Inmunoterapia en Vitíligo

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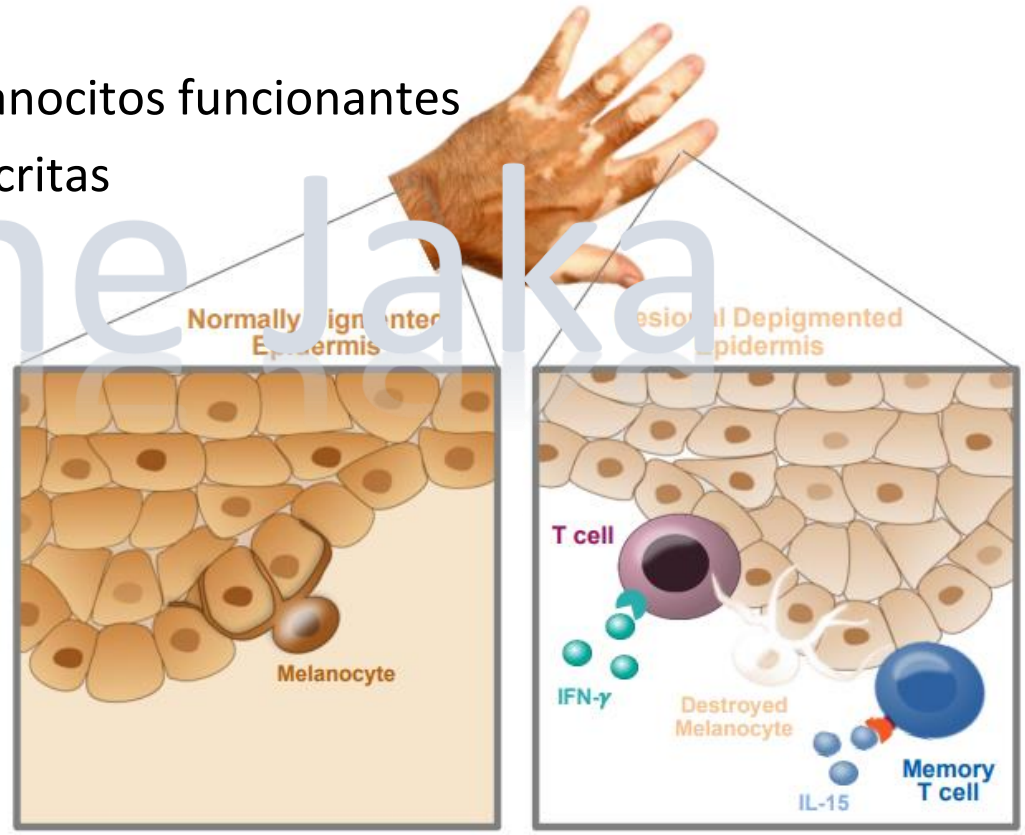
Conflictos de interés

- Participación en EC INCB18424-307/308 (True-V2) promovido por “ INCYTE corporation “

Introducción

- Enfermedad adquirida
  - Pérdida progresiva de melanocitos funcionantes
  - Máculas acrómicas circunscritas



Autoimmune destruction of melanocytes leading to skin depigmentation

- Prevalencia:
  - 0,5-2% población general

- Edad media aparición:
  - 20 años
- Sin diferencias entre sexo ni edad

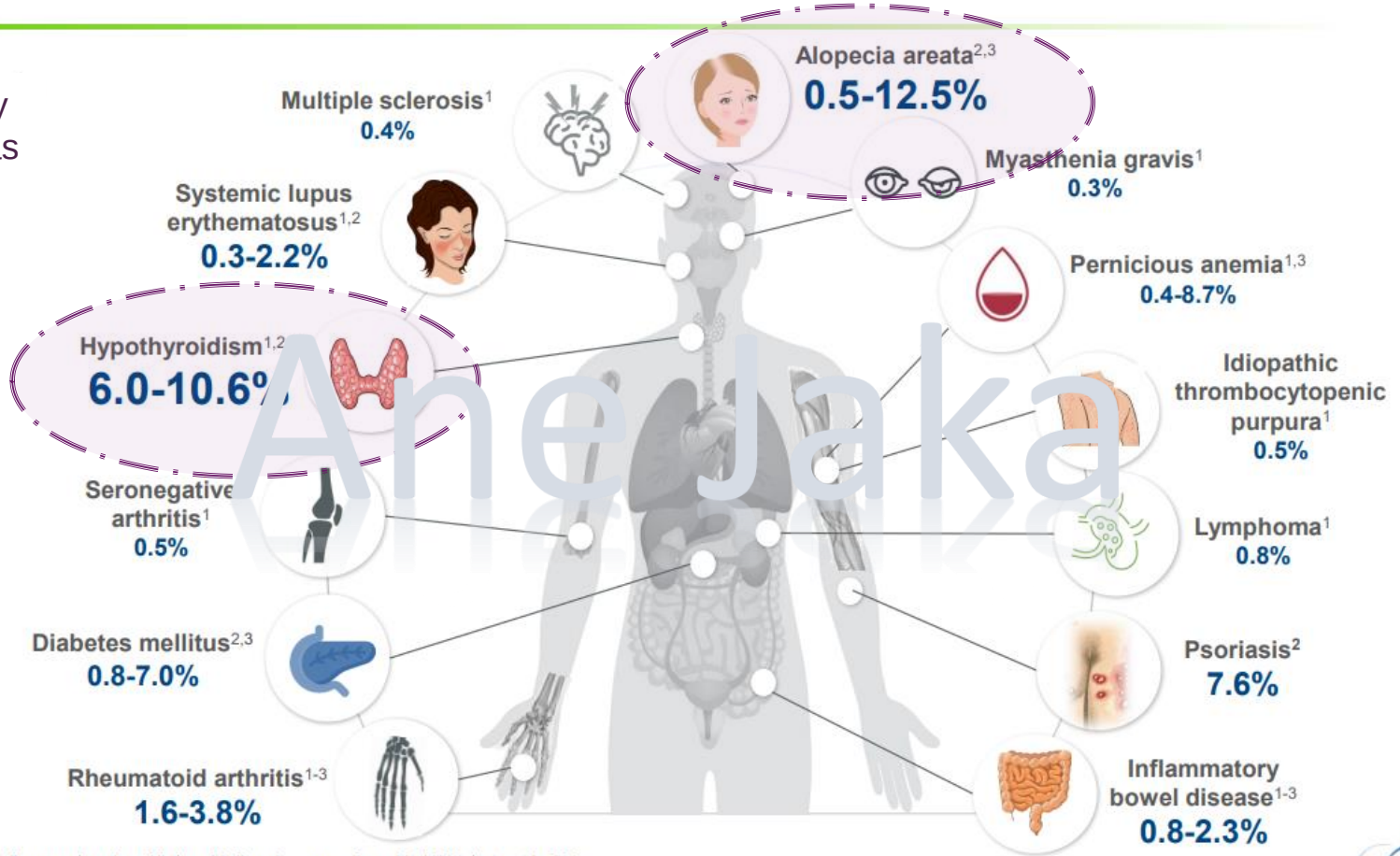
- Se intercalan largos períodos de estabilidad con períodos más cortos de progresión (semanas/meses)
- Patogénesis multifactorial

- Impacto psicológico

Asociación enfermedades autoinmunes

El vitíligo se asocia con diversas comorbilidades autoinmunes en el 20% de los pacientes [1,2]

La enfermedad tiroidea y la alopecia areata son las comorbilidades autoinmunes más comunes



[a] Risk increases with larger affected BSA and disease duration. All thyroid disorders were found in NSV, but not in SV.

1. Hadi A, et al. *J Am Acad Dermatol*. 2020;82:628-633. 2. Sheth VM, et al. *Dermatol*. 2013;227:311-315. 3. Dahir AM, et al. *Int J Dermatol*. 2018;57:1157-1164. 4. Ma SH, et al. *J Am Acad Dermatol*. 2021;85:1465-1472. 5. Yuan J, et al. *Front Endocrinol* (Lausanne). 2019;9:803.

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Check for updates

DERMATOLOGIC THERAPY WILEY

REVIEW ARTICLE

Psychodermatology of vitiligo: Psychological impact and consequences

Robert E. Simons | Danna L. Zevy | Mohammad Jafferany

Ezzedine K et al. American Journal of Clinical Dermatology (2021) 22:757–774

Psychosocial Comorbidities in Patients With Vitiligo: A Systematic Literature Review

Calidad de vida

Baja autoestima

Estigma

Depresión

Estrés

Ansiedad

Received: 12 April 2020 | Accepted: 13 April 2020
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Psychodermatology of vitiligo: Psychological impact and consequences

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Diagnóstico

CLÍNICO

Exploración

- Fototipo
- Exploración física+/- lámpara de Wood
- Leucotriquia
- Halo nevus

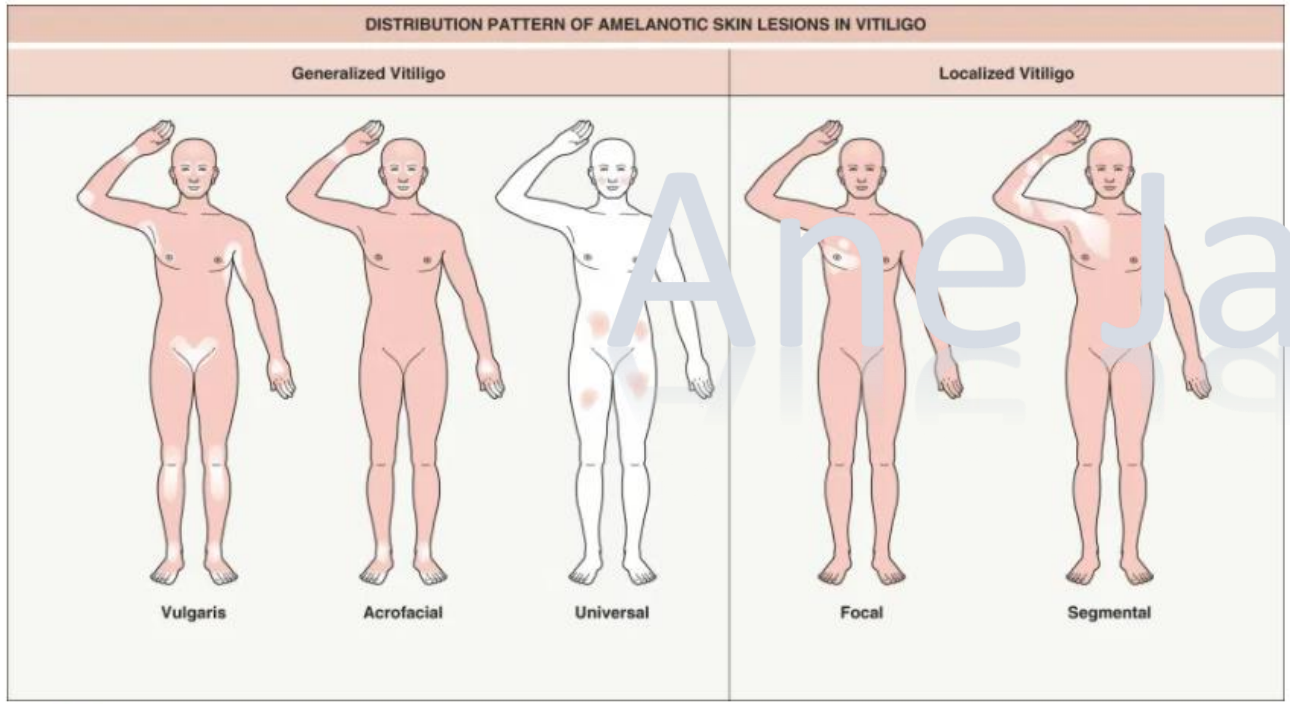
Historia médica

- Atc personales y familiares
- Enfermedades autoinmunes asociadas
- Historia familiar de vitíligo
- Tratamientos previos

Impacto en la calidad de vida

- Impacto psico-social

Clasificación



Classification of Koebner's phenomenon as proposed by the Vitiligo European Task Force in 2011 (van Geel et al., 2011b).

Bordeaux VGICC classification and consensus nomenclature

	Subtypes
Vitiligo/NSV	Acrofacial
	Mucosal (more than one mucosal site)
	Generalized
	Universal
	Mixed (associated with SV)
	Rare variants
Segmental Vitiligo	Uni-, bi-, or plurisegmental
Undetermined/unclassified Vitiligo	Focal
	Mucosal (one site in isolation)

NSV, non-segmental vitiligo; SV, segmental vitiligo; VGICC, Vitiligo Global Issues Consensus Conference.

Pigment Cell Melanoma Res. 25; E1–E13 ORIGINAL ARTICLE

Revised classification/nomenclature of vitiligo and related issues: the Vitiligo Global Issues Consensus Conference

K. Ezzedine[1,2], H. W. Lim[3], T. Suzuki[4], I. Katayama[5], I. Hamzavi[3], C. C. E. Lan[6], B. K. Goh[7], T. Anbar[8], C. Silva de Castro[9], A. Y. Lee[10], D. Parsad[11], N. van Geel[12], I. C. Le Poole[13], N. Oiso[14], L. Benzekri[15], R. Spritz[16], Y. Gauthier[1,2], S. K. Hann[17], M. Picardo[18] and A. Taieb[1,2]; on behalf of the Vitiligo Global Issue Consensus Conference panelists

Medidas –índice de gravedad

- Actualmente no hay consenso en los métodos para evaluar el vitíligo, ya sea para el diagnóstico o para los resultados de tratamiento.
- Las escalas más utilizadas:

El éxito del tratamiento se define como >75 % de repigmentación, con mantenimiento de ≥80 % de la repigmentación ganada más allá de los 6 meses[4,5,9]

BSA[b] — Body Surface Area

The percentage of vitiligo involvement determined by the palmar or handprint (palm+5 digits) method

VASI[b] — Vitiligo Area Scoring Index

A validated quantitative scale that measures the extent of vitiligo involvement as a % of BSA multiplied by the degree of depigmentation[2,3,6]

VES

A validated scoring system where 19 body areas are scored separately, depending on the extent of depigmentation[3]

Global Vitiligo Assessment

PhGVA,[b] PaGVA[b]

A 5-point scale where the severity of vitiligo is assessed by the physician or by the patient[6]

PaGIC-V

A 7-point scale comparing a patient's impression of their disease from baseline[6]

VNS

A new 5-point scale patient-reported outcome that takes into account skin color matching[7,8]

[a] According to the Vitiligo Global Issues Consensus Conference (VGICC), expectations for treatments may differ greatly between patients and doctors in setting thresholds for outcome research.[4] [b] This outcome measure can be further specified as facial (F) or total body (T).
BSA, body surface area; PaGIC-V, Patient Global Impression of Change–Vitiligo; PaGVA, Patient's Global Vitiligo Assessment; PhGVA, Physician's Global Vitiligo Assessment; PRO, patient-reported outcomes; VASI, Vitiligo Area Scoring Index; VNS, Vitiligo Noticeability Scale; VES, Vitiligo Extent Score.

1. Eleftheriadou V, et al. *Br J Dermatol*. 2012;167:804-814. 2. Dicle O. *J Pigment Disorders*. 2015;2:1. 3. van Geel N, et al. *J Invest Dermatol*. 2016;136:978-984. 4. Gan EY, et al. *Pigment Cell Melanoma Res*. 2017;30:28-40. 5. Eleftheriadou V, et al. *Br J Dermatol*. 2022;186:18-29. 6. Rosmarin D, et al. *Lancet*. 2020;396:110-120, Supplement. 7. Tour SK, et al. *BMC Dermatol*. 2014;14:10. 8. Batchelor JM, et al. *Br J Dermatol*. 2016;174:386-394. 9. Narayan VS, et al. *Br J Dermatol*. 2021;184:165-166.

Medidas –índice de gravedad

Body Surface Area

BSA

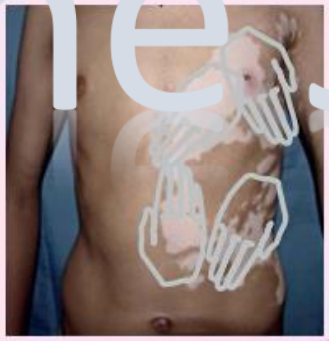
- Commonly used method to assess skin disease extent as a % of total body surface area[1]
- Estimated by the investigator using the Palmar Method to mimic the patient's hand size[2]
  - Vitiligo depigmented area determined to the nearest 0.1% using[2]:
    - **Handprint as 1% BSA** (palm + 5 digits, with fingers tucked together & thumb tucked to the side)
    - **Thumbprint as 0.1% BSA**

Total BSA (T-BSA) takes into account the depigmented areas for each of the following body regions:
head/neck (incl. F-BSA), upper limbs (incl. hands), trunk, lower limbs (incl. feet)[2]

Example:

T-BSA with skin lesions
= [(½ handprint x 3) + 1 handprint] × 1% BSA

→ **T-BSA = 2.5**



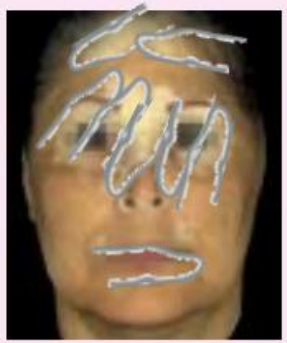
Facial BSA (F-BSA) takes into account the depigmented areas on the face as a % of the total body area[2,a]

Example:

F-BSA with skin lesions
=6.5 thumbprints ×0.1% BSA

→ **F-BSA = 0.65**

Note: Max. F-BSA =3
(i.e. depigmentation on 100% of the face)



In the US, Opzelura™ (ruxolitinib) cream 1.5% bid is approved for the topical treatment of NSV in adult and pediatric patients ≥12 years of age.[3] Outside of the US, ruxolitinib cream is considered an investigational compound. There is no guarantee that ruxolitinib cream will become commercially available for the use(s) under investigation.

BSA, Body Surface Area.

[a] "Face" includes the area on the forehead to the original hairline, on the cheek to the jawline vertically and laterally from the corner of the mouth to the tragus. It does not include the surface area of the lips, scalp, ears, or neck. In the Phase 2 trial of ruxolitinib cream in vitiligo (INCB 18424-211), the face included the nose but not the eyelids while in the Phase 3 trials of ruxolitinib cream in vitiligo (INCB 18424-306/307), the nose and eyelids were included.[2]

1. Gooderham MJ, et al. *J Cutan Med Surg*. 2018;22:10S-16S. 2. Rosmarin D, et al. *Lancet*. 2020;396:110-120. 3. Opzelura® (ruxolitinib) cream. US prescribing Information. Incyte Corporation; revised July 2022.

Medidas –índice de gravedad

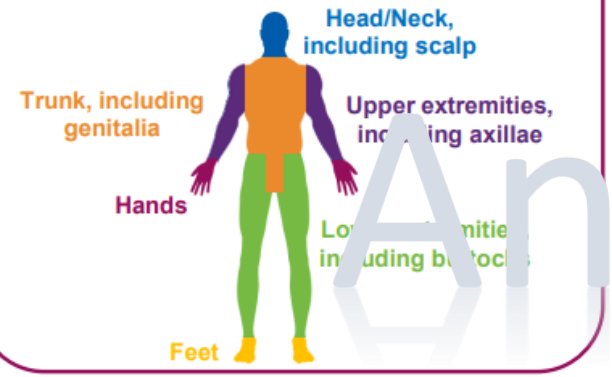
Vitiligo Area Scoring Index

T-VASI

- T-VASI is a validated quantitative scale that measures the extent of vitiligo involvement as a percentage of affected BSA multiplied by the degree of depigmentation[1-5]

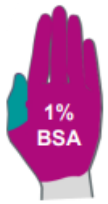
Step 1

Segment the body in 6 anatomic regions



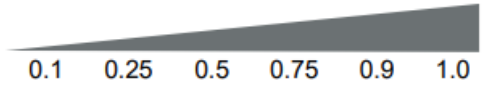
Step 2

Assess affected BSA using the Palmar Method

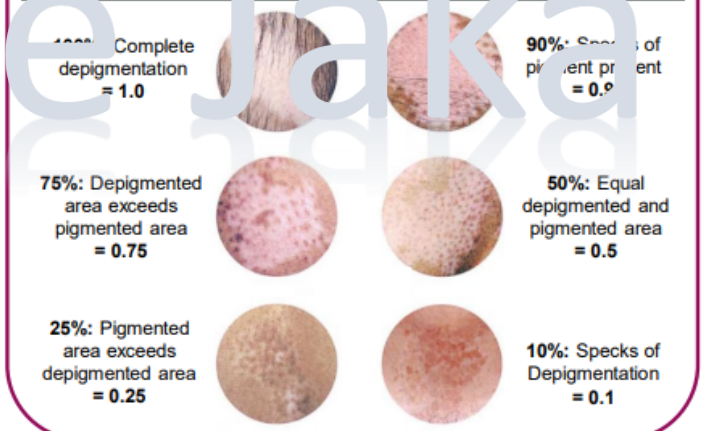


Step 3

Assess the degree of depigmentation



Standardized assessments for estimating the degree of pigmentation to derive VASI[5]



Step 4

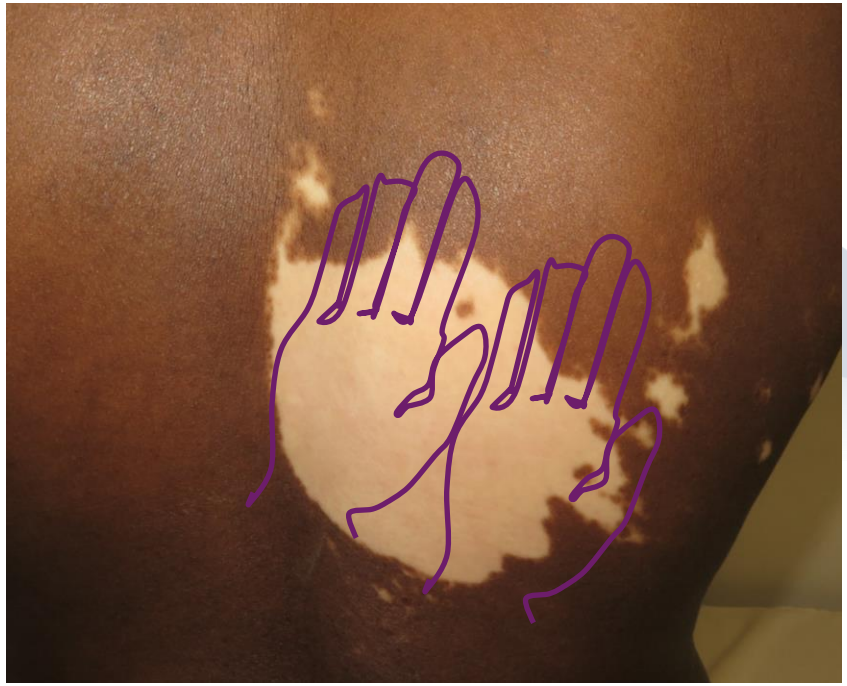
- Multiply the T-BSA by the degree of depigmentation for each body region
- Add the product of all body regions

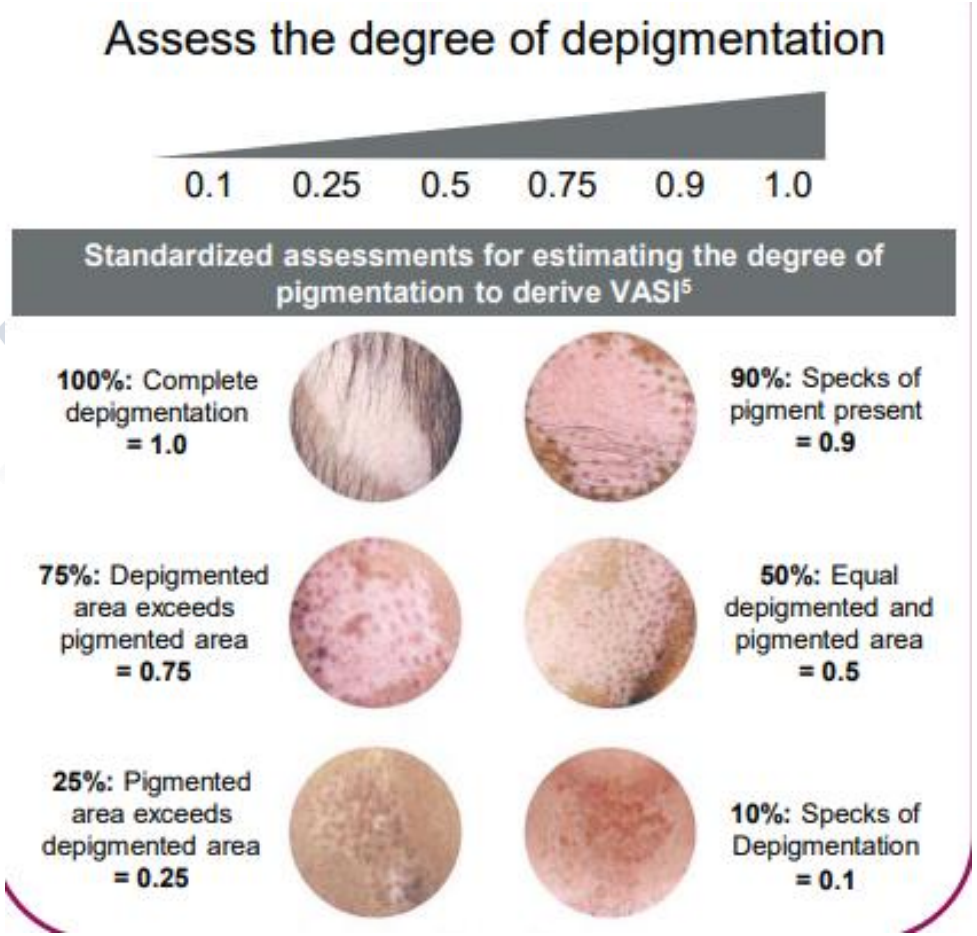
Location	T-BSA	Degree of depigmentation	VASI score per region
Head/Neck, including scalp	Max: 9.0	0.1/0.25/0.5/0.75/ 0.9/1.0	
Upper extremities, including axillae (excludes hands)	Max: 14		
Hands	Max: 4		
Trunk, including genitalia (excludes buttocks)	Max: 33		
Lower extremities, including buttocks (excludes feet)	Max: 36		
Feet	Max: 4		
TOTAL			T-VASI score

$$T-VASI = \sum_{\substack{Depigmented\ lesions \\ on\ all\ body\ sites}} (T-BSA)\ (degree\ of\ depigmentation)$$

T-VASI, Total Body Vitiligo Area Scoring Index.
1. Suppl to: Rosmarin D, et al. *Lancet*. 2020;396:110-120. 2. Dicle O. *J Pigment Disorders*. 2015;2:1. 3. van Geel N, et al. *J Invest Dermatol*. 2016;136:978-984. 4. DermNet NZ.com. Accessed Jun 2022. https://www.dermnetnz.org/topics/vitiligo/. 5. Hamzavi I, et al. *Arch Dermatol*. 2004;140:677-83.

Medidas –índice de gravedad



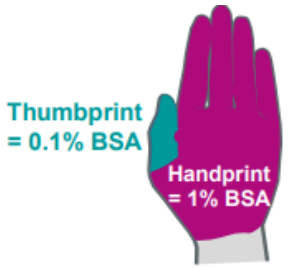


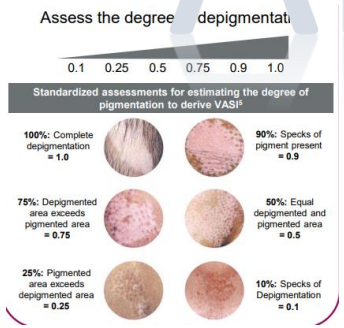
$$\text{VASI} = \sum_{\text{All Body Sites}} [\text{Hand Units}] \times [\text{Residual Depigmentation}]$$

Medidas –índice de gravedad

F-VASI

- F-VASI was developed by Incyte to assess the extent of depigmentation on the face[1,a]
- It is calculated by multiplying F-BSA (i.e. affected areas on the face as a percentage of the total body area) by the degree of depigmentation[1]



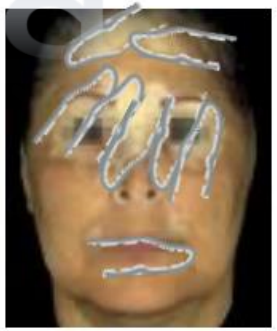


$$F-VASI = \sum_{\text{Depigmented lesions on the face}} (F-\text{BSA}) \, (\text{degree of depigmentation})$$

Example:

(6.5 thumbprints x 0.1% BSA)
× (90% depigmentation)
=0.65 x 0.9

→ **F-VASI score =0.6**



In the US, Opzelura™ (ruxolitinib) cream 1.5% bid is approved for the topical treatment of NSV in adult and pediatric patients ≥12 years of age.[2] Outside of the US, ruxolitinib cream is considered an investigational compound. There is no guarantee that ruxolitinib cream will become commercially available for the use(s) under investigation.

F-VASI, Facial Vitiligo Area Scoring Index.

[a] The F-VASI score is distinct from the T-VASI head/neck subscore.

1. Suppl to: Rosmarin D, et al. *Lancet*. 2020;396:110-120. 2. Opzelura® (ruxolitinib) cream. US prescribing Information. Incyte Corporation; revised July 2022.

Medidas –índice de gravedad

Ph/Pa-GVA

Global Vitiligo Assessment

PhGVA[1]

- A **5-point scale** where the severity of vitiligo is assessed by the **physician** (PhGVA)
- Scale can be for the face or total body (F/T-PhGVA)
- Treatment success is achieved when GVA score is 0 (clear or complete repigmentation) or 1 (almost clear/only specks of depigmentation present)

Score	Severity	Description
0	Clear	No signs of vitiligo
1	Almost Clear	Only specks of depigmentation present
2	Mild Disease	Pigmented and depigmented areas are equal
3	Moderate Disease	More or complete depigmentation (may include <30% hair whitening)
4	Severe Disease	Complete depigmentation plus >30% hair whitening

PaGVA[1]

- A **5-point PRO scale** where the severity of vitiligo is assessed by the **patient** (PaGVA)
- Scale can be for the face or total body (F/T-PaGVA)
- Patients answer this question:

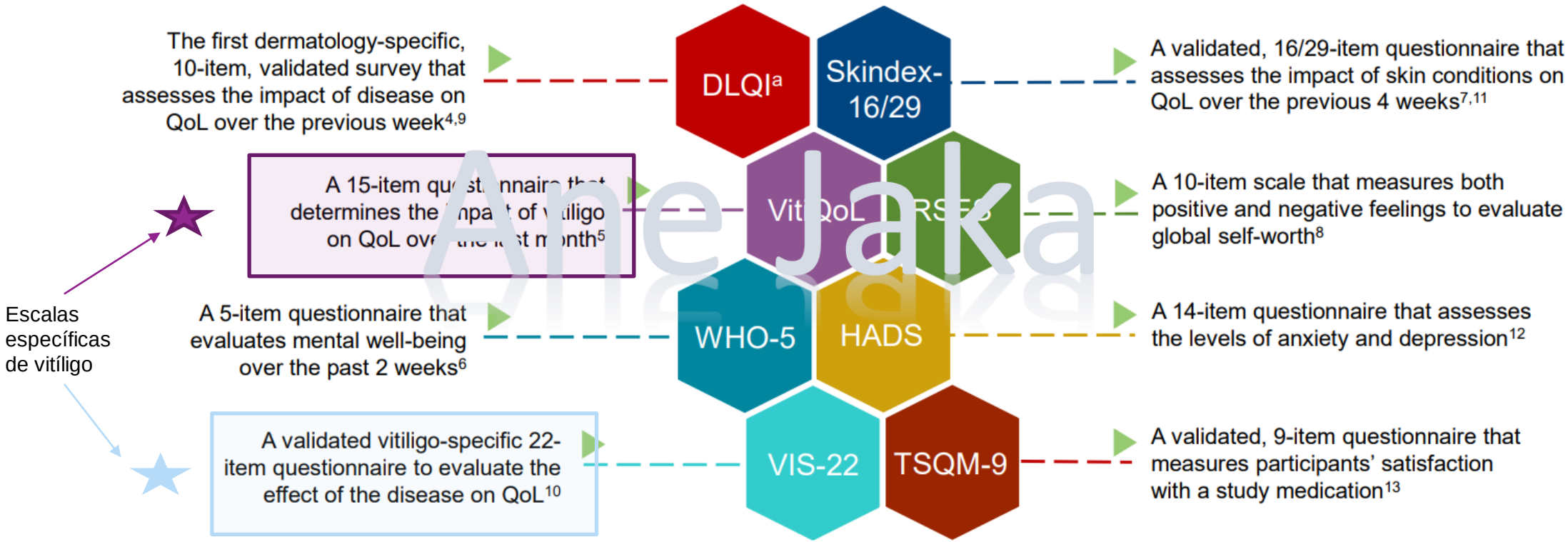
How severe is the vitiligo on your face (or total body) with respect to the area covered by white skin

Score	Answer
0	No white patches (no vitiligo)
1	Mild
2	Moderate
3	Severe
4	Very severe

Ph/Pa-GVA, Physician/Patient Global Vitiligo Assessment.

1. Suppl to: Rosmarin D, et al. *Lancet*. 2020;396:110-120.

Medidas –Calidad de vida

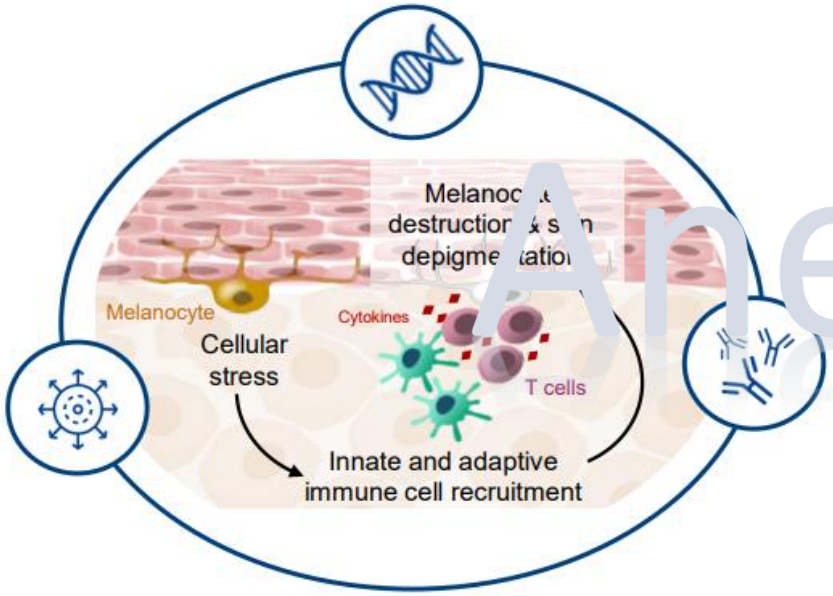


[a] Pediatric version or Children DLQI (CDLQI).[11]

DLQI, Dermatology Life Quality Index; HADS, Hospital Anxiety and Depression Scale; RSES, Rosenberg Self-Esteem Scale; TSQM-9, 9-item Treatment Satisfaction Questionnaire for Medication; VitiQoL, Vitiligo-specific health-related quality of life; WHO-5, 5-item World Health Organization Well-Being Index.

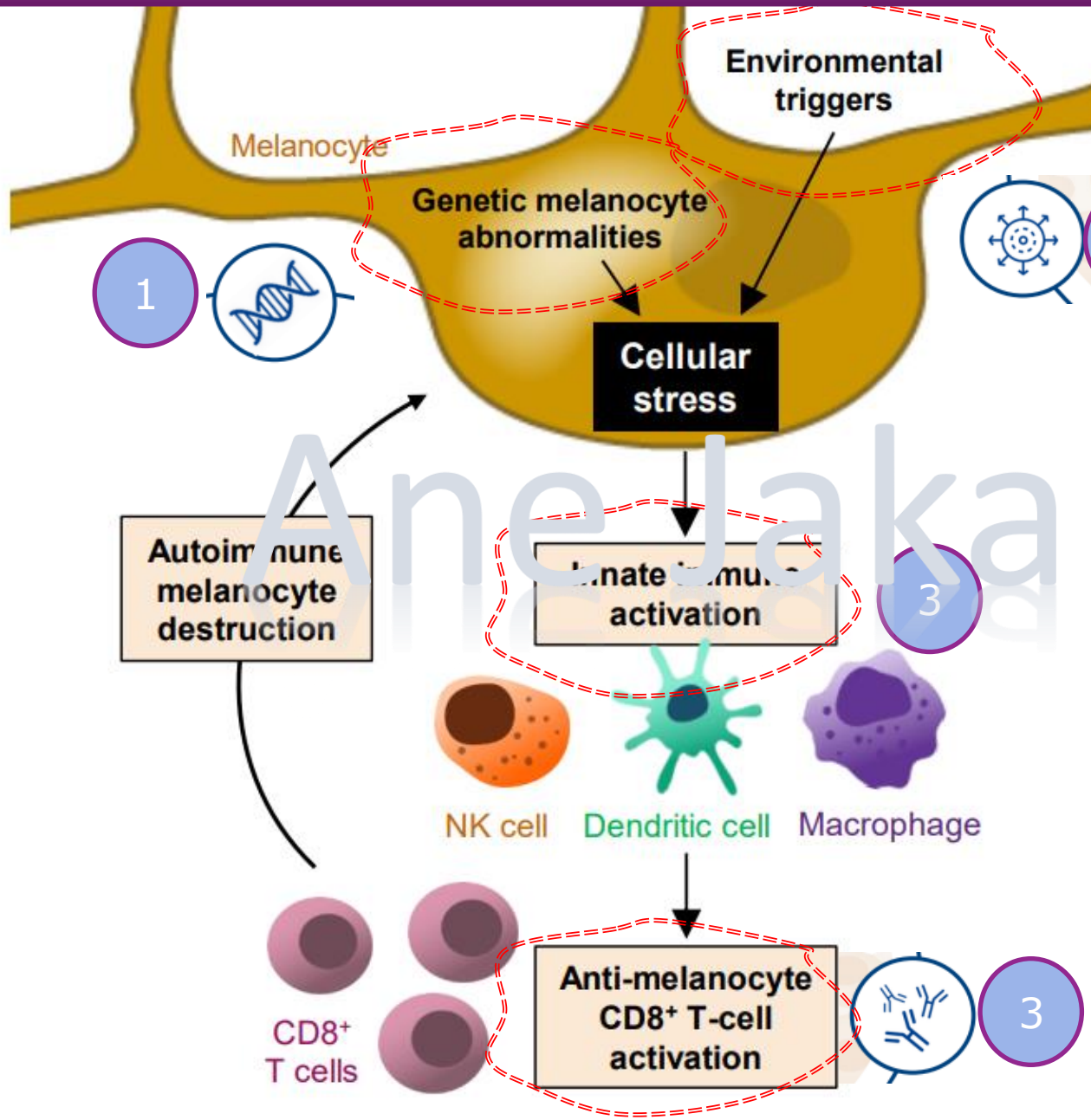
1. Ezzedine K, et al. *Pigment Cell Melanoma Res*. 2012;25:E1-E13. 2. Eleftheriadou V, et al. *Br J Dermatol*. 2012;167:804-814. 3. Whitton ME, et al. *Cochrane Database Syst Rev*. 2015:CD003263. 4. Finlay AY, Khan GK. *Clin Exp Dermatol*. 1994;19:210-216. 5. Lilly E, et al. *J Am Acad Dermatol*. 2013;69:e11-e18. 6. Topp CW, et al. *Psychother Psychosom*. 2015;84:167-176. 7. Chren MM. *Dermatol Clin*. 2012;30:231-236. 8. Rosenberg M. *Society and the Adolescent Self-Image*. Princeton University Press; 1965. 9. Lewis-Jones MS, Finlay AY. *Br J Dermatol*. 1995;132:942-949. 10. Gupta V, et al. *Br J Dermatol*. 2014;171:1084-1090. 11. Chren MM, et al. *J Cutan Med Surg*. 2001;5:105-110. 12. Zigmond AS. *Acta Psychiatr Scand*. 1983;67:361-370. 13. Bharmal M, et al. *Health Qual Life Outcomes*. 2009;7:36.

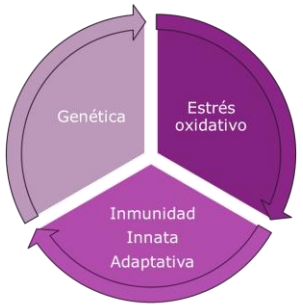
Patogénesis



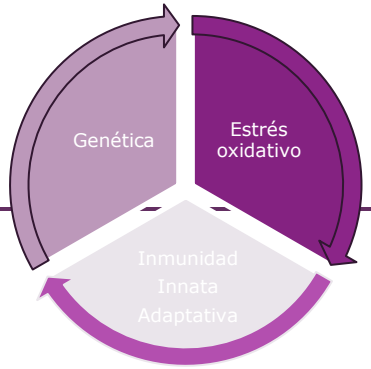
multifactorial

VITÍLIGO





Annu Rev Immunol, Frisoli ML, et al, 2020 (38), Pages 621-648

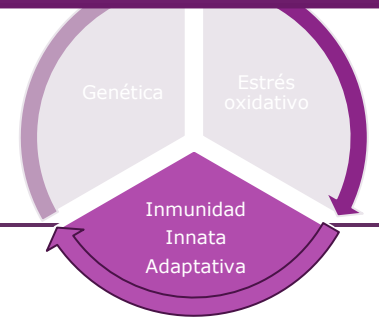


Genética

- Alrededor del 20% de los pacientes con vitíligo tiene al menos 1 familiar de primer grado con vitíligo
- El riesgo relativo de vitíligo para los familiares de primer grado aumenta de 7 a 10
- Riesgo herman@s de desarrollar vitíligo 6%
  - Si gemelos idénticos 23% –**importancia de los factores ambientales** adicionales
- Varios genes relevantes identificados- involucrados en la regulación inmunológica/melanogénesis y apoptosis

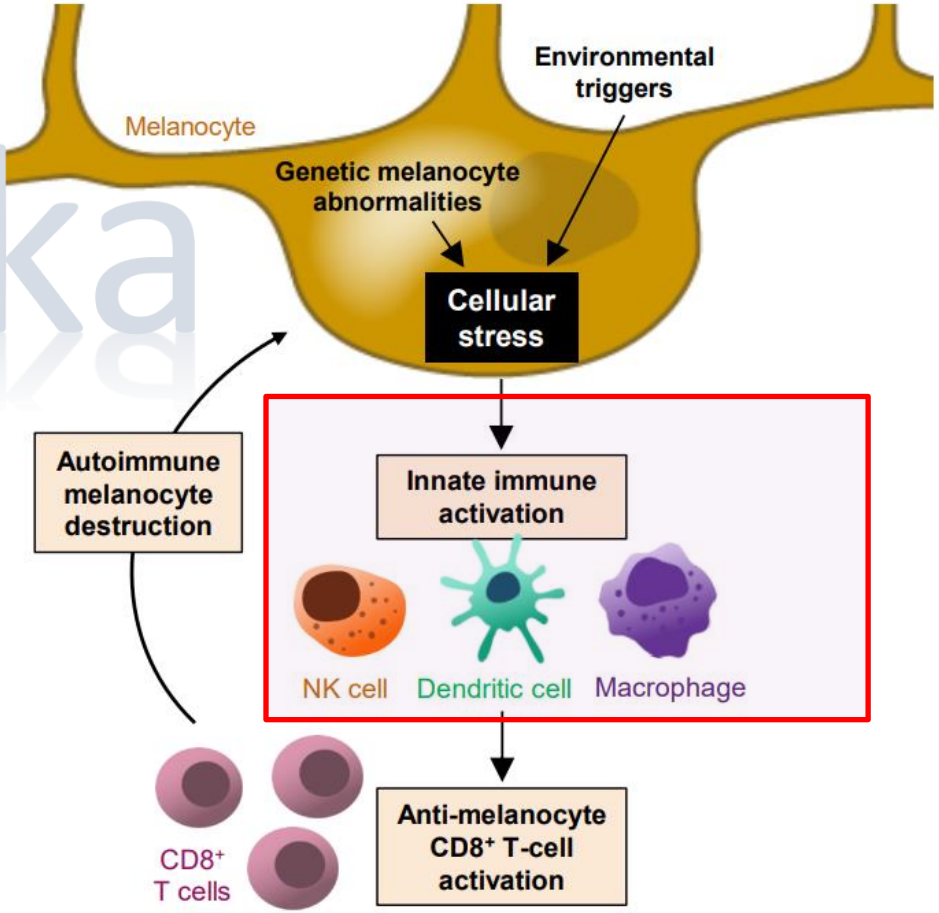
Estrés oxidativo

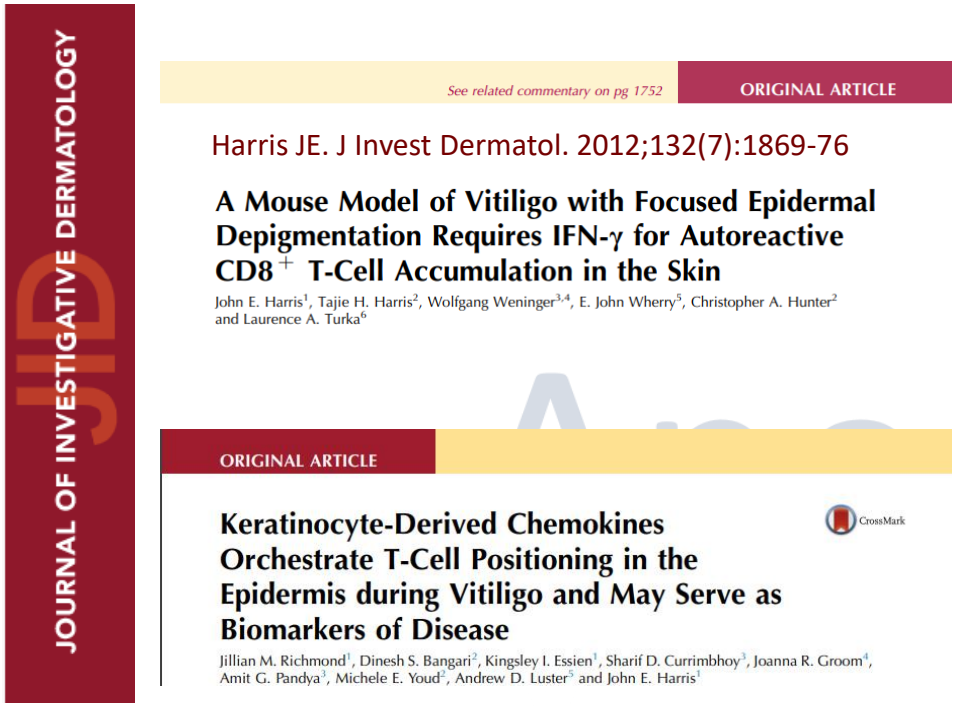
Bergqvist y cols 2019
Rashigi y cols. 2017



Inmunidad innata

- Reconoce señales de estrés oxidativo y las traduce en señales pro-inflamatorias
- Inducen linfocitos T CD8+ melanocito específicos




JOURNAL OF INVESTIGATIVE DERMATOLOGY

See related commentary on pg 1752 ORIGINAL ARTICLE

Harris JE. J Invest Dermatol. 2012;132(7):1869-76

A Mouse Model of Vitiligo with Focused Epidermal Depigmentation Requires IFN-γ for Autoreactive CD8 + T-Cell Accumulation in the Skin

John E. Harris[1], Tajie H. Harris[2], Wolfgang Weninger[3,4], E. John Wherry[5], Christopher A. Hunter[2] and Laurence A. Turka[6]

ORIGINAL ARTICLE

Keratinocyte-Derived Chemokines Orchestrate T-Cell Positioning in the Epidermis during Vitiligo and May Serve as Biomarkers of Disease

Jillian M. Richmond[1], Dinesh S. Bangari[2], Kingsley I. Essien[1], Sharif D. Currimbhoy[3], Joanna R. Groom[4], Amit G. Pandya[3], Michele E. Youd[2], Andrew D. Luster[5] and John E. Harris[1]

IFN gamma y citocinas inducidas por IFN gamma en queratinocitos promueven el reclutamiento de células T CD8+ antimelanocito


BJD British Journal of Dermatology
IMPROVING PATIENT OUTCOMES IN SKIN DISEASE WORLDWIDE

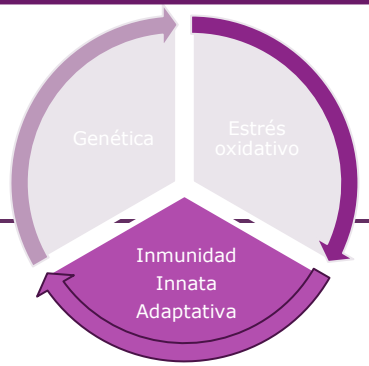
Translational Research

Increased expression of CXCR3 and its ligands in patients with vitiligo and CXCL10 as a potential clinical marker for vitiligo†

X. X. Wang, Q. Q. Wang, J. Q. Wu, M. Jiang, L. Chen, C. F. Zhang, L. H. Xiang

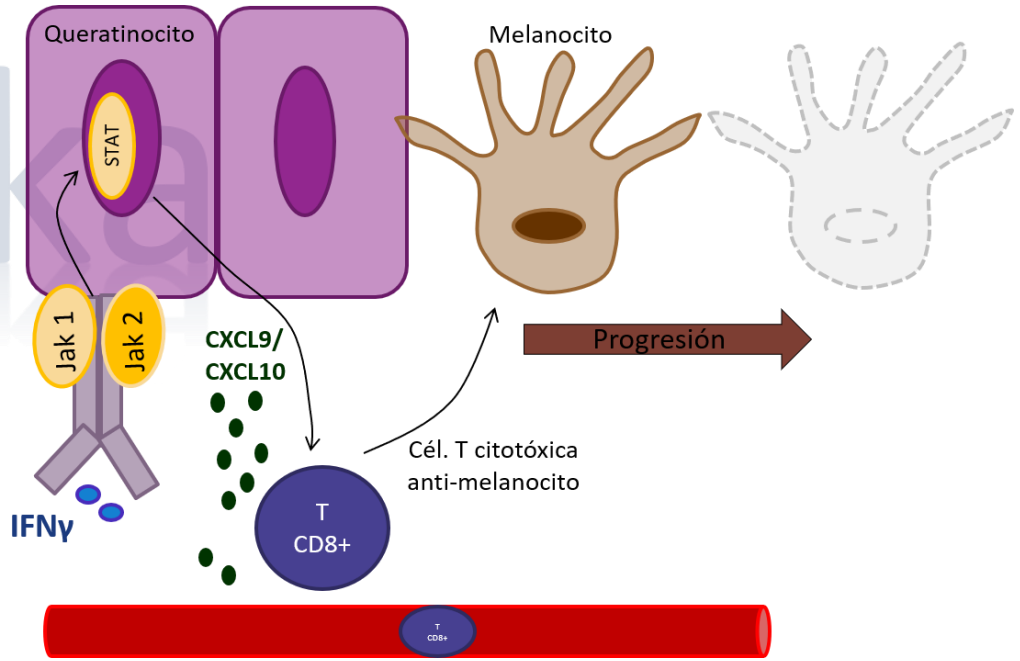
CXCL10 (en suero) puede ser un nuevo biomarcador para controlar la actividad de la enfermedad y guiar el tratamiento del vitiligo.

El eje IFN gamma- JAK STAT1- CXCL10 conlleva la destrucción de melanocitos



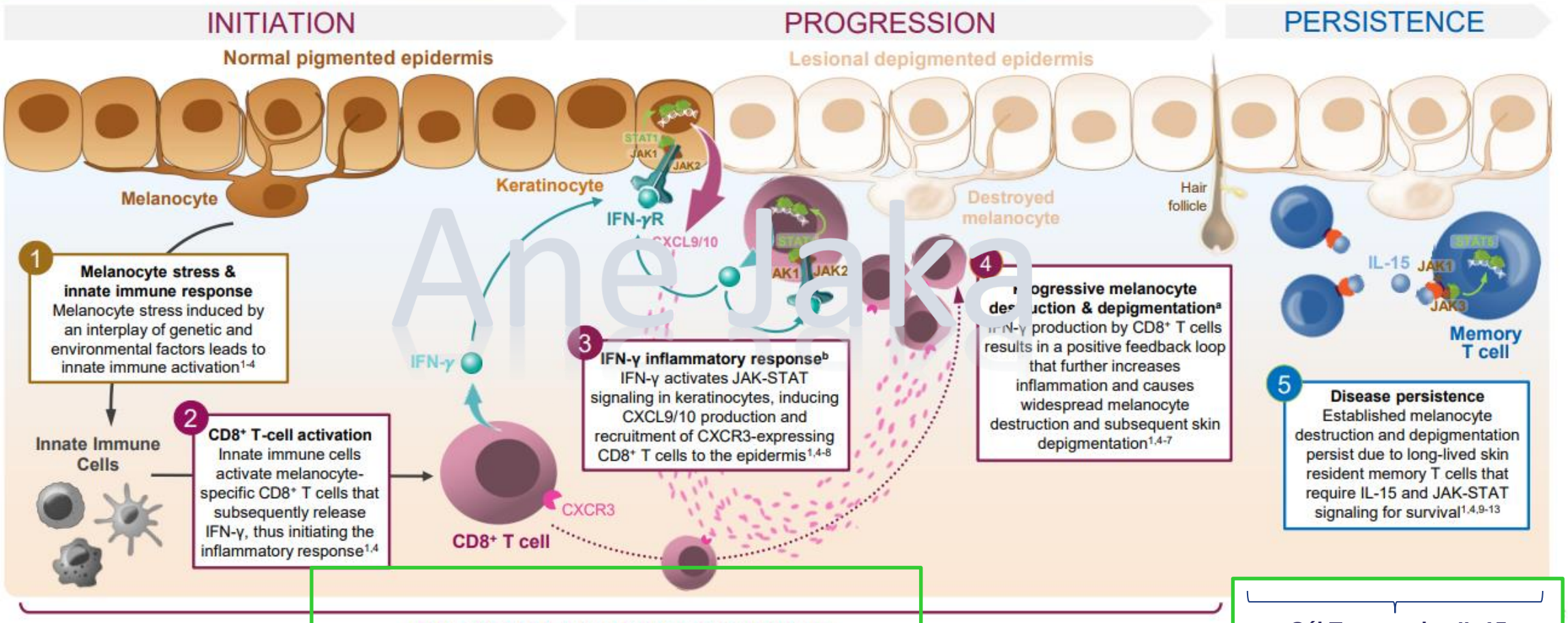
Inmunidad adaptativa

- Linfocitos T CD8+ melanocito específicos
  - Apoptosis
  - Producen IFN gamma
- IFN gamma
  - Mediante JAK-STAT
    - Induce producción quimiocinas CXCL9, CXCL10
- CXCL9/10
  - Promueven reclutamiento linfocitos T CD8+



Adaptado de Strassner et al. Curr Opin Immunol. 2016; 43: 81–88.

Depigmentation in Vitiligo Is The Result of T-Cell–Mediated Autoimmune Destruction of Melanocytes[1-13]



Célula T memoria –IL 15

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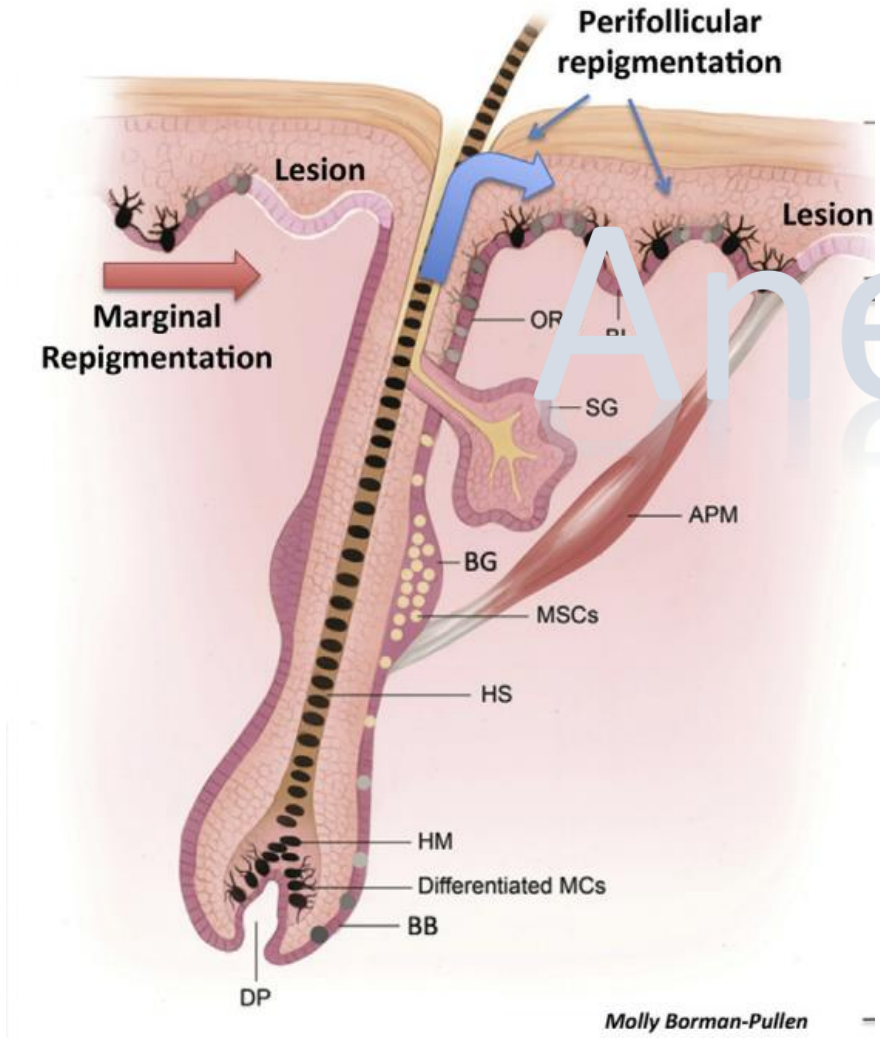
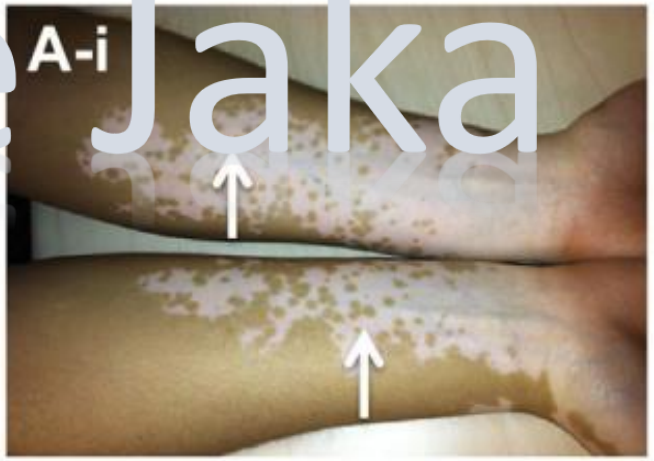
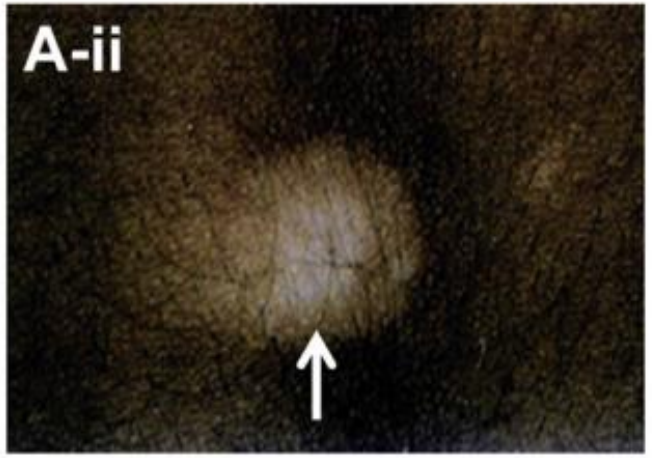
CXCL, C-X-C motif chemokine ligand; CXCR, C-X-C motif chemokine receptor.

1. Bergqvist C, Ezzedine K. *J Dermatol*. 2021;48:252-270. 2. Strassner JP and Harris JE. *Curr Opin Immunol*. 2016;43:81-88. 3. Richmond JM, et al. *Curr Opin Immunol*. 2013;25:676-682. 4. Frisoli ML, et al. *Annu Rev Immunol*. 2020;38:621-648. 5. Howell MD, et al. *Front Immunol*. 2019;10:2342. 6. Rashighi M and Harris JE. *Dermatol Clin*. 2017;35:257-265. 7. Rosmarin D, et al. *Lancet*. 2020;396:110-120. 8. Martins C, et al. *J Invest Dermatol*. 2022;142:1194-1205. 9. Chen X, et al. *Free Radical Biology Med*. 2019;139:80-91. 10. Richmond JM, et al. *Sci Transl Med*. 2018;10:eaam7710. 11. Atwa MA, et al. *J Cosmet Dermatol*. 2021;20:2640-2644. 12. Nolz JC and Richer MJ. *Mol Immunol*. 2020;117:180-188. 13. Riding RL, Harris JE. *J Immunol*. 2019;203:11-19.

Repigmentación



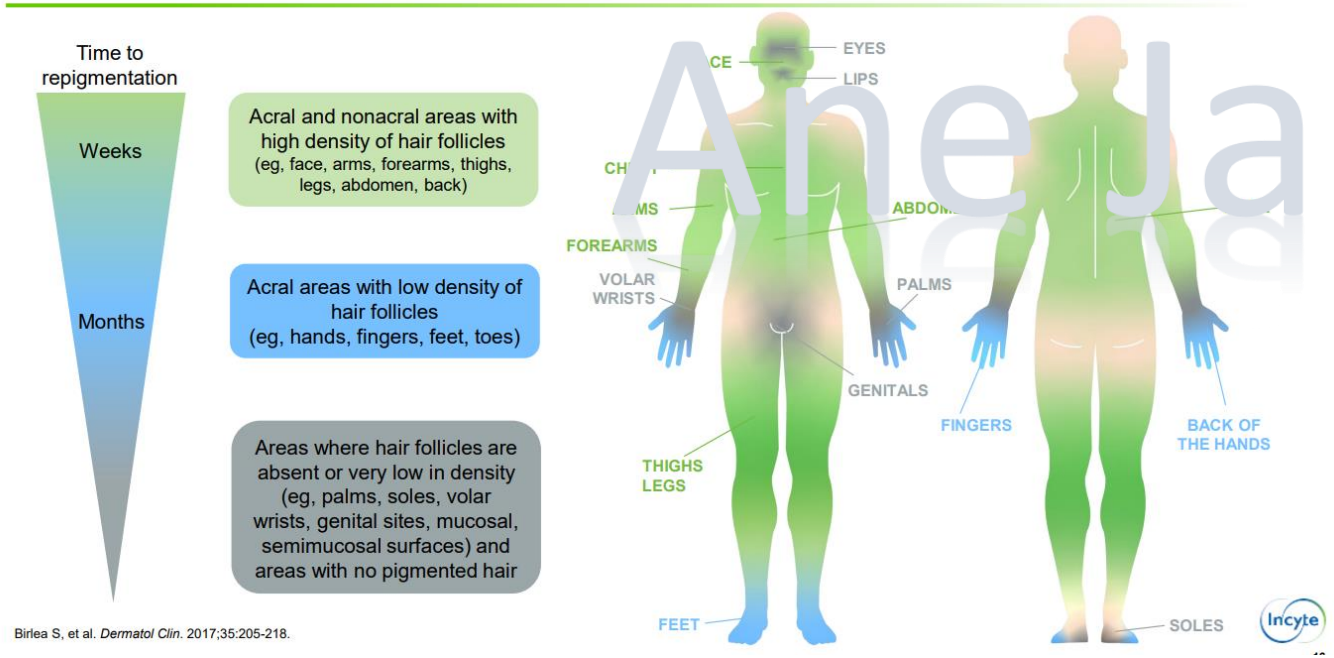




Birlea S et al. Dermatol Clin. 2017;35:205-218

Repigmentación

Repigmentation Is a Slow Process That Can Take Weeks to Months Depending on Lesion Location



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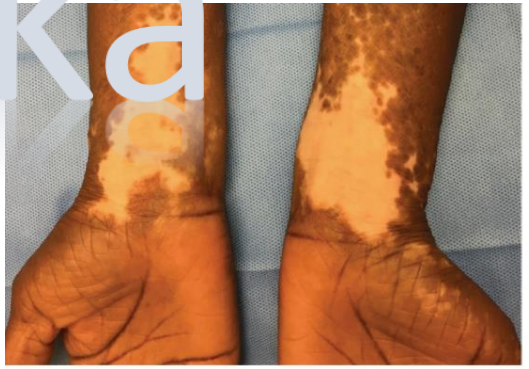
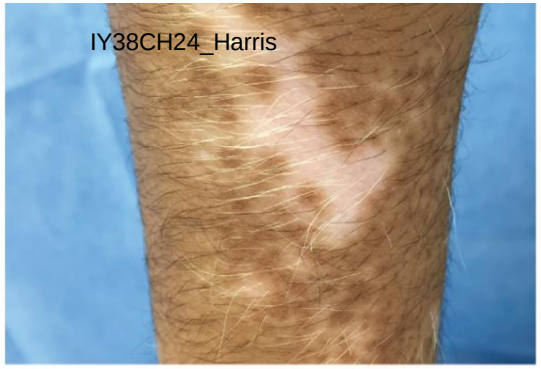




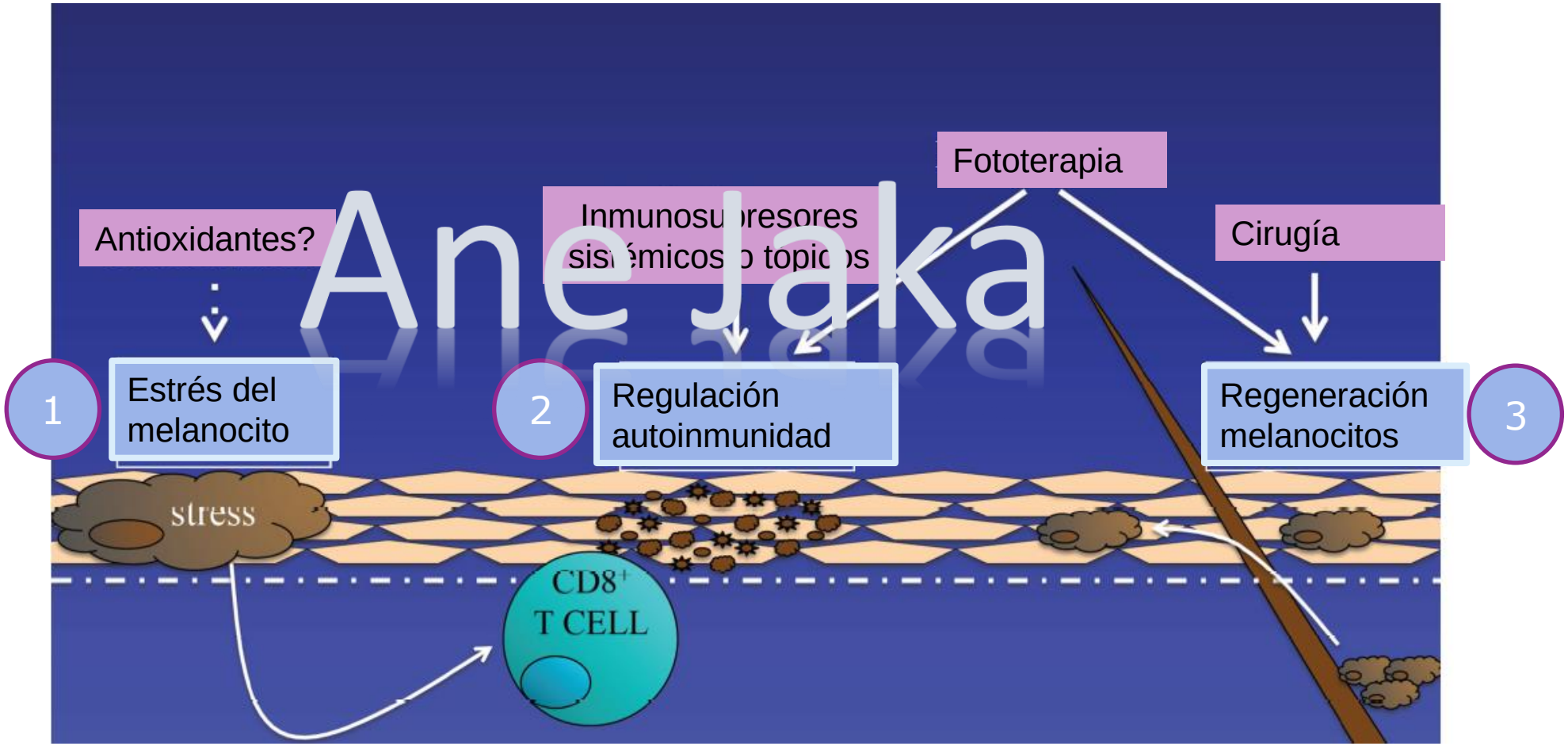
Terapias actuales

GUIDELINES BJD British Journal of Dermatology

Guideline for the diagnosis and management of vitiligo

D.J. Gawkrodger, A.D. Ormerod, L. Shaw, I. Mauri-Sole, M.E. Whitton,*† M.J. Watts, A.V. Anstey, J. Ingham‡ and K. Young‡

British Association of Dermatologists, 4 Fitzroy Square, London W1T 5HQ, U.K.
*Vitiligo Society, 125 Kennington Road, London SE11 6SF, U.K.
†Cochrane Skin Group, Centre of Evidence Based Dermatology, King's Meadow Campus, University of Nottingham NG7 2NR, U.K.
‡Royal College of Physicians, St Andrew's Place, Regent's Park, London NW1 4LE, U.K.



Rashigui. Dermatol Clin. 2017 Apr;35(2):257-265.

Reducción de estrés oxidativo del melanocito

- **Antioxidantes**

(Vit E, Vit C, Ac alfalipoico, gingko biloba, polypodium leucotomos)

Regulación de la autoinmunidad

- **Esteroides**
- **Inhibidores calcineurina**
- **Terapia dirigida a blancos inmunológicos**

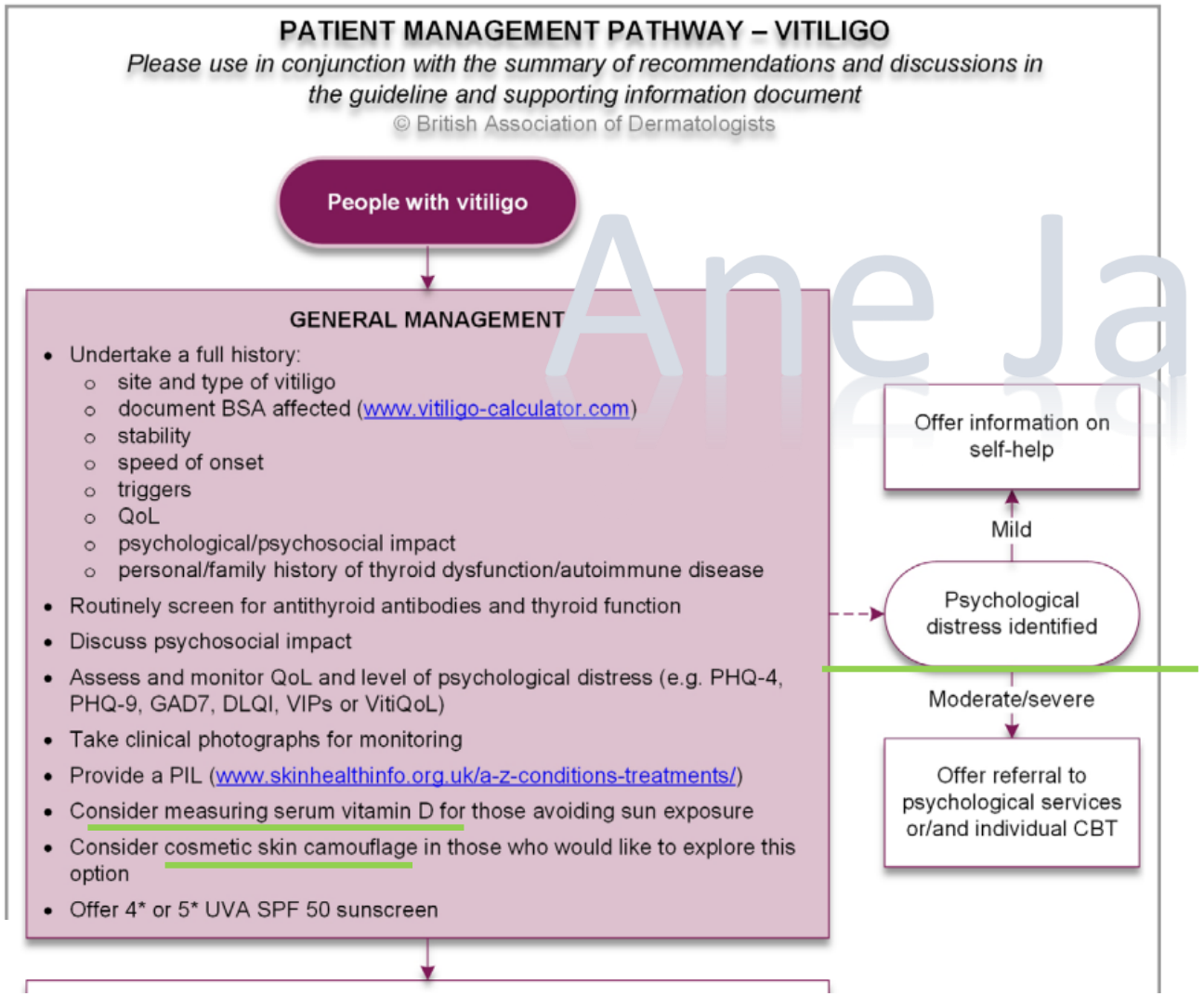
- **Fototerapia**

- **Cirugía** (trasplante melanocitos)
- **Láser excimer**
- **Aflamelanotide** (análogo de αMSH)
- **Activadores WNT**

Estimulación de la regeneración del melanocito

Adaptado de Rasighi y cols.

Terapias actuales



GUIDELINES
BJD British Journal of Dermatology

British Association of Dermatologists guidelines for the management of people with vitiligo 2021*

V. Eleftheriadou[1] R. Atkar,[2] J. Batchelor,[3] B. McDonald[4] L. Novakovic,[5,6] J.V. Patel,[7] J. Ravenscroft[8] E. Rush,[7,9] D. Shah,[10] R. Shah,[11,12] L. Shaw,[13] A.R. Thompson[12,14] M. Hashme,[15] L.S. Exton[15] M.F. Mohd Mustapa[15] L. Manounah[15] and the British Association of Dermatologists' Clinical Standards Unit

FIRST LINE

- Offer potent or very potent topical corticosteroid once daily (to minimize potential side-effects); avoid periocular area
- Consider topical tacrolimus 0.1% BD for ***facial*** vitiligo, especially the periocular region
- Consider topical tacrolimus 0.1% BD ***under occlusion*** on photoexposed areas only for ***nonfacial*** vitiligo
- Consider intermittent regimen, e.g. alternating weeks of once-daily application of potent or very potent topical corticosteroids +/- topical tacrolimus for areas with thinner skin

SECOND LINE

- Offer NB-UVB (whole-body or localized) +/- topical corticosteroid or calcineurin inhibitors
- For ***rapidly progressive*** disease, consider oral betamethasone 0.1 mg/kg twice weekly on two consecutive days for 3 months; then taper the dose by 1 mg/month for a further 3 months in combination with NB-UVB

THIRD LINE

(These treatments are not widely available on the NHS but in a limited number of centres with a specialist interest)

- Consider excimer laser/light + topical calcineurin inhibitors for ***localized*** vitiligo
- Consider cellular grafting for ***stable***, ***segmental*** or ***nonsegmental*** vitiligo
- Consider CO_2 laser + 5-FU in ***adults*** with ***nonsegmental*** vitiligo on hands and feet
- Consider depigmentation therapies for ***extensive*** vitiligo on visible sites

Quality of life in pediatric patients before and after cosmetic camouflage of visible skin conditions

Michele L. Ramien, MD,[a,b] Sandra Ondrejchak, RN,[a] Roxanne Gendron, BSc,[a] Afshin Hatami, MD,[a] Catherine C. McCuaig, MD,[a] Julie Powell, MD,[a] and Danielle Marcoux, MD[a]
Montreal, Quebec, and Ottawa, Ontario, Canada

Conclusions: Children and teenagers with visible vascular and pigmentary anomalies experience an impairment of QoL that is abrogated by introduction to use of cosmetic camouflage. (J Am Acad Dermatol 2014;71:935-40.)

Dermatol Clin. 2017 April ; 35(2): 257–265. doi:10.1016/j.det.2016.11.014.

Vitiligo pathogenesis and emerging treatments

Mehdi Rashighi, MD and **John E. Harris, MD, PhD**
University of Massachusetts Medical School Worcester, Massachusetts, USA

Reducción de estrés oxidativo del melanocito

- **Antioxidantes**

(Vit E, Vit C, Ac alfalipoico, gingko biloba, polypodium leucotomos)

Regulación de la autoinmunidad

- Esteroides
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- **Terapia dirigida a blancos inmunológicos**

- Fototerapia

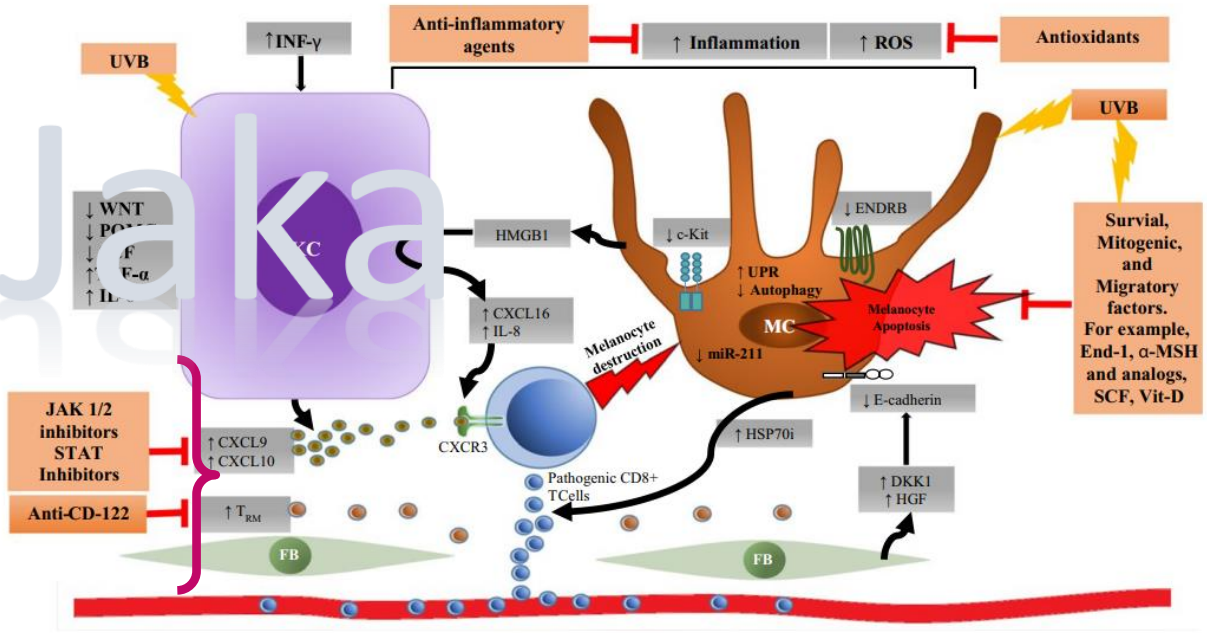
- **Cirugía** (trasplante melanocitos)
- **Láser excimer**
- **Aflamelanotide** (análogo de αMSH)
- **Activadores WNT**

Estimulación de la regeneración del melanocito

Adaptado de Rasighi y cols.

- **Terapias dirigidas a blancos inmunológicos**

  - **IFN gamma –CXCL10- JAK-STAT**
  - **IL-15/CD122**



Pigment Cell Melanoma Res. 2020;33(6):778-787. doi: 10.1111/pcmr.12878.

IFN gamma/CXCL 10/ JAK-STAT

Letter to the Editor

Interfering with the IFN-γ/CXCL10 pathway to develop new targeted treatments for vitiligo

Mehdi Rashighi, John E. Harris

RESEARCH ARTICLE

VITILIGO

CXCL10 Is Critical for the Progression and Maintenance of Depigmentation in a Mouse Model of Vitiligo

Mehdi Rashighi,[1] Priti Agarwal,[1] Jillian M. Richmond,[1] Tajie H. Harris,[2]* Karen Dresser,[3] Ming-Wan Su,[4] Youwen Zhou,[4] April Deng,[3] Christopher A. Hunter,[2] Andrew D. Luster,[5] John E. Harris[1†]

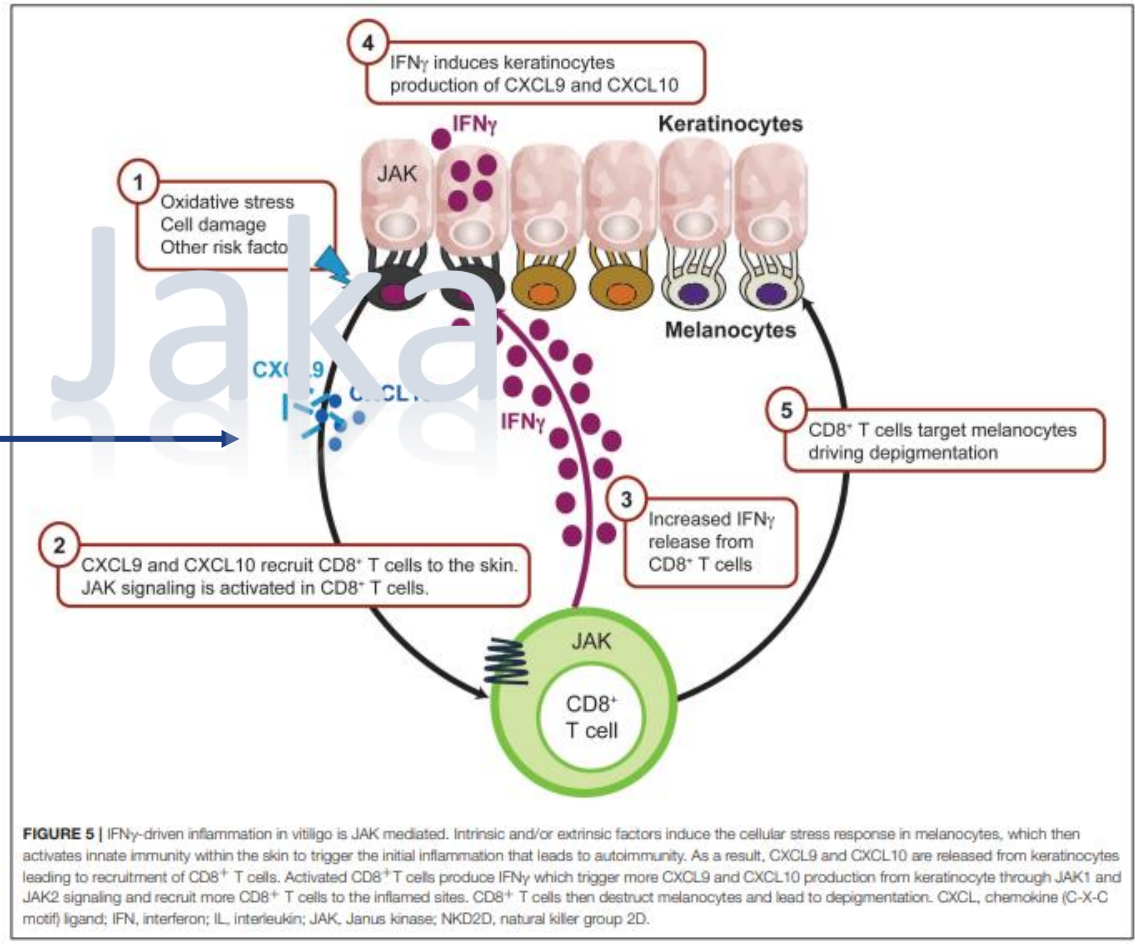
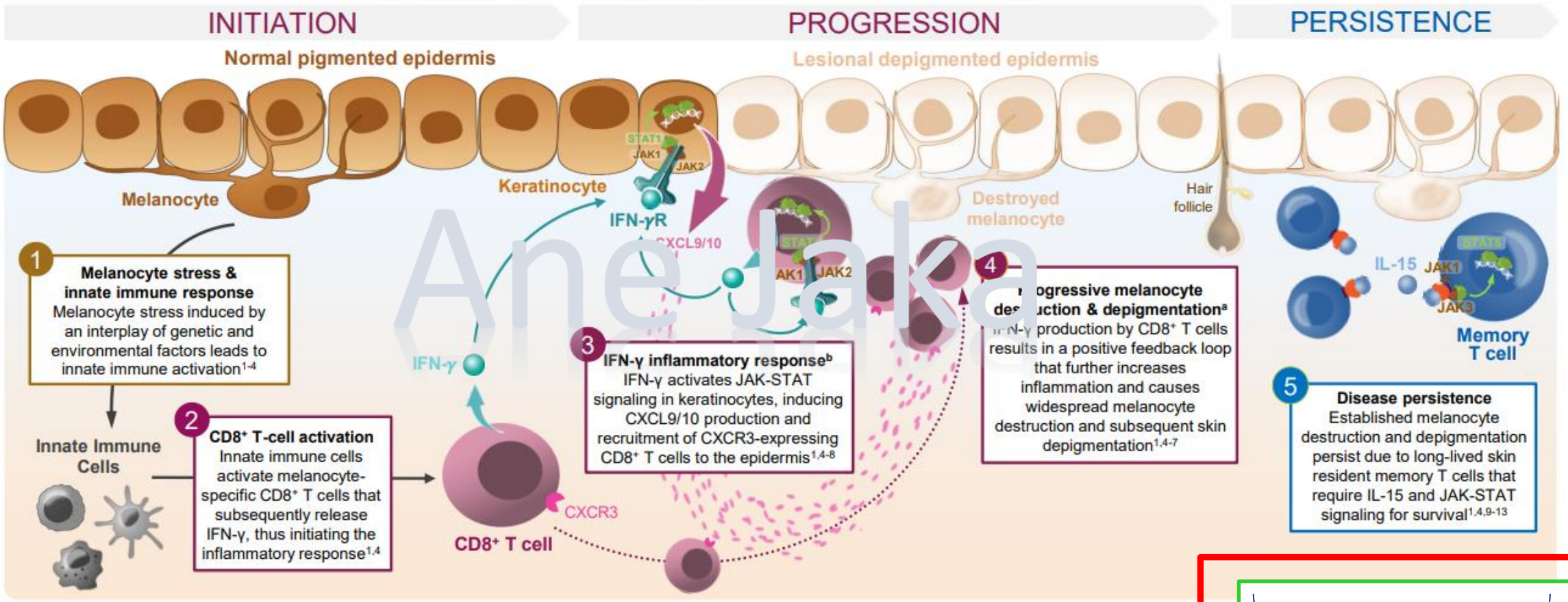


FIGURE 5 | IFNγ-driven inflammation in vitiligo is JAK mediated. Intrinsic and/or extrinsic factors induce the cellular stress response in melanocytes, which then activates innate immunity within the skin to trigger the initial inflammation that leads to autoimmunity. As a result, CXCL9 and CXCL10 are released from keratinocytes leading to recruitment of $CD8^+$ T cells. Activated $CD8^+$ T cells produce IFNγ which trigger more CXCL9 and CXCL10 production from keratinocyte through JAK1 and JAK2 signaling and recruit more $CD8^+$ T cells to the inflamed sites. $CD8^+$ T cells then destruct melanocytes and lead to depigmentation. CXCL, chemokine (C-X-C motif) ligand; IFN, interferon; IL, interleukin; JAK, Janus kinase; NKD2D, natural killer group 2D.

Howell. Front Immunol. 2019;10:2342.

Depigmentation in Vitiligo Is The Result of T-Cell–Mediated Autoimmune Destruction of Melanocytes[1-13]



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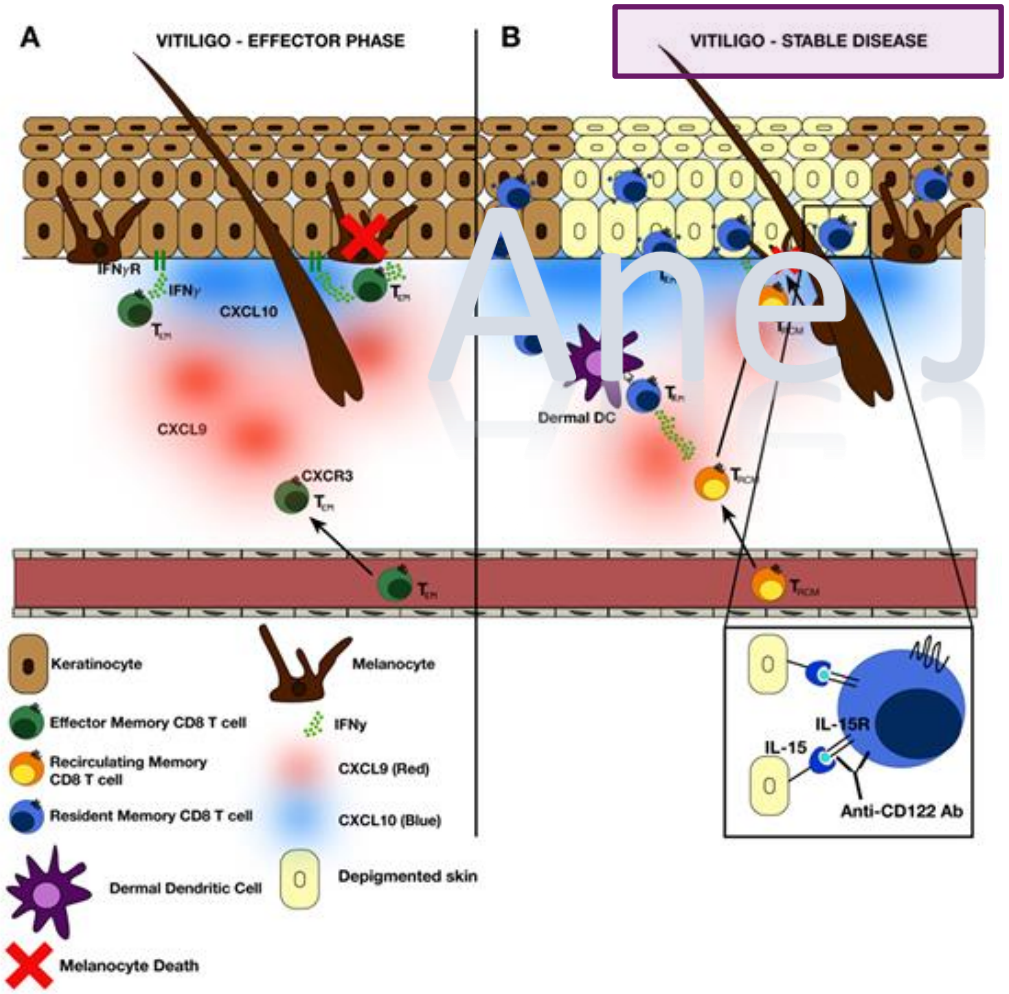
IL-15

La IL-15 estimula la proliferación de células T humanas de memoria
Células T CD8+ de memoria efectoras anti- melanocito



Published in final edited form as:
J Immunol. 2019 July 01; 203(1): 11–19. doi:10.4049/jimmunol.1900027.

The role of Memory CD8+ T cells in Human Vitiligo

Rebe a L. Riding*, John E. Harris*,†
Depa ner of D logy, University of Massachusetts Medical School

iginal icle

Oxidative s induced IL-15 *trans*-presentation in keratinocytes contributes to CD8+ T cells activation via JAK-STAT pathway in vitiligo

Xuguang Chen [1], Weinan Guo [1], Yuqian Chang [1], Jiaxi Chen, Pan Kang, Xiuli Yi, Tingting Cui, Sen Guo, Qian Xiao, Zhe Jian, Kai Li, Tianwen Gao, Shuli Li, Ling Liu, Chunying Li

J Cosmet Dermatol. 2021 Aug;20(8):2640-2644. doi: 10.1111/jocd.13908. Epub 2020 Dec 23.

Elevated serum level of interleukin-15 in vitiligo patients and its correlation with disease severity but not activity

Mona A Atwa [1], Sara Mohammed Mohammed Ali [2], Nahed Youssef [3], Radwa El-Sayed Mahmoud Marie [1]

Affiliations + expand

PMID: 33355977 DOI: 10.1111/jocd.13908

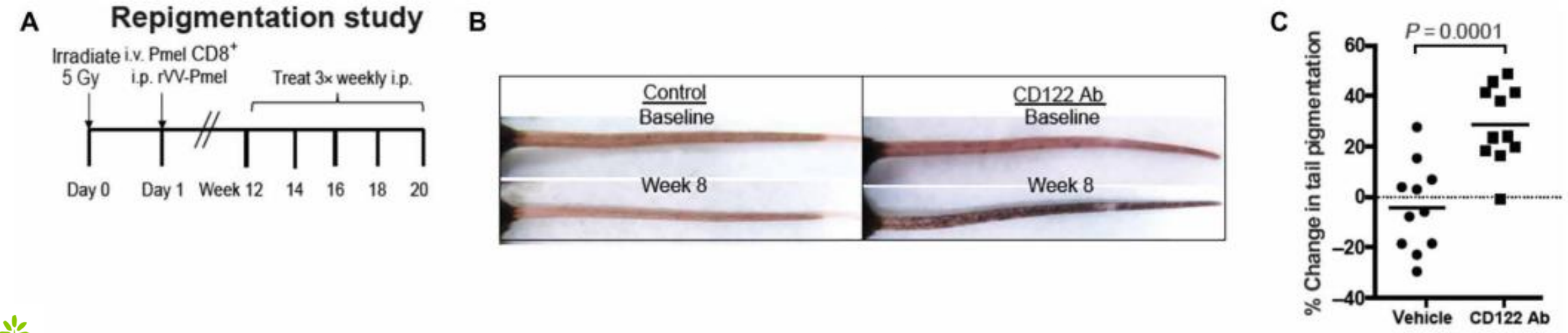
Published in final edited form as:
Sci Transl Med. 2018 July 18; 10(450): . doi:10.1126/scitranslmed.aam7710.

Antibody blockade of IL-15 signaling has the potential to durably reverse vitiligo

Jillian M. Richmond[1], **James P. Strassner**[1], **Lucio Zapata Jr.**[1], **Madhuri Garg**[1], **Rebecca L. Riding**[1], **Maggi A. Refat**[1], **Xueli Fan**[1], **Vincent Azzolino**[1], **Andrea Tovar-Garza**[2], **Naoya Tsurushita**[3], **Amit G. Pandya**[2], **J. Yun Tso**[3], and **John E. Harris**[1,*]

[1]Department of Dermatology, University of Massachusetts Medical School, Worcester, MA 01605, USA.

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE



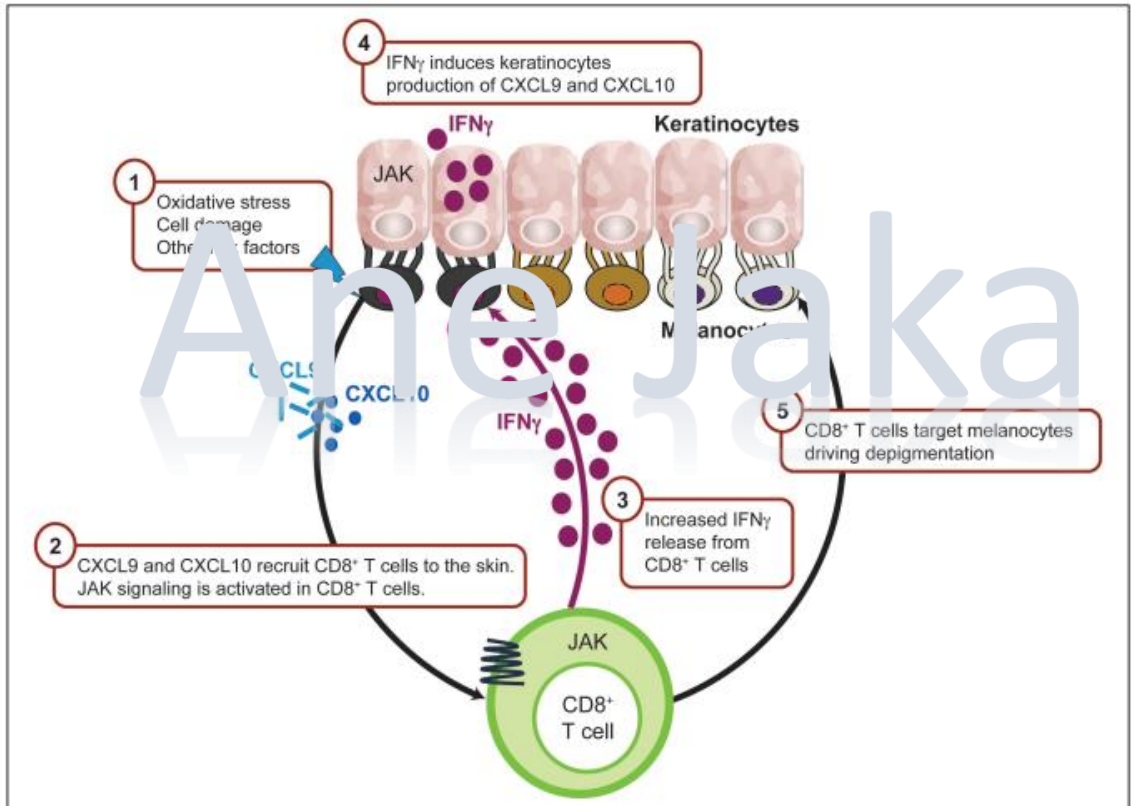
IL-15

NIH U.S. National Library of Medicine
ClinicalTrials.gov

Row	Saved	Status	Title	Conditions	Interventions	Locations
1	☐	Completed	Effect of NB-UVB on the Tissu Level IL 15 nd IL- Ra Activ on Segmental **Vitiligo** Cases.	• Ac e Non Se men **Vitili**	• R diation: Narrov band ul. violet	• Nourhan Emad Cairo, Helwan, Egypt
2	☐	Not yet recruiting	Evaluation of Serum **Interleukin-15** and Interleukin-22 Levels in Patients With Non-segmental **Vitiligo**	• **Vitiligo**	• Diagnostic Test: **Interleukin-15** and Interleukin-22	
3	☐	Recruiting	Evaluation of AMG 714 for **Vitiligo**	• **Vitiligo**	• Biological: AMG 714 • Biological: Placebo • Procedure: nbUVB phototherapy	• University of California, Irvine: Department of Dermatology Irvine, California, United States • University of California Davis Health System: Department of Dermatology Sacramento, California, United States • Yale University School of Medicine: Department of Dermatology New Haven, Connecticut, United States • (and 5 more...)

Determine the efficacy of IL-15 inhibition with AMG 714 at inducing total body skin repigmentation in vitiligo
A **Phase 2a** Randomized Double Blind Placebo Controlled Trial (ITN086AI)

IFN gamma/CXCL 10/ JAK-STAT



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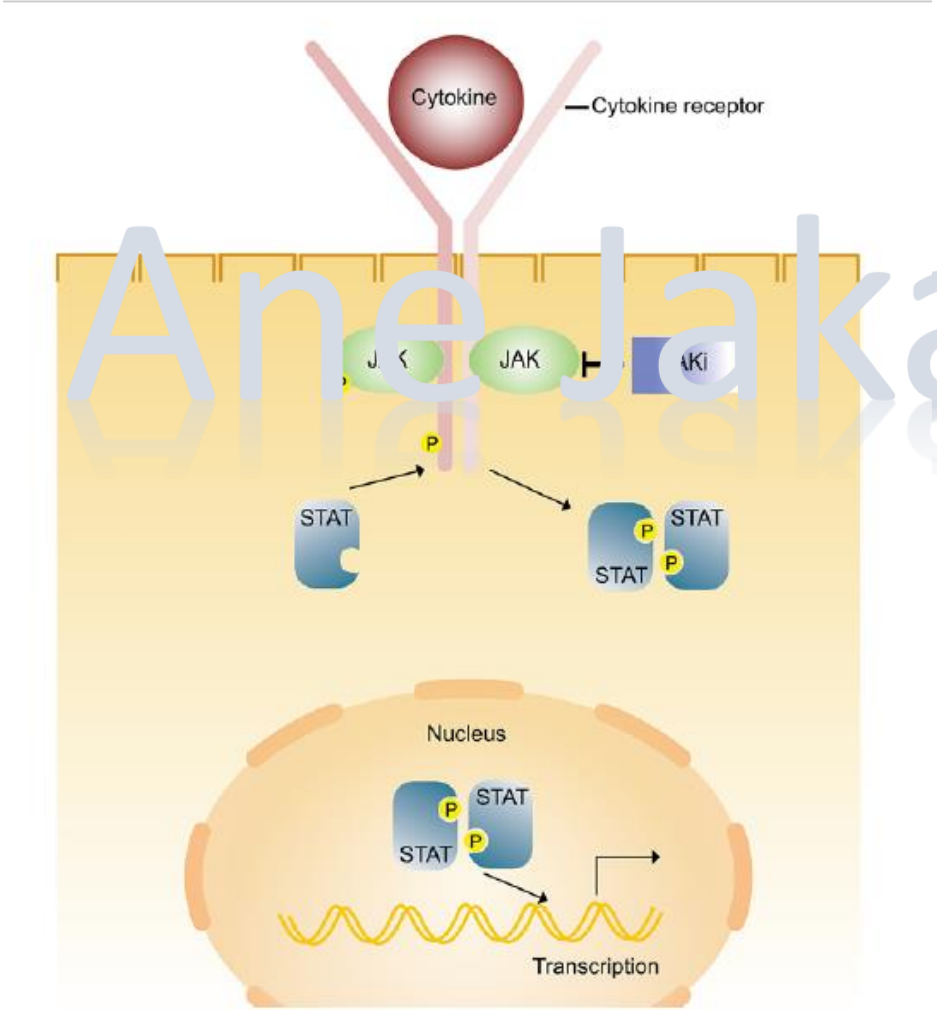
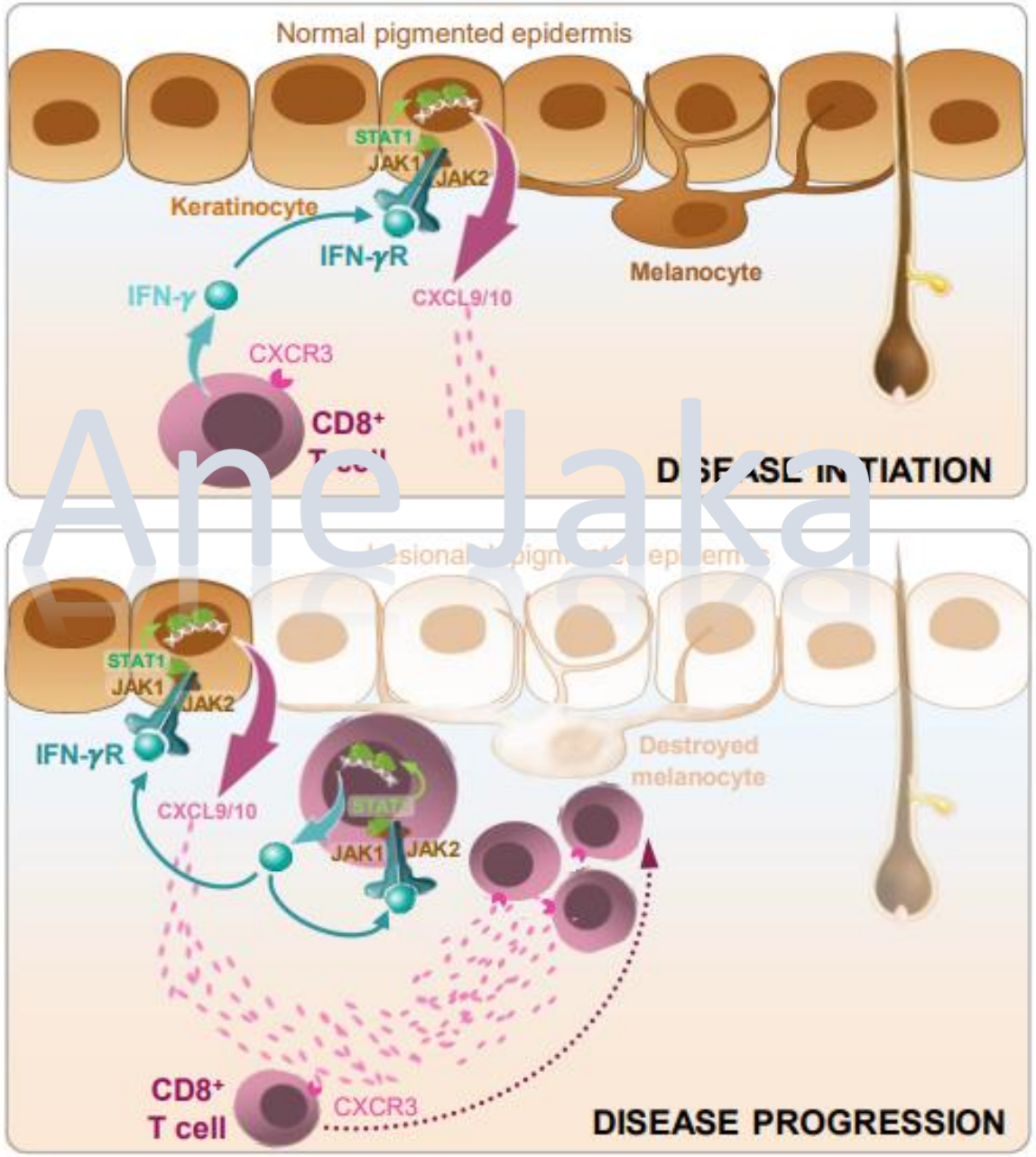
Howell. Front Immunol. 2019;10:2342.

Inhibidores Janus quinasa (JAK)

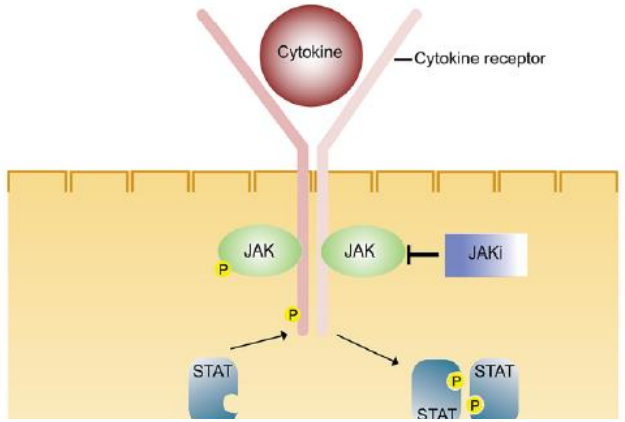


Welsch et al.Eur. J. Immunol. 2017. 47: 1096–1107


Normal pigmented epidermis
STAT1
JAK1
JAK2
Keratinocyte
IFN-γR
IFN-γ
CXCL9/10
Melanocyte
CXCR3
CD8+
DISEASE PROGRESSION
STAT1
JAK1
JAK2
IFN-γR
CXCL9/10
Destroyed melanocyte
CD8+
T cell
CXCR3
DISEASE PROGRESSION

Inhibidores JAK

- Vía señalización JAK/STAT: regula la **expresión de > 50 citocinas y factores de crecimiento**
  - Clave en Inmunidad y hematopoyesis
  - Aprobado: Neoplasias mieloproliferativas (mielofibrosis/PV), EICH, artritis reumatoide, artritis psoriásica, colitis ulcerosa.
- En estudio diferentes aplicaciones en dermatología (**dermatitis atópica, alopecia areata, psoriasis y vitíligo**)
  - Muchas citocinas dermatológicamente relevantes se basan en la vía JAK-STAT (IFN-α / β, IFN-γ,(IL-2, IL-4, IL-7, IL-9, IL-15 e IL-21) e IL-5, IL-6, IL-12, IL-13 e IL-23)
- **Otros**: dermatomiositis, dermatitis actínica crónica, eritema multiforme, síndrome hipereosinofílico, enfermedad de injerto contra huésped cutáneo, LPP y lupus, entre otros.

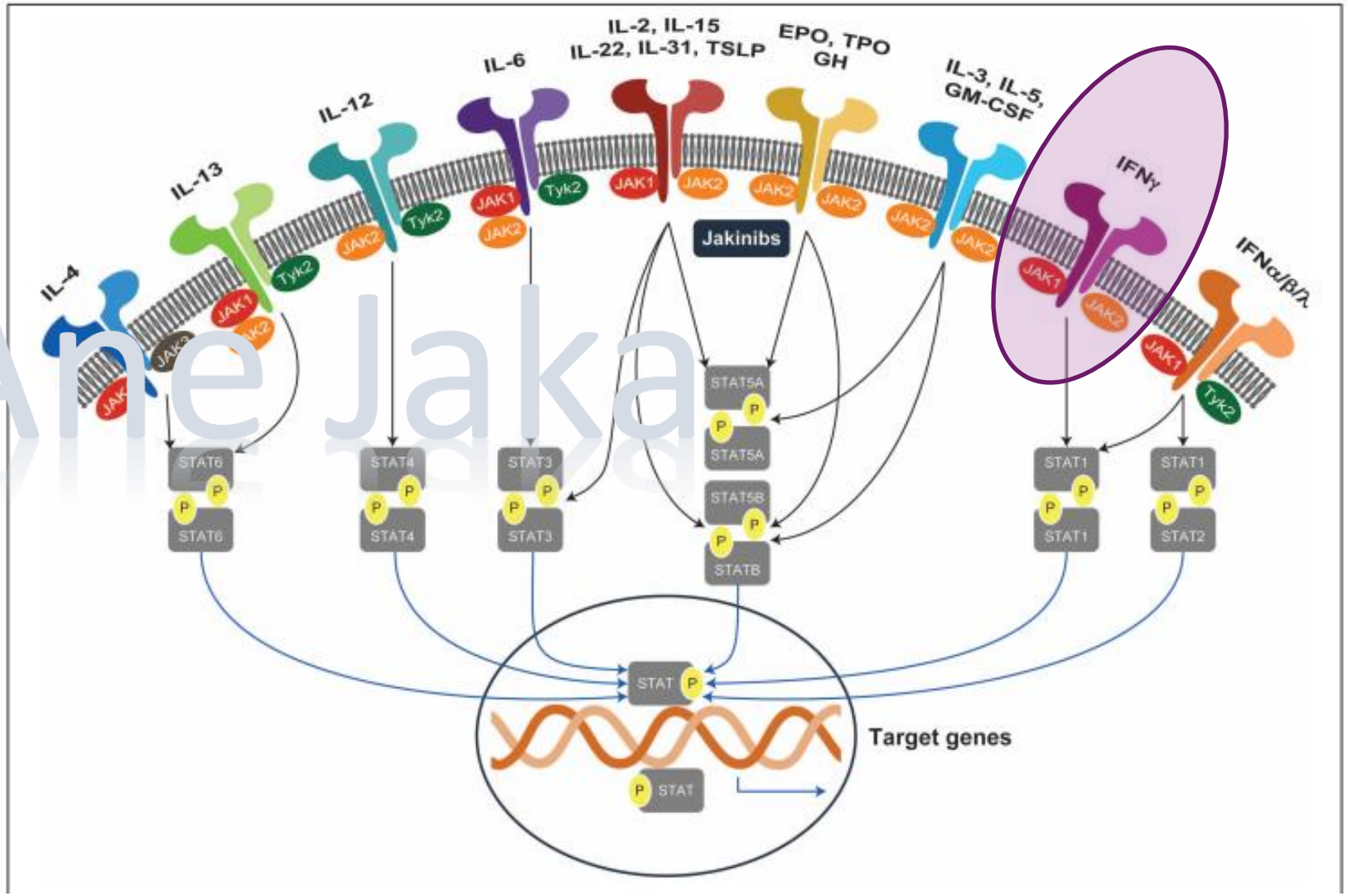


Cytokine /cytokine receptor families	Example	Associated JAKs
Type I interferons	IFN-α	JAK1, TYK2
Type II interferons	IFN-γ	JAK1, JAK2
IL-12 receptor β1 cytokines	IL-23	JAK2, TYK2
gp130 receptor cytokine family	IL-6	JAK1, JAK2, TYK2
IL-10 family cytokines	IL-22	JAK1, JAK2, TYK2
Common γ chain cytokines	IL-4	JAK1, JAK3
βc receptor cytokine family	GM-CSF	JAK2
Homodimeric receptor cytokine family	EPO	JAK2

Welsch et al.Eur. J. Immunol. 2017. 47: 1096–1107

Inhibidores JAK

Hay cuatro enzimas Janus Quinasa (JAK) conocidas:
JAK1, JAK2, JAK3 y TYK2
-cada miembro es utilizado por receptores diferentes-



Howell. Front Immunol. 2019;10:2342.

Inhibidores JAK

Research

Craiglow et al. JAMA Dermatology October 2015 ; 151 (10)

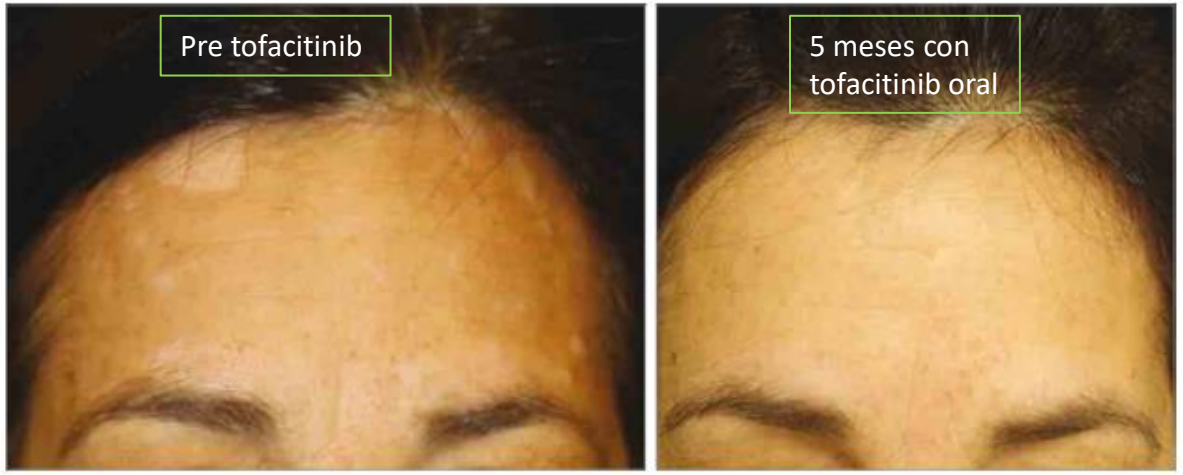
Case Report/Case Series

Tofacitinib Citrate for the Treatment of Vitiligo
A Pathogenesis-Directed Therapy

Brittany G. Craiglow, MD; Brett A. King, MD, PhD

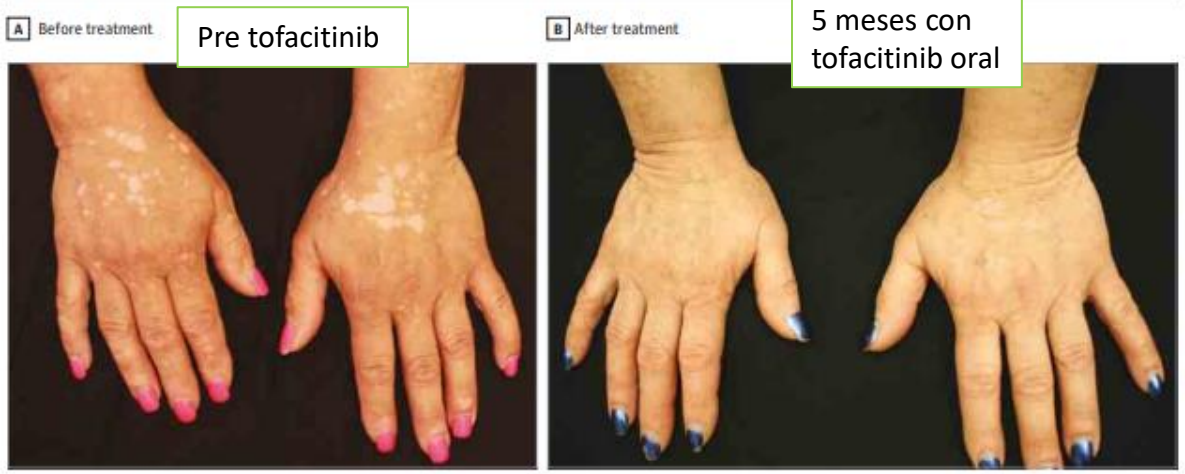
CASO CLÍNICO

- Mujer 50 años, sin AP
- Vitíligo progresivo, 1 año evolución → **BSA 10%**
- Tratamientos previos: corticoides tópicos, tacrolimus 0,1%pda y UVBBE
- **Tofacitinib oral:** 5mg/48h durante 3 semanas →5mg/24h hasta completar 5 meses
- Resultados: **REPIGMENTA un 5% del BSA→ el 50% de las áreas afectas**.



A, At baseline, numerous white macules and patches are evident. B, After 5 months of treatment, repigmentation is nearly complete.

Figure 2. Hands of the Patient Before and After Treatment With Tofacitinib Citrate



A, At baseline, numerous white macules and patches are evident. B, After 5 months of treatment, repigmentation is nearly complete.

Inhibidores JAK

ELSEVIER

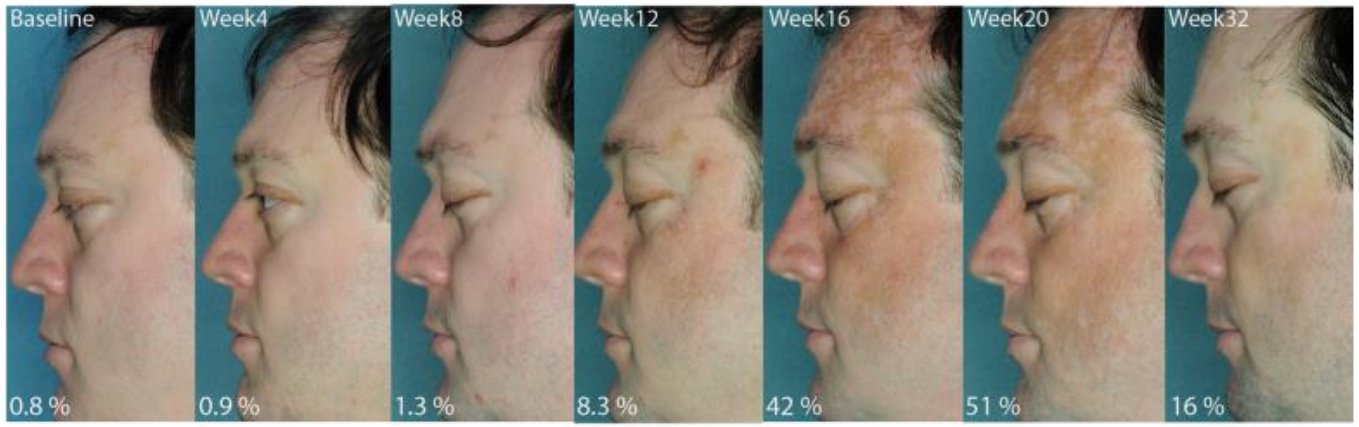
Journal of the American Academy of Dermatology

Volume 74, Issue 2, February 2016, Pages 370-371

Letter

Rapid skin repigmentation on oral ruxolitinib in a patient with coexistent vitiligo and alopecia areata (AA)

John E. Harris MD, PhD [a], Mehdi Rashighi MD [a], Nhan Nguyen MD [b], Ali Jabbari MD, PhD [b], Grace Ulerio BA [b], Raphael Clynes MD, PhD [b], Angela M. Christiano PhD [b, c], Julian Mackay-Wiggan MD, MS [b]



CASO CLÍNICO

- Hombre 35 años con AA y vitíligo.
- Estudio Fase 2 para evaluar la eficacia de ruxolitinib (Jakafi,Incyte,Wilmington, DE) en AA moderada-severa
- **Ruxolitinib oral:** 20 mg/12h durante 20 sem
- **Resultados: Semana 20 repigmentación facial del 51%**
- 12 semanas tras suspensión: repigmentación regresó.

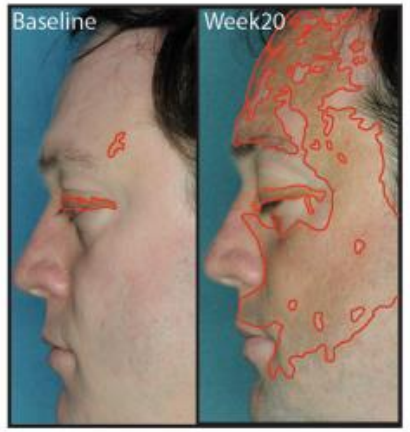


Fig 1. Vitiligo repigmentation during treatment with ruxolitinib. Screening skin examination reveals near-complete depigmentation of the patient's face at baseline. The first evidence of skin repigmentation appeared after 12 weeks of therapy, which continued until week 20, when ruxolitinib was discontinued. Follow-up visit 12 weeks after stopping the treatment shows recurrent depigmentation in the majority of previously repigmented areas. Pigmented areas of the face were outlined using the freehand selection tool followed by calculation of the percent selected area using ImageJ software (National Institutes of Health, Bethesda, MD).

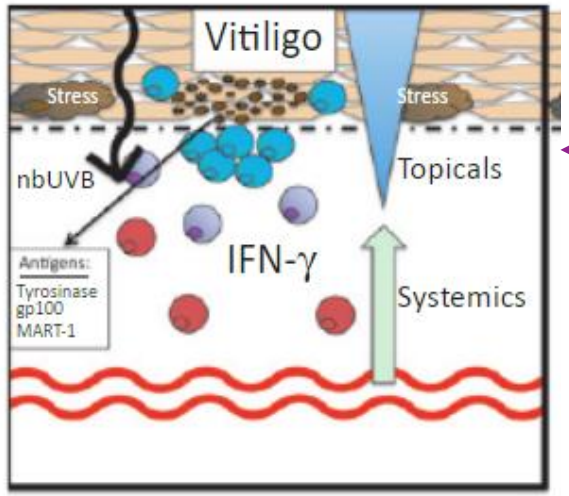
ORIGINAL ARTICLE

Keratinocyte-Derived Chemokines Orchestrate T-Cell Positioning in the Epidermis during Vitiligo and May Serve as Biomarkers of Disease

Jillian M. Richmond[1], Dinesh S. Bangari[2], Kingsley I. Essien[1], Sharif D. Currimbhoy[3], Joanna R. Groom[4], Amit G. Pandya[3], Michele E. Youd[2], Andrew D. Luster[5] and John E. Harris[1]

QUERATINOCITOS: fuente principal de producción de quimiocinas en el vitíligo

- **Sugiere que el tratamiento tópico dirigido a inhibir la señalización de IFN-g en los queratinocitos, puede ser una estrategia eficaz**



Harris. ExpD 2013

Inhibidores JAK

Adverse events were minor and included erythema, hyperpigmentation, and transient acne

JAAD Journal of the American Academy of Dermatology

REVIEW | VOLUME 79, ISSUE 3, P535-544, SEPTEMBER 01, 2018

Purchase

Topical Janus kinase inhibitors: A review of applications in dermatology

Anna-Marie Hosking, BS • Margit Juhasz, MD • Natasha Atanaskova Mesinkovska, MD, PhD

Published: April 16, 2018 • DOI: https://doi.org/10.1016/j.jaad.2018.04.018 • Check for updates

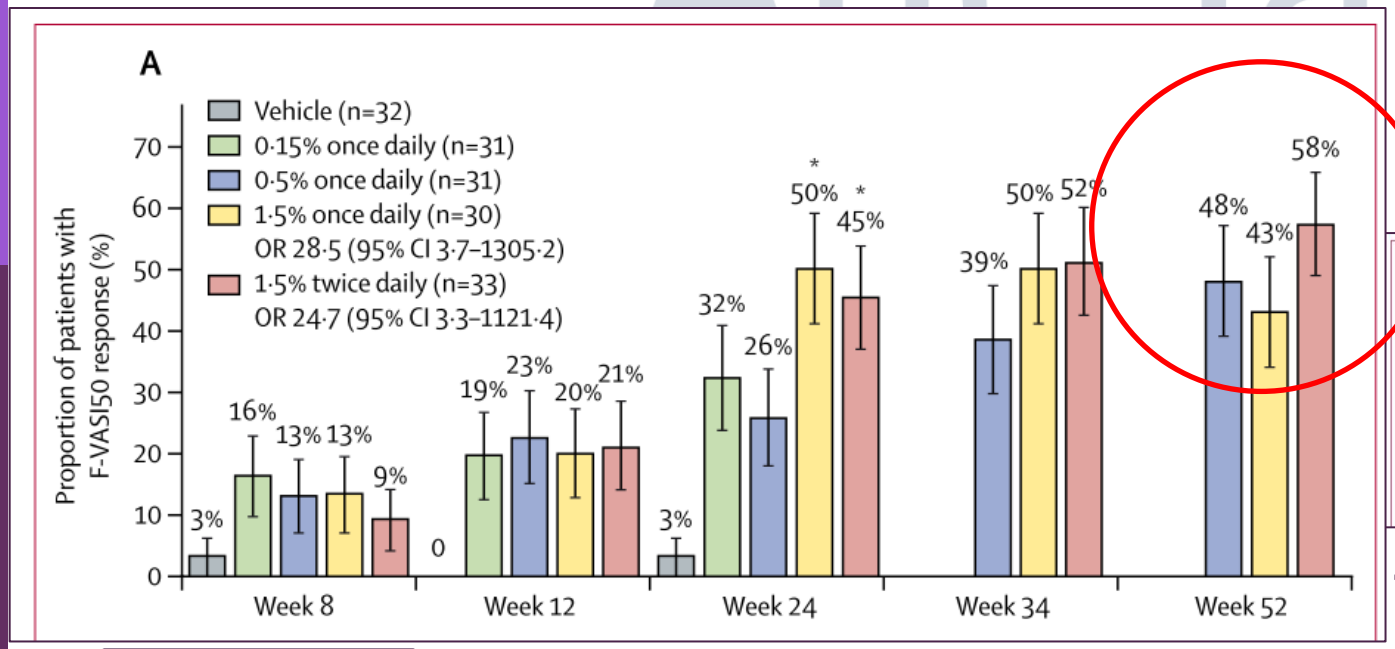
Inhibidores JAK

Ruxolitinib crema
Fase II

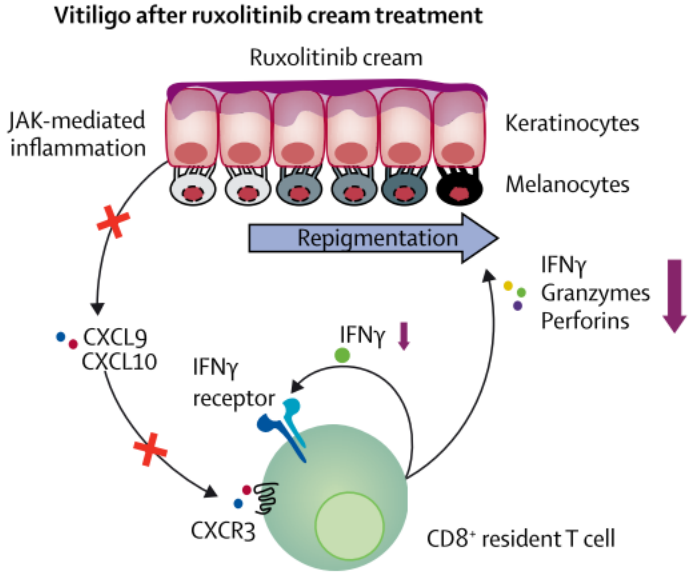
Articles Lancet 2020; 396:110-20

Ruxolitinib cream for treatment of vitiligo: a randomised, controlled, phase 2 trial

David Rosmarin, Amit G Pandya, Mark Lebwohl, Pearl Grimes, Iltefat Hamzavi, Alice B Gottlieb, Kathleen Butler, Fiona Kuo, Kang Sun, Tao Ji, Michael D Howell, John E Harris



Respuesta F-VASI 50



EA relacionados con el tratamiento

- **Prurito** en zona de aplicación
- **Acné**

The NEW ENGLAND JOURNAL of MEDICINE

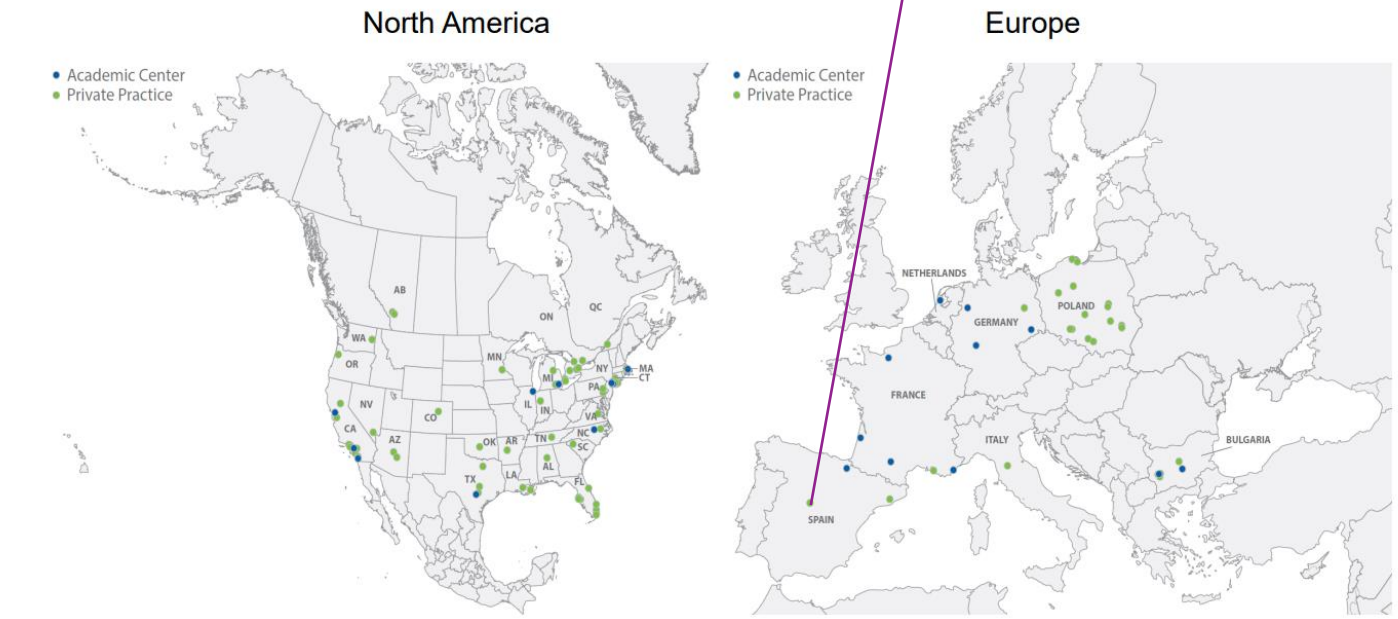
ESTABLISHED IN 1812 OCTOBER 20, 2022 VOL. 387 NO. 16

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

David Rosmarin, M.D., Thierry Passeron, M.D., Ph.D., Amit G. Pandya, M.D., Pearl Grimes, M.D., John E. Harris, M.D., Ph.D., Seemal R. Desai, M.D., Mark Lebwohl, M.D., Mireille Ruer-Mulard, M.D., Julien Seneschal, M.D., Ph.D., Albert Wolkerstorfer, M.D., Ph.D., Deanna Kornacki, Ph.D., Kang Sun, Ph.D., Kathleen Butler, M.D., and Khaled Ezzedine, M.D., Ph.D., for the TRuE-V Study Group*

Ruxolitinib crema
Fase III

Hospital Universitario Fundación Alcorcón **(Madrid)**
Hospital Universitari Germans Trias i Pujol **(Barcelona)**
Clínica Universitaria de Navarra **(Navarra/Madrid**)



Rosmarin D, et al. EADV 2021. Oral presentation 2931.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 20, 2022 VOL. 387 NO. 16

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

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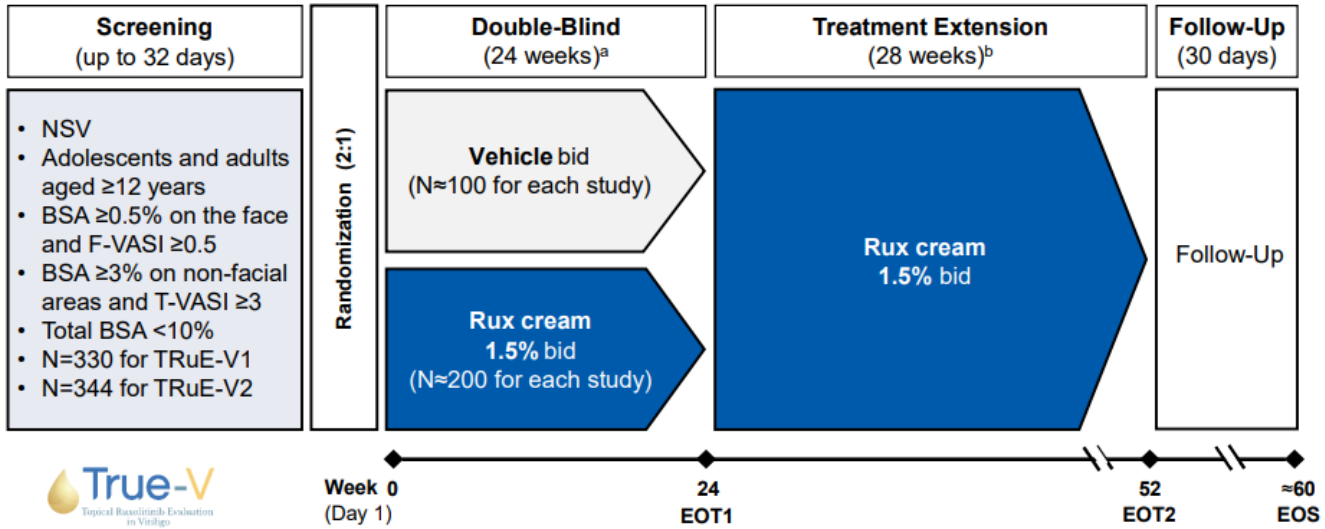
Eligibility Criteria

Key Inclusion Criteria

- Patients aged ≥12 years with nonsegmental vitiligo
- Depigmented areas including the following
  - ≥0.5% of total BSA on the face and ≥3% of total BSA on nonfacial areas
  - Scores ≥0.5 on F-VASI and ≥3 on T-VASI

TRuE-V1 and TRuE-V2

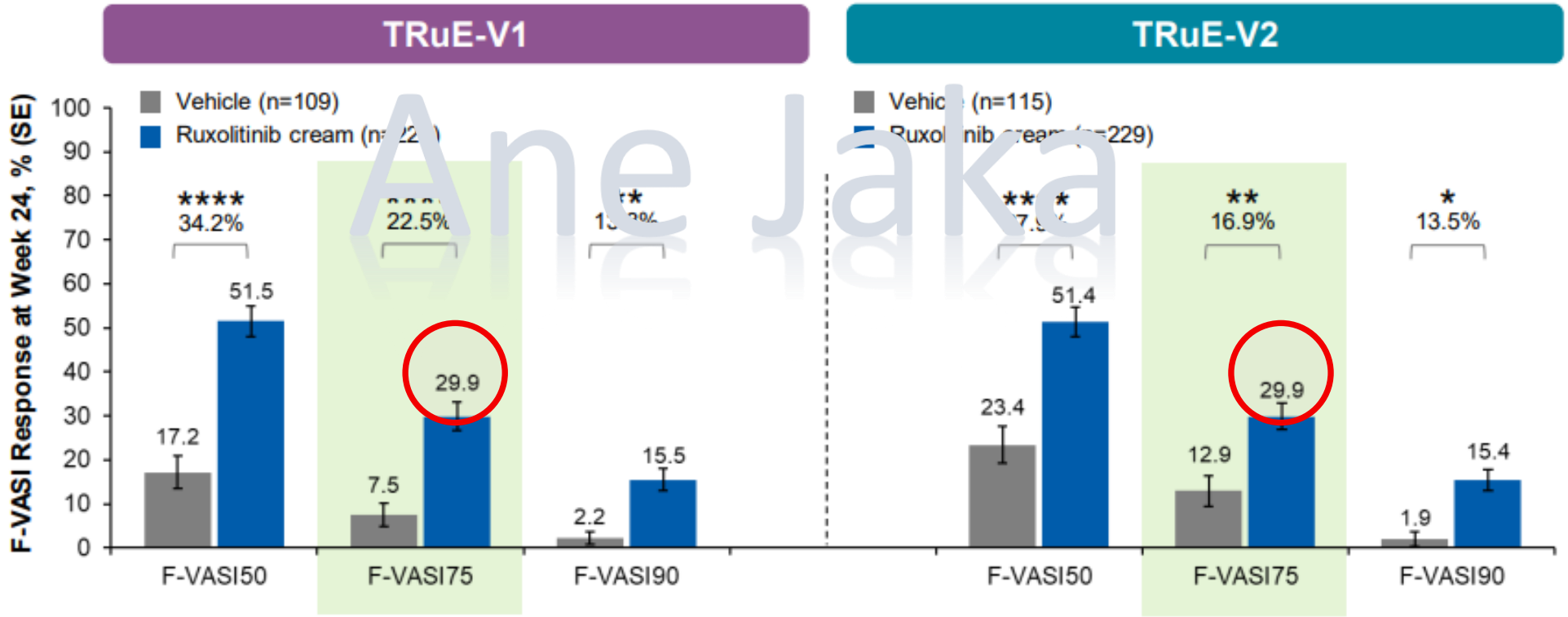
Two Phase 3, Randomized, Double-Blind, 52-Week, Vehicle-Controlled Studies of Ruxolitinib Cream[1-3]



F-VASI Responses at Week 24

N Engl J Med . 2022 20;387(16):1445-55

- F-VASI75 (primary endpoint), F-VASI50, and F-VASI90 responses at week 24 were achieved by a significantly greater proportion of patients applying ruxolitinib cream vs vehicle[1,a,b]



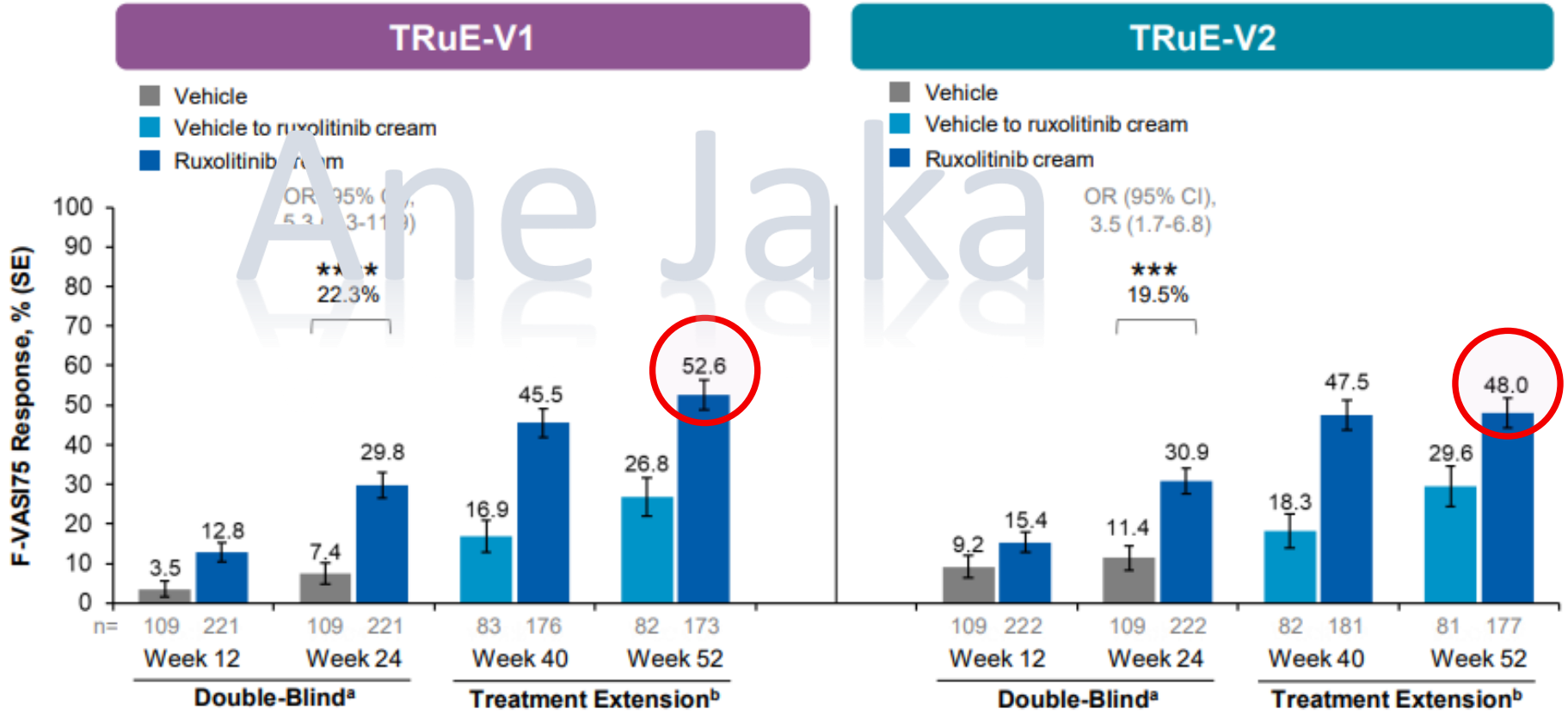
* $P<0.05$, ** $P<0.01$, **** $P<0.0001$ for response rate difference for ruxolitinib cream vs vehicle.
[a] Statistical analysis at week 24 used multiple imputation to account for any missing values. [b] A ≥50% improvement in facial repigmentation was considered clinically meaningful by patients based on analysis of TRuE-V1 and TRuE-V2 exit interviews.[2]

1. Rosmarin D, et al. EADV 2021. Oral presentation 2931. 2. Pandya AG, et al. Maui Derm 2022. ePoster.

N Engl J Med . 2022 20;387(16):1445-55

F-VASI75 Responses
Individual Study Analyses Through 52 Weeks

Aproximadamente **1/2** de los pacientes que aplicaron ruxolitinib crema desde el día 1 alcanzaron F-VASI75 en la semana 52



*** $P<0.001$, **** $P<0.0001$ for response rate difference for ruxolitinib cream vs vehicle.
[a] During the double-blind period (up to week 24), multiple imputation was applied to account for missing values. [b] During the open-label extension (after week 24), responses were reported as observed. Rosmarin D, et al. AAD 2022. Late-breaking oral presentation.

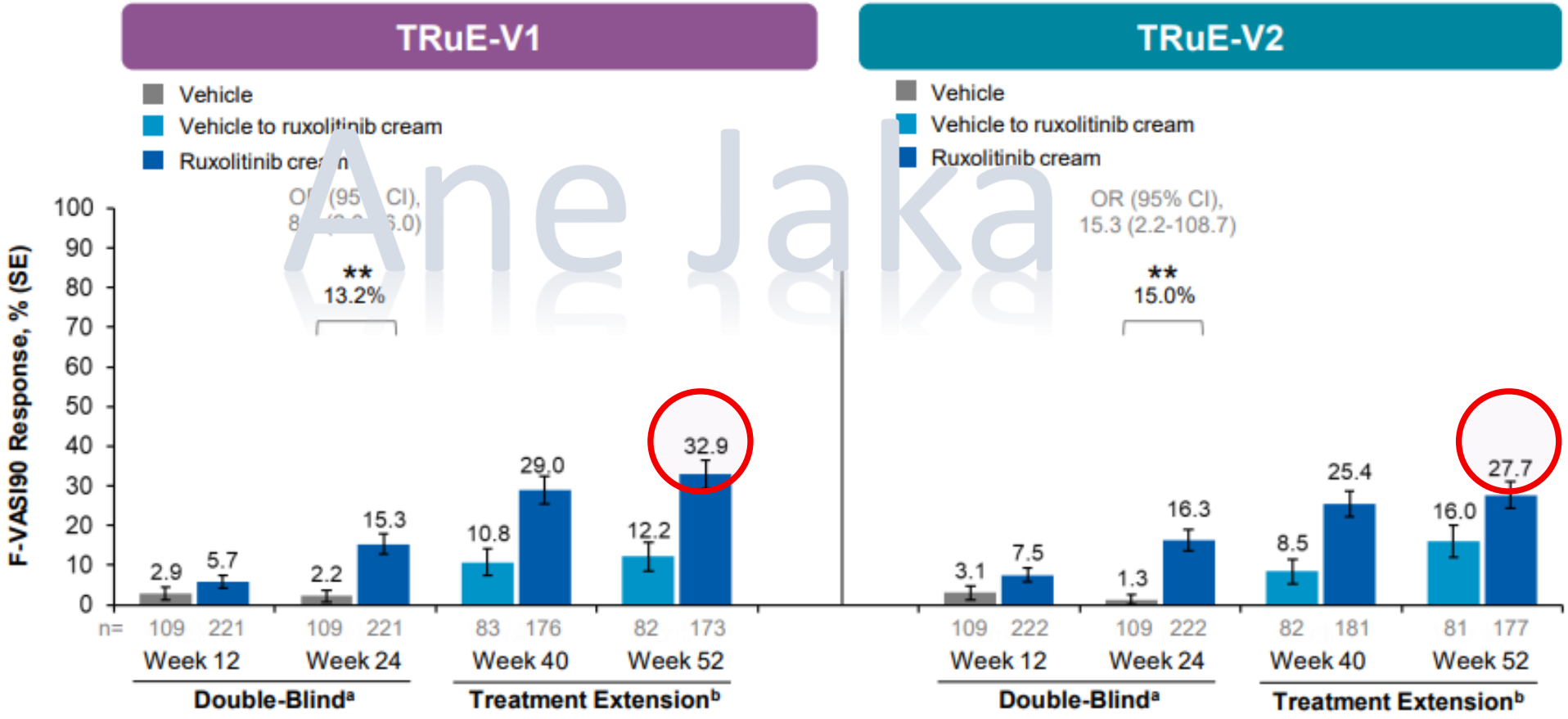
Click on the green arrow for the baseline characteristics

F-VASI90 Responses

Individual Study Analyses Through 52 Weeks

N Engl J Med . 2022 20;387(16):1445-55

Aproximadamente 1 de cada 3 pacientes que aplicaron ruxolitinib crema desde el día 1 alcanzaron F-VASI90 en la semana 52



** $P<0.01$ for response rate difference for ruxolitinib cream vs vehicle.

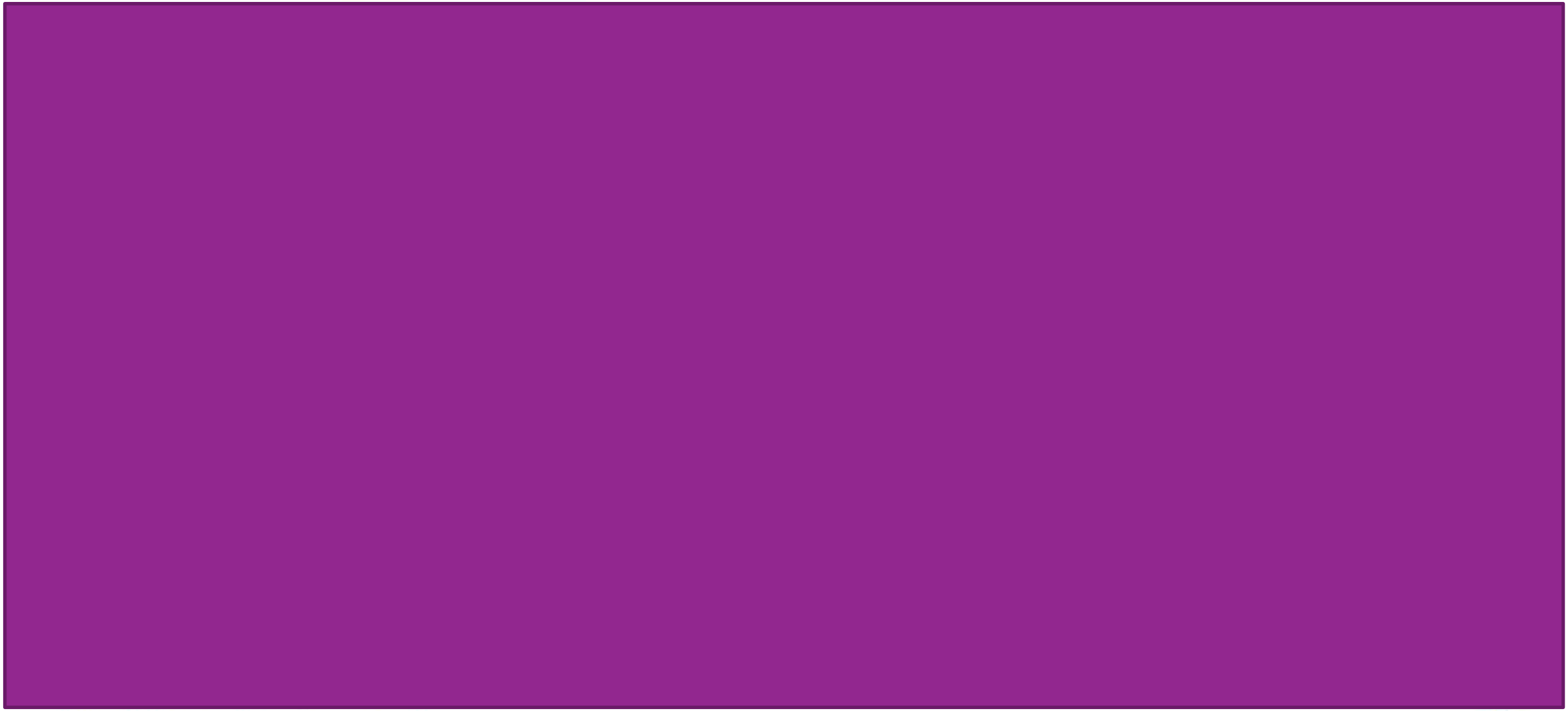
[a] During the double-blind period (up to week 24), multiple imputation was applied to account for missing values. [b] During the open-label extension (after week 24), responses were reported as observed.

Rosmarin D, et al. AAD 2022. Late-breaking oral presentation.

N Engl J Med . 2022 20;387(16):1445-55

Representative Clinical Images Showing F-VASI Response

Ruxolitinib Cream 1.5% bid

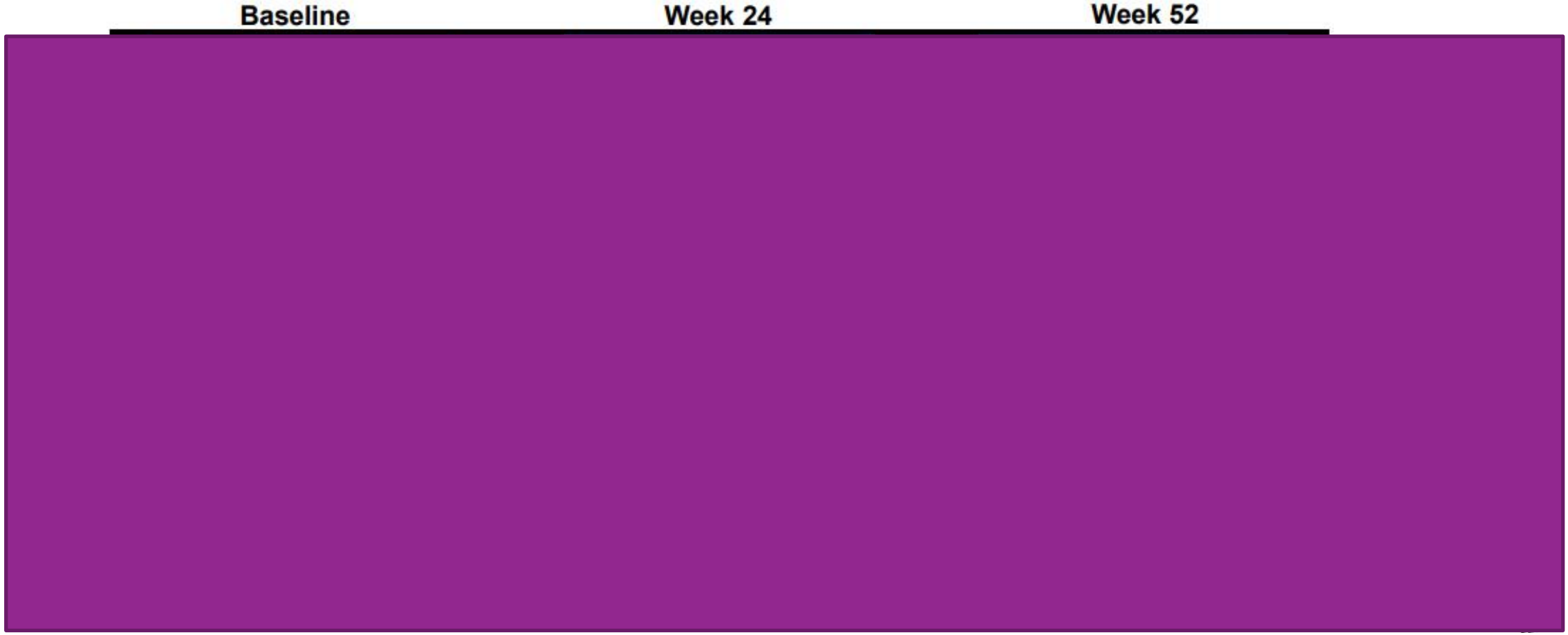


N Engl J Med . 2022 20;387(16):1445-55

Representative Clinical Images Showing F-VASI Responses

Ruxolitinib Cream 1.5% bid

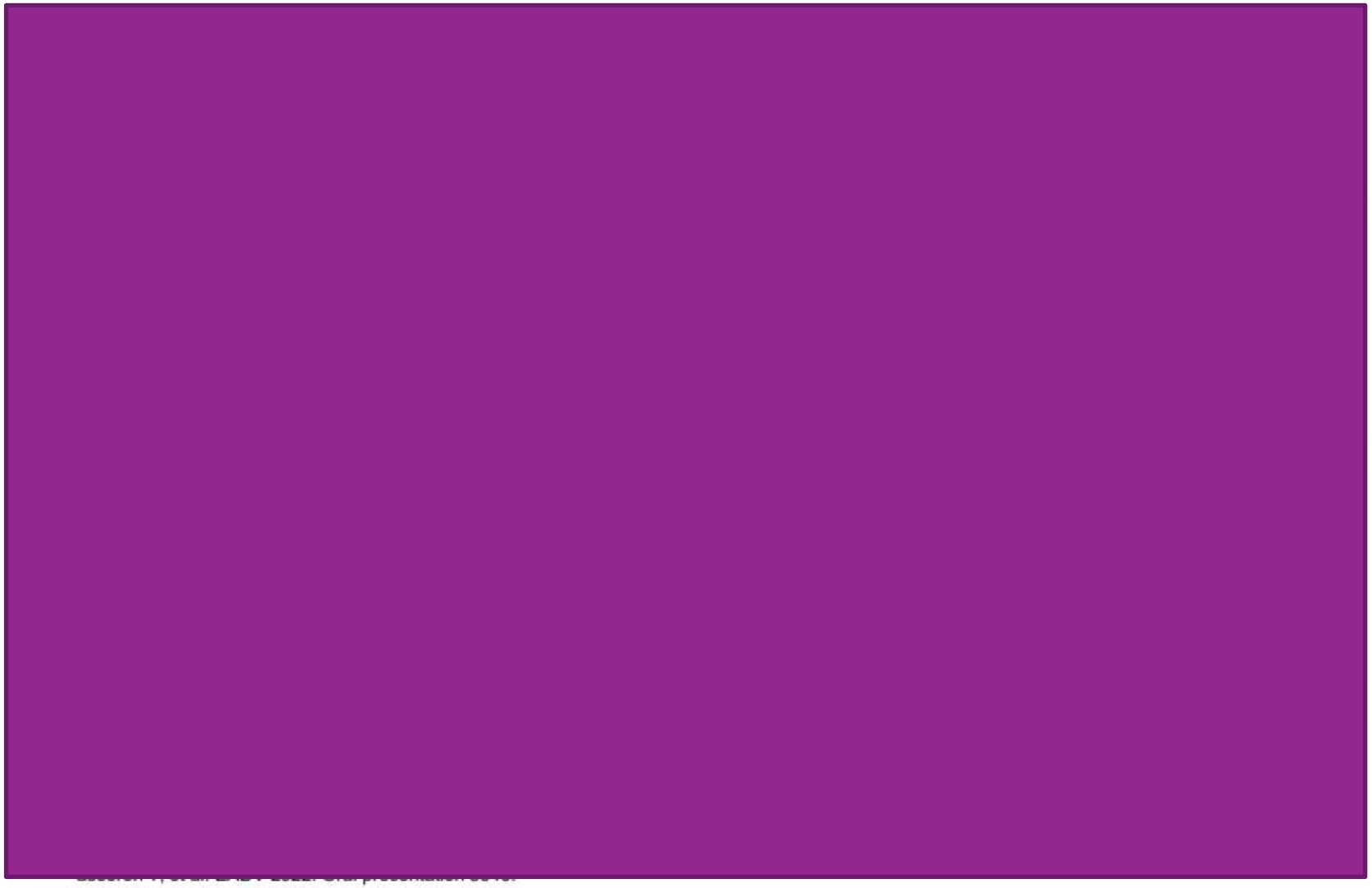
56 year-old male patient; disease duration, 21.6 years



N Engl J Med . 2022 20;387(16):1445-55

Clinical Images Showing Repigmentation of Body Regions

Ruxolitinib Cream 1.5% bid



VASI improvement from baseline at week 52

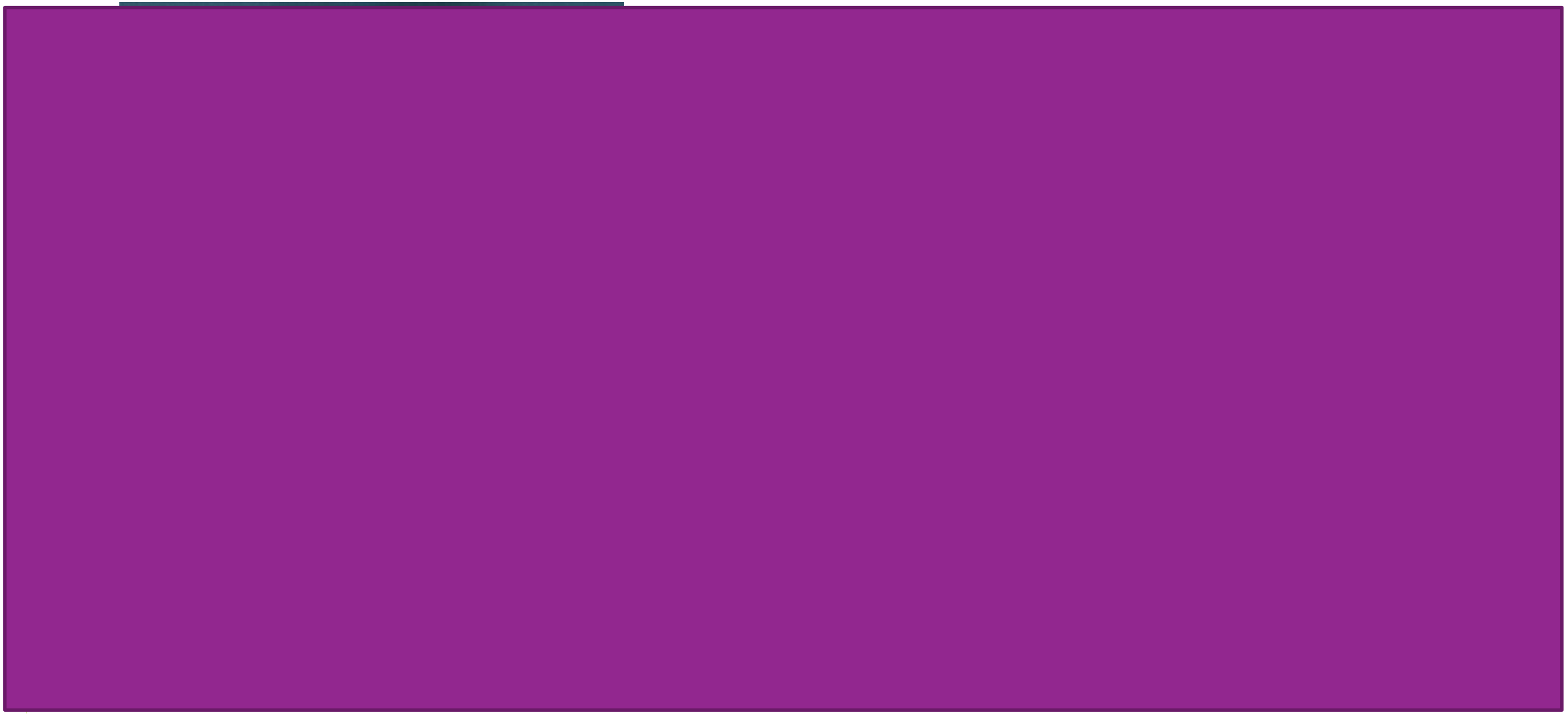
T-VASI[a]: **58.6%**
VASI of upper extremities: **45.8%**

T-VASI[a]: **60.9%**
VASI of hands: **50.0%**

T-VASI[a]: **54.0%**
VASI of lower extremities: **86.4%**

Baseline

Semana 52


Baseline
Semana 52

Safety
Pooled Analysis Through 52 Weeks

N Engl J Med . 2022 20;387(16):1445-55

- Application site reactions, including acne and pruritus, were all mild or moderate
- No serious TEAEs were considered related to treatment with ruxolitinib cream

Characteristic, n (%)	Vehicle up to week 24 (n=224)	Ruxolitinib cream up to week 52[a] (n=637)
Patients with TEAE	8[illegible] (36.2)	332 (52.1)
Most common TEAEs[b]		
COVID-19	[illegible].1)	39 (6.1)
Application site acne	[illegible] (1.[illegible])	34 (5.3)
Nasopharyngitis	5 (2.2)	31 (4.9)
Application site pruritus	6 (2.7)	25 (3.9)
Headache	6 (2.7)	25 (3.9)
Upper respiratory tract infection	5 (2.2)	20 (3.1)
Patients with treatment-related TEAE	16 (7.1)	87 (13.7)
Most common treatment-related TEAEs[b]		
Application site acne	2 (0.9)	28 (4.4)
Application site pruritus	6 (2.7)	22 (3.5)
Patients with serious TEAE	1 (0.4)	14 (2.2)
Patients with TEAE leading to discontinuation	1 (0.4)	3 (0.5)

[a] Including patients who crossed over from vehicle to ruxolitinib cream after week 24. [b] Occurring in ≥3% of patients in any treatment group.

1. Wolkerstorfer A, et al. EADV 2022. Oral presentation FC01.04. 2. Passeron T, et al. EADV 2022. Oral presentation 3640.

American Academy of Dermatology Association

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2023 Annual Meeting

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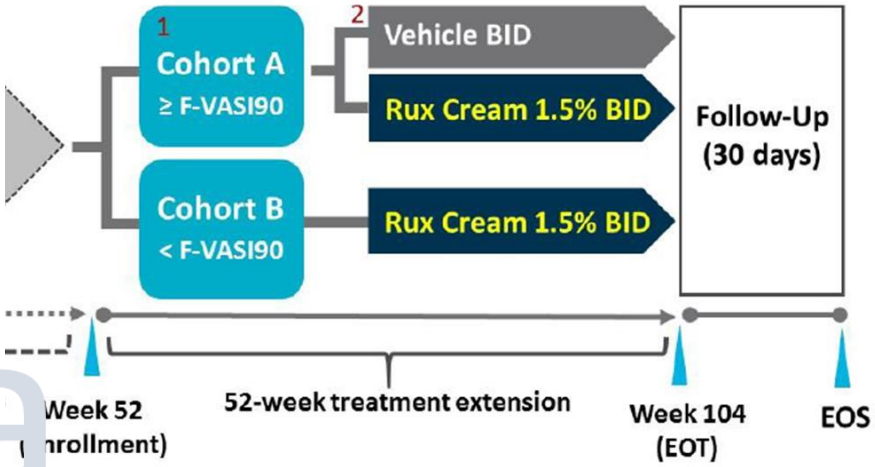
- Sessions
- Speakers
- CME / Evaluations

Randomized, Double-Blind, Placebo-Controlled Trial
Eric Lawrence Simpson, MD, FAAD

9:20 AM **Relapse and Maintenance of Clinical Response In the Randomized Withdrawal Arm of the TRuE-V Long-Term Extension Phase 3 Study of Ruxolitinib Cream in Vitiligo**
John Harris, MD, PhD, FAAD

9:30 **Facial and Total Vitiligo Ar[illegible] Scoring Inde[illegible] During 104 Wee[illegible] Ruxo[illegible]tinib Crea[illegible] T[illegible]atme[illegible]t for Vitilig[illegible]: Results [illegible]ron[illegible] Ope[illegible]-La[illegible]el Arm of the TR[illegible]E-V[illegible]ong-[illegible]erm Exte[illegible]sion [illegible]ase 3 Stud**
David Rosmarin, MD, FAAD

AAD 2023 New Orleans
S025 - LATE-BREAKING RESEARCH: SESSION 1



The 104-week long-term extension (LTE) data build on the positive 52-week TRuE-V1 and TRuE-V2

Many patients who achieved a high level of facial repigmentation (≥F-VASI90) in TRuE-V1/TRuE-V2 were able to **maintain durable response for one year after discontinuing Opzelura treatment.**

Approximately 29% of patients randomized to the withdrawal arm (i.e., applying vehicle cream) relapsed (<F-VASI75) during the extension period (through Week 104).
- 75% of patients regained ≥F-VASI75 once treatment with Opzelura was reinitiated (median 12 weeks) and 69% of patients regained ≥F-VASI90.

For those continuing Opzelura treatment, approximately 62% of patients who achieved **≥F-VASI90 at Week 52 maintained response for one year with ongoing Opzelura** treatment.

In patients who did not achieve near complete facial repigmentation (<F-VASI90) at Week 52 and continued treatment with Opzelura, improvements in facial and total body repigmentation, as shown by greater proportions of patients reaching F-VASI75 and T-VASI50, were observed through Week 104.

Opzelura was well tolerated with no serious treatment-related adverse events through Week 104

FDA U.S. FOOD & DRUG ADMINISTRATION

Search Menu

← Home / Drugs / News & Events for Human Drugs / FDA approves topical treatment addressing repigmentation in vitiligo in patients aged 12 and older

07/2022

FDA approves topical treatment addressing repigmentation in vitiligo in patients aged 12 and older

Safety and effectiveness of Opzelura were demonstrated in two clinical trials, NCT04052425 and NCT04057573. In both trials, subjects with non-segmental vitiligo were randomized to treatment with Opzelura or placebo cream twice daily for 24 weeks, followed by an additional 28 weeks of treatment with Opzelura for all subjects. At the end of the 24-week treatment period, 30% of Opzelura patients had at least 75% improvement in the facial Vitiligo Area Scoring Index, compared with 10% of placebo patients.

TWICE A DAY—EVERY DAY

Consistently apply OPZELURA two times each day to the affected skin on up to 10% of body surface area, perhaps as part of your morning and evening routines.

NIH U.S. National Library of Medicine

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Save this study

Topical Ruxolitinib Evaluation in Vitiligo Study 1 (TRuE-V1)

Topical Ruxolitinib Evaluation in Vitiligo Study 2 (TRuE-V2)

RUXOLITINIB 1,5 crema

Pacientes >65a
Fumadores
Riesgo CV
Riesgo de cáncer

INFORMACIÓN IMPORTANTE DE SEGURIDAD (CONTINUACIÓN)

Aumento del riesgo de eventos cardiovasculares importantes: Ha habido un mayor riesgo de eventos cardiovasculares importantes como infarto, accidente cerebrovascular o muerte en personas de 50 años de edad o más que tienen al menos 1 factor de riesgo de enfermedad cardíaca (cardiovascular) y están tomando un medicamento de la clase de medicamentos denominados inhibidores de JAK por vía oral, especialmente si son o fueron fumadoras.

Coágulos de sangre: pueden producirse coágulos de sangre en las venas de las piernas (trombosis venosa profunda, TVP) o en los pulmones (embolia pulmonar, EP), en algunas personas que reciben OPZELURA. Es posible que ser portador inicial en el coágulo de sangre en las venas de las piernas (trombosis venosa profunda, TVP) y en los pulmones (embolia pulmonar, EP) haya ocurrido con mayor frecuencia en personas de 50 años de edad o más y con al menos 1 factor de riesgo de cardiopatía (cardiovascular) que toman un medicamento de la clase de medicamentos denominados inhibidores de la JAK por vía oral.

Recuentos bajos de células sanguíneas: OPZELURA puede causar recuentos bajos de plaquetas (trombocitopenia), recuentos bajos de glóbulos rojos (anemia) y recuentos bajos de glóbulos blancos (neutropenia). Si es necesario, su proveedor de atención médica le hará un análisis de sangre para controlar sus recuentos de células sanguíneas durante su tratamiento con OPZELURA y podrá interrumpir su tratamiento si se producen signos o síntomas de recuentos bajos de células sanguíneas.

Aumentos de colesterol: se produjo un aumento del colesterol en personas cuando tomaban ruxolitinib por vía oral. Informe a su proveedor de atención médica si tiene niveles altos de colesterol o triglicéridos.

Antes de empezar a tomar OPZELURA, informe a su proveedor de atención médica si:

- tiene una infección, está siendo tratado por una o ha tenido una infección que no desaparece o sigue reapareciendo
- tiene diabetes, enfermedad pulmonar crónica, virus de inmunodeficiencia humana (VIH) o un sistema inmunitario débil
- tiene TB, o tuvo un contacto estrecho con alguien con TB
- ha tenido zóster (herpes zóster)
- tiene o ha tenido hepatitis B o C
- vive, vivió o viajó a ciertas partes del país (como los valles de los ríos Ohio y Mississippi y el Suroeste) donde hay una mayor probabilidad de contraer ciertos tipos de infecciones fúngicas. Estas infecciones pueden producirse o volverse más graves si usa OPZELURA. Pregunte a su proveedor de atención médica si no sabe si vivió en un área en la que estas infecciones son frecuentes.
- cree que tiene una infección o tiene síntomas de una infección, como fiebre, sudoración o escalofríos, dolores musculares, tos o falta de aire, sangre en la flema, pérdida de peso, piel caliente, roja o dolorosa o llagas en el cuerpo, diarrea o dolor estomacal, ardor al orinar u orinar con más frecuencia de lo habitual o se siente muy cansado.
- alguna vez tuvo algún tipo de cáncer, o es o fue fumador
- ha tenido un ataque cardíaco, otros problemas cardíacos o un accidente cerebrovascular
- tuvo coágulos de sangre en las venas de las piernas o en los pulmones en el pasado
- tiene niveles altos de colesterol o triglicéridos
- tiene o tuvo recuentos bajos de glóbulos blancos o rojos
- está embarazada o planea quedar embarazada. Se desconoce si OPZELURA dañará al bebé en gestación. Hay un registro de exposición durante el embarazo para personas que usan OPZELURA durante el embarazo. El propósito de este registro es recopilar información sobre su salud y la de su bebé. Si se expone a OPZELURA durante el embarazo, usted y su proveedor de atención médica deben informar la exposición a Incyte Corporation, llamando al 1-855-463-3463.
- está amamantando o planea amamantar. Se desconoce si OPZELURA pasa a la leche materna. No amamante durante el tratamiento con OPZELURA ni durante unas 4 semanas después de la última dosis.

Después de iniciar OPZELURA:

- Llame a su proveedor de atención médica de inmediato si tiene algún síntoma de infección. OPZELURA puede hacer que tenga más probabilidades de contraer infecciones o puede empeorar cualquier infección que tenga.

12

(continúan en la página siguiente)

Ensayos Clínicos Inhibidores JAK

Drug	Generation	Target	Status	Dermatologic Conditions
Ruxolitinib	1st	JAK1, JAK2	Phase II Phase III Phase II Phase III FDA-approved	Alopecia areata Vitiligo (topical) Psoriasis (topical) Graft-versus-host disease Atopic dermatitis (topical)
Tofacitinib	1st	JAK3, JAK1, JAK2 (with less selectivity)	Phase I Phase II Phase II Phase IV FDA-approved	Dermatomyositis Atopic dermatitis (topical) Psoriasis Alopecia areata Psoriatic arthritis
Baricitinib	1st	JAK1, JAK2	Phase II Phase II Phase III Phase III	Psoriasis Graft-versus-host disease Systemic lupus erythematosus Atopic dermatitis
Oclacitinib	1st	JAK1	FDA-approved	Canine allergic dermatitis
Upadacitinib	2nd	JAK1	Phase III FDA-approved	Atopic dermatitis Active psoriatic arthritis
Itacitinib	2nd	JAK1, JAK2	Phase II Phase II	Psoriasis Graft-versus-host disease

Skin Therapy Lett. 2022 Jan;27(1):4-9.

Filgotinib	2nd	JAK1	Phase II Phase II	Psoriatic arthritis Cutaneous lupus erythematosus
Abrocitinib	2nd	JAK1	Phase III	Atopic dermatitis
INCB54707	2nd	JAK1	Phase II	Hidradenitis suppurativa
Deucravacitinib	2nd	TYK2	Phase II Phase II Phase III	Systemic lupus erythematosus Psoriatic arthritis Psoriasis
Ritlecitinib	2nd	JAK3	Phase II Phase III	Vitiligo Alopecia areata
Brepocitinib	2nd	JAK1, TYK2	Phase II Phase II Phase II Phase II Phase II Phase II	Vitiligo Systemic lupus erythematosus Atopic dermatitis (topical) Alopecia areata Psoriatic arthritis Psoriasis
Gusacinitib	2nd	JAK1, JAK2, JAK3, TYK2, SYK	Phase IIb Phase IIb	Chronic hand eczema Atopic dermatitis
Delgocitinib	2nd	JAK1, JAK2, JAK3, TYK2	Phase IIb Phase IIb	Chronic hand eczema Atopic dermatitis
CTP-543	2nd	JAK1, JAK2	Phase III	Alopecia areata

TABLE 1A | Trials of emerging JAK inhibitors in vitiligo.

NCT number	Sponsor	Nationality	Trial phase	Treatment group	Drug type	Subject	Allocation	Status	Results	Side effect
NCT04896385	Incyte Corporation	The United States and Canada	2	Group1: ruxolitinib cream Group2: vehicle	JAK1/2 inhibitor	60	Randomized, double-blind	Recruiting	Not available	Not available
NCT02809976	Tufts Medical Center	The United States	2	Group 1: ruxolitinib 1.5% phosphate cream twice daily	JAK1/2 inhibitor	11	Single group, open-label	Completed	4 patients presented significant facial improvement, 23% of patients decreased VASI	Only mild side effects
NCT03099304	Incyte Corporation	The United Kingdom	2	Group 1: ruxolitinib cream 1.5% twice daily Group 2: ruxolitinib cream 1.5% once daily Group 3: ruxolitinib eam 0.5% once daily up 4: ru li 0. % once aily Gr p 5: ve cle	JAK1/2 inhibitor	157	Randomized, double-blind	Completed	More patients in cream 1.5% twice daily, 1.5% once daily, 0.5% e-daily ups achieved ASI5 an t ol	Only mild side effects
NCT04052425	Incyte Corporation	The United States	3	Gro 1: ru itinib eam Group 2: vehicle	JA 1/2 inhi	330	Ran nized -blind	Active	Not av ble	Not e
NCT04057573	Incyte Corporation	The United States	3	Group1: ruxolitinib cream Group 2: vehicle	JAK1/2 inhibitor	334	Randomized, double-blind	Active	Not available	Not available
NCT04530344	Incyte Corporation	The United States	3	Group 1: ruxolitinib cream Grorup2: vehicle	JAK1/2 inhibitor	500	Randomized, double-blind	Recruiting	Not available	Not available
NCT04822584	University Hospital, Bordeaux	France	2	Group 1: baricitinib Group 2: placebo	JAK1/2 inhibitor	48	Randomized, double-blind	Not yet recruiting	Not available	Not available
NCT04103060	Dermavant Sciences GmbH	The United States	2	Group 1: cerdulatinib, 0.37% gel, twice daily Group 2: vehicle gel, twice daily	SYK and JAK inhibitor (without JAK2)	33	Randomized, double-blind	Completed	Not available	Not available
NCT03715829	Pfizer	The United States	2	Group 1: PF-06651600 ritlecitinib Group 2: placebo Group 3: PF06700841 brepocitinib	Brepocitinib: TYK2/JAK1 inhibitor Ritlecitinib: JAK3/TEC	366	Randomized, double-blind	Completed	Not available	Not available
NCT03468855	Aclaris Therapeutics, Inc.	The United States	2	Group: **ATI-50002** ifidancitinib twice daily	JAK1 and JAK3 inhibitor	34	Single group, open-label	Completed	Mean change in F-VASI: -0.067 (0.2411) VNS: 2.2 (0.66)	1 Acute myocardial infarction, 1 Alcoholic Pancreatitis

VASI, Vitiligo Area Scoring Index; F-VASI, Facial Vitiligo Area Scoring Index; VNS, Vitiligo Noticeability Scale.

Janus Kinase Inhibitors in the Treatment of Vitiligo: A Review. Qi F, et al. Front Immunol. 2021. PMID: 34868078

Inhibidores JAK y fotoactivación

JAAD Journal of the American Academy of Dermatology

Repigmentation in vitiligo using the Janus kinase inhibitor tofacitinib may require concomitant light exposur

Lucy Y. Liu, BA • James P. Strassner, BS • Maggi A. Refat, [illegible] • Jo[illegible]E. Ha[illegible]s, MD, PhD
Brett A. King, MD, PhD

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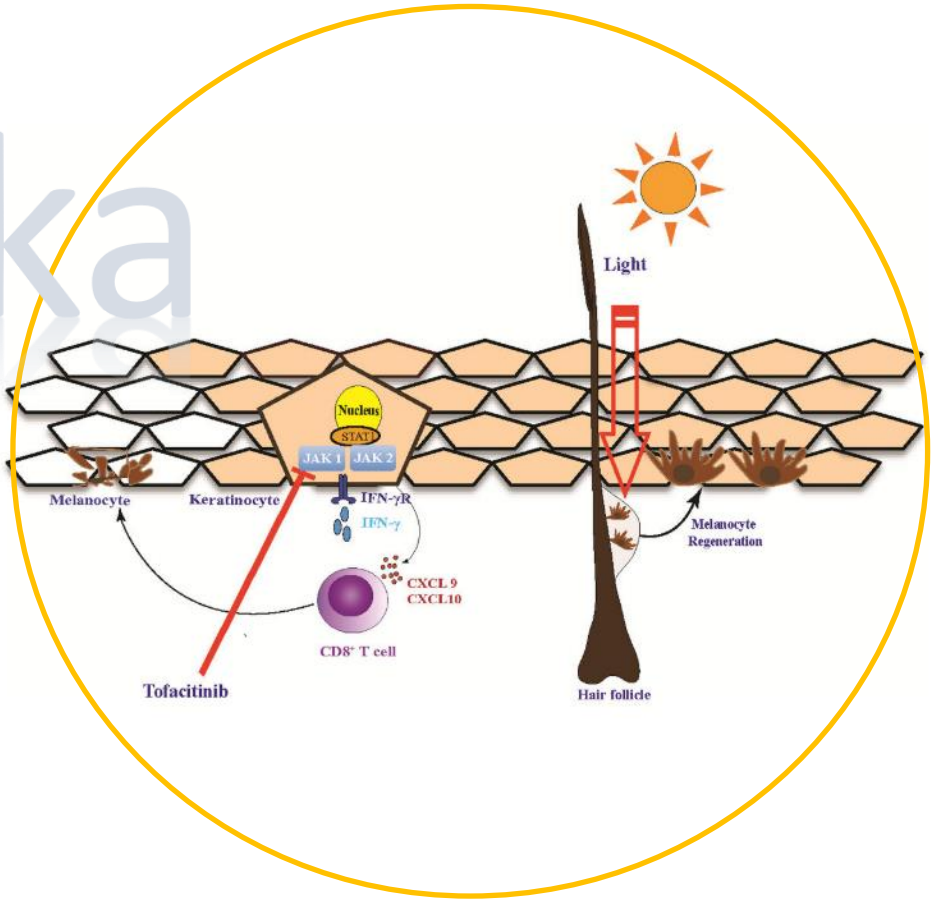
La repigmentación requiere tanto la supresión de la inflamación en la piel (inhibidores de JAK), como la **estimulación de los melanocitos mediante la exposición a la luz solar**



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Row	Saved	Status	Study Title	Conditions	Interventions	Locations
1	☐	Active, not recruiting	A Study to Evaluate the Safety and Efficacy of Ruxolitinib Cream With Phototherapy in Participants With **Vitiligo**	• **Vitiligo** • **JAK Inhibitor**	• Drug: Ruxolitinib 1.5% cream • Device: NB-UVB phototherapy	• First Oc Dermatology Fountain Valley, California, United States • UC Davis Health Sacramento, California, United States • Palo Alto Medical Foundation Sunnyvale, California, United States

Row	Saved	Status	Study Title	Conditions	Interventions	Locations
1	☐	Completed	A Phase 2b Study To Evaluate T e Effi cy An Safety rofil Of PF- 651600 And PF-06700841 In Active Non-se ligo ubject	• Active lon-segm tal	• Drug: PF- 651600 • Dr g: plac bo • Drug: F 700841 • Device: narrow-band UVB phototherapy	• Marvel Research, LLC Huntington Beach, California, United States • University of California, Irvine, Dermatology Clinical Research Center Irvine, California, United States • Vitiligo and Pigmentation Institute Of Southern California

Row	Saved	Status	Study Title	Conditions	Interventions	Locations
1	☐	Completed	A Phase 2b Study To Evaluate The Efficacy And Safety Profile Of PF-06651600 And PF-06700841 In Active Non-segmental **Vitiligo** Subjects	• Active Non-segmental **Vitiligo**	• Drug: PF-06651600 • Drug: placebo • Drug: **PF06700841** • Device: narrow-band UVB phototherapy	• Marvel Research, LLC Huntington Beach, California, United States • University of California, Irvine, Dermatology Clinical Research Center Irvine, California, United States • Vitiligo and Pigmentation Institute Of Southern California Los Angeles, California, United States • (and 88 more...)

CONCLUSIONES

Objetivos del tratamiento en el vitíligo

1. Regulación de la inmunidad
2. Promover la repigmentación
3. Evitar las recidivas.

- La inhibición de la señalización de IFNγ mediada por JAK quinasa es un tratamiento prometedor en vitíligo.
  - Tratamiento tópico: buena tolerancia, escasos efectos adversos
  - Buena respuesta –fVASI
- Fotoactivación como ayuda para estimular la repigmentación?
  - Asociar UVB-BE
- Durabilidad de la repigmentación ?
  - Estudios a largo plazo para valorar duración de respuesta
    - Tratamientos prolongados - mejor respuesta
  - Asociar otras dianas: anti- IL -15 (cél T memoria) ?


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INMUNOTERAPIA EN DERMATOLOGÍA

30 de marzo de 2023

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Gràcies,