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 andSeverity 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
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 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 [1]. 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].

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| 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*| 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/mm³) | 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/mm³) | 30 mg bid | 24.5    | PASI50 week 24 | 56 (SoD) | Transient nausea |
| 13   | M   | 44  | HIV positive (2002) (CD4+ 550 cells/mm³) | 30 mg bid | 33.6    | PASI90³ week 52 | 104 (SoD) | Transient diarrhea |
| 14   | M   | 32  | HIV positive (2009) (CD4+ 702 cells/mm³) | 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.

*aDeceased.
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                 |
| Zarbaian 2019 [5]       | HIV positive (CD4+ >1000 cells/mm³)                                        | 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| 14.7     | PASI100 W6 | None, stable CD4+ count                 |
| Sacchelli 2018 [32]     | HIV positive (2002) (CD4+ 566/µl), past Hepatitis B and C                  | 55/M    | 30 mg bid|          | PASI75M6 NAPSI 7 M6                       | None                                      |
| Apalla 2019 [11]        | Metastatic lung adenocarcinoma, stage IIIB (2013)                          | 67/F    | 30 mg bid|          | PASI75 W6 | None, cancer course not affected by APR  |
| Reddy 2019 [17]         | HIV positive (CD4+ 460 cells/mm³)                                          | 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     | PASI90W24 | None, normal HBload and LFTs           |
| Jeon 2017 [34]          | Active hepatitis C, decompensated viral load                              | 55/M    | 30 mg bid|          | PASI100 W6 | Initial nausea                           |
| González-Cantero 2018   | 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 | 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     | PASI90W24 | 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
| Report                  | Age/Sex   | APR dose | Bas PASI | Tx outcome | AEs                                                                 |
|------------------------|-----------|----------|----------|------------|----------------------------------------------------------------------|
| Ighani 2018 (3) [58]   | >65 y     | NR       | NR       | NR         | Malignancy hx: 5, liver disease: 4, psychiatric disorder: 4          |
| Phan 2020 [59]         | NR        | NR       | NR       | NR         | Malignancy: 40 >65 y                                                |
| Del Alcázar 2020 [62]  | NR        | NR       | NR       | NR         | Lung cancer: 20, latent tuberculosis: 20, hepatitis C: 17, hepatitis |
| Megna 2020 [61]        | NR        | NR       | NR       | NR         | Malignancy: 9, hepatitis C: 4, latent tuberculosis: 3, hepatitis C: 4, |
| Ighani 2018 (4) [60]   | NR        | NR       | NR       | NR         | hepatitis C: 17, hepatitis B: 13, hepatitis B and C: 2, hepatitis C: 2, |
| Megna 2020 [61]        | NR        | NR       | NR       | NR         | hepatitis C: 4, latent tuberculous: 3, hepatitis C: 2, previous malignancy (unspecified number) |
| Fremlin 2017 [63]      | NR        | NR       | NR       | NR         | Malignancy: 14 (6 in last 5 years), hepatitis B, hepatitis C: 3, liver disease: 20, renal insufficiency: 3, current malignancy: 1, previous malignancy: 5 |
| Kungurov 2019 [66]     | 47, F     | NR       | NR       | NR         | Hepatitis B: 1, chronic pancreatitis, diabetes, Peyrier's disease, back pain, current malignancy: 1, previous malignancy: 4 |
| Arzén-Miguel 2019 [67] | 51, M     | NR       | NR       | NR         | breast cancer, gallbladder cancer, treated latent tuberculosis: 3     |
| Bülte 2019 [68]        | 74, F     | NR       | NR       | NR         | Non-metastatic non-small cell lung cancer under nivolumab             |
| Magdaleno 2019 [70]    | NR        | NR       | NR       | NR         | Chronic liver disease: 13, severe infection: 1, previous malignancy: 8 |
| Report                  | Comorbidity                                                                 | Age/Sex | APR dose  | Bas PASI | Tx outcome | AEs                        |
|------------------------|----------------------------------------------------------------------------|---------|-----------|----------|------------|----------------------------|
| Magdaleno-Tapia 2019   | Chronic active alcoholism and hyper-transaminasemia                        | 61, M   | N/R       | N/R      | PASI<5 M6  | No serious AEs             |
|                        |                                                                           |         |           | NAPSI 32 |            |                            |
| Gioe 2021 [72]         | Chronic hepatitis B, bipolar disorder, acute MRSA* bacteremia, pulmonary   | 34, F   | N/R       | N/R      | PASI<5 M6  | No serious AEs             |
|                        | embolus                                                                   |         |           | >95% BSA|            |                            |
| Ibarguren 2021 [73]    | 1. Stage IV uveal melanoma                                                | 50, M   | 30 mg bid | 12       | PASI50 M12 | 1. diarrhea                |
|                        | 2. Stage IV laryngeal carcinoma                                            | 70, M   |           | 13.8     | PASI75 (time |
|                        | 3. Stage IV squamous cell lung carcinoma                                   | 60, M   |           | 6.4      | N/R)       |
|                        | all 3 under nivolumab                                                    |         |           |          | PASI50 not | 2. headache, cancer        |
|                        |                                                                           |         |           |          | achieved   | progression after 10      |
|                        |                                                                           |         |           |          |            | months                    |
|                        |                                                                           |         |           |          |            | 3. cancer progression      |
|                        |                                                                           |         |           |          |            | after 10 months           |
| Kurata 2021 [74]       | Colorectal cancer within past year                                        | 82, F   | N/R       | 5.5      | PASI90 and | γ-GT increase after 8 weeks |
|                        |                                                                           |         |           | NAPSI 77 | NAPSI50 W8 | & 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] | Zarbaian 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] | Kahl 2019 [37] | Nagata 2019 [38] | Uvais 2020 [39] | Vco-Alonso 2020 [40] | Melis 2020 [41] | Perrone 2017 [42] | Carpentieri 2020 [43] | Peitsch 2019 [44] |
| Quality               | Good                | Good               | Good              | Good           | Fair          | Good              | Fair           | Good           | Fair             | Good            |
| Report                | Takama 2020 [45] | Foi 2021 [46] | Di Lernia 2021 [47] | Aragon-Miguel 2019 [48] | Tampouratzis 2019 [49] | Papadavid 2018 [50] | Sahuquillo-Torrallba 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-Tapia 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              | Good           | Good          | Good              | Good           | 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 eventful 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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