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COVID-19 vaccine does not trigger psoriasis flares in psoriatic patients treated with apremilast

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Dear Editor,

Although COVID-19 vaccination is warmly suggested for psoriatic patients by several dermatological societies worldwide, only a recently published Italian case-series has sustained a safe and effective role of the vaccine in this patients' subset. Remarkably, vaccines information highlights that limited data are present for immunosuppressed patients and the vaccination should be performed in agreement with the vaccinator [1].

Furthermore, psoriasis itself is not considered an immunosuppressive status, but some anti-psoriatic, effective and safe drugs are codified as immunosuppressants. Thus, patients with moderate-to-severe psoriasis (PsO) undergoing target therapies [Interleukin (IL)-17 inhibitor (i), IL-12/23i, IL-23i and Tumor Necrosis Factor (TNF)-α], small molecules (apremilast, dimethyl fumarate) and conventional therapies (methotrexate, ciclosporin) are considered immunosuppressed by the World Health Organization (https://www.whocc.no/atc_ddd_methodology/who_collaborating_centre/). Among systemic anti-psoriatic treatments, only acitretin is not considered an immunosuppressant (Table 1).

Apremilast, a phosphodiesterase (PDE)-4 inhibitor, displays immunomodulatory effect on both keratinocytes and immune cells, decreasing cutaneous hyperplasia and mitigating the pro-inflammatory microenvironment. Noteworthy, apremilast is orally delivered and well-tolerated in young patients, neddle-phobics and in other circumstances that represent a relative contraindication for biologics (i.e. neoplasia or HIV) [2]. COVID-19 pandemic impacted on psoriatic patients adherence [3], anti-vax tendencies and lifestyles [4], complicating chronic immunosuppressive therapy monitoring. No data are present on apremilast and COVID-19 vaccines interaction to orient physician daily practice during the ongoing pandemic, so here we report three cases of PsO patients under apremilast that also underwent anti-COVID-19 vaccination.

Case 1. A 48-year-old male PsO patient with psoriatic arthritis (PsA), previously non-responder to ixekizumab and etanercept, underwent apremilast achieving stable remission for 8 months. Recently, he experienced a PsO and PsA flare during asymptomatic COVID-19 infection that

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resolved spontaneously 10 days after COVID-19 remission. Six months after it, he underwent the first and second doses of Pfizer mRNABNT162b2 vaccine without experiencing any PsO remitting.

Case 2. A 76-years-old male PsO patients under apremilast from 2017 with a stable residual Psoriasis Area Severity Index (PASI) 3. After the first dose of AZD1222 (AstraZeneca-Oxford vaccine) he experienced fever (38.5°C) and myalgia for 3 days, whilst the second dose was not complicated by side-effects. In both occasions he did not experience any psoriasis flare.

Case 3. A 36-years-old female with plaque psoriasis (PASI 3) and concurrent pustular psoriasis (Palmoplantar Psoriasis Area and Severity Index (PPPASI 2.3)) was stably treated with apremilast and narrow-band UVB for 3 years. She underwent Pfizer mRNABNT162b2 vaccine without any side-effects or psoriatic flare.

All patients developed IgG anti- SARS-CoV-2 S1- Receptor Binding Domain (RBD), suggesting that apremilast does not interfere with the acquisition of SARS-CoV-2 immunity. Furthermore, COVID-19 vaccines, both mRNA and viral vector based, did not trigger PsO or PsA flares in patients treated with apremilast. Interestingly, real-life data also highlighted the potential protective effect against SARS-CoV-2 in these patients' subset [5,6] and, at the same time, warning about the possible gastrointestinal and tasting side effects apremilast-related that may be misinterpreted as suggestive of COVID-19 [7,8].

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Table 1. The Anatomical Therapeutic Chemical (ATC) Classification System for the main systemic anti-psoriatic drugs published by the World Health Organization Collaborating Centre for Drug Statistics Methodology (WHOCC).

Systemic Drug	ATC five levels code					Immunosuppressant
	I[1]	II[2]	III[3]	IV[4]	V[5]	
Conventional therapies						
MTX	L	04	A	X	03	✓
Ciclosporin	L	04	A	D	01	✓
Acitretin	D	05	B	B	02	
Small molecules						
Apremilast	L	04	A	A	32	✓
Dimethyl fumarate	L	04	A	X	03	✓
Biologics						
Etanercept[6]	L	04	A	B	01	✓
Infliximab[6]	L	04	A	B	02	✓
Certolizumab	L	04	A	B	05	✓
Adalimumab[6]	L	04	A	B	04	✓
Ustekinumab	L	04	A	C	05	✓
Secukinumab	L	04	A	C	10	✓
Ixekizumab	L	04	A	C	13	✓
Brodalumab	L	04	A	C	12	✓
Guselkumab	L	04	A	C	16	✓
Tildrakizumab	L	04	A	C	17	✓
Risankizumab	L	04	A	C	18	✓

[1]One letter that indicates the anatomical main group among the 14 codified.

[2]Two digits that indicate the therapeutic subgroup.

[3]One letter that indicates the therapeutic/pharmacological subgroup.

[4]One letter that indicates the chemical/therapeutic/pharmacological subgroup.

[5]Two digits that indicate the chemical substance.

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[6] Included its biosimilars

https://www.whocc.no/atc_ddd_index/

Legend: MTX: Methotrexate, ATC: Anatomical Therapeutic Chemical Classification System

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