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# Treatment of Psoriasis in Patients With Psoriatic Arthritis: An Updated Literature Review Informing the 2021 GRAPPA Treatment Recommendations

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***ABSTRACT.*** ***Objective.*** Our aim was to summarize and evaluate the current quality of evidence regarding the efficacy of therapies for cutaneous psoriasis (PsO) in patients with psoriatic arthritis (PsA).

***Methods.*** A literature search of MEDLINE, Embase, Cochrane Library databases, and conference abstracts was conducted to identify interventional randomized controlled trials in patients with PsA between February 2013 and December 2021. Studies were included if PsO outcomes included achieving at least 75% improvement in the Psoriasis Area and Severity Index and the blinded comparison period was ≥ 10 weeks. The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology was employed to assess quality of the evidence to inform and update the 2021 Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) treatment recommendations.

***Results.*** A total of 116 studies and 36 abstracts identified in the initial search were screened. A total of 37 studies (40 treatment arms) met the criteria for final inclusion. Phosphodiesterase 4 inhibitors, Janus kinase inhibitors, and tyrosine kinase 2 inhibitors, interleukin 17 inhibitors (IL-17i), IL-12/23i, IL-23i, and tumor necrosis factor inhibitors (TNFi) had high-quality data broadly supporting the efficacy of each class for plaque PsO over placebo. Head-to-head studies with high-quality data supported both IL-17i and IL-23i over TNFi.

***Conclusion.*** Several pharmacologic therapeutic classes have high-quality evidence demonstrating efficacy for cutaneous PsO in the PsA population. The findings will be integrated into the 2021 GRAPPA treatment recommendations, intended to guide selection of a therapeutic class where efficacy in 1 or more cutaneous or musculoskeletal domains is required.

*Key Indexing Terms:* GRAPPA, psoriasis, psoriatic arthritis

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The goal of selecting therapy for psoriasis (PsO) among patients with psoriatic arthritis (PsA) is to achieve the lowest possible level of disease activity in all relevant domains of disease. Over the last several years, many new therapeutic agents have been developed to treat skin and nail PsO, as well as other PsA domains (peripheral arthritis, axial arthritis, enthesitis, and dactylitis). The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) has previously published treatment recommendations for the 6 PsA domains.[1,2] The recommendations are based on the assessment of the quality of evidence from randomized controlled trials (RCTs) using Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology to inform the overarching recommendations.[3]

The objective of this study was to systematically review the current literature and assess efficacy of treatments for cutaneous PsO in patients with PsA published between 2013 and 2021 to inform the 2021 GRAPPA treatment recommendations update.

## METHODS

Experts from GRAPPA conducted a systematic literature search and data extraction for 6 different domains of PsA, including the skin. The search was performed to identify interventional clinical RCTs in patients with PsA in the MEDLINE, Embase, and Cochrane Library databases between February 2013 and August 2020. Additional searches of MEDLINE and abstracts from annual meetings of the American College of Rheumatology (ACR) and the European Alliance of Associations for Rheumatology were performed through December 2021 to extract data from full manuscripts of previously identified abstracts to ensure completeness of data review. Data extraction and bias assessment using the GRADE methodology were performed, with high quality implying there is high confidence the true effect lies close to that of the estimate of the effect.[3]

Criteria for final inclusion were as follows: (1) reported 75%, 90%, or 100% improvement of Psoriasis Area and Severity Index (PASI75, PASI90, PASI100, respectively) or static physician global assessment (sPGA) clear or almost clear (0 or 1); and (2) included a blinded comparator arm > 10 weeks or a direct head-to-head comparison of 2 treatments > 10 weeks.

*Ethics.* This paper does not require IRB/animal approval.

## RESULTS

Formal quality review was conducted on 32 placebo-controlled RCTs (35 treatment arms), as shown in Table 1.[4-35] In addition, 5 head-to-head studies were included, as shown in Table 2.[36-40] The efficacy of 7 different classes of treatments compared to placebo (PBO) was assessed for the following pharmaceutical interventions: phosphodiesterase-4 inhibitors (PDE4i; apremilast [APR]), Janus kinase inhibitors (JAKi; tofacitinib [TOF], filgotinib [FILGO], and upadacitinib [UPA])/tyrosine kinase 2 inhibitors (TYK2i; deucravacitinib), tumor necrosis factor inhibitors (TNFi; certolizumab pegol [CZP], golimumab [GOL], and adalimumab [ADA]), interleukin 12/23 inhibitors (IL-12/23i; ustekinumab [UST]), IL-23i (guselkumab [GUS], risankizumab [RZB], and tildrakizumab [TIL]), IL-17i (ixekizumab [IXE], secukinumab [SEC], bimekizumab, and brodalumab [BRO]), and cytotoxic T lymphocyte-associated protein 4 immunoglobulin inhibitor (CTLA4-Igi; abatacept [ABA]).[4-35] Head-to-head studies of IL-17i vs TNFi and IL-12/23i vs TNFi were also included.[36-38] Additionally, 2 high-quality trials, the Study of Etanercept and Methotrexate in Subjects with Psoriatic Arthritis (SEAM-PsA) trial (etanercept [ETN] monotherapy vs ETN combination with methotrexate [MTX] vs MTX monotherapy) and the Tight Control of Psoriatic Arthritis (TICOPA) study were also included.[39,40] Studies of remtolumab (ABT-22), clazakizumab, and nonpharmacologic interventions in this timeframe (hypocaloric diet, marine polyunsaturated fatty acids, mud baths, and whole-body hyperthermia) were reviewed but did not meet inclusion criteria, and all were judged as low quality.[41-45]

*Evidence from RCTs*. For nearly all studies, the skin endpoints (PASI75, PASI90, PASI100, or sPGA 0 or 1) were secondary endpoints. Most studies included only patients in the PsO efficacy analyses if baseline body surface area (BSA) involvement was ≥ 3%. Many PsA trials allowed stable doses of MTX or other conventional synthetic disease-modifying drugs (csDMARDs) to be continued while taking interventional agents. Data for subgroups of patients using concomitant MTX or other conventional oral agents were generally descriptive and statistical analyses were not done or not reported. These and other limitations of assessing PsO efficacy in PsA trials are summarized in Table 3.

*PDE4i.*

- *APR*. Four trials comparing APR (20 mg or 30 mg BID) to PBO in patients with PsA were reviewed.[4-7] In all 4 trials, a significant improvement in PASI75 for APR (at 30 mg BID) compared to PBO was observed (21-25.7% and 2.7-10.8%, respectively). In 1 study, the lower dose (20 mg BID) was not significantly different from PBO.[7]

*JAKi and TYK2i.*

- *TOF.* Two trials of TOF, a JAK1 and JAK3 selective inhibitor, were reviewed.[8,9] In the Oral Psoriatic Arthritis Trial (OPAL) Beyond study, TOF (5 mg and 10 mg BID) were compared to PBO in patients with PsA.[8] At week 12, 17 out of 80 (21%) receiving 5 mg BID (not significant), 35 out of 81 (43%) receiving 10 mg BID ($P < 0.001$), and 12 out of 86 (14%) receiving PBO met PASI75 endpoints. In the OPAL Broaden study, 35 out of 82 (43%) on TOF 5 mg BID, and 31 out of 70 (44%) on TOF 10 mg BID were statistically superior to PBO ($P \leq 0.001$).[9]
- *FILGO.* FILGO, a JAKi selective for JAK1, is approved for use for rheumatoid arthritis in some countries. A small phase II study of 131 patients found 82 had ≥ 3% BSA involvement at baseline.[10] At week 16, 19 out of 42 (45%) on FILGO (200 mg daily) vs 6 out of 40 (15%) on PBO met PASI75 ($P = 0.003$). This drug is not being pursued for psoriatic indications in the United States.
- *UPA.* UPA is a JAKi selective for JAK1 over JAK2, JAK3, and TYK2. Two trials, SELECT-PsA 1 and SELECT-PsA 2, were reviewed.[11,12] In SELECT-PsA 1, a biologic-naïve population received 1 of 2 doses of UPA, ADA (40 mg every other week), or PBO.[11] Significantly more patients reached PASI75 for both doses of UPA (63% on 15 mg/day and 62% on 30 mg/day, $P < 0.001$) compared to PBO (21%). In SELECT-PsA 2, significantly more patients on both doses of UPA reached PASI75 (52% on 15 mg/day and 57% on 30 mg/day, $P < 0.001$) compared to PBO (24%).[12]

*Table 1.* Summary of efficacy data and therapeutic effect by class of RCTs of PsA, from 2013 to 2021.

| Therapeutic Class | | | No. Eligible (Control) | | | No. Eligible (Intervention 1) | | | | No. Eligible (Intervention 2) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Author and Study | N | | Baseline PASI, mean (median or range) | No. Evaluable | n (%) | Baseline PASI, mean (median or range) | No. Evaluable | n (%) | *P* or CI | Baseline PASI, mean (median or range) | No. Evaluable | n (%) | *P* or CI |
| | Outcome | Wk | | | | | | | | | | | |
| **PDE4i** | | | | | | | | | | | | | |
| Kavanaugh 2014[4] PALACE 1 | N = 489 | | | PBO (N = 165) | | | APR 20 mg BID (N =163) | | | | APR 30 mg BID (N = 161) | | |
| | PASI75 | 24 | 9.1 (9.5) | 65 | 3 (4.6) | 7.4 (8.7) | 74 | 13 (17.6) | 0.02 | 9.2 (9.7) | 81 | 17 (21) | 0.004 |
| Cutolo 2016[5] PALACE 2 | N = 484 | | | PBO (N = 159) | | | APR 20 mg BID (N = 163) | | | | APR 30 mg BID (N = 162) | | |
| | PASI75 | 16 | 8.6 (10.0) | 74 | 2 (2.7) | 7.4 (6.5) | 80 | 15 (18.8) | ≤ 0.005 | 7.8 (7.3) | 77 | 17 (22.1) | ≤ 0.005 |
| Edwards 2016[6] PALACE 3 | N = 505 | | | PBO (N = 169) | | | APR 20 mg BID (N = 169) | | | | APR 30 mg BID (N = 167) | | |
| | PASI75 | 16 | 7.6 (7.2) | 89 | 7 (8) | 7.6 (5.2) | 91 | 18 (20) | 0.02 | 7.9 (6.3) | 90 | 19 (21) | 0.001 |
| Wells 2018[7] PALACE 4 | N = 527 | | | PBO (N = 176) | | | APR 20 mg BID (N = 175) | | | | APR 30 mg BID (N = 176) | | |
| | PASI75 | 16 | 6.6 (6.1) | 93 | 10 (10.8) | 8.3 (7.95) | 104 | 18 (17.3) | NS | 6.6 (5.1) | 109 | 28 (25.7) | < 0.05 |
| **JAKi/TYK2i** | | | | | | | | | | | | | |
| Gladman 2017[8] OPAL Beyond | N = 394 | | | PBO (N = 131) | | | TOF 5 mg BID (N =131) | | | | TOF 10 mg BID (N =132) | | |
| | PASI75 | 12 | 7.1 (1.6-66.0) | 86 | 12 (14) | 7.6 (0.6-32.2) | 80 | 17 (21) | NS | 8.8 (0.8-41.6) | 81 | 35 (43) | ≤ 0.001 |
| Mease 2017[9] OPAL Broaden | N =316 | | | PBO (N =105) | | | TOF 5 mg BID (N =107) | | | | TOF 10 mg BID (N = 104) | | |
| | PASI75 | 12 | 6.6 (0.8-41.4) | 82 | 12 (15) | 5.6 (0.4-46) | 82 | 35 (43) | ≤ 0.001 | 7.8 (0.3-24.3) | 70 | 31(44) | ≤ 0.001 |
| Mease 2018[10] EQUATOR | N = 131 | | | PBO (N = 66) | | | FILGO 200 mg QD (N = 65) | | | | | | |
| | PASI75 | 16 | 6.9 (3.8-18.6) | 40 | 6 (15) | 6.5 (2.6-15) | 42 | 19 (45) | 0.003 | | | | |
| McInnes 2021[11] SELECT-PsA 1 | N = 1275 | | | PBO (N = 423) | | | UPA 15 mg QD (N = 429) | | | | UPA 30 mg QD (N = 423) | | |
| | PASI75 | 16 | 11.2 ±11.4 | 211 | 21 | 9.8 ± 10.0 | 214 | 63 | < 0.001 | 9.5 ± 8.8 | 210 | 62 | < 0.001 |
| Mease 2020[12] SELECT-PsA 2 | N = 641 | | | PBO (N = 212) | | | UPA 15 mg QD (N = 211) | | | | UPA 30 mg QD (N = 218) | | |
| | PASI75 | 24 | 11.7 ± 11.4 | 131 | 16 | 10.1 ± 9.2 | 130 | 52 | < 0.001 | 8.9 ± 9.1 | 131 | 57 | < 0.001 |
| Mease 2021[13] NCT03881059 | N = 203 | | | PBO (N = 66) | | | Deucravacitinib 6 mg QD (N = 70) | | | | Deucravacitinib 12 mg QD (N = 67) | | |
| | PASI75 | 16 | NR | NR | 20 | NR | NR | 42 | ≤ 0.01 | NR | NR | 60 | ≤ 0.01 |
| **TNFi** | | | | | | | | | | | | | |
| Mease 2014[14] RAPID-PsA | N = 409 | | | PBO (N = 136) | | | CZP 200 Q2W (N = 138) | | | | CZP 400 Q4W (N = 135) | | |
| | PASI75 | 12 | 7.1 | 86 | 14 | 7.0 | 90 | 46.7 | < 0.005 | 8.1 | 76 | 47.4 | < 0.005 |
| | PASI90 | 12 | 7.1 | 86 | 4.7 | 7.0 | 90 | 22.2 | < 0.005 | 8.1 | 76 | 19.7 | < 0.005 |
| | PASI75 | 24 | 7.1 | 86 | 15.1 | 7.0 | 90 | 62.2 | < 0.005 | 8.1 | NR | 60.5 | < 0.005 |
| | PASI90 | 24 | 7.1 | 86 | 5.8 | 7.0 | 90 | 46.7 | < 0.005 | 8.1 | NR | 35.5 | < 0.005 |
| Kavanaugh 2017[15] GO-VIBRANT | N = 480 | | | PBO (N = 239) | | | GOL 2 mg/kg IV Q8W (N = 241) | | | | | | |
| | PASI75 | 14 | 8.9 | 198 | 27 (13.6) | 11.0 | 196 | 116 (59.2) | ≤ 0.001 | | | | |
| | PASI75 | 24 | 8.9 | 198 | 26 (13.1) | 11.0 | 196 | 127 (64.8) | ≤ 0.001 | | | | |
| | PASI90 | 24 | 8.9 | 198 | 15 (7.6) | 11.0 | 196 | 84 (42.9) | ≤ 0.001 | | | | |
| | PASI100 | 24 | 8.9 | 198 | 11 (5.6) | 11.0 | 196 | 50 (25.5) | ≤ 0.001 | | | | |

*Table 1.* Continued.

| Therapeutic Class | | | No. Eligible (Control) | | | No. Eligible (Intervention 1) | | | | No. Eligible (Intervention 2) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Author and Study | N | | Baseline PASI, mean (median or range) | No. Evaluable | n (%) | Baseline PASI, mean (median or range) | No. Evaluable | n (%) | *P* or CI | Baseline PASI, mean (median or range) | No. Evaluable | n (%) | *P* or CI |
| | Outcome | Wk | | | | | | | | | | | |
| Vieira-Sousa | N = 44 | | PBO (+ MTX QW) (N = 23) | | | GOL 50 mg SC Q4W + MTX QW (N = 21) | | | | | | | |
| 2020[16] | PASI75 | 12 | 2.4 | 22 | 8 (36.4) | 4 | 20 | 10 (50) | 0.53 | | | | |
| GO-DACT | PASI90 | 12 | 2.4 | 22 | 4 (18.2) | 4 | 20 | 5 (25) | 0.71 | | | | |
| | PASI50 | 24 | 2.4 | 20 | 12 (60) | 4 | 20 | 17 (85) | 0.16 | | | | |
| | PASI75 | 24 | 2.4 | 20 | 9 (45) | 4 | 20 | 12 (60) | 0.53 | | | | |
| | PASI90 | 24 | 2.4 | 20 | 8 (40) | 4 | 20 | 5 (25) | 0.50 | | | | |
| Mease 2017[17] | N = 207 | | PBO (N = 106) | | | ADA 40 mg Q2W (N = 101) | | | | | | | |
| SPIRIT-P1 | PASI75 | 12 | 6.2 | 67 | 7.5 | 5.5 | 68 | 33.8 | ≤ 0.001 | | | | |
| | PASI90 | 12 | 6.2 | 67 | 1.5 | 5.5 | 68 | 22.1 | ≤ 0.01 | | | | |
| | PASI100 | 12 | 6.2 | 67 | 1.5 | 5.5 | 68 | 14.7 | ≤ 0.03 | | | | |
| | PASI75 | 24 | 6.2 | 67 | 10.4 | 5.5 | 68 | 54.4 | ≤ 0.001 | | | | |
| | PASI90 | 24 | 6.2 | 67 | 6 | 5.5 | 68 | 36.8 | ≤ 0.001 | | | | |
| | PASI100 | 24 | 6.2 | 67 | 3 | 5.5 | 68 | 23.5 | ≤ 0.01 | | | | |
| Mease 2017[9] | N = 211 | | PBO (N = 105) | | | ADA 40 mg Q2W (N = 106) | | | | | | | |
| OPAL Broaden | PASI75 | 12 | 6.6 (0.8-41.4) | 82 | 12 (15) | 7.0 (2.0–47.1) | 77 | 30 (39) | NR | | | | |
| McInnes 2021[12] | N = 852 | | PBO (N = 423) | | | ADA 40 mg Q2W (N = 429) | | | | | | | |
| SELECT-PsA 1 | PASI75 | 16 | 11.2 ± 11.4 | 211 | 21 | 9.4 ± 8.5 | 211 | 53 | NR | | | | |
| **IL-12/23i** | | | | | | | | | | | | | |
| McInnes 2013[18] | N = 615 | | PBO (N = 206) | | | UST 45 mg Q12W (N = 205) | | | | UST 90 mg Q12W (N = 204) | | | |
| PSUMMIT 1 | PASI75 | 24 | 8.8 (4.4-14.3) | 146 | 16 (11) | 7.1 (3.3-15.3) [a] | 145 | 83 (57.2) | < 0.0001 | 8.4 (4.8-14.7) | 149 | 93 (62.4) | < 0.0001 |
| Ritchlin 2014[19] | N = 312 | | PBO (N = 104) | | | UST 45 mg Q12W (N = 103) | | | | UST 90 mg Q12W (N = 105) | | | |
| PSUMMIT 2 | PASI75 | 24 | 7.9 (4.5-16.0) | 80 | 4 (5) | 8.6 (4.5-18.3) | 80 | 41 (51.3) | < 0.0001 | 8.8 (4.5-18.0) | 81 | 45 (55.6) | < 0.0001 |
| | PASI90 | 24 | 7.9 (4.5-16.0) | 80 | 3 (4) | 8.6 (4.5-18.3) | 80 | 24 (30) | < 0.001 | 8.8 (4.5-18.0) | 81 | 36 (44.4) | < 0.001 |
| **IL-23i** | | | | | | | | | | | | | |
| Deodhar 2018[20] | N = 149 | | PBO (N = 49) | | | GUS 100 mg Q8W (N = 100) | | | | | | | |
| NCT02319759 | PASI75 | 24 | 9.9 (8.0) | 48 | 6 (13) | 12.0 (10.5) | 98 | 77 (79) | < 0.0001 | | | | |
| | PASI90 | 24 | 9.9 (8.0) | 48 | 3 (6) | 12.0 (10.5) | 98 | 65 (66) | < 0.0001 | | | | |
| | PASI100 | 24 | 9.9 (8.0) | 48 | 3 (6) | 12.0 (10.5) | 98 | 39 (40) | < 0.0001 | | | | |
| Deodhar 2020[21] | N = 381 | | PBO (N = 126) | | | GUS 100 mg Q4W (N = 128) | | | | GUS 100 mg Q8W (N = 127) | | | |
| DISCOVER-1 | PASI75 | 24 | 7.7 (8.8) | 78 | 11 (14) | 9.5 (10.1) | 89 | 77 (86) | < 0.0001 | 8.4 (9.8) | 82 | 62 (76) | < 0.0001 |
| | PASI90 | 24 | 7.7 (8.8) | 78 | 9 (12) | 9.5 (10.1) | 89 | 56 (63) | < 0.0001 | 8.4 (9.8) | 82 | 41 (50) | < 0.0001 |
| | PASI100 | 24 | 7.7 (8.8) | 78 | 5 (6) | 9.5 (10.1) | 89 | 40 (45) | < 0.0001 | 8.4 (9.8) | 82 | 21 (26) | 0.0005 |
| Mease 2020[22] | N = 739 | | PBO (N = 246) | | | GUS 100 mg Q4W (N = 245) | | | | GUS 100 mg Q8W (N = 248) | | | |
| DISCOVER-2 | PASI75 | 24 | 9.3 (9.8) | 183 | 42 (23) | 10.8 (11.7) | 184 | 144 (78) | < 0.0001 | 9.7 (1.7) | 176 | 139 (79) | < 0.0001 |
| | PASI90 | 24 | 9.3 (9.8) | 183 | 18 (10) | 10.8 (11.7) | 184 | 112 (61) | < 0.0001 | 9.7 (1.7) | 176 | 121 (69) | < 0.0001 |
| | PASI100 | 24 | 9.3 (9.8) | 183 | 5 (3) | 10.8 (11.7) | 184 | 82 (45) | < 0.0001 | 9.7 (1.7) | 176 | 80 (45) | < 0.0001 |
| Kristensen 2022[23] | N = 964 | | PBO (N = 481) | | | RZB 150 mg Q12W (N = 483) | | | | | | | |
| KEEPsAKE 1 | PASI90 | 16 | 10.0 (10.4) | 272 | 27 (9.9) | 10.9 (10.1) | 273 | 52.3 | < 0.001 | | | | |

*Table 1.* Continued.

| Therapeutic Class | | | No. Eligible (Control) | | | No. Eligible (Intervention 1) | | | | No. Eligible (Intervention 2) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Author and Study | N | | Baseline PASI, mean (median or range) | No. Evaluable | n (%) | Baseline PASI, mean (median or range) | No. Evaluable | n (%) | *P* or CI | Baseline PASI, mean (median or range) | No. Evaluable | n (%) | *P* or CI |
| | Outcome | Wk | | | | | | | | | | | |
| Ostor 2021[24] | N = 443 | | | PBO (N = 219) | | RZB 150 mg Q12W (N = 224) | | | | | | | |
| KEEPsAKE 2 | PASI90 | 24 | 8.4 (9.9) | 119 | 12 (10.2) | 7.7 (6.7) | 123 | 68 (55) | < 0.001 | | | | |
| Mease 2021[25] NCT02980692 | N = 392 [a] | | | PBO (N = 79) | | TIL 100 mg Q12W (N = 77) | | | | TIL 200 mg Q4W (N = 78)/ TIL 200 mg Q12W (N = 79) | | | |
| | PASI75 | 24 | 5.0 ± 6.5 | 42 | 16.7 | 8.8 ± 9.5 | 55 | 56.4 | < 0.0001 | 7.6 ± 9.8/ 6.2 ± 7.4 | 53/44 | 64.2/79.6 | < 0.0001/ < 0.0001 |
| | PASI90 | 24 | 5.0 ± 6.5 | 42 | 7.1 | 8.8 ± 9.5 | 55 | 40 | < 0.001 | 7.6 ± 9.8/ 6.2 ± 7.4 | 53/44 | 47.2/50.0 | < 0.0001/ < 0.0001 |
| | PASI100 | 24 | 5.0 ± 6.5 | 42 | 4.8 | 8.8 ± 9.5 | 55 | 27.3 | < 0.05 | 7.6 ± 9.8/ 6.2 ± 7.4 | 53/44 | 30.2/25.0 | < 0.05/ < 0.05 |
| **IL-17i** | | | | | | | | | | | | | |
| Mease 2017[17] | N = 316 | | | PBO (N = 106) | | IXE 80 mg Q4W (N = 107) | | | | IXE 80 mg Q2W (N = 103) | | | |
| SPIRIT-P1 | PASI75 | 12 | 6.2 | 67 | 7.5 | 6.9 | 73 | 75.3 | ≤ 0.001 | 6 | 59 | 69.5 | ≤ 0.001 |
| | PASI90 | 12 | 6.2 | 67 | 1.5 | 6.9 | 73 | 52.1 | ≤ 0.001 | 6 | 59 | 57.6 | ≤ 0.001 |
| | PASI00 | 12 | 6.2 | 67 | 1.5 | 6.9 | 73 | 31.5 | ≤ 0.001 | 6 | 59 | 40.7 | ≤ 0.001 |
| | PASI75 | 24 | 6.2 | 67 | 10.4 | 6.9 | 73 | 71.2 | ≤ 0.001 | 6 | 59 | 79.7 | ≤ 0.001 |
| | PASI90 | 24 | 6.2 | 67 | 6 | 6.9 | 73 | 56.2 | ≤ 0.001 | 6 | 59 | 67.8 | ≤ 0.001 |
| | PASI100 | 24 | 6.2 | 67 | 3 | 6.9 | 73 | 42.5 | ≤ 0.001 | 6 | 59 | 52.5 | ≤ 0.001 |
| Nash 2017[26] | N = 363 | | | PBO (N = 118) | | IXE 80 mg Q4W (N = 122) | | | | IXE 80 mg Q2W (N = 123) | | | |
| SPIRIT-P2 | PASI75 | 24 | 5.2 | 67 | 10 (15) | 6.4 | 68 | 38 (56) | < 0.0001 | 6.2 | 68 | 41 (60) | < 0.0001 |
| | PASI90 | 24 | 5.2 | 67 | 8 (12) | 6.4 | 68 | 30 (44) | < 0.0001 | 6.2 | 68 | 34 (50) | < 0.0001 |
| | PASI100 | 24 | 5.2 | 67 | 3 (4) | 6.4 | 68 | 24 (35) | 0.0001 | 6.2 | 68 | 19 (28) | 0.0006 |
| Mease 2015[27] | N = 606 | | | PBO (N = 202) | | SEC 75 mg Q4W (N = 202) | | | | SEC 150 mg Q4W (N = 202) | | | |
| FUTURE 1 | PASI75 | 24 | 15.1 ± 11.6 | 109 | 9 (8.3) | 15.6 ± 13.9 | 108 | 70 (64.8) | < 0.001 | 10.6 ± 8.8 | 108 | 66 (61.1) | < 0.001 |
| | PASI90 | 24 | 15.1 ± 11.6 | 109 | 4 (3.7) | 15.6 ± 13.9 | 108 | 53 (49.1) | < 0.001 | 10.6 ± 8.8 | 108 | 49 (45.4) | < 0.001 |
| McInnes 2015[28] | N = 297 | | | PBO (N = 98) | | SEC 150 mg Q4W (N = 100) | | | | SEC 300 mg Q4W (N = 99) | | | |
| FUTURE 2 | PASI75 | 24 | 11.6 | 43 | 7 (16) | 16.2 | 58 | 28 (48) | 0.002 | 12.1 | 41 | 26 (63) | < 0.0001 |
| | PASI90 | 24 | 11.6 | 43 | 4 (9) | 16.2 | 58 | 19 (33) | 0.006 | 12.1 | 41 | 20 (49) | 0.0005 |
| Nash 2018[29] | N = 414 | | | PBO (N = 137) | | SEC 150 mg Q4W (N = 139) | | | | SEC 300 mg Q4W (N = 138) | | | |
| FUTURE 3 | PASI75 | 24 | 10.4 | 59 | 6 (10.2) | 10.1 | 68 | 34 (50) | < 0.05 | 8.8 | 62 | 29 (46.8) | < 0.001 |
| | PASI90 | 24 | 10.4 | 59 | 4 (6.8) | 10.1 | 68 | 25 (36.8) | NR | 8.8 | 62 | 21 (33.9) | < 0.01 |
| Kivitz 2019[30] | N = 341 | | | PBO (N = 114) | | SEC 150 mg Q4W with load (N = 114) | | | | SEC 150 mg Q4W no load (N = 113) | | | |
| FUTURE 4 | PASI75 | 16 | NR | 62 | 5 (8.1) | NR | 55 | 29 (52.7) | < 0.001 | NR | 54 | 27 (50) | < 0.001 |
| | PASI90 | 16 | NR | 62 | 1 (1.6) | NR | 55 | 20 (36.4) | < 0.001 | NR | 54 | 11 (20.4) | < 0.01 |
| Mease 2018[31] | N = 764 | | | PBO (N = 332) | | SEC 150 mg Q4W with/without load (N = 220) | | | | SEC 300 mg Q4W with load (N = 222) | | | |
| FUTURE 5 | PASI75 | 16 | NR | 332 | 41 (12.3) | NR | 125 | 75 (60)/ 68 (58.1) | < 0.05 | NR | 110 | 77 (70) | < 0.05 |
| | PASI90 | 16 | NR | 332 | 31 (9.3) | NR | 125 | 46 (36.8)/ 37 (31.6) | < 0.05 | NR | 110 | 59 (53.6) | < 0.05 |

*Table 1.* Continued.

| Therapeutic Class / Author and Study | N / Outcome | Wk | No. Eligible (Control) Baseline PASI, mean (median or range) | No. Evaluable | n (%) | No. Eligible (Intervention 1) Baseline PASI, mean (median or range) | No. Evaluable | n (%) | *P* or CI | No. Eligible (Intervention 2) Baseline PASI, mean (median or range) | No. Evaluable | n (%) | *P* or CI |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Glatt 2018[32] | N = 122 | | | PBO (N = 14) | | | Bimekizumab pooled (N = 108) | | | | | | |
| NCT02141763 | PASI75 | 8 | NR | 5 | 0 (0) | NR | 55 | 15 (100) | 79.6-100 | | | | |
| | PASI100 | 8 | NR | 5 | 0 (0) | NR | 55 | 13 (86.7) | 9.6-100 | | | | |
| | PASI75 | 20 | NR | 5 | 0 (0) | NR | 55 | 15 (100) | 62.1-96.3 | | | | |
| | PASI100 | 20 | NR | 5 | 0 (0) | NR | 55 | 11 (73.3) | 48.0-89.1 | | | | |
| Ritchlin 2020[33] | N = 206 [b] | | | PBO (N = 42) | | Bimekizumab 160 mg Q4W with load (N = 41) | | | | Bimekizumab 320 mg Q4W (N = 41) | | | |
| BE ACTIVE | PASI75 | 12 | NR | 28 | 2 (7) | NR | 26 | 20 (77) | < 0.0001 | NR | 26 | 19 (73) | < 0.0001 |
| | PASI90 | 12 | NR | 28 | 2 (7) | NR | 26 | 14 (54) | 0.001 | NR | 26 | 14 (54) | 0.001 |
| Mease 2021[34] | N = 962 | | | PBO (N = 322) | | BRO 140 mg Q2W pooled (N = 318) | | | | BRO 210 mg Q2W pooled (N = 322) | | | |
| AMVISION-1/ | PASI75 | 16 | 7.7 (9.0) | 221 | 10.4 | 8.6 (10.0) | 220 | 52.4 | ≤ 0.0001 | 7.8 (9.3) | 219 | 75.5 | ≤ 0.0001 |
| AMVISION-2 | PASI90 | 16 | 7.7 (9.0) | 221 | 6.1 | 8.6 (10.0) | 220 | 38.5 | ≤ 0.0001 | 7.8 (9.3) | 219 | 58.8 | ≤ 0.0001 |
| POOLED | PASI100 | 16 | 7.7 (9.0) | 221 | 3.9 | 8.6 (10.0) | 220 | 20.7 | ≤ 0.0001 | 7.8 (9.3) | 219 | 40.8 | ≤ 0.0001 |
| | PASI75 | 24 | 7.7 (9.0) | 221 | 9.6 | 8.6 (10.0) | 220 | 50.5 | ≤ 0.0001 | 7.8 (9.3) | 219 | 70.5 | ≤ 0.0001 |
| | PASI90 | 24 | 7.7 (9.0) | 221 | 3.8 | 8.6 (10.0) | 220 | 36.6 | ≤ 0.0001 | 7.8 (9.3) | 219 | 57.1 | ≤ 0.0001 |
| | PASI100 | 24 | 7.7 (9.0) | 221 | 1.9 | 8.6 (10.0) | 220 | 26 | ≤ 0.0001 | 7.8 (9.3) | 219 | 48.6 | ≤ 0.0001 |
| **CTLA4-Igi** | | | | | | | | | | | | | |
| Mease 2017[35] | N = 424 | | | PBO (N = 211) | | ABA 125 mg QW (N = 213) | | | | | | | |
| ASTRAEA | PASI50 | 24 | 7.2 (7.8) | 148 | 19.6 | 7.4 (8.0) | 145 | 26.7 | 0.14 | | | | |
| | PASI75 | 24 | 7.2 (7.8) | 148 | 10.1 | 7.4 (8.0) | 145 | 16.4 | NR | | | | |

Not all dosing regimens may include loading doses. [a] Tildrakizumab 20 mg dose (no. randomized = 78) data not shown. [b] Bimekizumab 160 without load (no. randomized = 41) not shown. N is the total no. of patients randomized; no. eligible is the no. of eligible patients (≥ 3% BSA involvement at baseline) randomized to treatment arm; n (%) is the no. of evaluable patients meeting endpoint; wk is the week at which timepoint the outcome was performed. ABA: abatacept; ADA: adalimumab; APR: apremilast; ASTRAEA: Active Psoriatic Arthritis Randomized Trial; BRO: brodalumab; BSA: body surface area; CTLA4Igi: cytotoxic T lymphocyte-associated protein 4 immunoglobulin inhibitor; CZP: certolizumab pegol; FILGO: filgotinib; GOL: golimumab; GUS: guselkumab; IL-12/23i: interleukin 12/23 inhibitor; IL-17i: interleukin 17 inhibitor (includes IL-17 A and F subtypes, and receptor blockade); IL23i: interleukin-23 inhibitor; IV: intravenous; IXE: ixekizumab; JAKi: Janus kinase inhibitor; MTX: methotrexate; NR: not reported; OPAL: Opal Psoriatic Arthritis Trial; PALACE: Psoriatic Arthritis Long-term Assessment of Clinical Efficacy; PASI: Psoriasis Area and Severity Index; PASI100: 100% improvement in PASI score from baseline; PASI75: 75% improvement in PASI score from baseline; PASI90: 90% improvement in PASI score from baseline; PBO: placebo; PDE4i: phosphodiesterase-4 inhibitor; PsA: psoriatic arthritis; Q12W: every 12 weeks; Q2W: every 2 weeks; Q4W: every 4 weeks; Q8W: every 8 weeks; QD: daily; QW: every week; RCT: randomized controlled trial; RZB: risankizumab; SC: subcutaneous; SEAM-PsA: Study of Etanercept and Methotrexate in Subjects with Psoriatic Arthritis; SEC: secukinumab; TIL: tildrakizumab; TNFi: tumor necrosis factor inhibitor; TOF: tofacitinib; TYK2i: tyrosine kinase 2 inhibitor; UPA: upadacitinib; UST: ustekinumab.

*Table 2.* Efficacy data and therapeutic effect by class of randomized head-to-head trials of PsA, from 2013 to2021.

| Therapeutic Class | | | No. Eligible (Intervention 1) | | | No. Eligible (Intervention 2) | | | | No. Eligible (Intervention 3) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Author and Study | N Outcome | Wk | Baseline PASI: mean (median or range) | No. Evaluable | n (%) | Baseline PASI: mean (median or range) | No. Evaluable | n (%) | *P* | Baseline PASI: mean (median or range) | No. Evaluable | n (%) | *P* |
| Mease 2019[36] | | | | | | | | | | | | | |
| SPIRIT-H2H | N = 566 | | ADA 40 mg Q2W (N = 283) | | | IXE 80 mg Q4W (N = 283) | | | | | | | |
| | PASI75 | 24 | 7.7 (7.3) | 283 | 195 (68.9) | 7.9 (8.7) | 283 | 227 (80.2) | 0.002 | | | | |
| | PASI90 | 24 | 7.7 (7.3) | 283 | 158 (55.8) | 7.9 (8.7) | 283 | 203 (71.7) | < 0.001 | | | | |
| | PASI100 | 24 | 7.7 (7.3) | 283 | 132 (46.6) | 7.9 (8.7) | 283 | 170 (60.1) | 0.001 | | | | |
| McInnes 2020[37] | | | | | | | | | | | | | |
| EXCEED | N = 853 | | ADA 40 mg Q2W (N = 427) | | | SEC 300 mg Q4W (N = 426) | | | | | | | |
| | PASI75 | 52 | 10 | 202 | 61 | 10.6 | 215 | 79 | 0.0002 | | | | |
| | PASI100 | 52 | 10 | 202 | 30 | 10.6 | 215 | 46 | 0.0007 | | | | |
| Araujo 2019[38] | | | | | | | | | | | | | |
| ECLIPSA | N = 47 | | UST 45/90 mg Q12W (N = 23) | | | TNFi (N = 24) | | | | | | | |
| | PASI90 | 12 | 3 (6.6) | NR | 86 | 2.8 (3.6) | NR | 29 | < 0.0001 | | | | |
| | PASI100 | 12 | 3 (6.6) | NR | 59 | 2.8 (3.6) | NR | 29 | 0.04 | | | | |
| Mease 2019[39] | | | | | | | | | | | | | |
| SEAM-PsA | N = 851 | | MTX QW (N = 284) | | | ETN 50 mg QW (N = 284) | | | | ETN 50 mg QW + MTX (N = 283) | | | |
| | sPGA 0/1 | 24 | 2.9 ± 0.1 | 178 | 118 (66.3) | 2.9 ± 0.1 | 166 | 120 (72.3) | 0.4 | 2.9 ± 0.1 | 161 | 125 (77.6) | 0.02 |
| Coates 2015[40] | | | | | | | | | | | | | |
| TICOPA | N = 207 | | Standard control (N = 105) | | | Tight control (N = 101) | | | | | | | |
| | PASI75 | 48 | 2.5 | 81 | 27 (33) | 2.6 | 75 | 44 (59) | 0.002 | | | | |

N is the total no. of patients randomized; no. eligible represents no. of evaluable patients (≥ 3% BSA involvement at baseline) randomized to treatment arm; n (%) is the no. of evaluable patients meeting endpoint; wk is the week at which timepoint the outcome was performed. ADA: adalimumab; ECLIPSA: Enthesial Clearance in Psoriatic Arthritis; ETN: etanercept; IXE: ixekizumab; MTX: methotrexate; NR: not reported; PASI: Psoriasis Area and Severity Index; PASI100: 100% improvement in PASI score from baseline; PASI75: 75% improvement in PASI score from baseline; PASI90: 90% improvement in PASI score from baseline; Q12W: every 12 weeks; Q2W: every 2 weeks; Q4W: every 4 weeks; QW: every week; SEAM-PsA: Study of Etanercept and Methotrexate in Subjects with Psoriatic Arthritis; SEC: secukinumab; sPGA: static physician global assessment; TICOPA: Tight Control of Psoriatic Arthritis; TNFi: tumor necrosis factor inhibitor; UST: ustekinumab.

*Table 3.* Comparison of potential limitations when evaluating cutaneous psoriasis in trials with patients with psoriasis vs PsA.

| Variable or Factor | Psoriasis Trials | PsA Trials | Potential Risk of Bias |
|---|---|---|---|
| Primary endpoint | Psoriasis severity endpoint (eg, % reaching PASI75 or clear/almost clear compared to PBO) | Rheumatologic endpoint (eg, % reaching ACR20 compared to PBO) | Differences in statistical methodologies of evaluating primary and secondary endpoints |
| Baseline psoriasis severity | Moderate-severe (PASI12, BSA 10%, and sPGA ≥ 3 or moderate) | Presence or history of plaque psoriasis | Median baseline PASI scores in mild-moderate range, affecting validity (sensitivity to change) of metrics like PASI |
| Inclusion of patients in analysis | All randomized patients included in analysis | Some randomized patients excluded in analysis if baseline involvement is < 3% BSA | Potential inconsistency |
| Concomitant therapies | Washouts required for all DMARDs/systemic immunomodulatory agents (eg, MTX or prednisone) | Concomitant MTX, prednisone, or other csDMARD frequently allowed if on stable doses | Imprecision: small percentage of patients may reach PASI75, affecting effect size and confidence in effect |
| Typical efficacy assessor | Trained dermatologist | Trained rheumatologist | Imprecision: potential risk of interrater or intrarater reliability |
| Phenotype differences | Plaque psoriasis, typically without moderate-to-severe PsA | Plaque psoriasis with moderate-severe PsA | Plaque psoriasis may be biologically different in patients with PsA |
| Psoriasis morphology differences | Plaque, primarily on trunk and extremities | Plaque, but may have increased prevalence of nail, scalp, palmoplantar, intertriginous involvement | Imprecision and inconsistency: morphology of plaque psoriasis on the trunk and extremities differs from intertriginous or palmoplantar, affecting PASI metrics of induration, scale, and erythema, or responsiveness to therapy |

ACR20: American College of Rheumatology criteria of > 20% improvement since baseline; BSA: body surface area; csDMARD: conventional synthetic disease-modifying antirheumatic drugs; DMARD: disease-modifying antirheumatic drugs; MTX: methotrexate; PASI: Psoriasis Area and Severity Index; PASI75: ≥ 75% improvement of PASI since baseline; PBO: placebo; PsA: psoriatic arthritis; sPGA: static physician global assessment.

· *Deucravacitinib.* Deucravacitinib is a TYK2i that was investigated in 1 phase II, double-blind, placebo-controlled trial.[13] At week 16, significantly more patients on deucravacitinib achieved PASI75 (42% on 6 mg/day and 60% on 12 mg/day) compared to PBO (20%).

*TNFi.* TNFi are well known to be efficacious for cutaneous PsO and PsA, and as a class, have been considered to have high-quality data supporting "strong recommendation for" classification in prior studies. Three new placebo-controlled RCTs were published between 2013 and 2021 (RAPID-PsA, GO-VIBRANT, GO-DACT).[14-16]

· *CZP.* CZP is a pegylated Fab' fragment of a humanized monoclonal antibody that inhibits TNF. The RAPID-PsA study assessed the efficacy of CZP vs PBO in nonbiologic-naïve patients with active PsA.[14] By week 24, more patients on CZP met PASI75 (62.2% on 200 mg every 2 weeks [Q2W] and 62.5% on 400 mg [Q4W] compared to PBO (15.1%).

· *GOL.* Two studies were found for GOL, a human monoclonal antibody TNFi, available in either subcutaneous (SC) or intravenous (IV) formulations. The GO-VIBRANT study assessed efficacy of GOL (2 mg/kg IV, given day 1, week 4, then every 8 weeks) and found significantly more patients on GOL reached > PASI75 by week 24, as shown in Table 1.[15] The GO-DACT study compared the efficacy of GOL 50 mg SC every 4 weeks with MTX-to-MTX monotherapy for patients with PsA with dactylitis, but did not find a significant difference by week 12 or week 24.[16]

· *ADA.* ADA, a human monoclonal antibody TNFi, was previously reported as having high-quality data in phase III trials for PsA.[2] Statistically more patients on ADA in OPAL Broaden and SELECT-PsA1 studies met PASI75 compared to PBO (Table 1).[9,11]

*IL-12/23i.*

· *UST.* UST is a human monoclonal antibody that binds to the p40 subunit of both IL-12 and IL-23. We reviewed 2 studies of UST for PsA: PSUMMIT 1 and PSUMMIT 2.[18,19] Both studies included patients with inadequate response to csDMARDs, and the PSUMMIT 1 population was also biologic-naïve. In PSUMMIT 1, more patients reached PASI75 by week 24 at both doses (57.2% on 45 mg and 62.4% on 90 mg, given day 1, week 4, then every 12 weeks) compared to PBO (11%).[18] In the PSUMMIT 2 study, significantly more patients on either 45 mg or 90 mg reached PASI75 (51.3% and 55.6%, respectively, $P < 0.001$) compared to PBO (5%).[19]

*IL-23i.*

· *GUS.* GUS is a human monoclonal antibody that binds to the p19 subunit of IL-23. Three studies of GUS were reviewed.[20-22] In a phase II trial of GUS (100 mg every 8 weeks), statistically more patients met PASI75/90/100 by week 24 compared to PBO.[20] The phase III DISCOVER-1 and DISCOVER-2 studies, which evaluated efficacy of GUS (100 mg every 4 weeks or 100 mg every 8 weeks), found that statistically more patients in both dosing regimens met PASI75/90/100 by week 24 compared to PBO.[21,22]

· *RZB.* RZB is a human monoclonal antibody that binds to the p19 subunit of IL-23. Two phase III studies reporting results of RZB were included.[23,24] The KEEPsAKE 1 study found significantly more patients on RZB (150 mg at weeks 0, 4, and 16) reached PASI90 by week 16 vs PBO (52.3% and 9.9%, respectively).[23] In KEEPsAKE-2 (150 mg vs PBO, given weeks 0, 4, 16, then every 12 weeks), statistically more patients met PASI90 at week 24 compared to patients on PBO (55% vs 10.2%, $P < 0.001$).[24]

· *TIL.* TIL is a human monoclonal antibody that binds to the p19 subunit of IL-23. A 52-week phase III study reporting results of 4 doses of TIL (20 mg every 12 weeks, 100 mg every 12 weeks, 200 mg every 4 weeks, 200 mg every 12 weeks) vs PBO was reviewed.[25] All 4 doses were significantly more effective than PBO in reaching PASI75/90/100 by week 24 (only data for 100 and 200 mg doses shown; Table 1).[25]

*IL-17i.*

· *IXE.* IXE is a recombinant humanized immunoglobulin G4-κ-monoclonal antibody that selectively binds and neutralizes IL-17A. We reviewed 2 studies of IXE (SPIRIT-P1 and SPIRIT-P2).[17,26] SPIRIT-P1 is a phase III study that evaluated 2 SC dosing regimens (IXE 80 mg every 4 weeks or every 2 weeks) compared to PBO and an active comparator, ADA.[17] By week 24, significantly more patients on either dose regimen of IXE reached PASI75/90/100 compared to PBO. A slightly better response was seen when IXE was given every 2 weeks (79.7% reached PASI75) compared to IXE given every 4 weeks (71.2% reached PASI75). The SPIRIT-P2 study compared IXE 80 mg given every 4 weeks or every 2 weeks to PBO and found statistically higher proportions of patients in both IXE arms that met PASI75/90/100 at week 24 compared to PBO.[26]

· *SEC.* We reviewed 5 RCTs (FUTURE 1-5 trials) that evaluated the efficacy of SEC, an IL-17A inhibitor, at week 16 or week 24.[27-31] FUTURE 1 found more patients met PASI75 (64.8% on 75 mg and 61.1% on 150 mg, $P < 0.001$ for both doses) compared to PBO (8.3%).[27] In FUTURE 2, statistically more patients on 150 mg (48%, $P = 0.002$) and 300 mg (63%, $P < 0.001$) met PASI75 compared to PBO (16%); statistical significance was not met in patients on 75 mg (28%, $P = 0.16$).[28] Comparable results were seen in FUTURE 3 for the 150 mg dose, although response to the 300 mg dose was numerically lower (33.9%), as shown in Table 1.[29] FUTURE 4 and FUTURE 5 trials compared efficacy of 150 mg and 300 mg with and without loading doses.[30,31] In FUTURE 5, the 300 mg arm with loading had the highest proportion numerically of patients achieving PASI75 (70%).[31]

· *Bimekizumab.* Bimekizumab is a monoclonal antibody that neutralizes both IL-17A and IL-17F and has been studied in both PsO and PsA populations. A phase Ib dose-ranging study showed all patients on bimekizumab reached PASI75 by week 8 compared to none on PBO.[32] A phase IIb study evaluating 4 doses of bimekizumab (BE ACTIVE) demonstrated a statistically greater proportion of patients in all treatment arms achieved PASI75 by week 12 compared to PBO (45% on 16 mg, 64% on 160 mg, 77% on 160 mg, 73% on 320 mg, 7% on PBO).[33]

· *BRO.* BRO is a human monoclonal antibody that binds to the IL-17 receptor subunit A (IL-17RA) blocking the action of multiple IL-17 family proinflammatory cytokines. The pooled results of 2 studies (AMVISION-1 and AMVISION-2)

showed a significantly higher proportion of patients achieved PASI75/90/100 in both the 140 mg and 210 mg doses by either week 16 or week 24 compared to PBO.[34]

*CTLA4-Igi.*

· *ABA.* ABA, a CTLA4-Igi, is prescribed for PsA, and 1 trial (Active Psoriatic Arthritis Randomized Trial [ASTRAEA]) was reviewed.[35] By week 24, a similar proportion of patients on ABA (16.4%, $P = 0.14$) met PASI75 compared with PBO (10.1%).[35]

*Head-to-head trials.* We reviewed 5 studies that compared a therapeutic agent to 1 or more active comparators without a PBO arm (head-to-head; Table 2).[36-40]

· *IL-17Ai vs TNFi.* Two head-to-head studies compared the efficacy of an IL-17Ai to a TNFi (SPIRIT-H2H and EXCEED).[36,37] The SPIRIT-H2H study compared IXE (80 mg every 4 weeks) to ADA (40 mg every 2 weeks) in patients with PsA who were naïve to biologics, with a primary endpoint of simultaneous achievement of ≥ 50% improvement from baseline in the ACR criteria (ACR50) and PASI100. Fewer patients on ADA met PASI75 by week 24 (68.9%) compared to IXE (80.2%, $P = 0.002$).[36] The EXCEED study compared SEC (300 mg every 4 weeks) to ADA (40 mg every 2 weeks) in biologic-naïve patients with PsA. At week 52, its combined endpoint of ACR50 and PASI100 was met by 31% receiving SEC vs 19% receiving ADA ($P = 0.009$; data not shown).[37]

· *IL-12/23i vs TNFi.* The Enthesial Clearance in Psoriatic Arthritis (ECLIPSA) trial was designed as a randomized, open-label study to compare efficacy of UST to TNFi for enthesitis.[38] Significantly more patients on UST met PASI90 by week 12 (86%, $P < 0.001$) compared to those on a TNFi (29%). Assessors were blinded to drug assignment. It is unclear if evaluable patients had ≥ 3% BSA at baseline.

· *MTX vs ETN.* The SEAM-PsA trial compared the efficacy of MTX oral monotherapy vs ETN 50 mg weekly (monotherapy or combined with MTX) for 24 weeks.[39] This study's primary skin endpoint was a sPGA clear (0) or almost clear (1); PASI was not done.[39] For patients with ≥ 3% BSA, more patients on the combination treatment (MTX + ETN) reported clear/almost clear (77.6%, $P = 0.02$) compared to either MTX monotherapy (66.3%) or ETN monotherapy (72.3%).

· *Tight control vs standard of care.* The TICOPA study evaluated the efficacy of a tight control regimen vs standard of care for a variety of treatments for patients who were naïve to DMARDs.[40] Those randomized to tight control followed a protocol guiding escalation of therapy to achieve minimal disease activity criteria. At week 48, significantly more (44/75, 59%, $P = 0.02$) patients in the tight control arm achieved PASI75 compared to (27/81, 33%) the control arm.[40]

## DISCUSSION

The objective of this literature review was to summarize and evaluate the current quality of evidence supporting the efficacy of therapies for cutaneous PsO in the PsA population published since the 2015 GRAPPA treatment recommendations update.[2] Our review and recommendations (Table 4) support the use of PDE4i, JAKi/TYK2i, TNFi, IL-12/23i, IL-23i, and IL-17i for cutaneous PsO in patients with PsA; however, we could not recommend CTLA4-Igi. These findings are consistent with large systematic reviews and society guidelines for moderate-severe PsO.[46-50] Additionally, there were a limited number of non–placebo-controlled high-quality trials supporting the therapeutic benefit of IL-17i and IL-23i over TNFi.[36-39] Differences in efficacy were seen by different doses and dosing regimens within the same type of treatments.

Assessment of data quality using GRADE methodology for PsO efficacy in the PsA population had several inherent challenges, as summarized in Table 3. Rather than treating these as biases that would affect individual study quality rating, they were treated as systematic limitations to all PsA RCTs where PsO efficacy is reported. Placebo-controlled RCTs with active comparators, head-to-head trials, and network metaanalyses of plaque PsO are available, and may be more relevant, to clinicians making therapeutic decisions when plaque PsO is active and warrants systemic therapy.[46,48,49] This review, and the GRAPPA treatment recommendations, are not intended to inform order of therapy (eg, first-, second-, third-line). Clinicians addressing skin disease must use many variables including extent, morphology, location, failure of other therapies, comorbidities, clinical judgment, patient preference, availability, administration, cost, and other factors to select the appropriate therapy for the skin. In patients who have both PsO and PsA, therapeutic decision making ideally occurs as a collaborative, interdisciplinary process between dermatologists, rheumatologists, the patient, and other specialists as indicated.

For future iterations of GRAPPA treatment recommendations, more in-depth reviews should be conducted to provide further insight to clinicians caring for patients with PsA. Data from subphenotypes seen more commonly in patients with PsA (eg, inverse/genital, scalp, palmoplantar plaque, or pustular PsO) might be valuable, even if sourced from primarily psoriatic patient populations.

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*Table 4.* Summary of recommendations and bias risk by class in RCTs of PsA, from 2013 to 2021.

| Class | Study | Bias Risk [a] | Effect by Class | Recommendation for Treatment | Comments |
|---|---|---|---|---|---|
| PDE4i | PALACE 1 | N | Favor PDE4i | Strong for | Efficacy overall less than most biologics; studies lack active comparator |
| | PALACE 2 | N | | | |
| | PALACE 3 | N | | | |
| | PALACE 4 | N | | | |
| JAKi/TYK2i | OPAL Beyond | N | Favor JAKi | Strong for | Most countries without regulatory approval for psoriasis for JAKi, TYK2i |
| | OPAL Broaden | N | | | |
| | EQUATOR | N | | | |
| | NCT03881059 | N | | | |
| | SELECT-PsA 1 | N | | | |
| | SELECT-PsA 2 | N | | | |
| TNFi | RAPID-PsA | N | Favor TNFi | Strong for | Studies prior to 2013 not included in analysis; regulatory approval for CZP dosing in psoriasis different than PsA |
| | GO-VIBRANT | N | | | |
| | GO-DACT | Y | | | |
| | SPIRIT-P1 - ADA | N | | | |
| | OPAL Broaden ADA | N | | | |
| | SELECT-PsA 1 ADA | N | | | |
| IL-12/23i | PSUMMIT 1 | N | Favor IL-12/23i | Strong for | Regulatory approval for both psoriasis and PsA |
| | PSUMMIT 2 | N | | | |
| IL-23i | NCT02319759 | N | Favor IL-23i | Strong for | TIL without regulatory approval for PsA |
| | DISCOVER- 1 | N | | | |
| | DISCOVER- 2 | N | | | |
| | KEEPsAKE 1 | N | | | |
| | KEEPsAKE 2 | N | | | |
| | NCT02980692 | N | | | |
| IL-17i | SPIRIT-P1 | N | Favor IL-17i | Strong for | Regulatory approval for psoriasis but not PsA in some countries; approved dosing for SEC for psoriasis differs from PsA |
| | SPIRIT-P2 | N | | | |
| | FUTURE 1 | N | | | |
| | FUTURE 2 | N | | | |
| | FUTURE 3 | N | | | |
| | FUTURE 4 | N | | | |
| | FUTURE 5 | N | | | |
| | BE ACTIVE | N | | | |
| | NCT02141763 | Y | | | |
| | AMVISION-1/2 | N | | | |
| CTLA4Igi | ASTRAEA | Y | No efficacy over PBO | No recommendation | Single small study; lack of efficacy over PBO |

[a] Overall risk of serious bias (Y = yes, N = no, for serious risk of bias) based on summary of risk assessment considering limitations, inconsistency, indirectness, publication bias. ADA: adalimumab; ASTRAEA: Active Psoriatic Arthritis Randomized Trial; CTLA4Igi: cytotoxic T-lymphocyte-associated protein 4-immunoglobulin g inhibitor; CZP: certolizumab pegol; IL-12/23i: interleukin 12/23 inhibitor; JAKi: Janus kinase inhibitor; OPAL: Opal Psoriatic Arthritis Trial; PALACE: Psoriatic Arthritis Long-term Assessment of Clinical Efficacy; PBO: placebo; PDE4i: phosphodiesterase 4 inhibitor; PsA: psoriatic arthritis; RCT: randomized controlled trial; SEC: secukinumab; TIL: tildrakizumab; TNFi: tumor necrosis factor-α inhibitor; TYK2i: tyrosine kinase 2 inhibitor.

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