligenik kalıtım paterni HLA- (A2, DR4, DR7, DQ7, DR1, B13, DQW3, CW6, and A30), *PTPN22*, *LPP*, *IL2RA*, *UBASH3A*, *C1QTNF6*AIS1, FOXD3, 4q13-q21, 2p16 (vitiligo associated protein-1), NALP1
Otoimmün	Diğer otoimmün hastalıklar ile sık birliktelik Organ spesifik otoantikor sıklığında artış (antitiroglobulin, antitiroid peroksidaz, antipariyetal hücre ve antinükleer antikorlar) Melanosit yüzey ve sitoplazmik antijenlerine karşı antikorlar **Melanosit destrüksiyonunda sitotoksik $CD8^+$ T lenfositlerin rol oynaması** **Lezyonel deride, artmış IFN-γ, TNF-α, IL-1β, 6, 15, 17, 21, 22, 23, 33 ekspresyonu** **Melanosit destrüksiyonunda anahtar mediatör ? IFN-γ induced protein-10 (CXCL-10)**
Nöral	Sinir uçlarından, etrafındaki melanositlere karşı sitotoksik olan mediatörlerin salgılanması? Stres ve ciddi emosyonel travma ile vitiligonun tetiklenmesi, segmental vitiligodaki dermatomal dağılım, lezyonel deride dermal akson dejenerasyonu, viral ensefalit, multipl skleroz ve periferik sinir hasarından sonra vitiligo gelişimi
Oksidatif Stres	Epidermiste hücre içi oksidasyon/redüksiyon dengesinde bozulma ve antioksidan düzeyinde azalma Reaktif oksijen metabolitlerinde artış ile inflamasyon ve hücre içi bileşenlerin oksidasyonunun uyarılması sonucu melanosit yıkımı
Self Destrüksiyon	Melanin sentezi sırasında oluşan toksik fenolik bileşiklerden kaynaklanan oksidatif strese karşı artmış duyarlılık nedeniyle oluşan melanosit yıkımı?
Melanositoraji	Travma, reaktif oksijen ürünleri, hücre dışı matriks proteinlerinin anormal sentezi gibi kronik süreçler ile hücre adezyonunda bozulma ve bazal membrandan melanosit dekolmanı
Azalmış Melanosit Ömrü	Melanositlerin sağ kalımından sorumlu SCF, MITF ve C-KIT gibi önemli faktörlerin eksikliği ile ilişkili
Viral	HIV, HCV, EBV, CMV, HHV, HEV ile birliktelikleri bildirilen vitiligo olguları

VİTİLİGO PATOGENEZ



VİTİLİGO TEDAVİ



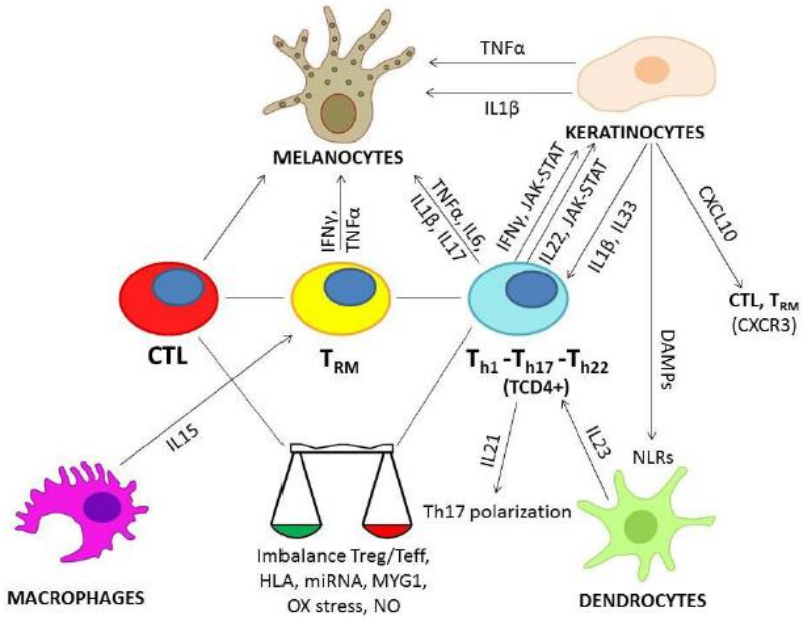
Bergqwist C, Ezzedine K. Vitiligo: A focus on pathogenesis and its therapeutic implications. J Dermatol 2021; 48: 252-270.

GÜNCEL TEDAVİLER

«Akıllı İlaçlarla Dermatolojide Güncellemeler»

Biyolojik ve Hedefe Yönelik Tedaviler

* JAK inhibitörleri
* STAT inhibitörleri
* TNF-α inhibitörleri
* Anti IL-17
* Anti IL-23
* Diğer hedefe yönelik tedaviler



JAK İNHİBİTÖRLERİ

JAK İNHİBİTÖRLERİ

* **IFN-γ,** JAK-STAT yolağı üzerinden etkili
* CXCL9 ve CXCL10 kemokinlerinin üretimi
* CXCR3 bulunan CD8+ T hücre birikimi
* Melanogenez inhibisyonu ve melanosit apoptozunun indüklenmesi
* **Tofacitinib** (JAK1/3 inh), **ruxolitinib** (JAK1/2 inh), **delgocitinib** (JAK1/2/3, tirozin kinaz 2 inh) ve **baricitinib** (JAK1/2 inh)

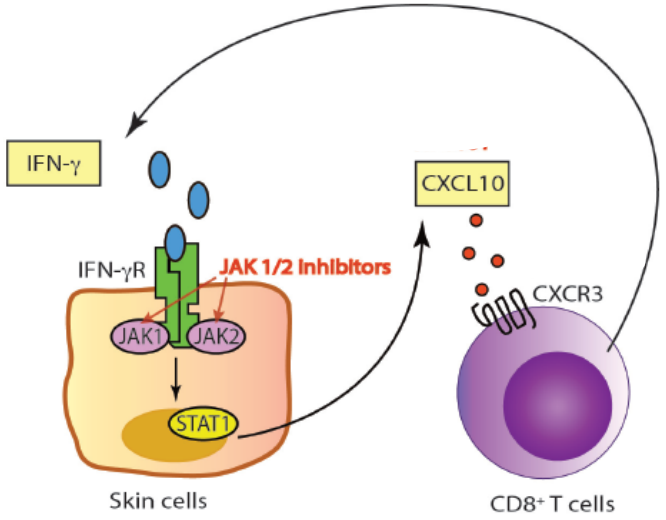


Figure 1 IFN-γ/CXCL10 signaling pathway in vitiligo. Binding of IFN-γ to its receptor (IFN-γR) activates the JAK-STAT pathway and leads to CXCL10 secretion in the skin. CXCL10 promotes recruitment of additional autoreactive $CD8^+$ T cells through its cognate receptor (CXCR3), which increases inflammation through a positive feedback loop. Compounds that have been developed to target each step are indicated in red.

TOFACITINIB (TOPİKAL)

Yayın	n	İlaç	Süre	Ek tedavi	Sonuç
Olamiju, 2020	1	Tofacitinib %2 krem	6 ay	DB-UVB	**%100 repigmentasyon (yüz)**
Ferreira, 2021	1	Tofacitinib %2 krem	9 ay	DB-UVB	**Belirgin repigmentasyon (yüz)**
Kim, 2021	1	Tofacitinib %2 krem	5 ay	-	**Tam repigmentasyon (göz kapağı)**
McKesey, 2019	11	Tofacitinib %2 krem	8-16h	DB-UVB	**VASI %70 düzelme**
Mobasher, 2020	16	Tofacitinib %2 krem	N/A	TCS, TCI, fototerapi ve lazer	**13/16 parsiyel repigmentasyon** **4 hastada >%90 düzelme** 5 hasta %25-75 düzelme 4 hasta %5-15 düzelme **Yüz bölgesinde ve koyu tenlilerde daha iyi yanıt**

Olamiju B, et al. Tofacitinib cream plus narrowband ultraviolet B phototherapy for segmental vitiligo in a child. Pediatr Dermatol . 2020 Jul; 37(4): 754-755.
Ferreira S, et al. Topical tofacitinib: a Janus kinase inhibitor for the treatment of vitiligo in an adolescent patient. Case Rep Dermatol. 2021; 13: 190–194.
Kim SR, et al. Repigmentation of vitiligo-associated eyelash Q1 leukotrichia with topical tofacitinib. JAAD Case Rep. 2021 Jul 27; 16: 90-91.
McKesey J, et al. A pilot study of 2% tofacitinib cream with narrowband ultraviolet B for the treatment of facial vitiligo. J Am Acad Dermatol. 2019 Aug; 81(2): 646-648.
Mobasher P, et al. Open label study of 2% tofacitinib for the treatment of refractory vitiligo. Br J Dermatol 2020; 182: 1047-9.

TOFACITINIB (TOPİKAL)

Yayın	n	İlaç	Süre	Ek tedavi	Sonuç
McKesey, 2019	11	Tofacitinib %2 krem	8-16h	DB-UVB	**VASI skorunda ort. %70 düzelme (%50-87)**

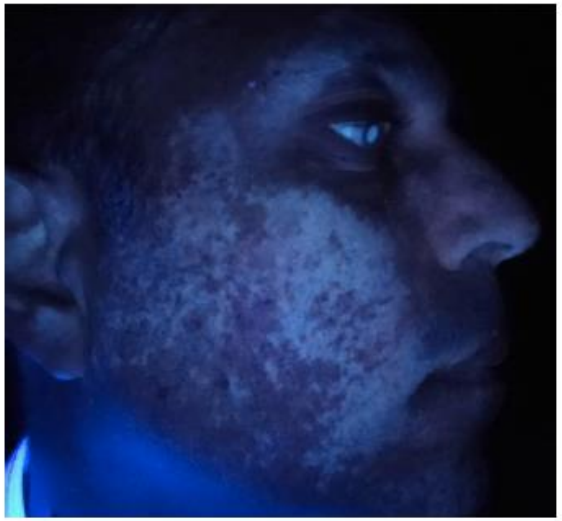


Fig 1. Nonsegmental vitiligo in a white man at baseline.

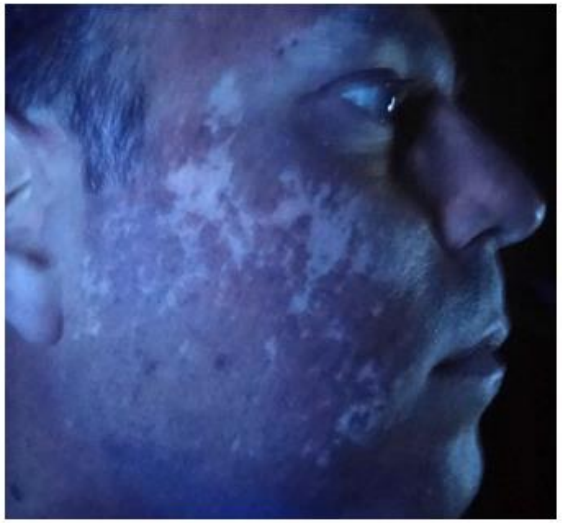


Fig 2. Nonsegmental vitiligo after 4 months of treatment

McKesey J, et al. A pilot study of 2% tofacitinib cream with narrowband ultraviolet B for the treatment of facial vitiligo. J Am Acad Dermatol. 2019 Aug; 81(2): 646-648.

TOFACITINIB (TOPİKAL)

Yayın	n	İlaç	Süre	Ek tedavi	Sonuç
Mobasher, 2020	16	Tofacitinib %2 krem	N/A	TCS, TCI, fototerapi ve lazer	**13/16 parsiyel repigmentasyon** **4 hastada >%90 düzelme** 5 hasta %25-75 düzelme 4 hasta %5-15 düzelme **Yüz bölgesinde ve koyu tenlilerde daha iyi yanıt**

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Open Label Pilot Study of 2% Tofacitinib for the Treatment of Refractory Vitiligo

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[1]University of California, Irvine, Department of Dermatology, Irvine, CA, USA
[2]Brigham and Women's Hospital, Department of Dermatology, Boston, MA, USA
[3]University of California, Davis, Department of Dermatology, Sacramento, CA, USA

TOFACITINIB (ORAL-1)

Yayın	N	İlaç	Süre	Klinik	Sonuç
Tajalli, 2020	1	Tofacitinib 5 mg, BID + NB-UVB	3 ay	GV, AA, PsO	**Vitiligo, AA ve PsO'te tam düzelme**
Aickara, 2022	1	Tofacitinib 5 mg, BID + NB-UVB	11 ay	GV	**Yüz ve saçlı deride tam düzelme**
Joshipura, 2018	1	Tofacitinib 5 mg, BID	3 ay	GV	**Güneş gören alanlarda belirgin pigmentasyon**
Craiglow, 2015	1	Tofacitinib 5 mg every other day for a week, then 5 mg daily	5 ay	Yüz, gövde, akral	**VYA %10'dan %5'e azalma (alında tam pigmentasyon)**
Vu, 2017	1	Tofacitinib 5 mg, BID	6 ay	NSV, AD, AA	**Minimal düzelme (VASI 4,68 → 3,95)**

Tajalli M, et al. Effective use of oral tofacitinib and phototherapy in a patient with concomitant alopecia areata, vitiligo, and plaque and inverse psoriasis. Clin Case Rep. 2020; 8(5): 819-822.
Aickara DJ, et al. Significant improvement of vitiligo with oral tofacitinib treatment. Int J Dermatol . 2022 Jul 11. doi: 10.1111/ijd.16323.
Joshipura D, et al. Importance of light in the treatment of vitiligo with JAK-inhibitors. J Dermatolog Treat. 2018 Feb; 29(1): 98–99.
Craiglow B, et al. Tofacitinib citrate for the treatment of vitiligo. JAMA Dermatol. 2015; 151(10): 1110.
Vu M, et al. Oral tofacitinib: a promising treatment in atopic dermatitis, alopecia areata and vitiligo. Clin Exp Dermatol. 2017; 42(8): 942-944.

TOFACITINIB (ORAL-2)

Yayın	N	İlaç	Süre	Klinik	Sonuç
Kim, 2018	2	Tofacitinib 2x5 mg daily, plus NB-UVB twice weekly	3 ay	Yüz, gövde, kollar	**Yüz bölgesinde bir hastada tama yakın, diğerinde ≥%75 düzelme**
Fang, 2022	3	Tofacitinib 5 mg, daily + Excimer laser	3 ay	GV	**Vitiligo Extent Score (VES)'da %33 azalma**
Liu, 2017	10	Tofacitinib 5–10 mg daily or twice daily	10 ay	8 GV, 2 akral	**Güneşe maruz kalan veya DB-UVB uygulanan 5 hastada repigmentasyon**
Song, 2022	19	Tofacitinib 5 mg, BID + NB-UVB + TKS + TKİ	4 ay	NSV	**VASI skorunda kontrol grubuna göre daha fazla düzelme**
Gianfaldoni, 2018	67	A, Phototherapy alone vs B, tofacitinib 10 mg, daily + Phototherapy	3 ay	GV vs GV+RA	**Repigmentasyon %77 vs %92**

Kim SR, et al. Rapid Repigmentation of Vitiligo Using Tofacitinib Plus Low-Dose, Narrowband UV-B Phototherapy. JAMA Dermatol. 2018 Mar 1; 154(3): 370-371.
Fang WC, et al. Low-dose tofacitinib with 308-nm excimer therapy successfully induced repigmentation in patients with refractory vitiligo. Clin Exp Dermatol. 2022; 47: 748–8.
Liu L, et al. Repigmentation in vitiligo using the Janus kinase inhibitor tofacitinib may require concomitant light exposure. J Am Acad Dermatol. 2017; 77(4): 675-682. e1.
Song H, et al. Effectiveness and safety of tofacitinib combined with narrowband ultraviolet B phototherapy for patients with refractory vitiligo in real-world clinical practice. Dermatologic Therapy. 2022; e15821.
Gianfaldoni S, et al. Micro - Focused Phototherapy Associated To Janus Kinase Inhibitor: A Promising Valid Therapeutic Option for Patients with Localized Vitiligo. Open Access Maced J Med Sci. 2018 Jan 21;6(1):46-48. doi: 10.3889/oamjms.2018.042. eCollection 2018 Jan 25.

TOFACITINIB (ORAL)

Yayın	n	İlaç	Süre	Klinik	Sonuç
Liu, 2017	10	Tofacitinib 5–10 mg daily or twice daily	10 ay	8 GV, 2 akral	**Güneşe maruz kalan veya DB-UVB uygulanan 5 hastada repigmentasyon**

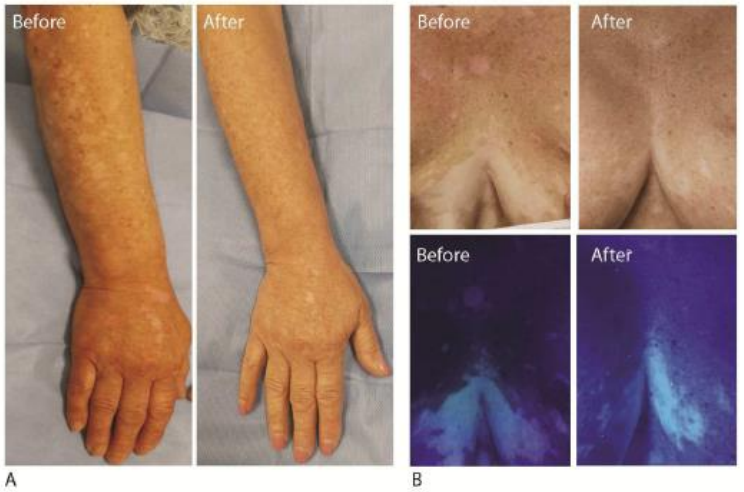


Figure 1.
Clinical images of patient 1: A) The sun-exposed forearm and dorsal hand, before and during treatment, demonstrates repigmentation. B) The chest, before and during treatment, under room light (top panels) and Wood's lamp (bottom panels), demonstrates repigmentation of sun-exposed lesions involving the upper chest but not sun-protected lesions involving the intermammary chest.

Liu L, et al. Repigmentation in vitiligo using the Janus kinase inhibitor tofacitinib may require concomitant light exposure. J Am Acad Dermatol. 2017; 77(4): 675-682. e1.

TOFACITINIB (ORAL)

Yayın	n	İlaç	Süre	Klinik	Sonuç
Song, 2022	19	Tofacitinib 5 mg, BID + NB-UVB + TKS + TKİ	4 ay	NSV	**VASI skorunda kontrol grubuna göre daha fazla düzelme (8-12-16.h'larda istatistiksel olarak anlamlı düzeyde)**

TABLE 2 Changes in total VASI prior to treatment and at 4th, 8th, 12th, and 16th week after beginning treatment

Group	Prior to treatment, mean ± SD	Fourth week after treatment, mean ± SD	Eighth week after treatment, mean ± SD	12th week after treatment, mean ± SD	16th week after treatment, mean ± SD
The controls	18.14 ± 17.78	18.19 ± 17.01			
Combination therapy	15.55 ± 13.40	9.80 ± 9.24	5.11 ± 3.80*	3.24 ± 3.17**	1.50 ± 1.52**
p-value	0.643	0.096	0.011	0.004	0.001

Abbreviations: SD, standard deviation; VASI, Vitiligo Area Scoring Index.
*$p < 0.05$ for VASI in combination group versus control group. **p 0.01 for VASI in combination group versus control group.

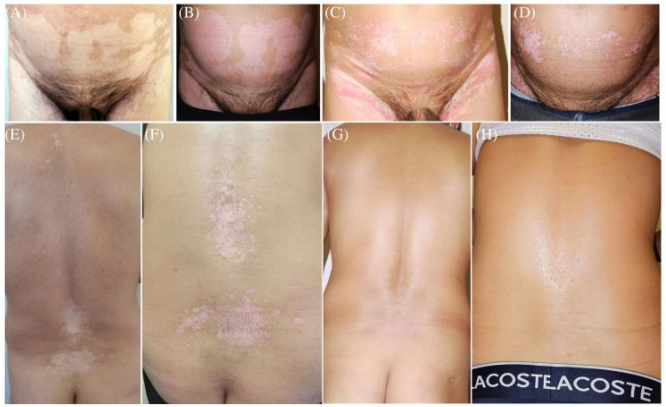
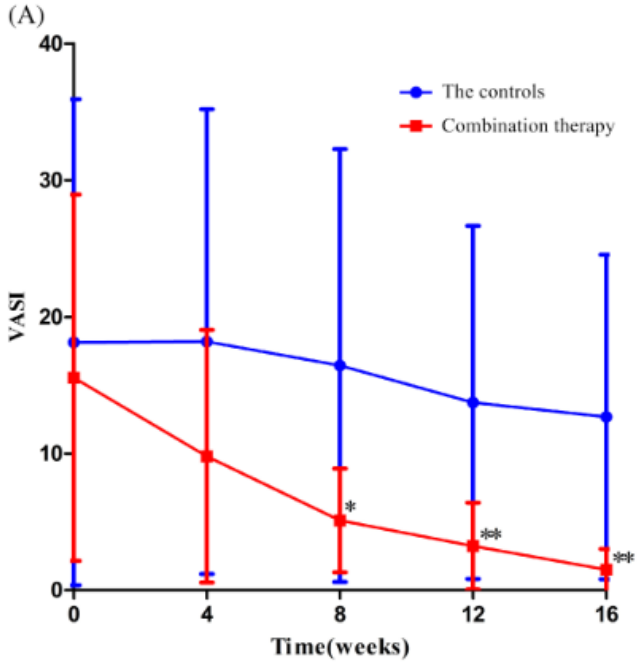


FIGURE 2 Repigmentation improvement during treatment of vitiligo using the combination of oral tofacitinib at 5 mg twice daily, topical cream (halometasone cream, tacrolimus 0.1% ointment, or pimecrolimus cream) twice daily, and NB-UVB three times per week. Abdomen and thigh: (A) prior to treatment, (B) fourth week after beginning treatment, (C) 12th week after beginning treatment, and (D) 16th week after beginning treatment. Back: (E) prior to treatment, (F) fourth week after beginning treatment, (G) 12th week after beginning treatment, and (H) 16th week after beginning treatment.



Song H, et al. Effectiveness and safety of tofacitinib combined with narrowband ultraviolet B phototherapy for patients with refractory vitiligo in real-world clinical practice. Dermatologic Therapy. 2022; e15821.

TOFACITINIB (ORAL)

Yayın	n	İlaç	Süre	Klinik	Sonuç
Gianfaldoni, 2018	67	A (GV, n=59), Phototherapy alone vs B (GV+RA, n=8), Tofacitinib 10 mg, daily + Phototherapy	3 ay	**GV** **vs** **GV+RA**	**Repigmentasyon** **%77 vs %92**

ID Design Press, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2018 Jan 25; 6(1):46-48.
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Clinical Science

Micro - Focused Phototherapy Associated To Janus Kinase Inhibitor: A Promising Valid Therapeutic Option for Patients with Localized Vitiligo

Serena Gianfaldoni[1*], Georgi Tchernev[2], Uwe Wollina[3], Maria Grazia Roccia[4], Massimo Fioranelli[5], Jacopo Lotti[5], Miriam Rovesti[6], Francesca Satolli[6], Yan Valle[7], Andy Goren[8], Michael Tirant[9], Mirna Situm[10], Maja Kovacevic[8,10], Katlein França[11], Torello Lotti[8]

Abstract

BACKGROUND: Vitiligo is an acquired pigmentary cutaneous disease, characterised by the progressive loss of melanocytes, resulting in hypopigmented skin areas which progressively become amelanotic. Classically, vitiligo treatments are unsatisfactory and challenging. Despite the continuous introduction of new therapies, phototherapy is still the mainstay for vitiligo repigmentation.

AIM: The aim of this multicenter observational retrospective study was to evaluate the efficacy and safety of the nb - UVB micro - phototherapy (BIOSKIN EVOLUTION®), used alone or in associations with an oral Janus kinase inhibitor (Tofacitinib citrate), in the treatment of stable or active forms of localised vitiligo.

MATERIAL AND METHODS: Fifty eight patients had been treated with n-UVB micro-photootherapy (Group A); 9 patients had been treated with phototherapy plus Tofacitinb citrate (Group B).

RESULTS: Among Group A, 42 patients (72%) obtained a re-pigmentation rate higher than 75%, with a medium value of 77%. 11 patients (19%) achieved a marked improvement of the clinical findings with a repigmentation rate between 50-75%; 4 patients (8%) showed a moderate response with a lesional repigmentation of 25-50%. Only one patient (1%) had a poor response to the phototherapeutic treatment

CONCLUSION: Nb - UVB micro-focused phototherapy is one of the most effective therapeutic options for vitiligo treatment. The association of micro-focused phototherapy to Tofacitinib citrate seems to provide better clinical results in term of repigmentation rate.

Gianfaldoni S, et al. Micro - Focused Phototherapy Associated To Janus Kinase Inhibitor: A Promising Valid Therapeutic Option for Patients with Localized Vitiligo. Open Access Maced J Med Sci. 2018 Jan 21;6(1):46-48. doi: 10.3889/oamjms.2018.042. eCollection 2018 Jan 25.

RUXOLITINIB (TOPİKAL-1)

Yayın	n	İlaç	Süre	Klinik	Sonuç
Joshipura, 2018	1	Ruxolitinib 1.5% cream BID	N/A	GV	**Yüz bölgesinde belirgin repigmentasyon**
Rothstein, 2017	12	Ruxolitinib 1.5% cream BID	20h	NSV	**VASI skorunda %27 düzelme (n=9)** **Yüz lezyonlarında %76 repigmentasyon (n=4)**
Joshipura, 2018	8	Ruxolitinib 1.5% cream BID	52h	NSV	**VASI skorunda %38 düzelme** **Yüz lezyonlarında VASI skorunda %92 düzelme**
Pandya, 2022	19	Ruxolitinib cream, 0.15-1.5% (BID/once daily) (+NB-UVB)	2 yıl	NSV	**15/19 hastada F-VASI skorunda iyileşme** **18/19 hastada T-VASI skorunda iyileşme** **104.h'da ort. iyileşme yüzdesi F-VASI %50, T-VASI %30**

Joshipura D, et al. Importance of light in the treatment of vitiligo with JAK-inhibitors. J Dermatolog Treat. 2018 Feb; 29(1): 98–99.
Rothstein B, et al. Treatment of vitiligo with the topical Janus kinase inhibitor ruxolitinib. J Am Acad Dermatol. 2017;76(6):1054–1060.
Joshipura D, et al. Treatment of vitiligo with the topical Janus kinase inhibitor ruxolitinib: a 32-week open-label extension study with optional narrow-band ultraviolet B. J Am Acad Dermatol. 2018; 78(6): 1205–1207.
Pandya AG, et al. Addition of narrow-band UVB phototherapy to ruxolitinib cream in patients with vitiligo. J Invest Dermatol. 2022 Dec;142(12):3352-3355.e4

RUXOLITINIB (TOPİKAL-2)

Yayın	n	İlaç	Süre	Klinik	Sonuç
Rosmarin, 2020	157	Ruxolitinib cream, 1.5% (BID/once daily), %0.5 once daily, 0.15% once daily, placebo	24h, 52h	NSV	**Multicentre, Randomised, Double-blind, Phase 2 Study** **F-VASI50 yanıtı 24.h'da %1,5 krem grubunda plaseboya göre yüksek (%45-50 vs %3)**
Hamzavi, 2022	157	Ruxolitinib cream, 1.5% BID	24h	NSV	**F-VASI50 yanıtı;** **50 yaş ve altında yüksek (%59 vs %31)** **Kadınlarda daha yüksek (%60 vs %33)** **T-VASI50 yanıtı;** **Baş-boyun %60, üst ve alt ekstremitelerde %53, ayak %29, el %15**
Rosmarin, 2022	674	Ruxolitinib cream, 1.5% BID	52h	NSV	**Phase 3, double-blind, vehicle-controlled trials (Topical Ruxolitinib Evaluation in Vitiligo Study 1 [TRuE-V1] and 2 [TRuE-V2])** **Ruksolitinib > Plasebo** **TRuE-V1 %29.8 vs %7.4 ve TRuE-V2 %30.9 vs %11.4**

Rosmarin D, et al. Ruxolitinib cream for treatment of vitiligo: a randomized, controlled, Phase 2 trial. Lancet. 2020; 396: 110–120.
Hamzavi I, et al. Efficacy of ruxolitinib cream in vitiligo by patient characteristics and affected body areas: Descriptive subgroup analyses from a phase 2, randomized, double-blind trial. J Am Acad Dermatol. 2022 Jun; 86(6): 1398-1401.
Rosmarin D, et al. Two Phase 3, Randomized, Controlled Trials of Ruxolitinib Cream for Vitiligo. N Engl J Med. 2022; 387: 1445-55.

RUXOLITINIB (TOPİKAL)

Yayın	n	İlaç	Süre	Klinik	Sonuç
Rothstein, 2017	12	Ruxolitinib 1.5% cream BID	20h	NSV	**VASI skorunda %27 düzelme (n=9)** **Yüz lezyonlarında %76 repigmentasyon (n=4)**
Joshipura, 2018	8	Ruxolitinib 1.5% cream BID	52h	NSV	**VASI skorunda %38 düzelme** **Yüz lezyonlarında VASI skorunda %92 düzelme**

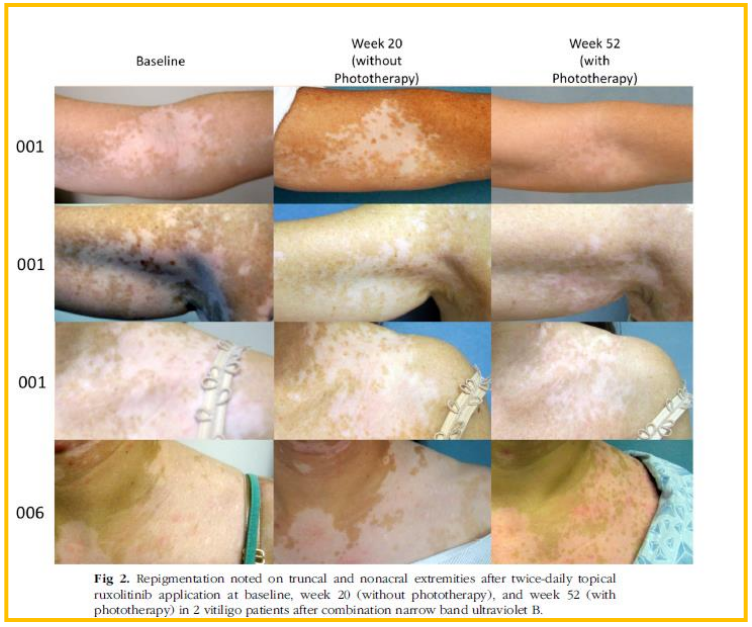
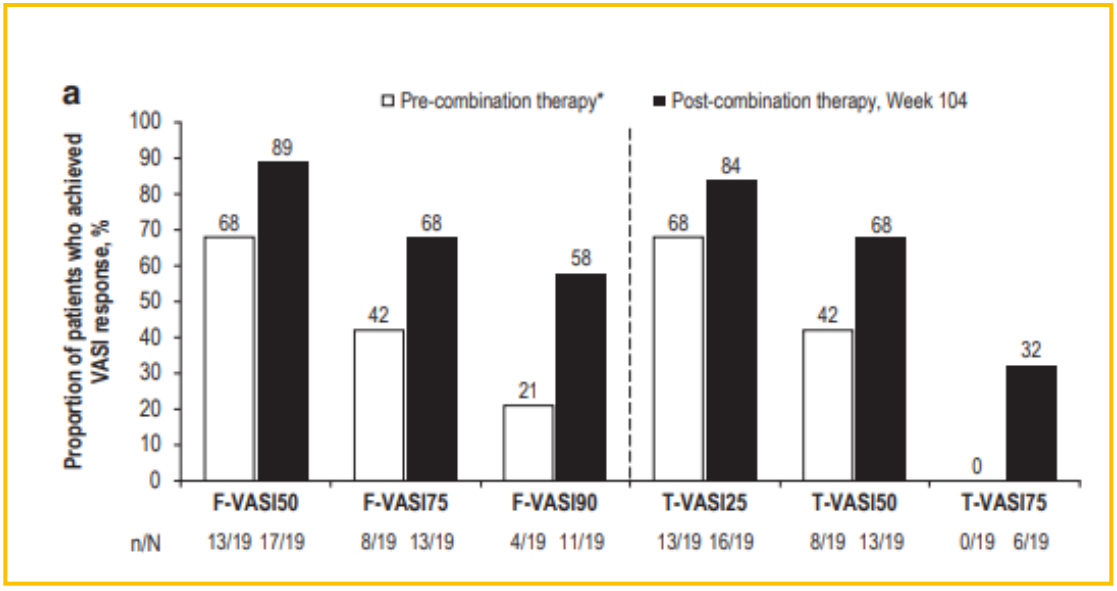


Fig 2. Repigmentation noted on truncal and nonacral extremities after twice-daily topical ruxolitinib application at baseline, week 20 (without phototherapy), and week 52 (with phototherapy) in 2 vitiligo patients after combination narrow band ultraviolet B.

Rothstein B, et al. Treatment of vitiligo with the topical Janus kinase inhibitor ruxolitinib. J Am Acad Dermatol. 2017;76(6):1054–1060.
Joshipura D, et al. Treatment of vitiligo with the topical Janus kinase inhibitor ruxolitinib: a 32-week open-label extension study with optional narrow-band ultraviolet B. J Am Acad Dermatol. 2018; 78(6): 1205–1207.

RUXOLITINIB (TOPİKAL)

Yayın	n	İlaç	Süre	Klinik	Sonuç
Pandya, 2022	19	Ruxolitinib cream, 0.15-1.5% (BID/once daily) (+NB-UVB)	2 yıl	NSV	**15/19 hastada F-VASI skorunda iyileşme** **18/19 hastada T-VASI skorunda iyileşme** **2 yıl sonunda ort. iyileşme yüzdesi F-VASI %50, T-VASI %30**

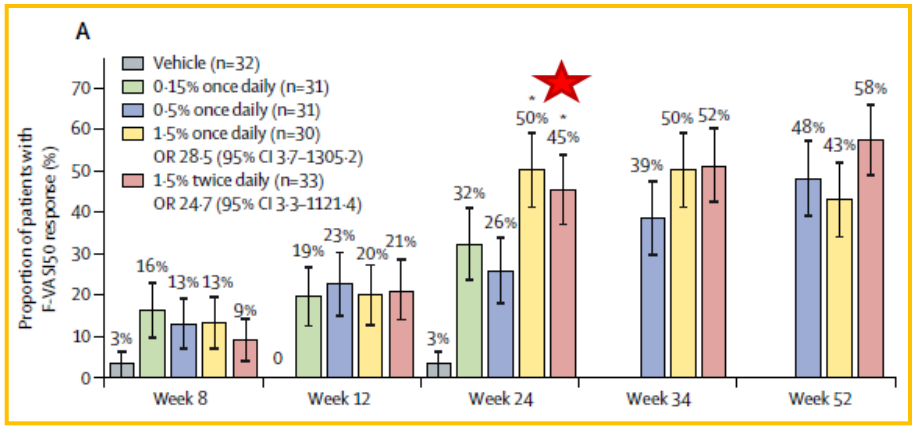


104. haftadaki tüm F-VASI ve T-VASI değerlerinde, NB-UVB eklendikten sonra kombinasyon tedavisinden önceki son vizite kıyasla artış

Pandya AG, et al. Addition of narrow-band UVB phototherapy to ruxolitinib cream in patients with vitiligo. J Invest Dermatol. 2022 Dec;142(12):3352-3355.e4

RUXOLITINIB (TOPİKAL)

Yayın	n	İlaç	Süre	Yerleşim	Sonuç
Rosmarin, 2020	157	Ruxolitinib cream, 1.5% (BID/once daily), %0.5 once daily, 0.15% once daily, placebo	24h, 52h	NSV	**Multicentre, Randomised, Double-blind, Phase 2 Study F-VASI50 yanıtı 24.h'da ruxolitinib %1,5 krem grubunda plaseboya göre yüksek yanıt (%45-50 vs %3)**



Rosmarin D, et al. Ruxolitinib cream for treatment of vitiligo: a randomized, controlled, Phase 2 trial. Lancet. 2020; 396: 110–120.

RUXOLITINIB (TOPİKAL)

Yayın	n	İlaç	Süre	Yerleşim	Sonuç
Hamzavi, 2022	157	Ruxolitinib cream, 1.5% BID	24h	NSV	**F-VASI50 yanıtı;** **50 yaş ve altında yüksek (%59 vs %31)** **Kadınlarda daha yüksek (%60 vs %33)** **T-VASI50 yanıtı;** **Baş-boyun %60, üst ve alt ekstremitelerde %53, ayak %29, el %15**

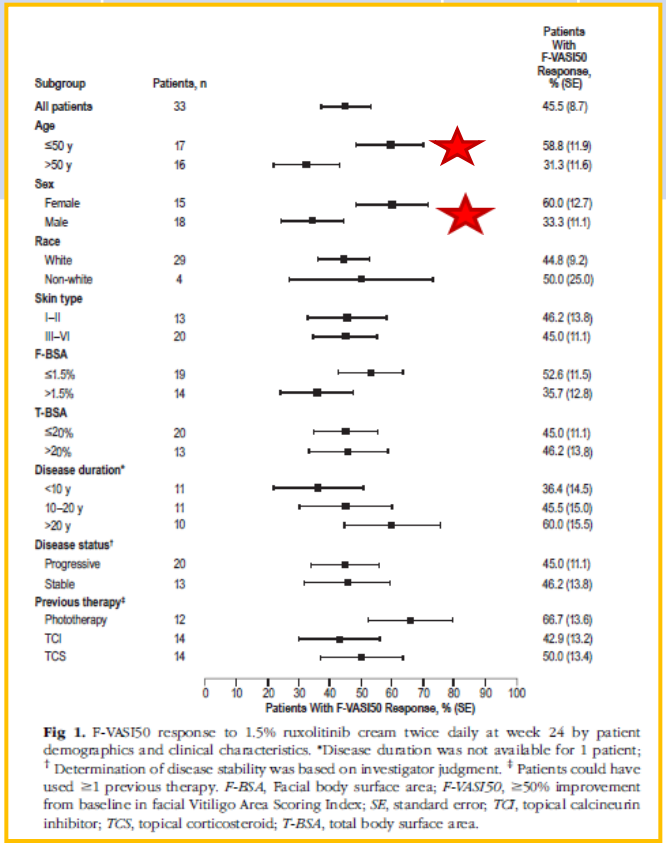


Fig 1. F-VASI50 response to 1.5% ruxolitinib cream twice daily at week 24 by patient demographics and clinical characteristics. *Disease duration was not available for 1 patient; † Determination of disease stability was based on investigator judgment. ‡ Patients could have used ≥1 previous therapy. *F-BSA*, Facial body surface area; *F-VASI50*, ≥50% improvement from baseline in facial Vitiligo Area Scoring Index; *SE*, standard error; *TCI*, topical calcineurin inhibitor; *TCS*, topical corticosteroid; *T-BSA*, total body surface area.

Efficacy of ruxolitinib cream in vitiligo by patient characteristics and affected body areas: Descriptive subgroup analyses from a phase 2, randomized, double-blind trial

Hamzavi I, et al. Efficacy of ruxolitinib cream in vitiligo by patient characteristics and affected body areas: Descriptive subgroup analyses from a phase 2, randomized, double-blind trial. J Am Acad Dermatol. 2022 Jun; 86(6): 1398-1401.

RUXOLITINIB (TOPİKAL)

Yayın	n	İlaç	Süre	Klinik	Sonuç
Rosmarin, 2022	674	Ruxolitinib cream, 1.5% BID	52h	NSV	**Phase 3, double-blind, vehicle-controlled trials (Topical Ruxolitinib Evaluation in Vitiligo Study 1 [TRuE-V1] and 2 [TRuE-V2])** **Ruksolitinib > Plasebo** **Adverse events:** Application-site acne (6.3-6.6%), nasopharyngitis (5.4-6.1% and 6.1%), and application-site pruritus (5.3-5.4)

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Two Phase 3, Randomized, Controlled Trials of Ruxolitinib Cream for Vitiligo

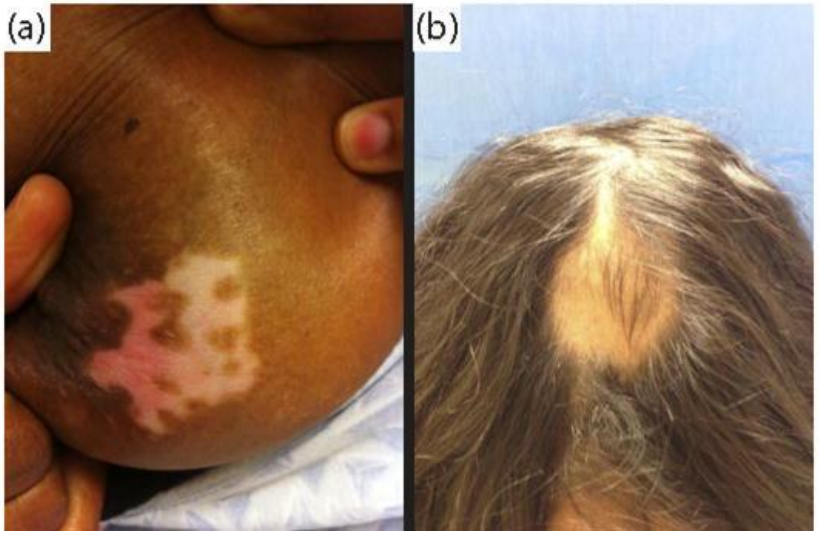
Table 2. Primary and Key Secondary Efficacy End Points (Double-Blind Period; Modified Intention-to-Treat Population).*

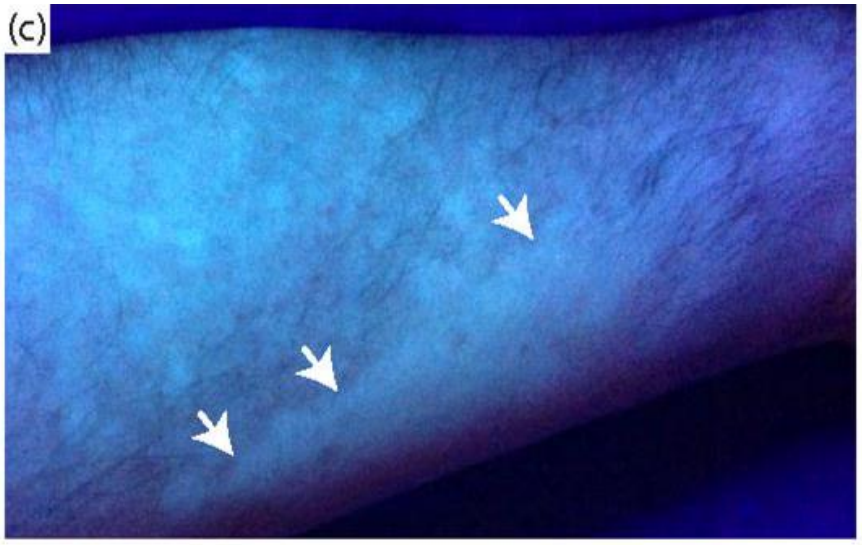
End Point	TRuE-V1				TRuE-V2			
	Vehicle (N=109)	1.5% Ruxolitinib Cream (N=221)	Relative Risk (95% CI)	P Value	Vehicle (N=109)	1.5% Ruxolitinib Cream (N=222)	Relative Risk (95% CI)	P Value
Primary end point								
F-VASI75 response at wk 24 — % (95% CI)†	7.4 (2.2 to 12.6)	29.8 (23.5 to 36.1)	4.0 (1.9 to 8.4)	<0.001	11.4 (5.2 to 17.7)	30.9 (24.5 to 37.3)	2.7 (1.5 to 4.9)	<0.001
Key secondary end points								
F-VASI50 response at wk 24 — % (95% CI)†	16.9 (9.3 to 24.6)	51.2 (44.4 to 58.0)	3.0 (1.9 to 4.8)	<0.001	20.9 (12.9 to 28.9)	51.4 (44.6 to 58.3)	2.5 (1.6 to 3.7)	<0.001
F-VASI90 response at wk 24 — % (95% CI)†	2.2 (0 to 5.1)	15.3 (10.4 to 20.2)	7.3 (1.8 to 29.5)	0.004	1.3 (0 to 3.8)	16.3 (11.2 to 21.5)	13.1 (1.9 to 90.2)	0.006
T-VASI50 response at wk 24 — % (95% CI)†	5.1 (0.6 to 9.7)	20.6 (15.2 to 26.0)	4.1 (1.6 to 10.5)	0.002	6.8 (1.9 to 11.7)	23.9 (18.1 to 29.8)	3.5 (1.7 to 7.5)	<0.001
VNS response at wk 24 — % (95% CI)†‡	3.3 (0 to 6.9)	24.5 (18.5 to 30.4)	7.5 (2.4 to 23.5)	<0.001	4.9 (0.7 to 9.2)	20.5 (14.9 to 26.1)	4.2 (1.7 to 10.2)	0.001
LSM percentage change from baseline in facial BSA affected by vitiligo at wk 24 (95% CI)§	−9.5 (−15.9 to −3.2)	−28.9 (−33.2 to −24.5)	NA	<0.001	−7.0 (−14.5 to 0.5)	−26.4 (−31.5 to −21.4)	NA	<0.001

* F-VASI50 denotes a decrease (improvement) of at least 50% in the F-VASI from baseline, F-VASI75 a decrease of at least 75% in the F-VASI from baseline, F-VASI90 a decrease of at least 90% in the F-VASI from baseline, NA not applicable, and T-VASI50 a decrease of at least 50% in the T-VASI from baseline.
† Multiple imputation was applied to account for missing values.
‡ A Vitiligo Noticeability Scale (VNS) response was defined as a rating of a lot less noticeable or no longer noticeable.
§ An analysis of covariance model was applied to determine least-squares mean (LSM) and P value.

RUXOLITINIB (ORAL)

Yayın	n	İlaç	Süre	Yerleşim	Sonuç
Harris, 2013	1	Ruxolitinib 20 mg, PO BID	5 ay	Yüz, gövde, akral	**Yüzdeki depigmentasyonda düzelme (%0,8'den %51) Tedavi sonlandırıldıktan 12 hafta sonra kötüleşme**





Harris JE. Vitiligo and alopecia areata: apples and oranges? Exp Dermatol. 2013; 22(12): 785-789.

DİĞER JAK İNHİBİTÖRLERİ

Yayın	N	İlaç	Süre	Yerleşim	Sonuç
Mumford, 2020	1	Baricitinib 4 mg, PO	8 ay	Eller ve ön kollar	**Tam repigmentasyon**
Yagi, 2021	2	Delgocitinib krem	8-12h	Eller (C1) BSA%20 (C2)	**C1 belirgin repigmentasyon C2 anlamlı değişiklik yok**
Li, 2023	2	Baricitinib 4 mg, PO	6-8 ay	NSV	**NB-UVB ve topikal tedaviler ile birlikte %75'e varan repigmentasyon**
Dong, 2022	4	Baricitinib (4 mg daily, first 4 weeks, then 2 mg daily for 8 weeks, PO)	12h	NSV	**Dört hafta sonunda belirgin repigmentasyon (%60-75) 3 aylık izlem sonunda iki hastada depigmentasyon**

Mumford BP, et al. Repigmentation of vitiligo with oral baricitinib. Australas J Dermatol 2020 Nov;61(4):374-376.
Yagi K, et al. Two cases of vitiligo vulgaris treated with topical Janus kinase inhibitor delgocitinib. Australas J Dermatol. 2021 Aug;62(3):433-434.
Li X, et al. Excellent Repigmentation of Generalized Vitiligo with Oral Baricitinib Combined with NB-UVB Phototherapy. Clin Cosmet Investig Dermatol . 2023 Mar 11;16:635-638.
Dong J, et al. Baricitinib is effective in treating progressing vitiligo in vivo and in vitro. Dose Response. 2022 May 31;20(2):15593258221105370.

STAT İNHİBİTÖRLERİ

STAT İNHİBİTÖRLERİ

Yayın	N	İlaç	Süre	Yerleşim	Sonuç
Noël, 2004	1	Simvastatin PO, 80 mg	6 ay	Yüz ve akral	**Orta derecede repigmentasyon**
Hu, 2022	1	Simvastatin topical sol. %0.11 twice daily and NB-UVB, twice a week	4 ay	NSV	**İki ay sonra perifoliküler repigmentasyon, dört ay sonra bariz iyileşme**
Vanderweil, 2017	15	Simvastatin PO, 40 mg daily for, 1 month, then 80 mg daily for 5 months	6 ay	NSV	**VASI skorunda ortalama artış %26 vs %0 (simvastatin vs plasebo)**
Shaker, 2022	**120**	**Simvastatin 80 mg daily (79 patients had dyslipidemia, till normalization of lipid profile or for 4 months, which came first)**	**6 ay**	**NSV**	**Vitiligo hastalık aktivitesi (VIDA) ve lipid seviyelerinde anlamlı azalma ($p < 0.011$) VASI skorunda azalma ($p=0.098$)**

Noël M, et al. Positive pleiotropic effects of HMG-CoA reductase inhibitor on vitiligo. Lipids Health Dis. 2004;3:7.
Hu W, et al. Narrowband Ultraviolet B Combined with Topical Simvastatin Solution in the Treatment of Vitiligo: A Case Report. Photobiomodul Photomed Laser Surg. 2022 May;40(5):362-364.
Vanderweil SG, et al. A double-blind, placebo-controlled, phase-II clinical trial to evaluate oral simvastatin as a treatment for vitiligo. J Am Acad Dermatol. 2017;76(1):150-151. e3.
Shaker ESE, et al. Simvastatin and non-segmental vitiligo: A new potential treatment option? Dermatol Ther. 2022 Dec;35(12):e15969.

TNF-α İNHİBİTÖRLERİ

TNF-α İNHİBİTÖRLERİ

Yayın	n	İlaç	Süre	Yerleşim	Sonuç
Kim, 2007	2	ETA	1 yıl	Dirençli, progresif vitiligo	**Vitiligo stabilizasyonu ve repigmentasyon**
Rigopoulos, 2007	4	ETA	4 ay	Progresif vitiligo	**Tüm olgularda vitiligo stabilizasyonu**
Alghamdi, 2012	6	INF (n=2), ADA (n=2), ETA (n=2)	2-6 ay	Progresif vitiligo	**Repigmentasyon yok** **Bir olguda (INF) vitiligoda progresyon**

Kim N, et al. Impaired PI3K/Akt activation-mediated NF-κB inactivation under elevated TNF-α is more vulnerable to apoptosis in vitiliginous keratinocytes. J Investig Dermatol. 2007;127(11):2612-2617.
Rigopoulos D, et al. Etanercept in the treatment of vitiligo. Dermatology. 2007;215(1):84-85.
Alghamdi KM, et al. Treatment of generalized vitiligo with anti-TNF- a agents. J Drugs Dermatol. 2012;11:534-539.

BİYOLOJİK AJAN KULLANIMINA BAĞLI GELİŞEN VİTİLİGO

A systematic review of vitiligo onset and exacerbation in patients receiving biologic therapy

Biologics (n, %)	
TNF-α inhibitor	71 (82.6)
Adalimumab	32
Infliximab	26
Etanercept	11
Certolizumab	2
CD52 inhibitor	6 (7.0)
Alemtuzumab	6
IL-12/23 inhibitor	4 (4.7)
Ustekinumab	4
IL-17A inhibitor	2 (2.3)
Secukinumab	1
Ixekizumab	1
CD20 inhibitor	1 (1.2)
Rituximab	1
IL-6 receptor inhibitor	1 (1.2)
Tocilizumab	1
CTLA-4 inhibitor	1 (1.2)
Abatacept	1
Reported Total	86

Tofacitinib (JAK inh.)

Pembrolizumab (Anti-PD1)

Durvalumab (Anti-PD1)

Nivolumab (Anti-PD1)

İmatinib (Tirozin kinaz inh.)

Mogalizumab (Anti-CCR4)

Ribociclib (Cyclin D1/CDK4 and CDK6 inh.)

Sachdeva M, et al. A systematic review of vitiligo onset and exacerbation in patients receiving biologic therapy JAAD Int. 2020 Dec 2; 2: 37-39.

IL-17 ve IL-23 İNHİBİTÖRLERİ

IL-17 ve IL-23 İNHİBİTÖRLERİ

Yayın	n	İlaç	Süre	Klinik	Sonuç
Katz, 2018	1	IXE	15 ay	Vitiligo, PsO	**Vitiligoda yanıt yok, PsO iyileşme**
Speeckaert, 2019	8	SEC	7 ay	Aktif NSV	**1 hastada orta derecede repigmentasyon 7 hastada progresyon yok**
Palazzo, 2020	1	SEC	12 ay	ADA sonrası vitiligo	**Tama yakın repigmentasyon**
Elkady, 2017	1	UST (90 mg)	5 ay	Generalize vitiligo, AA, PsO	**Tam iyileşme (PsO 16.hf, AA ve vitiligo 20.hf)**
Jerjen, 2020	1	TIL	12 AY	Akrofasiyal vitiligo	**%90 repigmentasyon**

Katz K, et al. Interleukin-17 inhibition in a patient with psoriasis and concurrent vitiligo. J Psoriasis Psoriatic Arthritis. 2018;3(4):126-130.
Speeckaert R, et al. IL-17A is not a treatment target in progressive vitiligo. Pigment Cell Melanoma Res. 2019;32(6):842-847.
Palazzo G. Resolution of post-adalimumab vitiligo with secukinumab in a patient with psoriasis vulgaris. Oxford Medical Case Reports, 2020;2020,13–16.
Elkady A, et al. Effective use of ustekinumab in a patient with concomitant psoriasis, vitiligo, and alopecia areata. JAAD Case Rep. 2017;3(6):477-479.
Jerjen R, et al. Repigmentation of acrofacial vitiligo with subcutaneous tildrakizumab. Australas J Dermatol . 2020 Nov;61(4):e446-e448.

DİĞER
HEDEFE YÖNELİK AJANLAR

DİĞER HEDEFE YÖNELİK AJANLAR

Yayın	n	İlaç	Süre	Klinik	Sonuç
Majid, 2019	13	Apremilast (PDE-4 inh)	3 ay	Progresif NSV	**8 hastada (%60) parsiyel repigmentasyon**
Khemis, 2020	80	Apremilast (PDE-4 inh)	12 ay	GV	**DB-UVB+apremilast ile DB-UVB+plasebo grupları arasında anlamlı fark yok**
Martinez-Cabriales, 2020	1	Eculizumab (C5 inh) Paroksismal nokturnal Hemoglobinüri	6 ay	GV	**Yüz ve ellerde repigmentasyon**
Grimes, 2013	4	Afamelanotid (α-MSH analog)	4 ay	GV	**%50-90 repigmentasyon (1-4. haftada başlayan)**
Lim, 2015	55	Afamelanotid (α-MSH analog)	6 ay	GV	**%49 vs %33 repigmentasyon (DB-UVB+AFA vs DB-UVB)**

Majid I, et al. Apremilast is effective in controlling the progression of adult vitiligo: A case series. Dermatologic Therapy. 2019;32:e12923.
Khemis A, et al. Apremilast in Combination with Narrowband UVB in the Treatment of Vitiligo: A 52-Week Monocentric Prospective Randomized Placebo-Controlled Study. J Invest Dermatol 2020; 140: 1533e1537.
Martinez-Cabriales SA, et al. Refractory vitiligo improving with eculizumab. Dermatologic Therapy. 2020;33:e13233.
Grimes PE, et al. The efficacy of afamelanotide and narrowband UV-B phototherapy for repigmentation of vitiligo. JAMA Dermatol. 2013; 149: 68–73.
Lim HW, et al. Afamelanotide and narrowband UV-B phototherapy for the treatment of vitiligo: a randomized multicenter trial. JAMA Dermatol. 2015; 151: 42–50.

ClinicalTrials.gov - 1

Ajan	Hedef	Phase	Uygulama	NCT no.	Durum
Ruxolitinib	JAK 1/2	3	Topikal	NCT04530344	Completed
Cerdulatinib	JAK/SYK	2	Topikal	NCT04103060	Completed
Ritlecitinib	JAK1/TYK2	2	Oral	NCT03715829	Completed
Ifidancitinib	JAK 1/3	2	Topikal	NCT03468855	Completed
Ritlecitinib /Brepocitinib	JAK 3 / JAK1/TYK2	2	Oral	NCT03715829	Completed
Ritlecitinib	JAK1/TYK2	3	Oral	NCT05583526	Recruiting
Baricitinib	JAK 1/2	2	Oral	NCT04822584	Active, not recruiting
Ruxolitinib	JAK 1/2	2	Topikal	NCT05247489 NCT04896385	Active, not recruiting
INCB054707	JAK1	2	Topikal	NCT04818346	Active, not recruiting
Upadacitinib	JAK1	2	Oral	NCT04927975	Active, not recruiting
Tofacitinib	JAK2	1	Oral	NCT05293119	Not yet recruiting
SHR0302	JAK1	2/3	Topikal	NCT04774809	Terminated (terminated by sponsor)
ARQ-252	JAK1	2	Topikal	NCT04811131	Terminated (Sponsor Decision)

ClinicalTrials.gov - 2

Ajan	Hedef	Phase	Uygulama	NCT no.	Durum
AMG 714	IL-15	2	Subkutan	NCT04338581	Recruiting
Secukinumab	IL-17	Pilot trial	Subkutan	EudraCT number: 2015–003552–48	No significant improvement
Apremilast (+ NB-UVB)	PDE-4	2	Oral	NCT03123016	No significant improvement
Apremilast (+ NB-UVB)	PDE-4	2	Oral	NCT03036995	No significant improvement
Simvastatin	STAT inh.	2	Oral	NCT01517893	No significant improvement
Atorvastatin (+ NB-UVB)	STAT inh.	2	Oral	NCT02432534	No significant improvement
Gastroprotected superoxide dismutase: glisodin	Antioxidant	2	Oral	NCT03941808	Completed
AS012	?	2	Oral	NCT04487860	Completed

GELECEKTEKİ MUHTEMEL HEDEFE YÖNELİK AJANLAR

TABLE 5 Potential vitiligo treatments for vitiligo

Targets	Treatment goal	Treatments	Mechanism
JAK	Immunosuppression	JAK inhibitors • Ruxolitinib (JAK1/2) • Tofacitinib (JAK1/3)	Disruption the IFN-γ–CXCR3–CXCL9/10 axis required for T Cell recruitment and function
IL-15	Immunosuppression and elimination of T_{RM} cells	Antibodies against IL-and CD122	Short-term treatment inhibits IFN-γ production by T_{RM}, and long-term treatment depletes T_{RM} from skin lesions. Potentially durable treatment agent which prevents relapses
T regulatory cells	Suppression of autoreactive effectors	Low dose IL-2	Increasing the pool of T regulatory cells to ultimately suppress the proliferation and activation of CD8+ T cells
HSP70	Block endogenous innate immune activation	Mutant DNA injections Plasmid HSP70i gene therapy	Mutant HSP70i counteracts innate immune activation by endogenous HSP70i
NK/CD8 (NKG2D)	Block endogenous innate immune activation Blocks cytolytic activity of CD8+ T cells	Anti-NKG2D type II integral membrane protein antibodies	Interfers with the recognition of NKG2D ligands by NK cells and $CD8^+$ T cells
CXCR3B	Preventing initial melanocyte apoptosis	Antibodies against CXCR3B	Inhibition of CXCR3B mediated apoptosis of melanocytes and activation of T cells
WNT pathway	Stimulation of repigmentation	WNT agonists or GSK3β inhibitors	Stimulation of melanocyte stem cell proliferation, differentiation and migration
Melanocortin 1 receptor agonist	Melanocyte regeneration	Afamelanotide	Stimulation of melanocyte stem cell proliferation, differentiation and migration

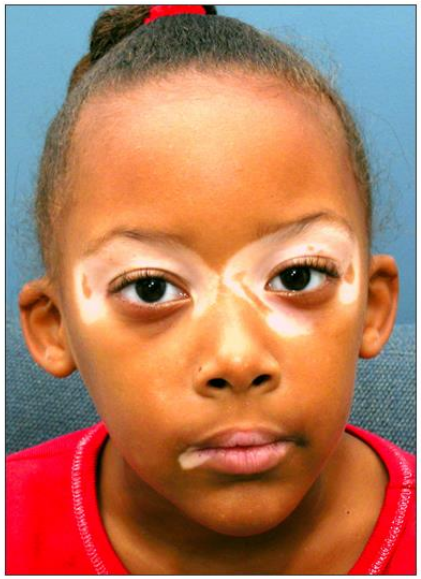
Abbreviation: T_{RM}, Tissue-resident memory T.

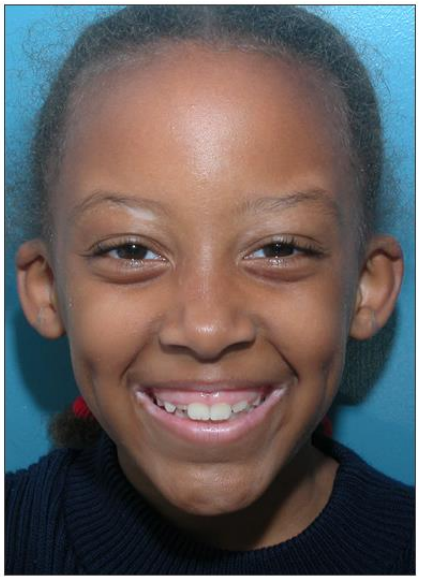
Bergqwist C, et al. Vitiligo: A focus on pathogenesis and its therapeutic implications. J Dermatol. 2021; 48: 252–270.

Table 2. Possible targets for the treatment of vitiligo, known effects on melanocytes, molecules related to the objectives, scientific rationale.

	Involvement	Possible Targets	Rationale
Pd-1	Immunity response and checkpoint function	PD-1, PD-L1	Regulating T-cell activation
IFN-gamma	Inflammation and promotion of autophagy	IFN-gamma soluble, CXCL10-CXCR3	Stopping specific CTLs killing of melanocytes
NOS	Production of oxygen radical species	Inducible synthase (iNOS)	Lower levels of oxidative stress
IL-15	Regulates level of IL-17	Soluble form and receptor CD122	Stopping crosstalk between T_{RM} cells and Tcm cells
S1PR1	Transit from tissues to blood vessels of T lymphocytes	S1PR1 (receptor) or S1P (ligand)	Allowing the recirculation of T memory cells and preventing the maintenance of inflammation

Custurone P, et al. Role of Cytokines in Vitiligo: Pathogenesis and Possible Targets for Old and New Treatments. Int J Mol Sci. 2021; 22: 11429 .





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Tıp Fakültesi

Teşekkürler...