Ixekizumab nel trattamento della PsO: caso clinico cardiologico

Dott.ssa Claudia Lasagni
Clinica Dermatologica, Policlinico di Modena

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Disclosures

Advisory board member, consulente o speaker per:

- Abbvie
- Almirall
- Leo Pharma
- Novartis
- Eli Lilly
- Janssen

Profilo paziente

PROFILO PAZIENTE

- Uomo, 65 anni
- Altezza: 197 cm; peso: 108 kg
- BMI: 27

ESORDIO STORIA PSORIASI

- **1996:** diagnosi di artrite psoriasica (terapia; CsA + steroide sistemico)
- **1998:** IMA (fumatore 40 sigarette/die)
- **2006:** secondo IMA (stenosi critica del tratto medio coronarico dx trattata con angioplastica e duplice stent coronarico quindi introduzione di doppia terapia antiaggregante

ANAMNESI FARMACOLOGICA (PsO)

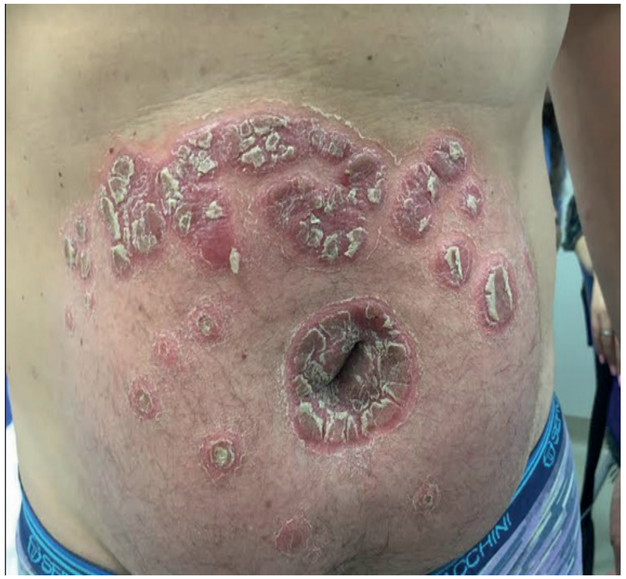
- A seguito di IMA viene sospesa terapia con Csa ed impostata terapia alternativa:
- **2000 - 2010: Infliximab**, sospesa per progressiva perdita di efficacia
- **2010 - 2012: Adalimumab**
- **2012 - 2017: Ustekinumab**
- **2017 - 2019: Secukinumab**, poi sospeso per perdita di efficacia

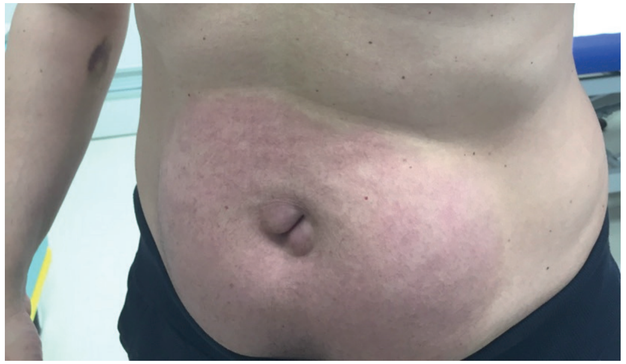
Comparsa di altre comorbidità…

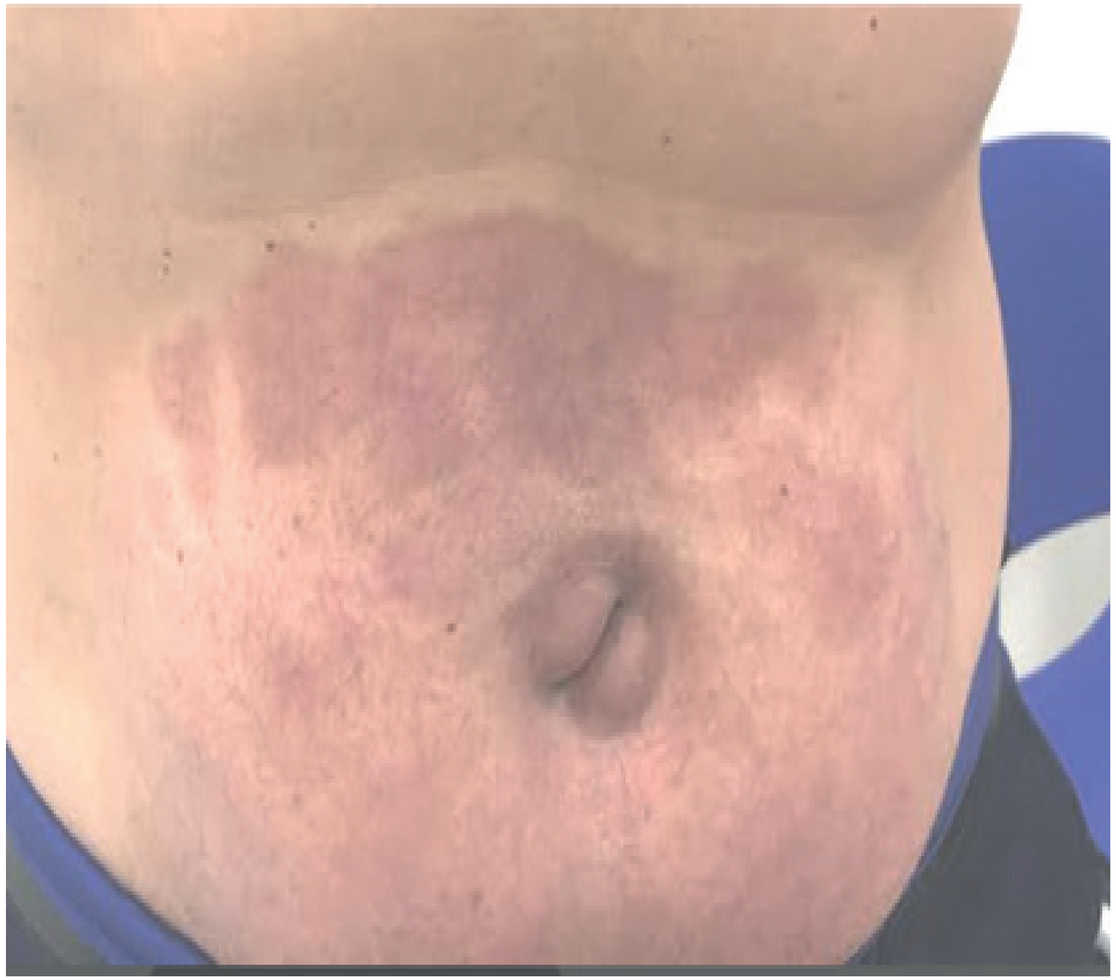
- **2019:** inizio terapia con ixekizumab
- **2020:** nodulo apicale polmonare di 6 mm fase stabile
- **2020:** nodulo apicale polmonare di 6 mm fase stabile alla medio coronaria di dx trattata con angioplastica ed impianto di singolo bms, inefficace tentativo di rivascolarizzazione e nuovo posizionamento stent coronarico

ULTIMO CONTROLLO CARDIOLOGICO

- **2022:** ecocardio ventricolo sx di normali dimensioni spessori e funzione contrattile globale nella norma
- **FE=55% e moderata dilatazione atriale sx**; sezione destra di normali dimensioni e funzione
- **Lieve rigurgito mitralico** funzionante
- Valvola aortica tricuspide con apertura conservata anche se **lieve insufficenza tricuspidale**; nessun versamento pericardico
- Vena cava inferiore di normali dimensioni
- Setti integri
- CONCLUSIONI; **FA permanente** attuale; **normale controllo della FC** in pazienti con **cardiopatia ischemica cronica** post infartuale in fase stabile







Esperienza clinica Dott.ssa Lasagni

DECISION GRID II.—Overview of "biologics" treatment options and the expert assessment of their suitability in specific treatment circumstances

Therapy	Small molecules	TNF inhibitors				Anti-IL-12/23	Anti-IL-17			Anti-IL-23		
Specific circumstances	Apremilast	Etanercept	Infliximab	Adalimumab	Certolizumab	Ustekinumab	Secukinumab	Ixekizumab	Brodalumab	Guselkumab	Tildrakizumab	Risankizumab
Concomitant psoriatic arthritis		↑↑ if non-responder to MTX										
Chronic inflammatory bowel disease: Crohn's disease			↑↑ 1st choice				↓			↑ 2nd choice if anti-TNF alpha not suitable		
Chronic inflammatory bowel disease: ulcerative colitis	↑ 2nd choice oral treatment		↑↑ 1st choice			↑↑ 1st choice	↓			↑ 2nd choice if anti-TNF alpha not suitable		
Diabetes mellitus/ metabolic syndrome												
Dyslipidemia												
Advanced heart failure	↑	↓↓				↑						
Heart disease: ischemic heart disease		↑										
Concomitant latent/ treated TB	↑	↓↓					↑			↑		
Pregnancy	↓				↑ preferred choice biologic							
Previous history of malignancies												

Symbols	Implication (adapted from GRADE)
↑↑	We believe that all or almost all informed people would make that choice
↑	We believe that most informed people would make that choice, but a substantial number would not
	See background text and specific recommendations
↓	We believe that most informed people would make a choice against that intervention, but a substantial number would not
↓↓	We believe that all or almost all informed people would make a choice against that choice

P.Gisondi et al. Italian Journal of Dermatology and Venereology 2022 February;157(Suppl. 1):1-78

Pazienti con insufficienza cardiaca congestizia

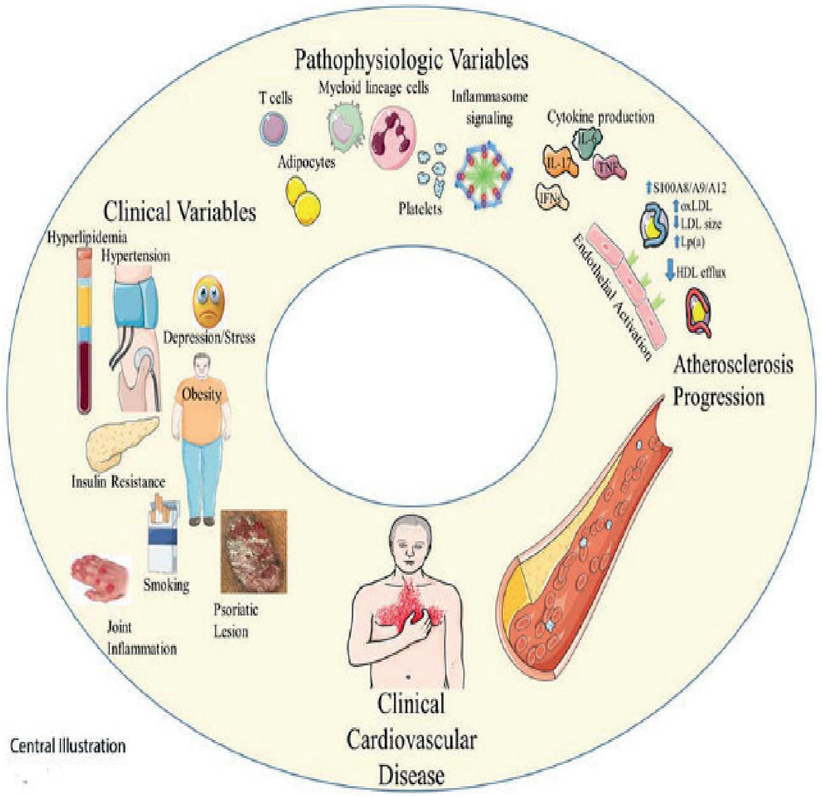
Algoritmo terapeutico:

- Inibitori IL-17 (prima opzione)
- Inibitori IL-23 (prima opzione)
- Ustekinumab (prima opzione)
- Evitare gli inibitori del TNF alfa:
    - In pazienti con classificazione NYHA classe III e IV
    - Ecocardiogramma raccomandato per le classi NYHA I e II
    - In pazienti con frazioni di eiezione <50%

P.Gisondi et al. Italian Journal of Dermatology and Venereology 2022 February;157(Suppl. 1):1-78

Terapia biologica e rischio di MACE

- **2012:** MGUS IgA lambda con immunofissazione urinaria positiva; rischio evolutivo in mieloma: **MEDIO-ALTO**
- **2014:** riscontro di FA trattata con cardioversione ma non risolta; **persiste FA cronica**
- **2016:** 2016 diabete mellito tipo 2 (metformina cloridrato)
- **2016:** piastrinopenia autoimmune
- **2018:** artroprotesi anca dx e diagnosi di multiradiculopatia cronica AAII



Rungapiromnan W, et al. Br J Dermatol. 2017

Terapia biologica e rischio di MACE

RISCHIO CARDIOVASCOLARE (MACE)

- Revisione sistematica di RCT (38 RCT con 12.024 pazienti
- **MACEs** (infarto del miocardio, incidente cerebrovascolare o morte cardiovascolare)
- Nessuna differenza statisticamente significativa nel rischio di MACE associato all'uso di terapie biologiche con anti-TNF, anti IL-12-23 o anti-IL17 in monoterapia.

Rungapiromnan W, et al. Br J Dermatol. 2017

› Postepy Dermatol Alergol. 2020 Dec;37(6):986-994. doi: 10.5114/ada.2020.102121. Epub 2021 Jan 6.

How current biologic therapies affect the risk of major adverse cardiovascular events in patients with plaque psoriasis? A systematic review and meta-analysis of randomized controlled trials

Sonia Nartowicz [1], Ewelina Jakielska [1], Monika Priadka [1], Zygmunt Adamski [1], Piotr Ratajczak [2], Krzysztof Kus [2]

Affiliations + expand

PMID: 33603620 PMCID: PMC7874875 DOI: 10.5114/ada.2020.102121

Free PMC article

Abstract

Introduction: Concerns have been raised about an increased risk of major adverse cardiovascular events (MACEs) - stroke, myocardial infarction and sudden cardiac death - in patients with plaque psoriasis receiving biologic therapies.

Aim: This review and meta-analysis of randomized controlled trials (RCTs) was to evaluate the risk difference of MACEs between experimental and comparator interventions.

Material and methods: We searched MEDLINE database for suitable trials. Prior to that we identified the search strategy and eligibility criteria. Each RCT was double-blind, placebo controlled and scored five points in Jadad scale. We calculated risk difference (RD) with use of the Mantel-Haenszel fixed-effect method with 95% confidence intervals (CIs) and calculated i2 statistic to assess heterogeneity. A total of 43 RCTs were included, involving 19,161 patients. Overall, the risk of MACEs in the included studies was 0.1% (n = 21).

Results: There were no statistically significant risk differences in patients treated with biologic therapy vs. placebo (RD = 0.0; Z = 1.09; 95% CI: 0.0-0.0; p = 0.28); tumour necrosis inhibitors vs. placebo (RD = 0.0; Z = 0.47; 95% CI: -0.0-0.0; p = 0.64); anti-IL-17A agents vs. placebo (RD = 0.0; Z = 1.25; 95% CI: -0.0-0.01; p = 0.21); anti-IL-23 agents vs. placebo (RD = 0; Z = 0.36; 95% CI: -0.0-0.01; p = 0.72); anti-IL-12/23 agents vs. placebo (RD = 0.0; Z = 0.73; 95% CI: -0.0-0.0; p = 0.46).

Multicenter Study › J Eur Acad Dermatol Venereol. 2020 Apr;34(4):769-778. doi: 10.1111/jdv.16018. Epub 2019 Nov 19.

Risk of major cardiovascular events in patients with psoriasis receiving biologic therapies: a prospective cohort study

W Rungapiromnan [1], K J Mason [2], M Lunt [2], K McElhone [2], A D Burden [3], M K Rutter [4 5], R B Warren [2 6], C E M Griffiths [2 6], D M Ashcroft [1], BADBIR Study Group

Collaborators, Affiliations + expand

PMID: 31633837 PMCID: PMC7155017 DOI: 10.1111/jdv.16018

Free PMC article

Abstract

Background: The cardiovascular safety profile of biologic therapies used for psoriasis is unclear.

Objectives: To compare the risk of major cardiovascular events (CVEs; acute coronary syndrome, unstable angina, myocardial infarction and stroke) in patients with chronic plaque psoriasis treated with adalimumab, etanercept or ustekinumab in a large prospective cohort.

Methods: Prospective cohort study examining the comparative risk of major CVEs was conducted using the British Association of Dermatologists Biologics and Immunomodulators Register. The main analysis compared adults with chronic plaque psoriasis receiving ustekinumab with tumour necrosis-α inhibitors (TNFi: etanercept and adalimumab), whilst the secondary analyses compared ustekinumab, etanercept or methotrexate against adalimumab. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated using overlap weights by propensity score to balance baseline covariates among comparison groups.

Results: We included 5468 biologic-naïve patients subsequently exposed (951 ustekinumab; 1313 etanercept; and 3204 adalimumab) in the main analysis. The secondary analyses also included 2189 patients receiving methotrexate. The median (p25-p75) follow-up times for patients using ustekinumab, TNFi, adalimumab, etanercept and methotrexate were as follows: 2.01 (1.16-3.21), 1.93 (1.05-3.34), 1.94 (1.09-3.32), 1.92 (0.93-3.45) and 1.43 (0.84-2.53) years, respectively. Ustekinumab, TNFi, adalimumab, etanercept and methotrexate groups had 7, 29, 23, 6 and 9 patients experiencing major CVEs, respectively. No differences in the risk of major CVEs were observed between biologic therapies [adjusted HR for ustekinumab vs. TNFi: 0.96 (95% CI 0.41-2.22); ustekinumab vs. adalimumab: 0.81 (0.30-2.17); etanercept vs. adalimumab: 0.81 (0.28-2.30)] and methotrexate against adalimumab [1.05 (0.34-3.28)].

Conclusions: In this large prospective cohort study, we found no significant differences in the risk of major CVEs between three different biologic therapies and methotrexate. Additional studies, with longer term follow-up, are needed to investigate the potential effects of biologic therapies on incidence of major CVEs.

ESC European Society of Cardiology
Cardiovascular Research (2019) 115, 721–728
doi:10.1093/cvr/cvz009

FAST-TRACK COMMUNICATION

Coronary artery plaque characteristics and treatment with biologic therapy in severe psoriasis: results from a prospective observational study

Youssef A. Elnabawi[1], Amit K. Dey[1], Aditya Goyal[1], Jacob W. Groenendyk[1], Jonathan H. Chung[1], Agastya D. Belur[1], Justin Rodante[1], Charlotte L. Harrington[1], Heather L. Teague[1], Yvonne Baumer[1], Andrew Keel[1], Martin P. Playford[1], Veit Sandfort[1], Marcus Y. Chen[1], Benjamin Lockshin[2], Joel M. Gelfand[3], David A. Bluemke[4], and Nehal N. Mehta[1]*

[1]Section of Inflammation and Cardiometabolic Disease, National Heart, Lung, and Blood Institute; National Institutes of Health, Bethesda, MD, USA; [2]DermAssociates, Silver Spring, MD, USA; [3]Department of Dermatology, University of Pennsylvania, Philadelphia, PA, USA; and [4]Department of Radiology, University of Wisconsin, Madison, WI, USA

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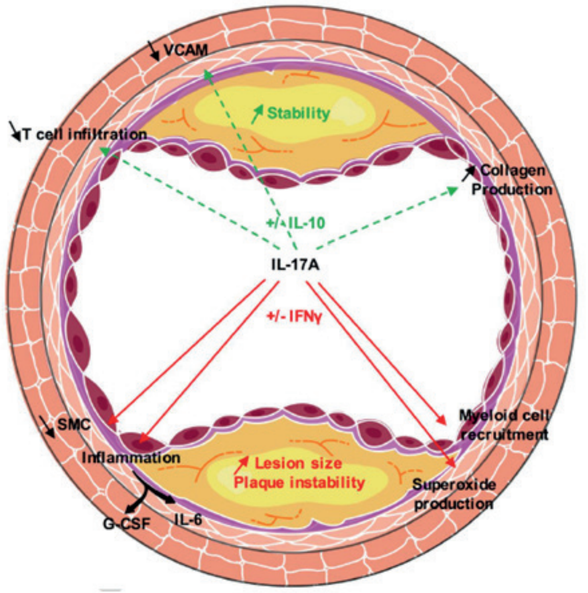


In uno studio osservazionale prospettico:

- Caratterizzazione della placca dell'arteria coronarica prima e dopo la terapia biologica in uno studio in aperto con 290 partecipanti, reclutati dal 1 gennaio 2013 al 31 ottobre 2018 dei quali 215 hanno completato il follow-up di un anno.
- **89 pazienti con psoriasi trattati con farmaci biologici vs 36 con topici (tutti i pazienti naive ai trattamenti sistemici)**
- Tutti i pazienti avevano **basso rischio di CVD**
- Angiografia con tomografia computerizzata ed esami del sangue (chimica di base, pannello lipidico completo, insulina e proteina C-reattiva ad alta sensibilità).

Elnabawi YA, et al JAMA Cardiol. 2019

Table 3 Coronary artery parameters by artery at baseline and one-year follow-up

Coronary characterization	Biologic treated (n = 267 arteries)				Non-biologic treated (n = 96 arteries)			
	Baseline	One-year	Change (%)	*P*-value	Baseline	One-year	Change (%)	*P*-value
Total plaque burden (mm^2)	1.30 ± 0.60	1.24 ± 0.60	-0.06 (-5)	**0.009**	1.28 ± 0.53	1.31 ± 0.48	0.03 (2)	0.22
Dense-calcified plaque burden (mm^2)	0.064 ± 0.12	0.067 ± 0.14	0.003 (5)	0.36	0.082 ± 0.17	0.084 ± 0.15	0.002 (2)	0.48
Non-calcified plaque burden (mm^2)	1.22 ± 0.59	1.15 ± 0.60	-0.07 (-6)	**0.005**	1.19 ± 0.41	1.25 ± 0.41	0.06 (5)	0.17
Plaque morphology index								
Fibrous burden (mm^2)	0.99 ± 0.45	0.98 ± 0.51	-0.01 (-1)	0.71	0.98 ± 0.32	0.94 ± .31	-0.04 (-4)	0.22
Fibro-fatty burden (mm^2)	0.22 ± 0.19	0.10 ± 0.14	-0.12 (-55)	**0.004**	0.16 ± 0.15	0.22 ± 0.14	0.06 (38)	**0.004**
Necrotic burden (mm^2)	0.07 ± 0.19	0.03 ± 0.09	-0.04 (-57)	**0.03**	0.06 ± 0.08	0.08 ± 0.22	0.02 (33)	0.27

Values are reported as mean ± SD for continuous data. Two-tailed *P*-values less than 0.05 deemed significant (bold values).

Elnabawi YA, et al JAMA Cardiol. 2019

Placche coronariche e farmaci biologici

- **Miglioramento significativo di hsCRP** con **anti-IL12/23** e **anti-IL17**
- Il **miglioramento del colesterolo HDL** è stato osservato solo nel **braccio trattato** con **anti-IL17**
- Una **riduzione del 5% del carico di placca non calcificata** con anti-TNF (P= 0,06), del 2% con anti-IL12/23 (P= 0,36) e del **12% con anti-IL17** (P= <0,001)
- Miglioramento della morfologia delle placche

Table 4 Change in non-calcified coronary plaque burden over one-year between treatment groups

Treatments	Change over one-year (mm^2) (%)		*P*-value
Anti-TNF therapy (*n* = 48)	-0.06 (-5)	–	
vs. Anti-IL12/23	–	-0.02 (-2)	0.27
vs. Anti-IL17	–	-0.15 (-12)	0.08
vs. NBT	–	0.06 (5)	**0.009**
Anti-IL12/23 therapy (*n* = 19)	-0.02 (-2)	–	
vs. Anti-IL17	–	-0.15 (-12)	**0.01**
vs. NBT	–	0.06 (5)	0.09
Anti-IL17 therapy (*n* = 22)	-0.15 (-12)	–	
vs. NBT	–	0.06 (5)	**0.005**

Values are reported as Mean (% change) for continuous data. Two-tailed *P*-values less than 0.05 significant (bold values).
IL, interleukin; NBT, non-biologic treated.

Elnabawi YA, et al JAMA Cardiol. 2019

› Life (Basel). 2021 Sep 5;11(9):919. doi: 10.3390/life11090919.

Impact of Interleukin-17 Inhibitor Therapy on Arterial Intima-media Thickness among Severe Psoriatic Patients

Éva Anna Piros [1 2], Ákos Szabó [2 3], Fanni Rencz [3], Valentin Brodszky [3], Klára Szalai [1], Noémi Galajda [1], Bálint Szilveszter [4], Edit Dósa [5 6], Béla Merkely [4], Péter Holló [1]

Affiliations + expand

PMID: 34575068 PMCID: PMC8471871 DOI: 10.3390/life11090919

Free PMC article

Abstract

Background: Psoriasis is frequently accompanied by cardiovascular diseases based on the shared immunopathogenic pathway. Authors determined the effect of interleukin (IL)-17 inhibitor therapy on arterial intima-media thickness (IMT) among severe psoriatic patients.

Methods: Thirty-one severe psoriatic patients were enrolled. Twenty received secukinumab and 11 received ixekizumab. Before treatment initiation and after 6 months, the carotid-brachial-femoral IMT, the Psoriasis Area Severity Index (PASI), the Dermatology Life Quality of Index (DLQI) and the EuroQol Visual Analogue Scale (EQ VAS) were evaluated.

Results: After 6 months, significant ameliorations were observed in PASI ($p < 0.001$) from 18 to 0, in DLQI ($p < 0.001$) from 17 to 0, in EQ VAS ($p < 0.001$) from 60 to 90, in right carotid IMT ($p < 0.001$) from 1.1 mm to 0.8 mm, in left carotid IMT ($p < 0.001$) from 1.1 mm to 0.7 mm, in right brachial IMT ($p < 0.001$) from 0.75 mm to 0.6 mm, in left brachial IMT ($p < 0.001$) from 0.8 mm to 0.5 mm, in right femoral IMT ($p < 0.001$) from 0.9 mm to 0.7 mm and in left femoral IMT ($p < 0.001$) from 0.8 mm to 0.7 mm.

Conclusions: By reducing the inflammation of the vascular wall, anti-IL-17 therapy may have a beneficial long-term effect on cardiovascular complications of systemic inflammation.

Randomized Controlled Trial › Can J Cardiol. 2020 Jan;36(1):100-111. doi: 10.1016/j.cjca.2019.06.021. Epub 2019 Jun 26.

Effects of Interleukin 17A Inhibition on Myocardial Deformation and Vascular Function in Psoriasis

George Makavos [1], Ignatios Ikonomidis [2], Ioanna Andreadou [3], Maria Varoudi [1], Irini Kapniari [4], Eleni Loukeri [3], Kostas Theodoropoulos [4], George Pavlidis [1], Helen Triantafyllidi [1], John Thymis [1], John Parissis [1], Maria Tsoumani [3], Pinelopi Rafouli-Stergiou [1], Pelagia Katsimbri [5], Evangelia Papadavid [4]

Affiliations + expand

PMID: 31606265 DOI: 10.1016/j.cjca.2019.06.021

Abstract

Background: Interleukin (IL)-17A activity is implicated in psoriasis. We investigated the effects of IL-17A inhibition on vascular and left ventricular (LV) function in patients with psoriasis.

Methods: A total of 150 patients with psoriasis received either an anti-IL-17A agent (secukinumab, n = 50), cyclosporine (n = 50), or methotrexate treatment (n = 50). At baseline and after 4 and 12 months of treatment, we measured (1) LV global longitudinal strain (GLS), GLS rate (GLSR), GLSR at early diastole, LV twisting, and untwisting; (2) coronary flow reserve (CFR); (3) pulse wave velocity (PWV); and (4) malondialdehyde and protein carbonyl as markers of oxidative stress.

Results: Compared with cyclosporine and methotrexate, anti-IL-17A treatment resulted in a greater increase in GLS at 4 and 12 months after treatment (10% and 14% with anti-IL-17A vs 2% and 2% with cyclosporine vs 4% and 4% with methotrexate, respectively), GLSR, GLSR at early diastole (45% and 41% vs 5% and 4% vs 7% and 9%, respectively), and LV twisting (32% and 28% vs 6% and 8% vs 7% and 6%, respectively) ($P < 0.05$). Anti-IL-17A treatment resulted in greater improvement of CFR and PWV than cyclosporine or methotrexate ($P < 0.05$). PWV increased after cyclosporine treatment (+11% at 4 and +14% and 12 months) ($P < 0.05$). Markers of oxidative stress were reduced only after anti-IL-17A treatment ($P < 0.05$). Changes of myocardial deformation markers and CFR after anti-IL-17A treatment correlated with a concomitant reduction of oxidative stress.

Conclusions: In psoriasis, inhibition of IL-17A results in a greater improvement of vascular and myocardial function compared with cyclosporine or methotrexate treatment, indicating a beneficial effect on overall cardiovascular function.

> Lipids Health Dis. 2021 Feb 18;20(1):16. doi: 10.1186/s12944-021-01441-9.

Metabolic profiling reveals interleukin-17A monoclonal antibody treatment ameliorate lipids metabolism with the potentiality to reduce cardiovascular risk in psoriasis patients

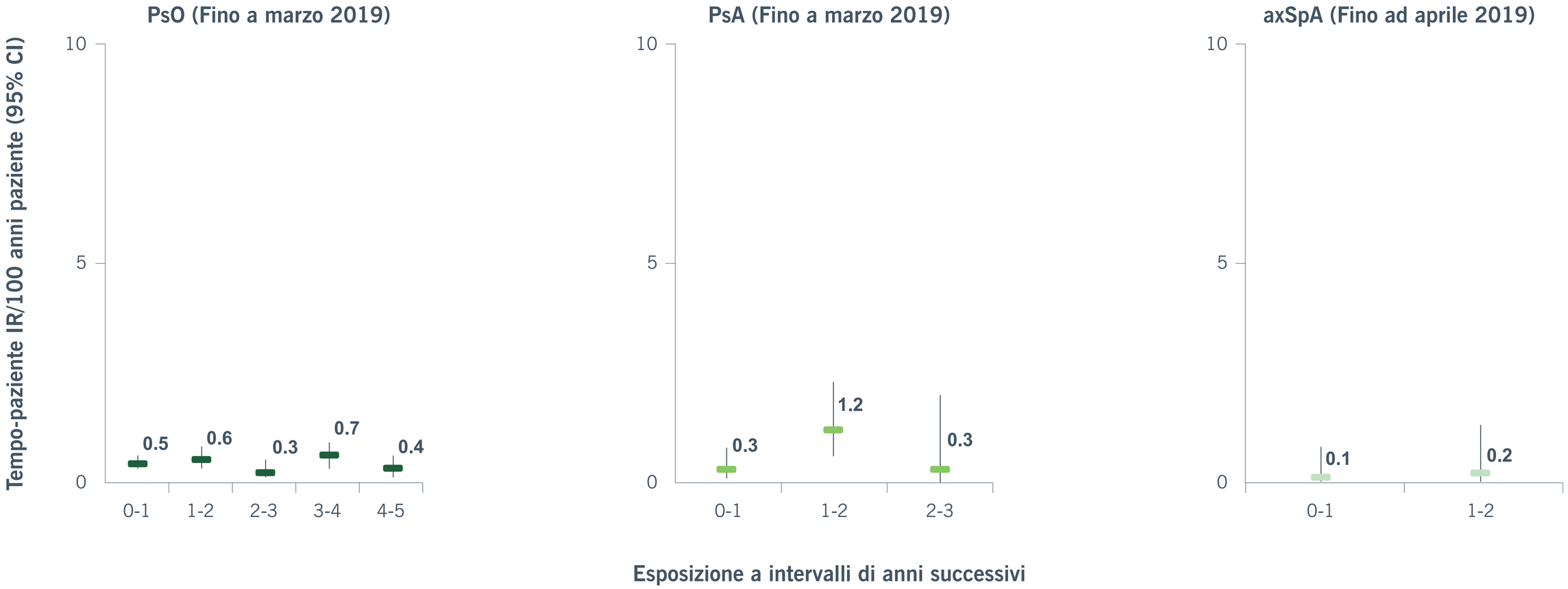
Han Cao [#1], Shengmin Su [#1], Qi Yang [2], Yunchen Le [2], Lihong Chen [2], Mengyan Hu [2], Xiaoyu Guo [1], Jie Zheng [2], Xia Li [3], Yunqiu Yu [4]

Affiliations + expand

PMID: 33602246 PMCID: PMC7890626 DOI: 10.1186/s12944-021-01441-9

Free PMC article

MACE: Risultati dagli studi di esposizione a ixekizumab nella PsO, nella PsA e nell'axSpA



Elnabawi YA, et al JAMA Cardiol. 2019

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Cardiovascular Risk in Patients with Psoriasis

Michael S. Garshick, MD, MS[a,b], Nicole L. Ward, PhD[c], James G. Krueger, MD, PhD[d], Jeffrey S. Berger, MD, MS[a,b,h,l]

SCREENING

Stile di vita errato
Fumo, dieta errata, inattività, depressione...

Comorbidità Cardiometaboliche

DIAGNOSTICA

Punteggio rischio CV
Fumo, dieta errata, inattività, depressione...

Severità psoriasi
Un maggiore coinvolgimento della malattia, la necessità di terapia sistemica o fototerapia identificano un rischio cv più elevato

INTERVENTO

Trattare i fattori di rischio CV tradizionali

Modulazione immunitaria
Terapie per ridurre il coinvolgimento cutaneo e articolare