Dermatology Practical & Conceptual

Apremilast in Psoriasis Patients With Serious Comorbidities: a Case Series and Systematic Review of Literature

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ABSTRACT

Introduction: Patients with serious comorbidities are traditionally excluded from clinical trials. Apremilast is not contraindicated in active infections, malignancy and serious hepatic or renal impairment, but real-life data is needed to support this recommendation.

Objectives: The aim of this paper is to present our personal as well as literature-sourced real-world evidenced on apremilast use in psoriasis patients with serious baseline comorbidities.

Methods: A case-series and systematic literature review were performed. The psoriasis archives of a tertiary-care hospital, four electronic databases (MEDLINE, ScienceDirect, Cochrane Library, Google scholar) and other sources were searched (January 2014 – July 2021). Identified records were considered eligible, if they reported on the use of apremilast monotherapy in psoriasis patients with chronic infections, history of malignancy, serious liver, renal, psychiatric, or other disease(s).

Results: At least 841 psoriasis patients with serious baseline diseases received apremilast. Only 3 cases of cancer progression and no infection reactivations or worsening of other diseases were documented. No increased frequency/severity of adverse events or reduced drug efficacy were noted. Main limitations of this study are the exclusion of a few reports due to inappropriately documented data and the fact that at least some patients might have been counted more than once.

Conclusions: Apremilast is a safe and adequately efficacious option for psoriasis that cannot be treated/is challenging to treat with classic systemic agents and/or biologics.

Introduction

Psoriasis is a chronic cutaneous disease of inflammatory nature, with a worldwide prevalence ranging between 1-3%; it has a substantial negative effect on patient physical well-being and quality-of-life, as well as on national health expenditure [1–3]. Apremilast (Otezla®, Amgen), a small molecular inhibitor of phosphodiesterase 4 (PDE4), has been used for the treatment of psoriatic arthritis and psoriasis since 2014 (first US Food and Drug Administration [FDA] approval). Contrary to biologics, it does not target any one specific component of the inflammatory process involved in the pathophysiology of psoriasis, but rather achieves some sort of equilibrium of pro-inflammatory and anti-inflammatory agents [4,5].

Apremilast comes with a set of favorable attributes, among which are the oral distribution, lower cost comparing to biologics and good safety profile [3,6]. It is not contraindicated in patients with active infections or serious liver impairment, nor is routine lab monitoring necessary. Similarly, it can be administered to patients with past or current malignancy [8]. Patients with severe renal impairment can still receive a reduced dose of apremilast [9]. A pooled analysis (≥ 156 weeks) from the 2 apremilast-approving (ESTEEM) trials showed that serious infection rate was low among patients receiving apremilast, while no serious opportunistic infections or cases of tuberculosis reactivation were noted [10]. However, as patients with chronic infections, cancers and serious co-existing diseases are traditionally excluded from clinical trials testing new drugs, conclusions regarding the use of said drugs in these occasions cannot always be safely drawn [7,11].

Objectives

The purpose of this study is to present our five-year experience in administering apremilast to psoriasis patients with serious comorbidities in the setting of a tertiary-care center in terms of drug safety and efficacy, as well as to concisely portray relevant real-life evidence sourced through a systematic literature search.

Methods

Case Series

The March 2016 (apremilast approval in Greece) to June 30th, 2021 archives of both the Psoriasis Outpatient Clinic and Afternoon Private Clinics of the First Dermatology Department, Aristotle University, Thessaloniki, Greece were consecutively searched for all psoriasis patients having received at least one dose of apremilast. Patients with an appropriately documented chronic/latent infection, recent (past 10 years) malignancy excluding basal cell carcinoma, serious kidney (stage IV and V) or liver (Child-Pugh C) disease, severe psychiatric disorder or other serious illness as was defined by Kelley [12] were included in the study. The following data were retrieved by two collaborating authors (AT and NS): age, gender, comorbidity(-ies), year of comorbidity diagnosis, apremilast dose, baseline Psoriasis Area and Severity Index (PASI), treatment outcome in terms of efficacy, duration of apremilast treatment (weeks) and adverse events (AEs) including adverse outcomes related to comorbidity(-ies) in question. Written informed consent was obtained by all participants. This project was designed and conducted based on the declaration of Helsinki and was approved by the Ethics Committee of the Hospital of Venereal and Cutaneous Diseases, Thessaloniki, Greece.

Systematic Review

Eligibility Criteria

We conducted this systematic review as stated by Meta-analyses Of Observational Studies in Epidemiology (MOOSE) statement. Published and unpublished prospective or retrospective observational studies reporting on the use of apremilast for the treatment of psoriasis patients with serious baseline comorbidities (chronic/latent infections such as tuberculosis, hepatitis and HIV, cancer diagnosis within past ten years excluding basal cell carcinoma, stage IV and V chronic kidney disease hemodialysis, Child-Pugh class C liver disease, serious psychiatric disorders or other serious illness as was defined by Kelley [12]) were considered eligible for inclusion in our study. Clinical trials or studies not presenting real-life data, as well as studies reporting on combination therapy of apremilast and other systemic agents aside from phototherapy, systemic corticosteroids or other medication administered systemically for existing comorbidities were excluded from our review. Only studies performed after 2014 (apremilast first FDA approval) were considered. No language restrictions were placed.

Information Sources

Three electronic databases were searched (MEDLINE, ScienceDirect, and the Cochrane Library electronic databases). Google scholar (https://scholar.google.com/) was also browsed. Abstract compendia of the World Congresses of Dermatology, World Psoriasis and Psoriatic Arthritis Congresses, American Academy of Dermatology Annual Meetings and European Academy of Dermatology and Venereology Annual Congresses of the last five years were examined (online browsing). Last search date for all above mentioned platforms was July 4th, 2021. Amgen® was

contacted and kindly asked to supply our team with any published or unpublished data abiding by our search criteria. The "Reference" section of studies included in our review was hand searched for additional eligible work.

Search Strategy

The following search strategy was used for MEDLINE database and modified accordingly for the rest of searched platforms: (apremilast[Title]) AND (psoriasis[Title/Abstract]) filtered by year of publication (2014 to 2021). The search was performed independently by two authors (AT and NS).

Study Endpoints

The primary endpoint of this study was the documentation of any safety-related outcomes in patients with serious comorbidities having received apremilast (for example comorbidity progression, AEs commonly related to apremilast use or other events). Secondary endpoint was treatment efficacy, without any limitations imposed on efficacy measures used.

Selection Process and Data Collection

Duplicate records were independently manually removed by two reviewers (NS and AT). Subsequently, two reviewers (AT and NS) independently screened titles and abstracts for relevance to the study objective. The full text of remaining records was read, and eligible studies were included in the review. AT and NS separately extracted the following data from included studies according to a pre-formulated sheet: first author, year of publication / research completion, comorbidity(-ies), age and gender of patient(-s), apremilast dose, baseline PASI, AEs including comorbidity-related events. Any disagreements were resolved in consultation with a third author (ES).

Quality Assessment

Two authors (AT and ES) independently assessed included reports based on two different tools, namely the Joanna Briggs Institute (JBI) critical appraisal tool for case reports/case series and the JBI critical appraisal tool for analytical cross-sectional studies, each comprising eight questions (Supplement). Each study was assigned an overall rating of poor, good or fair, if 0-5, 6-7 or 8 criteria were met respectively.

Results

The psoriasis-archives search returned 16 eligible cases, one of which was not included in the analysis due to incompletely documented patient data (Table 1). No progression of malignancy, reactivation of chronic / latent infection or deterioration of already deficient renal or hepatic function were noted. Apremilast was generally well-tolerated and only mild transient AEs were reported in 6 patients. Patient compliance to treatment was high (three cases of temporary drug discontinuation, < 14 days, due to Covid-19-related restrictions and consequent difficulties in drug prescription). Desired response (PASI50) was not achieved in 1 case and apremilast was therefore discontinued (primary drug failure).

The systematic literature search yielded 52 studies eligible for inclusion (Figure 1). One additional study was identified after the last search date (published July 8th 2021) and does not appear in the flow diagram (Figure 1) [13]. A total of at least 826 psoriasis patients with serious comorbidities (various malignancies – at least 456 patients –, latent / past tuberculosis – 49 patients –, hepatitis B, C and HIV infections – at least 83 patients –, serious renal – 7 patients – or liver impairment – at least 110 patients –, serious psychiatric disorders – 49 patients – or other serious illness as was defined by Kelley [12]) were prescribed apremilast twice or once daily (Table 2). The exact number of patients with serious comorbidities prescribed apremilast was not reported in a few studies, therefore, the numbers mentioned above are a conservative underestimation of the studied population. Included patients manifested all types of psoriasis and/or nail psoriasis. Overall, apremilast was hardly ever associated with negative comorbidity-related outcomes and reported AEs were apparently not more severe or frequent than those experienced by the average psoriasis patient. Sufficient response of psoriasis to apremilast was recorded in most cases. Overall, the quality of included studies was good (Table 3).

Conclusions

This case series and systematic review reports on the use of apremilast in 841 psoriasis patients with serious baseline comorbidities, which would have made the use of classic systemic agents and/or biologics inappropriate or challenging. According to our study, the use of apremilast in this group of patients apparently neither leads to deterioration / exacerbation of severe pre-existing comorbidity(-ies) nor is it associated with an increased risk of adverse events. What is more, drug efficacy does not seem to be affected by the underlying comorbidity, with cases of remarkable response even in erythrodermic patients with very serious underlying diseases.

A drug safety profile, especially in the context of pre-existing comorbidities, is one of its major attributes to be taken into consideration, when deciding on a treatment regimen [14]. Psoriasis patients receiving apremilast, as opposed to other systemic agents, seem to have a lower infection risk [15]. Rates of herpes zoster infection were lowest for users of apremilast among a cohort of psoriasis patients treated with biologics and/or small molecules (5.4, 95% CI 1.7-12.6) [16]. Comparing to methotrexate (MTX), as investigated in a cohort of 2845 psoriasis patients treated

Table 1. Cases of psoriasis patients with serious baseline comorbidities treated with apremilast.

Case	Sex	Age	Comorbidity (diagnosis)	APR Dose	Bas PASI	Tx outcome	APR duration	AEs
1	M	69	Prostate cancer (2013)	30 mg bid	10.3	PASI50 week 16	53 (LOoE)	None
2	M	76	Lung tuberculosis (1968)	30 mg bid	9	PASI50 week 16	52 (Lost to f/u)	None
3	M	73	Latent tuberculosis	30 mg bid	13.4	PASI75 week 16	72 (LOoE)	None
4	M	79[a]	Lung cancer (2015)	30 mg bid	15.9	PASI50 not achieved	21 (LAoE)	Abdominal pain
5	F	65	Breast cancer (2016), hepatitis B	30 mg bid	5.3	PASI100 24 weeks	35 (clear skin)	Dyspepsia
6	M	63	Hepatitis C and liver fibrosis	30 mg bid	6.7	PASI50 week 16	37 (LOoE)	None
7	M	44	Hemodialysis (Stage 5 Chronic kidney disease – IgA nephropathy)	30 mg od	13.2	PASI50 week 24	40 (LOoE)	None
8	F	66	Lung tuberculosis (1980)	30 mg bid	11.1	PASI50 week 16	4 (AEs)	Headache
9	M	33	HIV positive (2011) (CD4+ 602 cells/mm^3)	30 mg bid	15.8	PASI75 week 16	149 (SoD)	None
10	M	65	Urinary bladder cancer (2015), Stage 2 chronic kidney disease	30 mg bid	9.1	PASI50 week 16	31 (LOoE)	None
11	F	56	Cervical cancer (2013)	30 mg bid	10.8	PASI75 week 24	154 (SoD)	None
12	M	37	HIV positive (2009) (CD4+ 590 cells/mm^3)	30 mg bid	24.5	PASI50 week 24	56 (SoD)	Transient nausea
13	M	44	HIV positive (2002) (CD4+ 550 cells/mm^3)	30 mg bid	33.6	PASI90[q] week 52	104 (SoD)	Transient diarrhea
14	M	32	HIV positive (2009) (CD4+ 702 cells/mm^3)	30 mg bid	19.3	PASI90 week 24	34 (SoD)	Transient diarrhea
15	M	88	Hepatitis B	30 mg bid	28.6	PASI90 week 8	16 (SoD)	None

AEs = adverse events; APR = apremilast; Bas = baseline; F = female; f/u = follow-up; HIV = human immunodeficiency; LAoE = lack of efficacy; LOoE = loss of efficacy; M = male; o.d. = once daily; PASI = Psoriasis Area and Severity Index;; bid = twice daily (bis in die); PASI50 = 50% reduction of baseline PASI; PASI75 = 75% reduction of baseline PASI; virus; PASI90 = 90% reduction of baseline PASI; SoD = still on drug; Tx = treatment.

[a]Deceased.

with nine systemic agents in Spain, apremilast had a lower infection (incidence rate 0.3 [95% CI 0.1-0.9]) and malignant neoplasm risk (incidence rate 0.1 [95% CI 0-0.7]) [14].

Psoriasis may be more severe or difficult to treat in patients with HIV infection [17,18]. What is more, HIV-positive patients are immuno-compromised and prone to reactivation of latent infections [17]. According to the 2020 Belgian practical recommendations for the treatment of psoriasis in HIV-positive patients, apremilast and acitretin are considered first-line choices]. Furthermore, many biologics (adalimumab, certolizumab pegol, etanercept, infliximab, ustekinumab, guselkumab, risankizumab, brodalumab, secukinumab, ixekizumab) can be used in patients receiving highly active antiretroviral therapy (HAART) and having undetectable viral load [19]. In case of detectable viral load, discussion with an infectious-disease specialist is warranted, with apremilast and acitretin being the preferred options [19]. Based on the same recommendations, the preferred options for short-term systemic treatment of psoriasis patients with chronic hepatitis C infection are adalimumab and etanercept, as there is not enough evidence to support the use of other biologics and apremilast [19]. As far as chronic hepatitis B infection is concerned, ustekinumab, apremilast, cyclosporine and acitretin are preferred [19]. Apremilast has shown potential in the treatment of psoriasis patients with a history of malignancy. It may even help treat lung cancer, as PDE4 is expressed in lung cancer cells [20].

In the current pandemic era, it is important to examine a drug safety with regards to the COVID-19 infection. According to the World Health Organization, psoriasis patients on

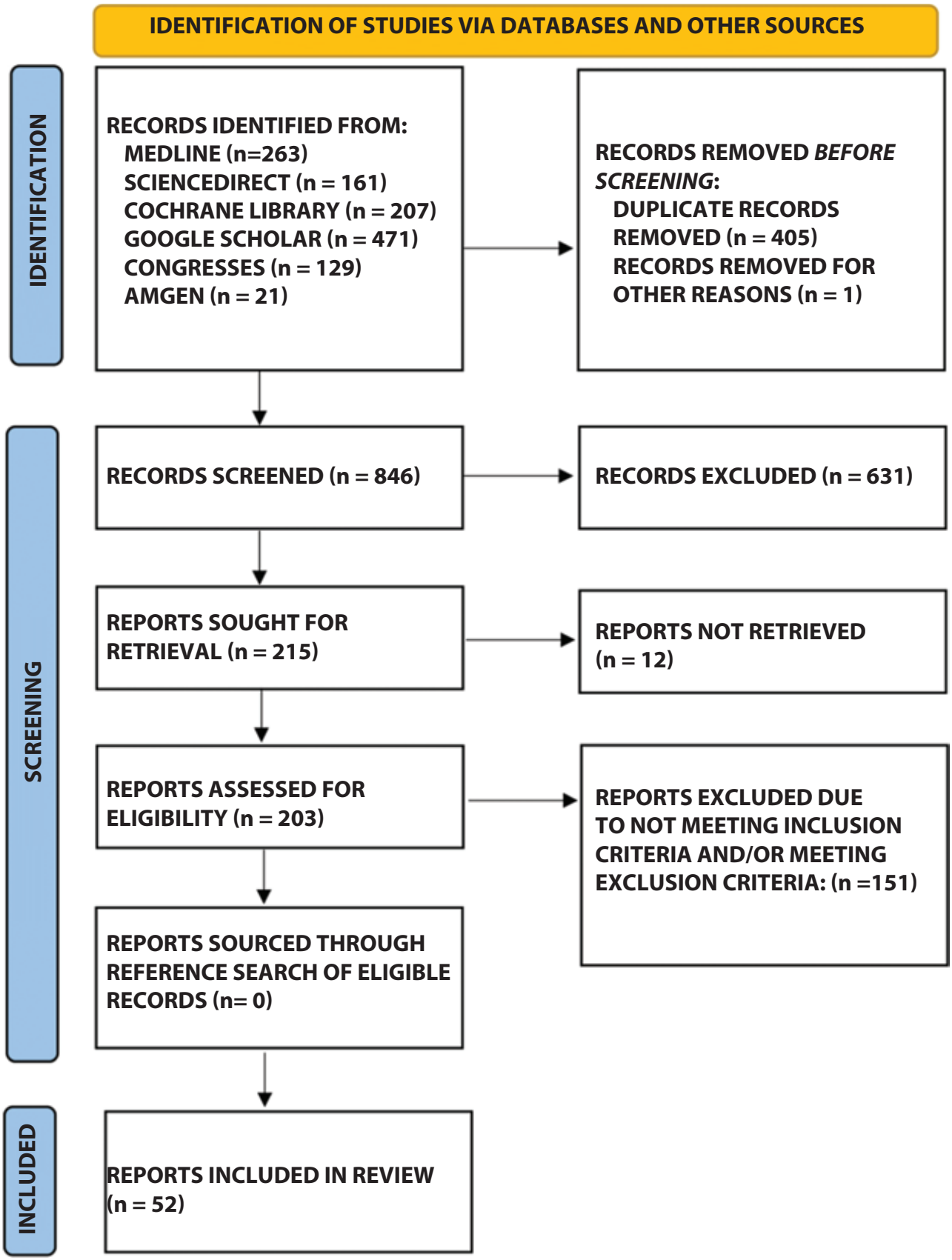

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram detailing the number and origin of records identified, included in and excluded from this systematic review, as well as the reasons for exclusion.

Table 2. Literature cases of apremilast administered to psoriasis patients with serious baseline comorbidities.

Report	Comorbidity	Age/Sex	APR dose	Bas PASI	Tx outcome	AEs
Mugheddu 2020 [22]	Recurrent brain oligodendroglioma under temozolomide and prednisone	45/M	30 mg bid	45	Improvement	N/R COVID-19 pneumonia, full recovery
Manfreda 2019 [15]	HIV positive (CD4+ 628 cells/mm3), Hepatitis B, drug addiction history	41/M	30 mg bid	12	PASI90W24	None, stable CD4+ count
Zarbafian 2019 [5]	HIV positive (CD4+ >1000 cells/mm^3)	54/M	30 mg bid	10.2	73% PASI reduction M7	Transient diarrhea, frequent URTIs, stable CD4+ count
Reddy 2017 [4]	HIV positive, Hepatitis C	46/M	30 mg bid	BSA 8%	BSA 1.5% M5	None
Shah 2019 [18]	HIV positive (CD4+ 742/µl)	35/M	30 mg bid, then od	14.7	PASI100 W6	None, stable CD4+ count
Sacchelli 2018 [32]	HIV positive (2002) (CD4+ 566/mc), past Hepatitis B and C	55/M	30 mg bid	8 NAPSI[q] 21	PASI75M6 NAPSI 7 M6	None
Apalla 2019 [11]	Metastatic lung adenocarcinoma, stage IIIB (2013)	67/F	30 mg bid	18	PASI75 W16	None, cancer course not affected by APR
Reddy 2019 [17]	HIV positive (CD4+ 460 cells/mm^3)	50/M	30 mg bid and then od	BSA 10%	BSA 0% M3	N/R
Fotiadou 2018 [33]	Chronic hepatitis B, undetectable viral load	52/F	30 mg b.i.d.	13.2	PASI90 W24	None, normal HBload and LFTs
Jeon 2017 [34]	Active hepatitis C, decompensated cirrhosis, metastatic HCC	55/M	30 mg bid	N/R	PASI100 W6	Initial nausea
González-Cantero 2018 [35]	Malignancy: 3, liver disease: 1, alcoholism: 1, infectious disease: 1, renal insufficiency: 1, demyelinating disease: 1	N/R	N/R	N/R	N/R	No changes in the course of comorbidities
Gottlieb 2021 [36]	Malignancy: 92, serious infection: 53	N/R	N/R	N/R	N/R	N/R
Kahn 2019 [37]	1. renal cell carcinoma 2. melanoma	63, N/R 64, N/R	N/R	BSA 10% BSA 5%	N/R	No clinical/radiographical signs of cancer recurrence
Nagata 2019 [38]	Hemodialysis	60, M	30 mg od	PSSI 36	PSSI 10 W12	Nausea (transient)
Uvais 2020 [39]	Bipolar affective disorder	30, F	30 mg/day	N/R	N/R	N/R
Vico-Alonso 2020 [40]	Chronic myeloid leukemia under imatinib, latent tuberculosis, alcoholism, steatohepatitis	58, M	30 mg bid	22.4	PASI90 W24	None, stable tumoral state, normal lab tests
Melis 2020 [41]	Malignancy (excl. NMSC): 13 (breast, bladder, colorectal), severe infection: 7 (HIV, HBV, HCV), psychiatric disorder: 6, liver disease: 3, latent tuberculosis: 2	N/R	30 mg bid	N/R	N/R	N/R
Perrone 2017 [42]	Chronic anemia and thrombocytopenia	71, M	N/R	N/R	N/R	Fanconi Syndrome

Report	Comorbidity	Age/Sex	APR dose	Bas PASI	Tx outcome	AEs
Carpentieri 2020 [43]	Malignancy (excl. NMSC): 10	N/R	N/R	N/R	Most patients showed improvement	no clinical or radiographic recurrence or progression of their cancer
Peitsch 2019 [44]	Mantel cell lymphoma under rituximab, hepatic and pulmonary aspergillosis	60, M	30 mg bid	17.2	PASI90 M5	None, lymphoma in remission
Takama 2020 [45]	Urinary bladder cancer under pembrolizumab	74, M	30 mg bid, then od	2.9	PASI50 W2, PASI90 M2	Nausea
Foti 2021 [46]	Melanoma with lymph node metastasis under nivolumab	62, M	30 mg bid	44	PASI50 M6, PASI90 M12	None, no worsening of melanoma
Di Lernia 2021 [47]	Malignancy: 3 colorectal, 2 GI stromal, 1 leukemia, 1 lymphoma,1 kidney, 1 uterus and thyroid, 2 melanoma,1 urinary bladder,1 metastatic SCC, 1 prostate	5 F, 9 M (age N/R)	30 mg bid	N/R	N/R	Diarrhea, headache (3 patients, disc. APR), urinary bladder cancer and metastatic SCC recurrence after APR disc.
Aragon-Miguel 2019 [48]	Malignancy hx: 6, latent tuberculosis: 16, hepatitis C or B (chronic or past): 7	N/R	N/R	N/R	N/R	N/R No infection reactivations
Tampouratzi 2019 [49]	Chronic hepatitis B, under entecavir	64, M	N/R	N/R	Excellent response	None
Papadavid 2018 [50]	Malignancy hx: 1, latent tuberculosis: 1, chronic latent hepatitis B: 1	N/R	N/R	N/R	N/R	N/R
Sahuquillo-Torralba 2020 [51]	Latent tuberculosis: 1, active hepatitis B: 1, spontaneous bacterial peritonitis: 1, immune hepatitis: 1	N/R	N/R	N/R	N/R	N/R
Siciliano 2020 [52]	Metastatic melanoma (2018)	75, M	30 mg bid	N/R	Improvement	None, melanoma remission
Lanna 2020 [53]	Tumors: 5	N/R	N/R	N/R	N/R	N/R
Lanna 2019 [54]	Hepatitis E	55, M	30 mg bid	18	PASI90 M6	None
Balato 2020 [55]	Malignancy: 40	N/R	N/R	N/R	N/R	Lower PASI50 and PASI75 response rates
Queiro Silva 2020 [21]	Hairy cell leukemia	55, M	N/R	N/R	N/R	Severe COVID-19 infection
Ighani 2018 (1) [56]	Malignancy hx: 15, liver disease: 8, psychiatric disorder: 9	N/R	N/R	N/R	N/R	N/R
Ighani 2018 (2) [57]	Malignancy hx: 31, liver disease: 27, psychiatric disorder: 29	N/R	N/R	N/R	N/R	N/R

Table 2 continues

Table 2. Literature cases of apremilast administered to psoriasis patients with serious baseline comorbidities. *(continued)*

Report	Comorbidity	Age/Sex	APR dose	Bas PASI	Tx outcome	AEs
Ighani 2018 (3) [58]	Malignancy hx: 5, liver disease: 4, psychiatric disorder: 4	N/R	N/R	N/R	N/R	N/R
Phan 2020 [59]	Malignancy: 40	>65 y	N/R	N/R	N/R	N/R
Ighani 2018 (4) [60]	hepatitis C: 2, breast cancer: 2, renal disease (unspecified): 2	N/R	N/R	N/R	N/R	N/R
Megna 2020 [61]	Malignancy: 9, hepatitis C: 4, latent tuberculosis: 3	N/R	N/R	N/R	N/R	N/R
Del Alcázar 2020 [62]	Lung cancer: 20, latent tuberculosis: 20, hepatitis C: 17, hepatitis B: 13, hepatitis B and C: 2, malignancy hx: 92, liver disease: 33	N/R	N/R	N/R	N/R	No cases of infection reactivation or cancer recurrence
Fremlin 2017 [63]	Cases of alcohol excess, alcoholic liver disease, previous malignancy (unspecified number)	N/R	N/R	N/R	N/R	N/R
Foulkes 2017 [64]	Cases of malignant melanoma and HIV (unspecified number)	N/R	N/R	N/R	N/R	N/R
Malara 2018 [65]	Latent tubercular skin infection: 2, previous hepatitis: 1, endocarditis-related cardiac valve failure: 1, malignancy: 4	N/R	N/R	N/R	N/R	None
Daudén 2020 [14]	Malignancy hx: 14 (6 in last 5 years), hepatitis B:12, hepatitis C: 5, chronic liver disease: 20, renal insufficiency: 3	N/R	N/R	N/R	N/R	N/R
Kungurov 2019 [66]	Hepatitis B: 1, chronic pancreatitis, cholecystitis and colitis: 1, hepatitis C: 1	47, F 38, F 31, M	N/R	27.3 29.9 33	PASI75 W24 PASI75 W6 PASI75 W28	None
Aragon-Miguel 2019 [67]	breast cancer: 1, gallbladder cancer: 1, treated latent tuberculosis: 3	N/R	N/R	N/R	N/R	N/R
Bulic 2019 [68]	1. laryngeal SCC (2013) 2. papillary thyroid cancer (2014) 3. liver cirrhosis (Child-Pugh B)/portal hypertension/ hepatocellular cancer (pT2pNxpMx)/ liver transplant (2017) 4. melanoma (pT1a, Breslow 0.81mm) (2013)	51, M 50, M 51, M 58, F	N/R	N/R	N/R	No recurrency of malignancy over a two-year follow-up
Fattore 2019 [69]	Non-metastatic non-small-cell lung cancer under nivolumab	74, F	30 mg bid	N/R	PASI100 W6	Transient nausea
Magdaleno 2019 [70]	Chronic liver disease: 13, severe infection: 11, previous malignancy: 8	N/R	N/R	N/R	N/R	N/R

Report	Comorbidity	Age/Sex	APR dose	Bas PASI	Tx outcome	AEs
Magdaleno-Tapial 2019 [71]	Chronic active alcoholism and hyper-transaminasemia	61, M	N/R	N/R NAPSI 32	PASI<5 M6	No serious AEs
Gioe 2021 [72]	Chronic hepatitis B, bipolar disorder, acute MRSA[ee] bacteremia, pulmonary embolus	34, F	N/R	N/R (>95% BSA)	BSA< 15% M1	N/R
Ibarguren 2021 [73]	1. Stage IV uveal melanoma 2. Stage IV laryngeal carcinoma 3. Stage IV squamous cell lung carcinoma all 3 under nivolumab	50, M 70, M 60, M	30 mg bid	12 13.8 6.4	PASI50 M12 PASI75 (time N/R) PASI50 not achieved	1. diarrhea 2. headache, cancer progression after 10 months 3. cancer progression after 10 months
Kurata 2021 [74]	Colorectal cancer within past year	82, F	N/R	5.5 NAPSI 77	PASI90 and NAPSI50 W8	γ-GT increase after 8 weeks & drug disc.
Cohen-Sors 2021 [13]	Hematologic malignancy: 10	N/R	N/R	N/R	N/R	Evolution of previously stable CLL (1 case)

AEs = adverse events; APR = apremilast; Bas = baseline; bid = twice daily; BSA = body surface area; F = female; CLL = chronic lymphocytic leukemia; disc. = discontinuation; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; HIV = human immunodeficiency virus; hx = history; LFTs = liver function tests; M = male; M = month; MRSA = methicillin resistant staphylococcus aureus; NAPSI = nail psoriasis severity index; NMSC = non-melanoma skin cancer; N/R = not reported; od = once daily; PASI = Psoriasis Area and Severity Index; PASI50 = 50% reduction of baseline PASI; PASI75 = 75% reduction of baseline PASI; PASI90 = 90% reduction of baseline PASI; PASI100 = 100% reduction of baseline PASI; PSSI = psoriasis scalp severity index; SCC = squamous cell carcinoma; Tx = treatment;y = years old; URTIs = upper respiratory tract infections; W = week.

Table 3. Methodological quality assessment of included reports.

Report	Mugheddu 2020 [22]	Manfreda 2019 [15]	Zarbafian 2019 [5]	Reddy 2017 [4]	Shah 2019 [18]	Sacchelli 2018 [32]	Apalla 2019 [11]	Reddy 2019 [17]	Fotiadou 2018 [33]	Jeon 2017 [34]
Quality	Fair	Fair	Fair	Fair	Fair	Fair	Fair	Fair	Fair	Fair
Report	Gonzalez-Cantero 2018 [35]	Gottlieb 2021 [36]	Kahn 2019 [37]	Nagata 2019 [38]	Uvais 2020 [39]	Vico-Alonso 2020 [40]	Melis 2020 [41]	Perrone 2017 [42]	Carpentieri 2020 [43]	Peitsch 2019 [44]
Quality	Good	Good	Good	Good	Good	Fair	Good	Fair	Good	Fair
Report	Takama 2020 [45]	Foti 2021 [46]	Di Lernia 2021 [47]	Aragon-Miguel 2019 [48]	Tampouratzi 2019 [49]	Papadavid 2018 [50]	Sahuquillo-Torralba 2020 [51]	Siciliano 2020 [52]	Lanna 2020 [53]	Lanna 2019 [54]
Quality	Fair	Fair	Good	Good	Good	Good	Good	Good	Good	Good
Report	Balato 2020 [55]	Queiro Silva 2020 [21]	Ighani 2018 (1) [56]	Ighani 2018 (2) [57]	Ighani 2018 (3) [58]	Phan 2020 [59]	Ighani 2018 (4) [60]	Megna 2020 [61]	Del Alcazar 2020 [62]	Fremlin 2017 [63]
Quality	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good
Report	Foulkes 2017 [64]	Malara 2018 [65]	Daudén 2020 [14]	Kungurov 2019 [66]	Aragon-Miguel 2019 [67]	Bulic 2019 [68]	Fattore 2019 [69]	Magdaleno 2019 [70]	Magdaleno-Tapial 2019 [71]	Gioe 2021 [72]
Quality	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good
Report	Ibarguren 2021 [73]	Kurata 2021 [74]	Cohen-Sors 2021 [13]							
Quality	Good	Good	Good							

Case reports have been assessed through the JBI critical appraisal checklist for case reports. Cross-sectional studies have been assessed through the NIH quality assessment tool for observational cohort and cross-sectional studies. Each report has been assigned an overall quality marking of poor, good or fair.

small molecules like apremilast are thought to be immunosuppressed [6]. There have been reports of asymptomatic, as well as of fast and uneventful resolution of COVID-19 infections in psoriasis patients under apremilast, even in the case of serious comorbidities [21-23]. What is more, it seems that apremilast use does not hinder the formation of antibodies against SARS-CoV-2 [6]. It is important to remember that common apremilast AEs like taste alteration and gastrointestinal symptoms can mimic COVID-19 manifestations [6].

A relatively new, special population of psoriatic patients are those receiving therapy with immune checkpoint inhibitors (ICPIs) for various types of cancer. ICPIs have revolutionized cancer treatment and their use expands constantly. They include monoclonal antibodies that target cytotoxic T lymphocyte–associated antigen-4 (CTLA-4), programmed cell death protein 1 (PD-1), or programmed death ligand 1 (PD-L1) [24]. Due to the unique nature of ICPIs, a new category of AEs emerged concurrently with their clinical use [24]. They are known as "immune-related adverse events" (irAEs) and although they can affect any organ, skin is the one most frequently involved [24]. Morbilliform exanthems, pruritus, vitiligo and lichenoid eruptions are by far the most common cutaneous irAEs [25,26]. Numerous others have been reported, among which newly occurring or exacerbating previous psoriasis.

In the majority of cases, cutaneous irAEs are mild-to-moderate (grade 1-2) and anti-cancer treatment is not interrupted, although severity may vary, up to life-threatening Stevens-Johnson syndrome/toxic epidermal necrolysis [27,28]. Similarly, psoriasis is usually managed with topical treatment [24,29]. In moderate/severe cases, treatment is more complicated since immunosuppression by anti-psoriatic drugs can theoretically lead to tumor escape. In those patients, apremilast seems to be a relatively safe and effective choice, however its use is supported only by case reports/small case series. Finally, an algorithm published recently by the ENCADO (European Network for Cutaneous Adverse Event to Oncologic Drugs) also suggests apremilast if the patient does not respond to phototherapy and/or acitretin [30].

Our study is not without its limitations. A few large studies like Armstrong and Levi were excluded from this review and potentially significant data was missed, because results were not reported separately for patients receiving apremilast monotherapy and those receiving combination treatment or other systemic agents [31]. On the other hand, it is fairly possible that some patients included in this review have been counted more than once, as they might have been sourced from the same databases or research centers (eg multiple publications by the same authors, Table 2). What is more, in studies reporting on multiple patients, efficacy and safety outcome measures were usually presented indistinguishably for all included patients and not individually, based on the comorbidity status, therefore the relevant fields of Table 2 could not be filled in. Last but not least, baseline comorbidity cases such as chronic infections were sometimes presented as a total number, without distinguishing among different types of eg infections.

All in all, according to this case series and systematic review, real-life use of apremilast so far suggests that the latter is indeed a safe and adequately efficacious option for moderate-to-severe psoriasis that cannot be treated/is challenging to treat with classic systemic agents and/or biologics. What is more, there seems to be no increased risk of COVID-19 infection in patients receiving apremilast, with evidence suggesting a smoother course of the disease.

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