Appendix B: Evidenzreport zur Leitlinie 'Therapie der Psoriasis vulgaris'

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Inhalt

APPENDIX 1 EVIDENCE TO DECISION FRAMEWORK PLAQUE TYPE PSORIASIS ........................................2
Plaque type psoriasis: Evidence to decision framework ........................................................................2

APPENDIX 2 EVIDENCE TO DECISION FRAMEWORK PSORIATIC ARTHRITIS ......................................25
Psoriatic arthritis: Update of a systematic review on the systemic treatment of psoriatic arthritis ..........25

APPENDIX 5 DIABETES MELLITUS ........................................................................................................44
Diabetes mellitus: Systematic review of the evidence on psoriasis treatment and diabetes mellitus ..........44

APPENDIX 7 VIRAL HEPATITIS ..............................................................................................................59
Hepatitis: Systematic review of the evidence on psoriasis treatment and viral hepatitis ..........................59
## APPENDIX 1 EVIDENCE TO DECISION FRAMEWORK PLAQUE TYPE PSORIASIS

### Plaque type psoriasis: Evidence to decision framework

For patients with plaque type psoriasis, what are the clinical effectiveness/efficacy, safety and tolerability of conventional treatments (acitretin, ciclosporin, fumaric acid esters, methotrexate), biologics (adalimumab, brodalumab, certolizumab pegol, etanercept, guselkumab, infliximab, ixekizumab, risankizumab, secukinumab, tildrakizumab or ustekinumab), small molecules (apremilast) compared with each other or with placebo?

**POPULATION:** Patients with moderate to severe psoriasis vulgaris

**INTERVENTION:**

<table>
<thead>
<tr>
<th>Systemic conventional treatments</th>
<th>Small molecules</th>
<th>Tnf inhibitors</th>
<th>Anti-IL12/23</th>
<th>Anti-IL17</th>
<th>Anti-IL23</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acitretin</td>
<td>Apremilast</td>
<td>Adalimumab</td>
<td>Ustekinumab</td>
<td>Brodalumab</td>
<td>Gusekumab</td>
</tr>
<tr>
<td>Ciclosporin</td>
<td>Certolizumab</td>
<td>Ixekizumab</td>
<td>Rizankizumab</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FAEs</td>
<td></td>
<td>Etanercept</td>
<td>Secukinumab</td>
<td>Tildrakizum</td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td></td>
<td>Infliximab</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**COMPARISON:** All systemic treatments and placebo

**MAIN OUTCOMES:**
- Psoriasis Area and Severity Index (PASI) 90% improvement
- Proportion of patients that experienced a severe adverse event (SAE)

**SETTING:**
- Region: Europe (study inclusion not limited to studies done in Europe)
- Setting: clinical and practice (private and public) dermatologists

**PERSPECTIVE:** Population perspective

**BACKGROUND:**
- Several new treatments have been developed and approved
- New statistical methods have become available to allow for comparisons where no head-to-head RCTs exists
- Knowledge on monitoring and management of new treatment options is limited and physicians need guidance on how to use these
- Many psoriasis patients have significant comorbidity and specific advise is necessary to treat these patients
- Hence, the objectives of the guideline are to:
  - Include new treatments and the evidence that has become available
  - Update the recommendations regarding biologic systemic treatment options (Part 1)
  - Develop a treatment algorithms including biologic and nonbiologic systemic treatment options
  - Provide clear recommendations on how to best monitor and manage patients considering the available treatment options
  - Develop several, short guidance documents with visual tools for ease of implementation
  - Provide guidance on the treatment of special populations and difficult clinical situations (mostly expert consensus; Part 2)

Evidence synthesis in cooperation with:
CONFLICT OF INTERESTS:

Less than 50% of the guideline development committee declared to have personal-financial conflicts of interests (see Methods & Evidence report of this guideline).

For the Cochrane Review author groups’ declaration of interests, see page 594 of the review.

Needs Assessment

RESEARCH EVIDENCE

- Differences between psoriasis guidelines exists, such as in the evaluation of the evidence (2)
- “There exists a disconnect between the European psoriasis treatment guidelines and the various central and eastern European country-specific biologic coverage eligibilities” (3);
- „Our results [comparing Czech Psoriasis register with others e.g. PsoBest] found a similar or higher prevalence of comorbidities, long disease duration, and high impact on the quality of life among patients included in Western European registries.” (4);

Desirable Effects

How substantial are the desirable anticipated effects?

RESEARCH EVIDENCE


The treatments are presented in the same order as the SUCRA ranking results. This does not automatically mean statistically significant difference.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Any systemic treatment compared to placebo for chronic plaque psoriasis - PASI 90

<table>
<thead>
<tr>
<th>Any systemic treatment compared to placebo for chronic plaque psoriasis - PASI 90a</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient or population</strong>: people with chronic plaque psoriasis</td>
</tr>
<tr>
<td><strong>Intervention</strong>: any systemic treatment</td>
</tr>
<tr>
<td><strong>Comparison</strong>: placebo</td>
</tr>
<tr>
<td><strong>Setting</strong>: Most trials recruited participants from hospital setting, but also in offices</td>
</tr>
<tr>
<td><strong>Timetable</strong>: from 8 to 24 weeks after randomisation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>SUCRA</th>
<th>nr of participants (studies)</th>
<th>Certainty of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk with placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk with any systemic treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).  
CI: Confidence interval; RR: Risk ratio;

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

aThe Psoriasis Area and Severity Index combines the assessment of the severity of lesions and the area affected into a single score in the range of 0 (no disease) to 72 (maximal disease); PASI 90: 90% improvement in the PASI.

bRisk with placebo: is the median placebo-group risk value in the included studies for the assumed risk with placebo.
### Undesirable Effects

How substantial are the undesirable anticipated effects?

**RESEARCH EVIDENCE**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects (95% CI)</th>
<th>Relative effect</th>
<th>SUCRA</th>
<th>C of participants (studies)</th>
<th>Certainty of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab Moderate</td>
<td>15 per 1000 443 per 1000 (189 to 806)</td>
<td>RR: 0.62 (94% to 97%)</td>
<td>88.5</td>
<td>3651 (5 RCTs)</td>
<td>MODERATE</td>
<td>Downgraded by 1 level due to inconsistency in consistent looses of evidence</td>
</tr>
<tr>
<td>Inetrazumab Moderate</td>
<td>15 per 1000 423 per 1000 (248 to 712)</td>
<td>RR: 0.62 (61% to 80%)</td>
<td>88.5</td>
<td>3268 (4 RCTs)</td>
<td>MODERATE</td>
<td>Downgraded by 1 level due to inconsistency in consistent looses of evidence</td>
</tr>
<tr>
<td>Riasinzumab Moderate</td>
<td>15 per 1000 415 per 1000 (242 to 692)</td>
<td>RR: 0.73 (62% to 87%)</td>
<td>87.5</td>
<td>3476 (4 RCTs)</td>
<td>HIGH</td>
<td>-</td>
</tr>
<tr>
<td>Brolinzumab Moderate</td>
<td>15 per 1000 390 per 1000 (254 to 680)</td>
<td>RR: 0.84 (71% to 92%)</td>
<td>85.3</td>
<td>250 (1 RCT)</td>
<td>HIGH</td>
<td>Downgraded by 2 levels due to depression in evidence</td>
</tr>
<tr>
<td>Quacizumab Moderate</td>
<td>15 per 1000 388 per 1000 (232 to 678)</td>
<td>RR: 0.84 (60% to 99%)</td>
<td>81</td>
<td>1767 (5 RCTs)</td>
<td>MODERATE</td>
<td>Downgraded by 1 level due to risk of bias: 1 study contributing to this estimate at high risk of bias in a sensitive reporting domain</td>
</tr>
<tr>
<td>Sucizumab Moderate</td>
<td>15 per 1000 370 per 1000 (220 to 602)</td>
<td>RR: 0.57 (38% to 70%)</td>
<td>75.4</td>
<td>3095 (8 RCTs)</td>
<td>HIGH</td>
<td>-</td>
</tr>
<tr>
<td>Eriliuzumab Moderate</td>
<td>15 per 1000 329 per 1000 (175 to 586)</td>
<td>RR: 0.89 (73% to 98%)</td>
<td>68.7</td>
<td>4200 (5 RCTs)</td>
<td>MODERATE</td>
<td>Downgraded by 1 level due to risk of bias: 2 studies contributing to this estimate at high risk of bias in selective reporting domain</td>
</tr>
<tr>
<td>Adiluzumab Moderate</td>
<td>15 per 1000 267 per 1000 (129 to 328)</td>
<td>RR: 0.84 (64% to 21%)</td>
<td>58.1</td>
<td>3621 (9 RCTs)</td>
<td>MODERATE</td>
<td>Downgraded by 1 level due to inconsistency in consistent looses of evidence</td>
</tr>
<tr>
<td>Unduluzumab Moderate</td>
<td>15 per 1000 268 per 1000 (127 to 346)</td>
<td>RR: 0.84 (57% to 28%)</td>
<td>55.6</td>
<td>4221 (9 RCTs)</td>
<td>MODERATE</td>
<td>-</td>
</tr>
<tr>
<td>Tolrikuzumab Moderate</td>
<td>15 per 1000 296 per 1000 (194 to 398)</td>
<td>RR: 0.84 (80% to 12%)</td>
<td>55.6</td>
<td>1405 (3 RCTs)</td>
<td>HIGH</td>
<td>-</td>
</tr>
<tr>
<td>Oral tars- teron kinase Z (TTK2)</td>
<td>15 per 1000 250 per 1000 (256 to 800)</td>
<td>RR: 0.84 (78.8 to 95.6)</td>
<td>55.5</td>
<td>287 (1 RCT)</td>
<td>HIGH</td>
<td>Downgraded by 2 levels due to depression in evidence</td>
</tr>
<tr>
<td>Cortizumab Moderate</td>
<td>15 per 1000 182 per 1000 (122 to 251)</td>
<td>RR: 0.84 (66% to 98%)</td>
<td>42.5</td>
<td>3506 (4 RCTs)</td>
<td>MODERATE</td>
<td>-</td>
</tr>
<tr>
<td>Cisizumab Moderate</td>
<td>15 per 1000 148 per 1000 (82 to 266)</td>
<td>RR: 0.84 (49% to 94%)</td>
<td>35.4</td>
<td>6 RCTs</td>
<td>LOW</td>
<td>Downgraded by 2 levels due to risk of bias: 5 studies contributing to this estimate are mostly at high risk of bias, high wide C</td>
</tr>
<tr>
<td>Enericcept Moderate</td>
<td>15 per 1000 132 per 1000 (107 to 274)</td>
<td>RR: 0.84 (31.3 to 41.5)</td>
<td>35</td>
<td>5512 (34 RCTs)</td>
<td>MODERATE</td>
<td>Downgraded by 1 level due to risk of bias: 1 study contributing to this estimate at high risk of bias in a sensitive reporting domain</td>
</tr>
<tr>
<td>Methotrexate Moderate</td>
<td>15 per 1000 110 per 1000 (61 to 188)</td>
<td>RR: 0.84 (76% to 93%)</td>
<td>32.8</td>
<td>318 (1 RCT)</td>
<td>LOW</td>
<td>Downgraded by 1 level due to inconsistency in consistent looses of evidence and 1 level due to risk of bias: 1 study at high risk of bias in the sensitive reporting bias results</td>
</tr>
<tr>
<td>Telhiazumab Moderate</td>
<td>15 per 1000 133 per 1000 (98 to 174)</td>
<td>RR: 0.84 (1.01 to 13.97)</td>
<td>25.4</td>
<td>3592 (5 RCTs)</td>
<td>LOW</td>
<td>Downgraded by 2 levels due to risk of bias: 2 studies contributing to this estimate at high risk of bias in inconsistent outcome data and 1 study at high risk of bias in inconsistent outcome data (sensitive reporting bias domain)</td>
</tr>
<tr>
<td>Arizumab Moderate</td>
<td>15 per 1000 110 per 1000 (61 to 188)</td>
<td>RR: 0.84 (1.01 to 13.97)</td>
<td>25.4</td>
<td>2020 (5 RCTs)</td>
<td>MODERATE</td>
<td>Downgraded by 1 level due to risk of bias: studies contributing to this estimate at high risk of bias in the sensitive reporting bias domain</td>
</tr>
<tr>
<td>Fumaric acid Moderate</td>
<td>15 per 1000 75 per 1000 (57 to 83)</td>
<td>RR: 0.84 (1.01 to 13.97)</td>
<td>25.4</td>
<td>2020 (5 RCTs)</td>
<td>MODERATE</td>
<td>Downgraded by 2 levels due to inconsistency in evidence (wide C) including 1 level due to risk of bias: 2 studies contributing to this estimate at high risk of bias in the sensitive reporting bias domain</td>
</tr>
<tr>
<td>Activin Moderate</td>
<td>15 per 1000 30 per 1000 (8 to 82)</td>
<td>RR: 0.84 (1.01 to 13.97)</td>
<td>25.4</td>
<td>2020 (5 RCTs)</td>
<td>MODERATE</td>
<td>Downgraded by 2 levels due to inconsistency in evidence (wide C) including 1 level due to risk of bias: 2 studies contributing to this estimate at high risk of bias in the sensitive reporting bias domain</td>
</tr>
</tbody>
</table>
Severe adverse events:

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>SUCRAb</th>
<th>No of participants (studies)c</th>
<th>Certainty of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk with placebo</td>
<td>Risk with any systemic treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; RR: Risk ratio

GRADE Working Group grades of evidence

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Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

aRisk with placebo is the median placebo-group risk value in the included studies for the assumed risk with placebo.

bSUCRA was expressed as a percentage between 0 (when a treatment is certain to be the worst) to 100% (when a treatment is certain to be the best).

cNumber of participants (studies) is from the direct comparisons.
<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>SUCRA*</th>
<th>C of participants (studies)**</th>
<th>Certainty of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>Moderate</td>
<td>RR 0.44 (0.20 to 0.91)</td>
<td>87.6</td>
<td>319 (3 RCTs)</td>
<td>MODERATE</td>
<td>Downgraded by 2 level due to imprecision (wide CI including 1)</td>
</tr>
<tr>
<td>Simukizumab</td>
<td>Moderate</td>
<td>RR 0.20 (0.01 to 0.41)</td>
<td>84.3</td>
<td>510 (1 RCT)</td>
<td>LOW</td>
<td>Downgraded by 2 levels due to imprecision (wide CI including 1)</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Moderate</td>
<td>RR 0.60 (0.37 to 0.96)</td>
<td>78.9</td>
<td>1476 (4 RCTs)</td>
<td>MODERATE</td>
<td>Downgraded by 1 level due to imprecision (wide CI)</td>
</tr>
<tr>
<td>Cetorizumab</td>
<td>Moderate</td>
<td>RR 0.70 (0.51 to 1.19)</td>
<td>81.4</td>
<td>1025 (4 RCTs)</td>
<td>LOW</td>
<td>Downgraded by 1 level due to risk of bias (1 study at high risk of bias in binding of participants and personnel (performance bias) and 1 level due to imprecision (wide CI including 1)</td>
</tr>
<tr>
<td>Oral Tyro-smine kinase 2 (TYK2) inhibitor</td>
<td>Moderate</td>
<td>RR 0.61 (0.56 to 0.71)</td>
<td>61.6</td>
<td>267 (1 RCT)</td>
<td>LOW</td>
<td>Downgraded by 2 levels due to imprecision (wide CI including 1)</td>
</tr>
<tr>
<td>Tildrakizumab</td>
<td>Moderate</td>
<td>RR 0.84 (0.39 to 1.81)</td>
<td>54.6</td>
<td>1904 (3 RCTs)</td>
<td>MODERATE</td>
<td>Downgraded by 1 level due to imprecision (wide CI including 1)</td>
</tr>
<tr>
<td>Apremilast</td>
<td>Moderate</td>
<td>RR 0.88 (0.48 to 1.51)</td>
<td>54.5</td>
<td>2200 (8 RCTs)</td>
<td>LOW</td>
<td>Downgraded by 1 level due to risk of bias and 1 level due to imprecision due to wide CI (including 1)</td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>Moderate</td>
<td>RR 0.90 (0.80 to 1.20)</td>
<td>52.7</td>
<td>4593 (15 RCTs)</td>
<td>MODERATE</td>
<td>Downgraded by 1 level due to imprecision (wide CI including 1)</td>
</tr>
<tr>
<td>Etanercept</td>
<td>Moderate</td>
<td>RR 0.69 (0.61 to 1.60)</td>
<td>52.6</td>
<td>4265 (17 RCTs)</td>
<td>MODERATE</td>
<td>Downgraded by 1 level due to imprecision (wide CI including 1)</td>
</tr>
<tr>
<td>Fumaric acid esters</td>
<td>Moderate</td>
<td>RR 0.98 (0.90 to 1.04)</td>
<td>43.5</td>
<td>704 (1 RCT)</td>
<td>VERY LOW</td>
<td>Reasons for downgrading by 2 level due to risk of bias and 1 level due to imprecision, and to wide CI including 1</td>
</tr>
<tr>
<td>Omalizumab</td>
<td>Moderate</td>
<td>RR 0.98 (0.94 to 1.02)</td>
<td>43.2</td>
<td>1797 (2 RCTs)</td>
<td>MODERATE</td>
<td>Downgraded by 1 level due to imprecision (wide CI including 1)</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>Moderate</td>
<td>RR 0.98 (0.94 to 1.02)</td>
<td>42.6</td>
<td>5485 (10 RCTs)</td>
<td>MODERATE</td>
<td>Downgraded by 1 level due to imprecision (wide CI including 1)</td>
</tr>
<tr>
<td>Tofacitinib</td>
<td>Moderate</td>
<td>RR 1.01 (0.97 to 1.07)</td>
<td>42.2</td>
<td>3122 (7 RCTs)</td>
<td>MODERATE</td>
<td>Downgraded by 1 level due to imprecision (wide CI including 1)</td>
</tr>
<tr>
<td>Brodalumab</td>
<td>Moderate</td>
<td>RR 1.05 (0.91 to 1.21)</td>
<td>38.4</td>
<td>4128 (5 RCTs)</td>
<td>MODERATE</td>
<td>Downgraded by 1 level due to imprecision (wide CI including 1)</td>
</tr>
<tr>
<td>Infliximab</td>
<td>Moderate</td>
<td>RR 1.11 (0.95 to 1.29)</td>
<td>39.9</td>
<td>1678 (6 RCTs)</td>
<td>MODERATE</td>
<td>Downgraded by 1 level due to imprecision (wide CI including 1)</td>
</tr>
<tr>
<td>Ixekizumab</td>
<td>Moderate</td>
<td>RR 1.09 (0.92 to 1.30)</td>
<td>35.4</td>
<td>3208 (4 RCTs)</td>
<td>MODERATE</td>
<td>Downgraded by 1 level due to imprecision (wide CI including 1)</td>
</tr>
<tr>
<td>Ciclosporin</td>
<td>Moderate</td>
<td>RR 1.47 (1.03 to 1.11)</td>
<td>52</td>
<td>(0 RCTs)</td>
<td>VERY LOW</td>
<td>Downgraded by 2 levels due to risk of bias/1 level due to imprecision (the studies contributing to this estimate are mostly at high risk of bias), and wide CI including 1</td>
</tr>
<tr>
<td>Activin</td>
<td>Moderate</td>
<td>RR 1.50 (1.25 to 1.85)</td>
<td>31.2</td>
<td>(0 RCTs)</td>
<td>VERY LOW</td>
<td>Downgraded by 2 levels due to imprecision (wide CI including 1) and 1 level due to risk of bias as the studies indirectly contributing to this estimate at high risk in binding domain</td>
</tr>
<tr>
<td>Secukinumab</td>
<td>Moderate</td>
<td>RR 1.12 (0.74 to 1.70)</td>
<td>30.4</td>
<td>2004 (8 RCTs)</td>
<td>MODERATE</td>
<td>Downgraded by 1 level due to imprecision (wide CI including 1)</td>
</tr>
</tbody>
</table>
### Certainty of evidence

What is the overall certainty of the evidence of effects?

Table below: Study bias distribution for PASI 90 using CINeMA (table provided by Emilie Sbidian, thank you)


<table>
<thead>
<tr>
<th>Comparison</th>
<th>Number of studies</th>
<th>Within-study bias</th>
<th>Across-studies bias</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Heterogeneity</th>
<th>Incoherence</th>
<th>Confidence rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACI: ETA</td>
<td>2</td>
<td>Major concerns</td>
<td>Undetected</td>
<td>No concerns</td>
<td>Some concerns</td>
<td>No concerns</td>
<td>Some concerns</td>
<td>Low</td>
</tr>
<tr>
<td>ADA: GUSEL</td>
<td>3</td>
<td>No concerns</td>
<td>Undetected</td>
<td>No concerns</td>
<td>No concerns</td>
<td>Some concerns</td>
<td>No concerns</td>
<td>High</td>
</tr>
<tr>
<td>ADA: MTX</td>
<td>1</td>
<td>No concerns</td>
<td>Undetected</td>
<td>No concerns</td>
<td>No concerns</td>
<td>Some concerns</td>
<td>No concerns</td>
<td>Moderate</td>
</tr>
<tr>
<td>ADA: PBO</td>
<td>9</td>
<td>No concerns</td>
<td>Undetected</td>
<td>No concerns</td>
<td>No concerns</td>
<td>No concerns</td>
<td>No concerns</td>
<td>High</td>
</tr>
<tr>
<td>ADA: RISAN</td>
<td>1</td>
<td>No concerns</td>
<td>Undetected</td>
<td>No concerns</td>
<td>No concerns</td>
<td>No concerns</td>
<td>No concerns</td>
<td>High</td>
</tr>
<tr>
<td>APRE: ETA</td>
<td>1</td>
<td>Some concerns</td>
<td>Undetected</td>
<td>No concerns</td>
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Values

Is there important uncertainty about or variability in how much people value the main outcomes?

RESEARCH EVIDENCE

Several different ways of classifying the severity of psoriasis exist.

According to a European consensus from 2011 (5), psoriasis is classified as:

- Moderate-to-severe disease: (PASI > 10 OR body surface area [BSA] > 10) AND DLQI > 10

In 2017, Llamas-Velasco et al. suggested the following psoriasis severity definitions(6):

- Mild, PASI<7 and DLQI<7;
- Moderate, PASI=7-15 and DLQI=5-15 (classified as severe when difficult-to-treat sites are affected or when there is a significant psychosocial impact);
- Severe, PASI >15, independently of the DLQI score.

The International Psoriasis Council Board Members and Councillors re-categorized psoriasis in 2020 as follows (page 121, Strober et al 2020 (7)):

Psoriasis patients should be classified as candidates for topical therapy or candidates for systemic therapy. The latter are patients who meet at least 1 of the following criteria:

1. BSA >10%
2. Disease involving special areas
3. Failure of topical therapy

Taking into account the impact of important psoriasis characteristics from the patient’s perspective criteria have been defined, which upgrade mild disease to moderate-to-severe when present. These include a major involvement of visible areas, major involvement of the scalp, involvement of genitals, onycholysis or onychodystrophy of at least two fingernails, presence of itch leading to scratching and the presence of recalcitrant plaques (8).

Since the European consensus group meeting, considerable progress has been made concerning the development of new treatment options for psoriasis. They had, for example, defined treatment success during induction treatment as PASI75 (5).

In many countries, higher treatment goals (e.g. PASI 90) are aimed for. In addition, the focus has shifted away from a percentage reduction towards a targeted final outcome (e.g. PASI < 2, DLQI < 2 or PGA clear or almost clear (9).

- Patients are first interested in safety followed by efficacy of biologic treatment, with some variations (10)
- Sociodemographic factors play a role; access and delivery are important attributes

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

RESEARCH EVIDENCE

Figure 7: PASI 90 (left/bottom) and SAEs (right/top). (assessment from 8 to 24 weeks after randomisation). Drugs are reported in order of primary benefit ranking. Each cell contains the risk ratio (RR) and 95% confidence interval for the two primary outcomes (PASI 90 and SAEs) [Copyright © 2020 The Cochrane Collaboration]

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(See Table 7 for full details and references.)
Figure 12: Ranking Plot (efficacy x-axis, safety y-axis). Optimal treatment should be characterised by both high efficacy and acceptability (upper right corner). [Copyright © 2020 The Cochrane Collaboration]
Equity

What would be the impact on health equity?

RESEARCH EVIDENCE

- Costs remain barrier to prescribing biologics (11)
- In addition, national regulations and reimbursement situation need to be taken into consideration and treatment algorithms need to be adapted to regional or national specific circumstances.

Acceptability

Is the intervention acceptable to key stakeholders?

RESEARCH EVIDENCE

- Patients are first interested in safety followed by efficacy of treatment, with some variations (10)
- Sociodemographic factors play a role; access and delivery are important attributes

Recommendations

For main recommendations and flow chart, see guideline document

Justification

All treatment options were found to be efficacious when compared to placebo.

Recommendations were drafted along the line of drug licensing, taking practical aspect of reimbursement into account. National societies may develop different recommendations reflecting the national reimbursement situation.

Following the label, for most patients a ‘conventional’ is considered as the first treatment option. Taking into consideration the higher efficacy of approved EMA first label biologics, a “first line use” of biologics is considered in patients with severe psoriasis.

For the selection of a treatment among the ‘conventionals’, first line biologics and biologics / small molecules in general, many different factors need to be taken into account (see also “specific treatment circumstances”) and no clear hierarchy has been decided upon by the guideline group.

Subgroup considerations

We considered the evidence alongside further research for patients with comorbidities and special patient populations.

Implementation considerations

The main barrier to implementation may be the national/local limitation to drug reimbursement, making the prescription of costly treatments such as the biologics and small molecules difficult.

Monitoring and evaluation
Monitoring and evaluation is to be done on national levels.

- Change in practice performance
- Change in health outcomes
- Change in end-user knowledge and understanding

As an example for national monitoring and evaluation strategies, see BAD (12) or for an example of a cross-sectional survey about psoriasis patient care (13)

Monitoring over two years following publication (done by EuroGuiDerm Team):

- Number of accesses and/or downloads from the EDF website
- Altmetric-Score of the journal publication
- Number of Web of Science citations
- Number of countries which adopted (translated the guideline as is, without change of content); this is presented separately for European countries, regions and non-European countries
- Number of countries which adapted the guideline (used parts of the guideline, or some recommendations); this is presented separately for European countries, regions and non-European countries

Research priorities

- Which are the predictors for treatment success or the occurrence of adverse events?
- What is the role of therapeutic drug monitoring?
- When should a treatment be stopped in case of clearance?
- Which treatments can be combined safely and lead to improved efficacy?
- What is the most suitable treatment option in given comorbid situations?
Appendix 2 Evidence to Decision Framework psoriatic arthritis

Psoriatic arthritis: Update of a systematic review on the systemic treatment of psoriatic arthritis

We updated existing systematic reviews from Dressler et al. (14) and Pham et al. (15), which had been developed by the same working group in parallel.

For the guideline, the recommendations focus on treatment options suitable and licensed for both conditions as the target group of this guideline are dermatologists, treating patients with moderate to severe psoriasis. The systematic review, however, was done for all treatment options licenced for psoriatic arthritis.

First we report the evidence to decision framework, thereafter the details of the systematic review update.

Evidence to decision framework

<table>
<thead>
<tr>
<th>POPULATION:</th>
<th>Patients with moderate to severe psoriasis vulgaris and concomitant psoriatic arthritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>INTERVENTION:</td>
<td>Considered for the guideline recommendation(s): only systemic treatments approved for both plaque type psoriasis and psoriatic arthritis</td>
</tr>
<tr>
<td></td>
<td>- conventional synthetic disease modifying anti rheumatic drugs (csDMARDs): MTX,</td>
</tr>
<tr>
<td></td>
<td>- targeted synthetic (ts)DMARDS: apremilast,</td>
</tr>
<tr>
<td></td>
<td>- biological (b)DMARDs: ADA, CZP, ETA, INF, UST, IXE, SEC</td>
</tr>
<tr>
<td>COMPARISON:</td>
<td>One of the above or placebo</td>
</tr>
<tr>
<td>MAIN OUTCOMES:</td>
<td>- Efficacy outcomes: 20% improvement in the mACR criteria</td>
</tr>
<tr>
<td></td>
<td>- Safety outcomes: proportion of patients with at least one AE</td>
</tr>
<tr>
<td>SETTING:</td>
<td>- Region: Europe (study inclusion not limited to studies done in Europe)</td>
</tr>
<tr>
<td></td>
<td>- Setting: clinical and practice (private and public) dermatologists</td>
</tr>
<tr>
<td>PERSPECTIVE:</td>
<td>- Population perspective</td>
</tr>
<tr>
<td>BACKGROUND:</td>
<td>- Concomitant psoriatic arthritis is frequent in patients with moderate to severe plaque type psoriasis.</td>
</tr>
<tr>
<td></td>
<td>- Several new treatments have been developed and approved since the last version of the guideline, additional evidence is available as further studies have been performed and published.</td>
</tr>
<tr>
<td></td>
<td>- Access to specialist care is limited and in many countries long waiting periods are required for specialist appointments, appropriate treatment choice from dermatologists for patients with concomitant psoriatic arthritis needs to be ensured.</td>
</tr>
<tr>
<td></td>
<td>- It is important to note that specific subtypes of psoriatic arthritis exist (e.g. peripheral, axial, enthesitis, dactylitis) and that response rates to drugs may vary based on the subtype.</td>
</tr>
</tbody>
</table>

Evidence synthesis updated based on Dressler et al and Pham et al. (14, 15)
CONFLICT OF INTERESTS: Less than 50% of the guideline development committee declared to have personal-financial conflicts of interests (see Methods & Evidence report of this guideline).

Needs Assessment

RESEARCH EVIDENCE

- Access to specialist care is limited and in many countries long waiting periods are required for specialist appointments, appropriate treatment choice from dermatologists for patients with concomitant psoriatic arthritis needs to be ensured.

Desirable Effects

How substantial are the desirable anticipated effects?

RESEARCH EVIDENCE

For details of systematic review, see below.
Psoriatic arthritis: Update of a systematic review on the systemic treatment of psoriatic arthritis (Dressler et al (14) updated, below)

Summary of the results for drugs approved for psoriasis of the skin and psoriatic arthritis (Dressler et al (14) updated, below)

<table>
<thead>
<tr>
<th>Patients achieving ACR20</th>
<th>RR</th>
<th>95% CI</th>
<th>Quality of the Evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Head-to-head comparisons</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ETA 50mg + MTX vs. MTX 20mg QW</td>
<td>1.28</td>
<td>1.11 to 1.48</td>
<td>LOW</td>
</tr>
<tr>
<td>INF 5mg/kg W 0,2,6,14 + MTX vs. MTX 15mg QW</td>
<td>1.40</td>
<td>1.07 to 1.84</td>
<td>VERY LOW</td>
</tr>
<tr>
<td>IXE 80mg Q2W vs. ADA 40mg Q2W</td>
<td>1.08</td>
<td>0.86 to 1.36</td>
<td>LOW</td>
</tr>
<tr>
<td>IXE 80mg Q4W vs. ADA 40mg Q2W</td>
<td>0.96</td>
<td>0.86 to 1.06</td>
<td>LOW</td>
</tr>
<tr>
<td><strong>Placebo comparisons</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADA 40mg EOW vs. PBO</td>
<td>3.35</td>
<td>2.24 to 4.99</td>
<td>MODERATE</td>
</tr>
<tr>
<td>APR 30mg BID vs. PBO</td>
<td>1.94</td>
<td>1.59 to 2.38</td>
<td>MODERATE</td>
</tr>
<tr>
<td>APR 20mg BID vs PBO</td>
<td>1.86</td>
<td>1.49 to 2.31</td>
<td>MODERATE</td>
</tr>
<tr>
<td>CZP 400mg Q4W vs. PBO</td>
<td>2.36</td>
<td>1.68 to 3.31</td>
<td>MODERATE</td>
</tr>
<tr>
<td>CZP 200mg Q2W vs. PBO</td>
<td>2.71</td>
<td>1.95 to 3.76</td>
<td>MODERATE</td>
</tr>
<tr>
<td>ETA 25mg BIW vs. PBO</td>
<td>4.05</td>
<td>2.56 to 6.40</td>
<td>LOW</td>
</tr>
<tr>
<td>INF 5mg/kg W0,2,6,14 vs. PBO</td>
<td>4.38</td>
<td>2.24 to 8.56</td>
<td>MODERATE</td>
</tr>
</tbody>
</table>
### Undesirable Effects

**How substantial are the undesirable anticipated effects?**

**RESEARCH EVIDENCE**

For details of systematic review, see below.

Psoriatic arthritis: Update of a systematic review on the systemic treatment of psoriatic arthritis

Summary of the results for drugs approved for psoriasis of the skin and psoriatic arthritis (Dressler et al (14) updated, below)

#### Patients with at least one adverse event

<table>
<thead>
<tr>
<th></th>
<th>RR</th>
<th>95% CI</th>
<th>Quality of the Evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Head-to-head comparisons</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ETA 50mg + MTX vs. MTX 20mg QW</td>
<td>1.01</td>
<td>0.92 to 1.11</td>
<td>MODERATE</td>
</tr>
<tr>
<td>INF 5mg/kg W 0, 2, 6, 14 + MTX vs. MTX 15mg QW. MTX 15mg QW</td>
<td>1.65</td>
<td>1.08 to 2.52</td>
<td>VERY LOW</td>
</tr>
<tr>
<td>IXE 80mg Q2W vs. ADA 40mg Q2W</td>
<td>1.02</td>
<td>0.83 to 1.25</td>
<td>MODERATE</td>
</tr>
<tr>
<td>IXE 80mg Q4W vs. ADA 40mg Q2W</td>
<td>1.14</td>
<td>1.01 to 1.28</td>
<td>VERY LOW</td>
</tr>
<tr>
<td><strong>Placebo comparisons</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADA 40mg EOW vs. PBO</td>
<td>0.67</td>
<td>0.50 to 0.89</td>
<td>VERY LOW</td>
</tr>
</tbody>
</table>

One study (Gottlieb et al. 2009) reported induction dose of QW (weeks 0-3). Abbreviations: ACR20 = 20% improvement in American College of Rheumatology response criteria; RR = risk ratio; 95% CI = 95% confidence interval; ETA = Etanercept; MTX = Methotrexate; mg = milligrams; QW= once a week; INF = Infliximab; kg = kilograms IXE = Ixekizumab; ADA = Adalimumab; Q2W = once every 2 weeks; EOW = every other week; PBO = placebo; APR = Apremilast; BID = twice a day; CZP = Certolizumab Pegol; Q4W = once every 4 weeks; BIW = twice a week; W = week; Sec = Secukinumab; LD = loading dose; UST = Ustekinumab; Q12W = every 12 weeks.

Effects with regard to ACR 20 response from included treatment options versus placebo were considered as relevant. Difference in the effects of anti-TNF antagonists versus IL 17 antagonists with regard to ACR 20 were considered as irrelevant or of minor importance (indirect comparisons with relevant methodological limitations).
**Certainty of evidence**

What is the overall certainty of the evidence of effects?

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>ACR20 - induction</th>
<th>Adverse Events - induction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Certainty assessment</td>
<td>Certainty assessment</td>
</tr>
</tbody>
</table>

**Head-to-head comparisons:**

- APR 30mg BID vs. PBO
  - RR: 1.24
  - 95% CI: 1.12 to 1.36
  - Certainty: LOW

- APR 20mg BID vs PBO
  - RR: 1.27
  - 95% CI: 1.15 to 1.41
  - Certainty: LOW

- CZP 400mg Q4W vs. PBO
  - RR: 1.05
  - 95% CI: 0.90 to 1.23
  - Certainty: MODERATE

- CZP 200mg Q2W vs. PBO
  - RR: 1.01
  - 95% CI: 0.86 to 1.19
  - Certainty: MODERATE

- ETA 25mg BIW vs. PBO
  - RR: n.d.

- INF 5mg/kg W 0, 2, 6, 14 vs. PBO
  - RR: 1.13
  - 95% CI: 0.87 to 1.47
  - Certainty: LOW

- IXE 80mg Q2W vs. PBO
  - RR: 1.39
  - 95% CI: 1.09 to 1.78
  - Certainty: LOW

- IXE 80mg Q4W vs. PBO
  - RR: 1.41
  - 95% CI: 1.10 to 1.79
  - Certainty: LOW

- MTX 7.5mg QW vs. PBO
  - RR: n.d.

- SEC 150mg Q4W vs. PBO
  - RR: 1.03
  - 95% CI: 0.95 to 1.12
  - Certainty: HIGH

- SEC 150mg Q4W + LD vs. PBO
  - RR: 1.01
  - 95% CI: 0.89 to 1.15
  - Certainty: MODERATE

- SEC 300mg Q4W + LD vs. PBO
  - RR: 1.02
  - 95% CI: 0.89 to 1.16
  - Certainty: MODERATE

- UST 45mg W 0, 4 and Q12W vs PBO
  - RR: n.d.

- UST 90mg W 0, 4 and Q12W* vs PBO
  - RR: 0.96
  - 95% CI: 0.75 to 1.24
  - Certainty: VERY LOW

*One study (Gottlieb et al. 2009) reported induction dose of QW (weeks 0–3). Abbreviations: RR = risk ratio; 95% CI = 95% confidence interval; ETA = Etanercept; MTX = Methotrexate; mg = milligrams; QW= once a week; INF = Infliximab; kg = kilograms IXE = Ixekizumab; ADA = Adalimumab; Q2W = once every 2 weeks; EOW = every other week; PBO = placebo; APR = Apremilast; BID = twice a day; CZP = Certolizumab Pegol; Q4W = once every 4 weeks; BIW = twice a week; W = week; Sec = Secukinumab; LD = loading dose; UST = Ustekinumab; Q12W = every 12 weeks.

Assessment of undesirable effects was limited due to limited direct comparability of safety results and safety reporting. The assessments of undesirable effect with regard to the available data on “Patients with at least one adverse event” were considered not to be specific enough to guide general treatment recommendations. A treatment safety profile needs to be individually matched to a specific patient (see also other chapters on comorbid situations).
<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Comparisons</th>
<th>Number of RCTs</th>
<th>Allocation Concealment</th>
<th>Randomization Method</th>
<th>Blinding</th>
<th>Difference</th>
<th>Clinical Importance</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etanercept 50mg + MTX vs. Methotrexate 20 mg QW + PBO</td>
<td>1 RCT</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>serious</td>
<td>serious</td>
<td>not serious</td>
</tr>
<tr>
<td>Infliximab 5mg/kg + MTX 15mg/w vs Methotrexate 15mg/w</td>
<td>1 RCT</td>
<td>serious</td>
<td>serious</td>
<td>not serious</td>
<td>not serious</td>
<td>serious</td>
<td>serious</td>
<td>not serious</td>
</tr>
<tr>
<td>Apremilast 20mg vs. placebo</td>
<td>1 RCT</td>
<td>serious</td>
<td>serious</td>
<td>not serious</td>
<td>not serious</td>
<td>serious</td>
<td>serious</td>
<td>not serious</td>
</tr>
<tr>
<td>Apremilast 30mg vs. placebo</td>
<td>1 RCT</td>
<td>very serious</td>
<td>very serious</td>
<td>not serious</td>
<td>not serious</td>
<td>serious</td>
<td>serious</td>
<td>not serious</td>
</tr>
<tr>
<td>Adalimumab 40mg Q2W vs Placebo</td>
<td>2 RCT</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>serious</td>
<td>serious</td>
<td>not serious</td>
</tr>
<tr>
<td>Certolizumab pegol 400mg Q4W vs placebo</td>
<td>1 RCT</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>serious</td>
<td>serious</td>
<td>not serious</td>
</tr>
<tr>
<td>Certolizumab pegol 200mg Q2W vs placebo</td>
<td>1 RCT</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>serious</td>
<td>serious</td>
<td>not serious</td>
</tr>
<tr>
<td>Etanercept 25mg BiW vs. placebo</td>
<td>2 RCT</td>
<td>very serious</td>
<td>very serious</td>
<td>not serious</td>
<td>not serious</td>
<td>serious</td>
<td>serious</td>
<td>not serious</td>
</tr>
<tr>
<td>Methotrexate 20mg Q2W vs Placebo</td>
<td>2 RCT</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>serious</td>
<td>serious</td>
<td>not serious</td>
</tr>
<tr>
<td>Certolizumab pegol 400mg Q4W vs placebo</td>
<td>1 RCT</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>serious</td>
<td>serious</td>
<td>not serious</td>
</tr>
<tr>
<td>Certolizumab pegol 200mg Q2W vs placebo</td>
<td>1 RCT</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>serious</td>
<td>serious</td>
<td>not serious</td>
</tr>
</tbody>
</table>

**Placebo comparisons:**

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Comparisons</th>
<th>Number of RCTs</th>
<th>Allocation Concealment</th>
<th>Randomization Method</th>
<th>Blinding</th>
<th>Difference</th>
<th>Clinical Importance</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab 40mg Q2W vs Placebo</td>
<td>5 RCT</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>serious</td>
<td>serious</td>
<td>not serious</td>
</tr>
<tr>
<td>Apremilast 30mg BiW vs. placebo</td>
<td>4 RCT</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>serious</td>
<td>serious</td>
<td>not serious</td>
</tr>
<tr>
<td>Certolizumab pegol 400mg Q4W vs placebo</td>
<td>1 RCT</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>serious</td>
<td>serious</td>
<td>not serious</td>
</tr>
</tbody>
</table>

**Notes:**
- A. only one study available;
- B. 95% confidence limit crosses MID threshold (1.25) uncertain whether it is clinical important;
- C. Only one study available;
- D. 95% confidence limit crosses lines of no effect and MID threshold (1.25); uncertain whether there is any difference;
- E. Data was pooled across 16 and 24 weeks (IMPACT: 16 weeks, IMPACT2: 24 weeks, the latter included early escape options and hence more NRI for early escapers);
- F. Only one study available; c. 95% confidence limit crosses lines of appreciable harm (1.25); statistically significant but clinical importance uncertain; d. 95% confidence limit crosses lines of appreciable harm (1.25); statistically significant but clinical importance uncertain; e. 95% confidence limit crosses lines of no effect and MID threshold (1.25); uncertain whether there is any difference;
Sekucinumab 150mg vs. placebo

- 5 RCTs: not serious, not serious, not serious, not serious, none
- 4 RCTs: not serious, not serious, not serious, not serious, none

Secukinumab 150mg+LD vs. placebo

- 2 RCTs a. Only one study: not serious, not serious, not serious, not serious, none

Secukinumab 300mg+LD vs. placebo

- 1 RCT a. Only one study: not serious, not serious, not serious, not serious, none

Ustekinumab 45mg W0, 4 and Q12W vs placebo

- 2 RCTs: not serious, not serious, not serious, not serious, none

Ustekinumab 90mg W0, 4 and Q12W vs placebo

- 3 RCTs: serious*, not serious, not serious, not serious, none

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

ACR 20 reflects on a minimum response of 20% improvement to baseline. Higher improvement percentages will be valued more. ACR is a composite score measuring number of tender and number of swollen joints but also includes patient/physician global assessment as well as pain and functional ability. A stronger focus on patient reported outcomes and quality of life measurements may be valued more by some people.

For safety outcomes see above. In general, direct comparison for safety are hampered by a lack of standardised importance and people may value adverse events and safety profile very differently.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

Indirect evidence for this from above (evidence to decision table for Plaque type psoriasis) can be taken into consideration for this.

Equity

What would be the impact on health equity?

RESEARCH EVIDENCE

- Costs remain barrier to prescribing biologics
- In addition, national regulations and reimbursement situation need to be taken into consideration and treatment algorithms need to be adapted to regional or national specific circumstances.

Acceptability

Is the intervention acceptable to key stakeholders?

RESEARCH EVIDENCE

- Patients are first interested in safety followed by efficacy of treatments, with some variations.

RESEARCH EVIDENCE

- Costs remain barrier to prescribing biologics
- In addition, national regulations and reimbursement situation need to be taken into consideration and treatment algorithms need to be adapted to regional or national specific circumstances.
- Sociodemographic factors play a role; access and delivery are important attributes.
- Costs and drug licencing limit the use of expensive treatment of treatments having a "second line label".
**Recommendations**

See main guideline

**Justification**

Recommendations were drafted along the line of drug licensing, taking practical aspect of reimbursement into account. National societies may develop different recommendations reflecting the national reimbursement situation.

For most patients MTX is considered as the first treatment option. (recommendation based on label, long term experience, price, efficacy, safety).

In case of non-response, TNFs, anti IL12/23 and anti IL17 are considered the alternatives (recommendation based on label, price, efficacy, safety).

Previously, guidelines have given a preference to TNF alpha antagonists over other bDMARDS. In the guideline group’s view, a preference for inhibitors of TNF treatments for PsA is no longer mandatory, since the IL-17A antibody treatments might be equally effective, however more data are needed for its real-life long term efficacy, safety and co-medication.

For the selection of a treatment among the anti TNF alpha antagonists and the anti IL17 directed antibodies, no clear hierarchy has been decided upon by the guideline group.

**Subgroup considerations**

This is already a subgroup, other comorbid conditions are discussed in other chapters.

**Implementation considerations**

The main barrier to implementation may be the national/local limitation to drug reimbursement, making the prescription of costly treatments difficult.

**Monitoring and evaluation**

Monitoring and evaluation is to be done on national levels.

- Change in practice performance
- Change in health outcomes
- Change in end-user knowledge and understanding

As an example for national monitoring and evaluation strategies, see BAD (12) or for an example of a cross sectional survey about psoriasis patient care (13)

**Research priorities**
- Which treatment is most suitable for specific subtypes of psoriatic arthritis exist (e.g. peripheral, axial, enthesitis, dactylitis)
- How can treatment response be predicted?
- What is the role of therapeutic drug monitoring?
- When should a treatment be stopped in case of ceased pain?
- Which treatments can be combined safely and lead to improved efficacy?

Details of the systematic review update (psoriatic arthritis, results above)

Eligibility criteria

We adhered to the methods as reported in both of the above mentioned reviews. However, we modified the inclusion criteria from Dressler et al. The assessment time of the efficacy outcome modified American College of Rheumatology (ACR) criteria, was not only after 24 weeks but after 12 to 24 weeks since the start of treatment. Hence, studies that were excluded before were also reviewed for inclusion. Studies that were included in both systematic reviews were included in the update.

As safety outcome, we used the proportion of participants with at least one adverse events. We did not take into account guselkumab, bimekizumab and abatacept, because the European Medicines Agency (EMA) has not approved them for the treatment of psoriatic arthritis. We only included randomized controlled trials (RCTs) reporting efficacy outcome and/or safety outcome. The eligibility criteria can be seen in table below.

<table>
<thead>
<tr>
<th>ELIGIBILITY CRITERIA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients</strong></td>
</tr>
<tr>
<td>Inclusion: diagnosis of PsA, Pso w/ PsA (at least 80% of the included patient population with PsA where no subgroup analysis was conducted)</td>
</tr>
<tr>
<td>Adults</td>
</tr>
<tr>
<td>Exclusion: Other diagnoses e.g. RA</td>
</tr>
<tr>
<td>Inpatients</td>
</tr>
<tr>
<td>≤ 15 patients per study arm at point of randomization</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
</tr>
<tr>
<td>Inclusion: DMARDs: methotrexate (MTX), sulfasalazin (SSZ), cyclosporine (CSA) or leflunomide (LEF) Biologics: adalimumab (ADA), etanercept (ETA), golimumab (GOL), infliximab (INF), ustekinumab (UST), secukinumab (SEC), ixekizumab (anti IL17), certolizumab pegol (CZ), including biosimilars for ADA, ETA, GOL and INF</td>
</tr>
<tr>
<td>Others: apremilast (APR) or tofacitinib (TOF)</td>
</tr>
<tr>
<td>Exclusion: Guselkumab, bimekizumab and abatacept</td>
</tr>
<tr>
<td><strong>Comparator</strong></td>
</tr>
<tr>
<td>Inclusion: Comparisons with another included drug and/or placebo</td>
</tr>
<tr>
<td>Dose comparison studies</td>
</tr>
<tr>
<td>Exclusion: Comparison with same systematic drug and only different topical drug (in case of patients with primary plaque type psoriasis with sub-analysis for joints)</td>
</tr>
</tbody>
</table>
Outcomes

Inclusion:
At least 1 of the following efficacy or safety outcomes at one time point within 12-24 weeks:
Efficacy outcomes: 20% improvement in the ACR criteria
Safety outcomes: percentage of patients with at least one AE

Study Design

Inclusion:
Only RCTs (cross-over, parallel, cluster, factorial)
Exclusion:
Observational studies
Abstracts

Information sources

We searched Medline (via Ovid) using the search strategy from Pham et al (15). The update was run the 25 October 2019. The search contained subject headings and terms for psoriatic arthritis and drugs see end of this section.

Study selection

Duplicates were removed. First, every hit underwent title and abstract screening. Secondly, records underwent full-text screening, both in accordance with the eligibility criteria. Only one reviewer conducted the update.

Data collection and reporting

All records identified were managed with Endnote X8. Data was then extracted using a shorter version of the standardized extraction sheet, as displayed below.

<table>
<thead>
<tr>
<th>Study characteristic</th>
<th>Inclusion criteria</th>
<th>Baseline data</th>
<th>Withdrawals</th>
<th>Induction (16-24w): ACR20/50/70</th>
<th>SAE</th>
</tr>
</thead>
<tbody>
<tr>
<td>First author</td>
<td>Drug</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>Study duration [w]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of AE; withrawals</td>
<td>Lost to follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of AE; withdrawals</td>
<td>Concurrent treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Withdrawal phase</td>
<td>Inclusion criteria as defined in the paper</td>
<td>Age</td>
<td>Age mean ±SD/ median (range)</td>
<td>TJC mean ±SD/ median (interquartile range)</td>
<td>SJC mean ±SD/ median (interquartile range)</td>
</tr>
<tr>
<td>n (%) of patients with at least one AE</td>
<td>Number of AE; withdrawals</td>
<td>Lost to follow-up</td>
<td>Discontinuation due to other reasons</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Induction (16-24w): ACR20/50/70</td>
<td>Time of assessment [w]</td>
<td>N (%) of patients with at least one SAE</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Methodological quality assessment/ Risk of bias assessment

One reviewer using the Cochrane risk of bias tool assessed the risk of bias of the included studies(16). Each study was evaluated according to the following categories: random sequence generation, allocation concealment, building of participant and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias.

Summary measures
We extracted data from the number of participants as intention to treat (ITT) or modified ITT if available. Review manager 5.3 (RevMan) was used to calculate risk ratios as effect measure for dichotomous outcomes and to estimate 95% confidence intervals. For meta-analyses, data was pooled using random effects model and heterogeneity was assessed with I².

Certainty of the evidence

We utilized the GRADE approach (17) to assess the quality of evidence. GradePro GDT was used to generate summary of findings table and data was imported from RevMan. We evaluated ACR20 and safety outcomes for each treatment comparison.

Results

The search yielded 217 records, 14 new studies were included.

<table>
<thead>
<tr>
<th>Title</th>
<th>Overall risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genovese 2007</td>
<td>Unclear RoB</td>
</tr>
<tr>
<td>Safety and efficacy of adalimumab in treatment of patients with psoriatic arthritis who had failed disease modifying antirheumatic drug therapy</td>
<td></td>
</tr>
<tr>
<td>Nash 2018</td>
<td>Unclear RoB</td>
</tr>
<tr>
<td>Study</td>
<td>Reference</td>
</tr>
<tr>
<td>----------------------------------------------------------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Early and sustained efficacy with apremilast monotherapy in biological-naive patients with psoriatic arthritis: a phase III B, randomised controlled trial (ACTIVE)</td>
<td>Wells 2018</td>
</tr>
<tr>
<td>Apremilast monotherapy in DMARD-naive psoriatic arthritis patients: results of the randomized, placebo-controlled PALACE 4 trial</td>
<td>Gladman 2017</td>
</tr>
<tr>
<td>Tofacitinib for Psoriatic Arthritis in Patients with an Inadequate Response to TNF Inhibitors. In REVMAN</td>
<td>Mease 2017</td>
</tr>
<tr>
<td>Tofacitinib or Adalimumab versus Placebo for Psoriatic Arthritis</td>
<td>Nash 2018</td>
</tr>
<tr>
<td>Efficacy and safety of secukinumab administration by autoinjector in patients with psoriatic arthritis: results from a randomized, placebo-controlled trial (FUTURE 3)</td>
<td>Mease 2018</td>
</tr>
<tr>
<td>Secukinumab improves active psoriatic arthritis symptoms and inhibits radiographic progression: primary results from the randomised, double-blind, phase III FUTURE 5 study</td>
<td>Kivitz 2019</td>
</tr>
<tr>
<td>Efficacy and Safety of Subcutaneous Secukinumab 150 mg with or Without Loading Regimen in Psoriatic Arthritis: Results from the FUTURE 4 Study</td>
<td>Kavaugh 2017</td>
</tr>
<tr>
<td>Safety and Efficacy of Intravenous Golimumab in Patients With Active Psoriatic Arthritis: Results Through Week Twenty-Four of the GO-VIBRANT Study</td>
<td>Gottlieb 2009</td>
</tr>
<tr>
<td>Ustekinumab, a human interleukin 12/23 monoclonal antibody, for psoriatic arthritis: randomised, double-blind, placebo-controlled, crossover trial</td>
<td>Mease 2019</td>
</tr>
<tr>
<td>A head-to-head comparison of the efficacy and safety of ixekizumab and adalimumab in biological-naive patients with active psoriatic arthritis: 24-week results of a randomised, open-label, blinded-assessor trial</td>
<td>Mease 2000</td>
</tr>
<tr>
<td>Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomised trial</td>
<td>Mease 2019</td>
</tr>
<tr>
<td>Etanercept and Methotrexate as Monotherapy or in Combination for Psoriatic Arthritis: Primary Results From a Randomized, Controlled Phase III Trial (SEAM-PsA)</td>
<td>Van Mense 2019</td>
</tr>
</tbody>
</table>
Achieving remission in psoriatic arthritis by early initiation of TNF inhibition: a double-blind, randomised, placebo-controlled trial of golimumab plus methotrexate versus placebo plus methotrexate

A summary of the results of the meta-analysis and the GRADE evaluation are shown below, all details are available upon request from euroguiderm@debm.de.

Included here were all treatments that are licensed for psoriatic arthritis to be congruent with the previous review. However, the guideline chapter only includes those that are licensed for psoriasis.

A brief overview of the newly included studies is also included below.

<table>
<thead>
<tr>
<th>Placebo comparisons</th>
<th>Patients achieving ARC20</th>
<th>Patients with at least one</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR</td>
<td>95% CI</td>
</tr>
<tr>
<td>SEC 150mg vs. PBO</td>
<td>2.44</td>
<td>2.10 to 2.84</td>
</tr>
<tr>
<td>SEC 150mg + LD vs. PBO</td>
<td>2.06</td>
<td>1.70 to 2.49</td>
</tr>
<tr>
<td>TOF 10mg BID vs. PBO</td>
<td>1.89</td>
<td>1.49 to 2.39</td>
</tr>
<tr>
<td>UST 45mg vs PBO</td>
<td>1.95</td>
<td>1.52 to 2.50</td>
</tr>
<tr>
<td>APR 30mg BID vs. PBO</td>
<td>1.94</td>
<td>1.59 to 2.38</td>
</tr>
<tr>
<td>ADA 40mg EOW vs. PBO</td>
<td>3.35</td>
<td>2.24 to 4.99</td>
</tr>
<tr>
<td>APR 20mg BID vs PBO</td>
<td>1.86</td>
<td>1.49 to 2.31</td>
</tr>
<tr>
<td>CZP 400mg vs. PBO</td>
<td>2.36</td>
<td>1.68 to 3.31</td>
</tr>
<tr>
<td>CZP 200mg vs. PBO</td>
<td>2.71</td>
<td>1.95 to 3.76</td>
</tr>
<tr>
<td>GOL 50mg vs. PBO</td>
<td>4.20</td>
<td>2.51 to 7.03</td>
</tr>
<tr>
<td>GOL 100mg vs. PBO</td>
<td>4.92</td>
<td>2.96 to 8.17</td>
</tr>
<tr>
<td>GOL 2mg/kg vs. PBO</td>
<td>3.45</td>
<td>2.69 to 4.44</td>
</tr>
<tr>
<td>INF 5mg/kg vs. PBO</td>
<td>4.38</td>
<td>2.24 to 8.56</td>
</tr>
<tr>
<td>IXE 80mg Q2W vs. PBO</td>
<td>2.21</td>
<td>1.71 to 2.86</td>
</tr>
<tr>
<td>IXE 80mg Q4W vs. PBO</td>
<td>2.25</td>
<td>1.59 to 3.18</td>
</tr>
<tr>
<td>SEC 300mg + LD vs. PBO</td>
<td>2.28</td>
<td>1.87 to 2.80</td>
</tr>
<tr>
<td>TOF 5mg BID vs. PBO</td>
<td>1.77</td>
<td>1.29 to 2.44</td>
</tr>
<tr>
<td>UST 90mg vs PBO</td>
<td>2.26</td>
<td>1.80 to 2.82</td>
</tr>
<tr>
<td>ETA 25mg BM vs. PBO</td>
<td>4.05</td>
<td>2.56 to 6.40</td>
</tr>
<tr>
<td>LIF 100mg vs. PBO</td>
<td>1.70</td>
<td>0.99 to 2.92</td>
</tr>
<tr>
<td>MTX 7.5mg vs. PBO</td>
<td>1.82</td>
<td>0.97 to 3.40</td>
</tr>
<tr>
<td>SSZ 0.2mg QD vs. PBO</td>
<td>1.29</td>
<td>0.90 to 1.86</td>
</tr>
</tbody>
</table>

Head-to-head comparisons:

<table>
<thead>
<tr>
<th></th>
<th>RR</th>
<th>95% CI</th>
<th>Quality of the Evidence (GRADE)</th>
<th>RR</th>
<th>95% CI</th>
<th>Quality of the Evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ETA 50mg + MTX vs. MTX 20mg QW</td>
<td>1.28</td>
<td>1.11 to 1.48</td>
<td>LOW</td>
<td>1.01</td>
<td>0.92 to 1.11</td>
<td>MODERATE</td>
</tr>
<tr>
<td>LIF 100mg vs. MTX 10mg</td>
<td>1.01</td>
<td>0.84 to 1.21</td>
<td>LOW</td>
<td>n.d.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOF 5mg BID vs ADA 40mg Q2W</td>
<td>0.97</td>
<td>0.75 to 1.26</td>
<td>LOW</td>
<td>0.85</td>
<td>0.62 to 1.16</td>
<td>LOW</td>
</tr>
<tr>
<td>GOL 50mg + MTX vs. MTX 25mg QW</td>
<td>1.45</td>
<td>1.00 to 2.11</td>
<td>VERY LOW</td>
<td>0.88</td>
<td>0.70 to 1.10</td>
<td>VERY LOW</td>
</tr>
<tr>
<td>INF 5mg/kg + MTX vs. MTX 15mg/kg</td>
<td>1.40</td>
<td>1.07 to 1.84</td>
<td>VERY LOW</td>
<td>1.65</td>
<td>1.08 to 2.52</td>
<td>VERY LOW</td>
</tr>
<tr>
<td>IXE 80mg Q2W vs. ADA 40mg Q2W</td>
<td>1.08</td>
<td>0.86 to 1.36</td>
<td>VERY LOW</td>
<td>1.02</td>
<td>0.83 to 1.25</td>
<td>MODERATE</td>
</tr>
<tr>
<td>IXE 80mg Q4W vs. ADA 40mg Q2W</td>
<td>0.96</td>
<td>0.86 to 1.06</td>
<td>VERY LOW</td>
<td>1.14</td>
<td>1.01 to 1.28</td>
<td>VERY LOW</td>
</tr>
<tr>
<td>LIF 100mg vs. MTX 10mg</td>
<td>1.01</td>
<td>0.84 to 1.21</td>
<td>LOW</td>
<td>n.d.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The results are summarized below. Full data extraction tables of the studies including during this update are available upon request from euroguiderm@debm.de

<table>
<thead>
<tr>
<th>First author</th>
<th>Drug</th>
<th>Number (n) randomized</th>
<th>Time of assessment [w]</th>
<th>N</th>
<th>ACR20 n(%)</th>
<th>ACR50 n(%)</th>
<th>ACR70 n(%)</th>
<th>Time of assessment [w]</th>
<th>N / % of patients with at least 1 AE</th>
<th>Time of assessment [w]</th>
<th>N (%) of patients with at least one SAE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genovese 2007</td>
<td>ADA 40mg (in 0.8ml syring) s.c. EOW for 12wks</td>
<td>51</td>
<td>12</td>
<td>51</td>
<td>20</td>
<td>13</td>
<td>7</td>
<td></td>
<td>27/51</td>
<td>52.9%</td>
<td>1/51</td>
</tr>
<tr>
<td></td>
<td>PBO (in 0.8ml syring) s.c. EOW for 12wks</td>
<td>51 (ITT 49)</td>
<td>12</td>
<td>51</td>
<td>8</td>
<td>1</td>
<td>0</td>
<td></td>
<td>39/49</td>
<td>79.6%</td>
<td>2/49</td>
</tr>
<tr>
<td>Mease 2000</td>
<td>ETN 25mg SC (twice weekly)</td>
<td>30</td>
<td>12</td>
<td>30</td>
<td>22</td>
<td>15</td>
<td>4</td>
<td></td>
<td>nr</td>
<td>0/30</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PBO SC (twice weekly)</td>
<td>30 (26 completed study last obs carried forward)</td>
<td>12</td>
<td>30</td>
<td>4</td>
<td>1</td>
<td>0</td>
<td></td>
<td>nr</td>
<td>1/30</td>
<td></td>
</tr>
<tr>
<td>Mease 2019</td>
<td>MTX 2.5mg p.o (starting 10mg/week up to 20mg/week) + SC PBO weekly</td>
<td>284</td>
<td>24</td>
<td>284</td>
<td>144/284</td>
<td>77/252</td>
<td>35/253</td>
<td></td>
<td>nr</td>
<td>nr</td>
<td></td>
</tr>
<tr>
<td>SEAM-PsA</td>
<td>ETN 50mg SC (weekly)</td>
<td>284</td>
<td>24</td>
<td>284</td>
<td>173/284</td>
<td>114/257</td>
<td>75/257</td>
<td></td>
<td>nr</td>
<td>nr</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ETN 50mg SC (weekly) + MTX p.o (target dose 20mg/wk)</td>
<td>283</td>
<td>24</td>
<td>283</td>
<td>184/283</td>
<td>117/256</td>
<td>71/256</td>
<td></td>
<td>nr</td>
<td>nr</td>
<td></td>
</tr>
<tr>
<td>Kavanaugh 2017</td>
<td>GOL i.v 2 mg/kg at weeks 0 and 4 and every 8 weeks</td>
<td>241 (240 received GOL)</td>
<td>14</td>
<td>241</td>
<td>181</td>
<td>105</td>
<td>59</td>
<td></td>
<td>111/240</td>
<td>46.3%</td>
<td>7/240</td>
</tr>
<tr>
<td>GO Vibrant</td>
<td>PBO i.v at weeks 0 and 4 and every 8 weeks</td>
<td>239</td>
<td>24</td>
<td>239</td>
<td>52</td>
<td>15</td>
<td>15</td>
<td></td>
<td>97/239</td>
<td>40.6%</td>
<td>8/239</td>
</tr>
<tr>
<td>van Mens 2019</td>
<td>GOL 50 mg monthly + MTX 15mg weekly up to 25 mg weekly</td>
<td>26</td>
<td>22</td>
<td>26</td>
<td>Circa 22</td>
<td>Circa 21</td>
<td>Circa 15</td>
<td></td>
<td>21/26</td>
<td>80.8%</td>
<td>0/26</td>
</tr>
<tr>
<td></td>
<td>MTX 15mg weekly up to 25 mg weekly + PBO</td>
<td>25 (ITT 24)</td>
<td>24</td>
<td>25</td>
<td>Circa 14</td>
<td>Circa 8</td>
<td>Circa 3</td>
<td></td>
<td>22/24</td>
<td>91.6%</td>
<td>1/24</td>
</tr>
<tr>
<td>First author</td>
<td>Drug</td>
<td>Number (n) randomized</td>
<td>Time of assessment (w)</td>
<td>N</td>
<td>ACR20 n(%)</td>
<td>ACR50 n(%)</td>
<td>ACR70 n(%)</td>
<td>Time of assessment (w)</td>
<td>N / % of patients with at least 1 AE</td>
<td>Time of assessment (w)</td>
<td>N / % of patients with at least one SAE</td>
</tr>
<tr>
<td>-------------</td>
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<td>------------</td>
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<td>------------</td>
<td>-----------------------</td>
<td>--------------------------------</td>
<td>-----------------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>Nash 2018</td>
<td>APR 30mg BID for 52 weeks</td>
<td>110</td>
<td>24</td>
<td>110</td>
<td>110</td>
<td>42 /38.2%</td>
<td>22 /20.2%</td>
<td>73 /109</td>
<td>3 /109</td>
<td></td>
<td>2.8%</td>
</tr>
<tr>
<td>Wells 2018</td>
<td>APR 20 mg tablets p.o. BID</td>
<td>175</td>
<td>24</td>
<td>175</td>
<td>175</td>
<td>49 /28%</td>
<td>20 /11.4%</td>
<td>87 /175</td>
<td>3 /175</td>
<td></td>
<td>1.7%</td>
</tr>
<tr>
<td>Wells 2018</td>
<td>APR 30mg tablets p.o. BID</td>
<td>176</td>
<td>24</td>
<td>176</td>
<td>176</td>
<td>54 /30.7%</td>
<td>7 /4.0%</td>
<td>99 /175</td>
<td>1 /175</td>
<td></td>
<td>0.6%</td>
</tr>
<tr>
<td>PALACE 4</td>
<td>PBO tablets BID p.o., EE if pts ≤ 20% improvement in SJC and TJC at wk 16, at w24 remaining PBO pts were re-randomised to APR20mg or APR30mg BID</td>
<td>176</td>
<td>24</td>
<td>176</td>
<td>176</td>
<td>28 /15.9%</td>
<td>8.5% /2.1%</td>
<td>73 /176</td>
<td>5 /176</td>
<td></td>
<td>2.8%</td>
</tr>
<tr>
<td>Gladmann 2017</td>
<td>tofacitinib 5 mg BID</td>
<td>131</td>
<td>12</td>
<td>131</td>
<td>131</td>
<td>65 /49.6%</td>
<td>39 /29.8%</td>
<td>72 /131</td>
<td>1 /131</td>
<td></td>
<td>1%</td>
</tr>
<tr>
<td>OPAL Beyond</td>
<td>tofacitinib 10 mg BID</td>
<td>132</td>
<td>12</td>
<td>132</td>
<td>132</td>
<td>62 /47.0%</td>
<td>37 /28.0%</td>
<td>70 /132</td>
<td>3 /132</td>
<td></td>
<td>2%</td>
</tr>
<tr>
<td>NCT01882439</td>
<td>PBO, advanced to TOF 5mg or 10mg in blinded manner at 3M</td>
<td>131</td>
<td>24</td>
<td>131</td>
<td>131</td>
<td>31 /23.7%</td>
<td>19 /14.5%</td>
<td>58 /131</td>
<td>3 /132</td>
<td></td>
<td>2%</td>
</tr>
<tr>
<td>Mease 2017</td>
<td>TOF 5mg BID</td>
<td>107</td>
<td>12</td>
<td>107</td>
<td>107</td>
<td>54 /50.5%</td>
<td>30 /28.0%</td>
<td>42 /107</td>
<td>3 /107</td>
<td></td>
<td>2.8%</td>
</tr>
<tr>
<td>OPAL BROADEN</td>
<td>TOF 10mg BID</td>
<td>104</td>
<td>12</td>
<td>104</td>
<td>104</td>
<td>63 /60.6%</td>
<td>42 /40.4%</td>
<td>47 /104</td>
<td>1 /104</td>
<td></td>
<td>1.0%</td>
</tr>
<tr>
<td>NCT0187766</td>
<td>ADA 40mg sc Q2W</td>
<td>106</td>
<td>12</td>
<td>106</td>
<td>106</td>
<td>55 /51.9%</td>
<td>35 /33.0%</td>
<td>49 /106</td>
<td>1 /106</td>
<td></td>
<td>0.9%</td>
</tr>
<tr>
<td>PBO</td>
<td>105</td>
<td>12</td>
<td>105</td>
<td>5 35 / 33.3%</td>
<td>10 / 09.5%</td>
<td>5 / 4.8%</td>
<td>37 /105</td>
<td>1 /105</td>
<td></td>
<td>1.0%</td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Drug</td>
<td>First author</td>
<td>Study</td>
<td>Number (n) randomized</td>
<td>Time of assessment [w]</td>
<td>N</td>
<td>ACR20 n(%)</td>
<td>ACR50 n(%)</td>
<td>ACR70 n(%)</td>
<td>Time of assessment [w]</td>
<td>N / % of patients with at least 1 AE</td>
</tr>
<tr>
<td>--------</td>
<td>------</td>
<td>--------------</td>
<td>-------</td>
<td>-----------------------</td>
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<td>-------------</td>
<td>-------------</td>
<td>-------------</td>
<td>-----------------------</td>
<td>----------------------------------------</td>
</tr>
<tr>
<td>Nash 2018</td>
<td>SEC 300mg SC QW w0,1,2,3,4 then every 4w</td>
<td>SEC 300mg SC QW w0,1,2,3,4 then every 4w</td>
<td>139</td>
<td>24</td>
<td>139</td>
<td>67</td>
<td>48.2%</td>
<td>48</td>
<td>34.5%</td>
<td>16</td>
<td>76/139 54.7%</td>
</tr>
<tr>
<td>Nash 2018</td>
<td>SEC 150mg SC QW w0,1,2,3,4 then every 4w</td>
<td>SEC 150mg SC QW w0,1,2,3,4 then every 4w</td>
<td>138</td>
<td>24</td>
<td>138</td>
<td>58</td>
<td>42.0%</td>
<td>26</td>
<td>18.8%</td>
<td>16</td>
<td>80/138 58.0%</td>
</tr>
<tr>
<td>Kivitz 2019</td>
<td>PBO w0,1,2,3,4 then every 4w</td>
<td>PBO w0,1,2,3,4 then every 4w</td>
<td>137</td>
<td>24</td>
<td>137</td>
<td>22</td>
<td>16.1%</td>
<td>12</td>
<td>8.8%</td>
<td>16</td>
<td>77/137 56.2%</td>
</tr>
<tr>
<td>Mease 2018</td>
<td>SEC 150mg QW with loading of 150mg, w0,1,2,3,4 then every 4w</td>
<td>SEC 150mg QW with loading of 150mg, w0,1,2,3,4 then every 4w</td>
<td>114</td>
<td>16</td>
<td>114</td>
<td>47</td>
<td>41.2%</td>
<td>26</td>
<td>22.8%</td>
<td>10</td>
<td>140/222 63.1%</td>
</tr>
<tr>
<td>Mease 2018</td>
<td>PBO QW, w0,1,2,3,4 then every 4w</td>
<td>PBO QW, w0,1,2,3,4 then every 4w</td>
<td>114</td>
<td>16</td>
<td>114</td>
<td>21</td>
<td>18.4%</td>
<td>7</td>
<td>6.1%</td>
<td>1</td>
<td>206/332 62.0%</td>
</tr>
<tr>
<td>Mease 2018</td>
<td>SEC 300mg QW with LD, w0,1,2,3,4 then every 4w</td>
<td>SEC 300mg QW with LD, w0,1,2,3,4 then every 4w</td>
<td>222</td>
<td>16</td>
<td>222</td>
<td>139</td>
<td>62.6%</td>
<td>39.6%</td>
<td>20.3%</td>
<td>24</td>
<td>197/283 69.6%</td>
</tr>
<tr>
<td>Mease 2018</td>
<td>SEC 150mg QW with LD, w0,1,2,3,4 then every 4w</td>
<td>SEC 150mg QW with LD, w0,1,2,3,4 then every 4w</td>
<td>220</td>
<td>16</td>
<td>220</td>
<td>122</td>
<td>55.5%</td>
<td>35.9%</td>
<td>18.2%</td>
<td>24</td>
<td>138/220 62.7%</td>
</tr>
<tr>
<td>Mease 2018</td>
<td>PBO QW, w0,1,2,3,4 then every 4w</td>
<td>PBO QW, w0,1,2,3,4 then every 4w</td>
<td>332</td>
<td>16</td>
<td>332</td>
<td>91</td>
<td>27.4%</td>
<td>8.1%</td>
<td>4.2%</td>
<td>24</td>
<td>206/332 62.0%</td>
</tr>
<tr>
<td>Mease 2019</td>
<td>IXE 80mg SC every Q4W with LD in w0, or Q2W if moderate to severe psoriasis</td>
<td>IXE 80mg SC every Q4W with LD in w0, or Q2W if moderate to severe psoriasis</td>
<td>283</td>
<td>24</td>
<td>283</td>
<td>195</td>
<td>68.9%</td>
<td>143</td>
<td>50.5%</td>
<td>90</td>
<td>197/283 69.6%</td>
</tr>
<tr>
<td>Mease 2019</td>
<td>ADA 40mg SC Q2W or 80mg LD then 40mg Q2W if moderate to severe psoriasis</td>
<td>ADA 40mg SC Q2W or 80mg LD then 40mg Q2W if moderate to severe psoriasis</td>
<td>283</td>
<td>24</td>
<td>283</td>
<td>204</td>
<td>72.1%</td>
<td>132</td>
<td>46.6%</td>
<td>73</td>
<td>173/283 61.1%</td>
</tr>
<tr>
<td>Gottlieb 2009</td>
<td>UST 90mg sc. Q1wk at wk 0,1,2,3; crossover to placebo at wk 12+16</td>
<td>UST 90mg sc. Q1wk at wk 0,1,2,3; crossover to placebo at wk 12+16</td>
<td>76</td>
<td>12</td>
<td>76</td>
<td>32</td>
<td>42%</td>
<td>19</td>
<td>25%</td>
<td>5</td>
<td>46/76 60.5%</td>
</tr>
<tr>
<td>Gottlieb 2009</td>
<td>PBO sc. Q1wk at wk 0,1,2,3, UST 90mg at wk 12+16</td>
<td>PBO sc. Q1wk at wk 0,1,2,3, UST 90mg at wk 12+16</td>
<td>70</td>
<td>12</td>
<td>70</td>
<td>10</td>
<td>14%</td>
<td>8</td>
<td>11%</td>
<td>0</td>
<td>44/70 62.9%</td>
</tr>
</tbody>
</table>
Search strategy for the review on psoriasis arthritis: MEDLINE OVID; from Pham et al 2019

<table>
<thead>
<tr>
<th>#</th>
<th>Searches</th>
<th>32</th>
<th>33 and 31</th>
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<tbody>
<tr>
<td>1</td>
<td>exp Arthritis, Psoriatic/</td>
<td>32</td>
<td>30 and 31</td>
</tr>
<tr>
<td>2</td>
<td>(Psoria* adj3 arthr*).ab,ti.</td>
<td>33</td>
<td>Randomized Controlled Trials as Topic/</td>
</tr>
<tr>
<td>3</td>
<td>exp Antibodies, Monoclonal/</td>
<td>34</td>
<td>randomized controlled trial/</td>
</tr>
<tr>
<td>4</td>
<td>exp Adalimumab/</td>
<td>35</td>
<td>Random Allocation/</td>
</tr>
<tr>
<td>5</td>
<td>adalimumab.ab,ti.</td>
<td>36</td>
<td>Double Blind Method/</td>
</tr>
<tr>
<td>6</td>
<td>exp Certolizumab Pegol/</td>
<td>37</td>
<td>Single Blind Method/</td>
</tr>
<tr>
<td>7</td>
<td>certolizumab pegol.ab,ti.</td>
<td>38</td>
<td>clinical trial/</td>
</tr>
<tr>
<td>8</td>
<td>exp Ustekinumab/</td>
<td>39</td>
<td>clinical trial, phase i.pt.</td>
</tr>
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<td>9</td>
<td>ustekinumab.ab,ti.</td>
<td>40</td>
<td>clinical trial, phase ii.pt.</td>
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<td>10</td>
<td>exp Infliximab/</td>
<td>41</td>
<td>clinical trial, phase iii.pt.</td>
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<td>infliximab.ab,ti.</td>
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<td>clinical trial, phase iv.pt.</td>
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<td>12</td>
<td>exp Etanercept/</td>
<td>43</td>
<td>controlled clinical trial.pt.</td>
</tr>
<tr>
<td>13</td>
<td>etanercept.ab,ti.</td>
<td>44</td>
<td>randomized controlled trial.pt.</td>
</tr>
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<td>14</td>
<td>golimumab.ab,ti.</td>
<td>45</td>
<td>multicenter study.pt.</td>
</tr>
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<td>15</td>
<td>secukinumab.ab,ti.</td>
<td>46</td>
<td>clinical trial.pt.</td>
</tr>
<tr>
<td>16</td>
<td>guselkumab.ab,ti.</td>
<td>47</td>
<td>exp Clinical Trials as topic/</td>
</tr>
<tr>
<td>17</td>
<td>ixekizumab.ab,ti.</td>
<td>48</td>
<td>or/33-47</td>
</tr>
<tr>
<td>18</td>
<td>apremilast.ab,ti.</td>
<td>49</td>
<td>(clinical adj trial$).tw.</td>
</tr>
<tr>
<td>19</td>
<td>tofacitinib.ab,ti.</td>
<td>50</td>
<td>((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.</td>
</tr>
<tr>
<td>20</td>
<td>biologic* ab,ti.</td>
<td>51</td>
<td>PLACEBOS/</td>
</tr>
<tr>
<td>21</td>
<td>(DMARD* or diseas* modif* anti?rheuma* drug* or (anti?rheuma* adj2 drug*) or (anti?rheuma* adj2 agent*) or (monoclonal adj2 antibod*)).ab,ti.</td>
<td>52</td>
<td>placebo$.tw.</td>
</tr>
<tr>
<td>22</td>
<td>exp Antirheumatic Agents/</td>
<td>53</td>
<td>randomly allocated.tw.</td>
</tr>
<tr>
<td>23</td>
<td>exp Methotrexate/</td>
<td>54</td>
<td>(allocated adj2 random$).tw.</td>
</tr>
<tr>
<td>24</td>
<td>(MTX* or methotrexat*).ab,ti.</td>
<td>55</td>
<td>or/49-54</td>
</tr>
<tr>
<td>25</td>
<td>exp Sulfasalazine/</td>
<td>56</td>
<td>48 or 55</td>
</tr>
<tr>
<td>26</td>
<td>(sulfazalazin* or sulphasalazin* or sulphazalazin* or sulfasalazin* or SSZ*).ab,ti.</td>
<td>57</td>
<td>case report.tw.</td>
</tr>
<tr>
<td>27</td>
<td>exp Cyclosporine/</td>
<td>58</td>
<td>letter/</td>
</tr>
<tr>
<td>28</td>
<td>(cyclosporin* or ciclosporin* or csa*).ab,ti.</td>
<td>59</td>
<td>historical article/</td>
</tr>
<tr>
<td>29</td>
<td>(leflunomid* or lef*).ab,ti.</td>
<td>60</td>
<td>or/57-59</td>
</tr>
<tr>
<td>30</td>
<td>1 or 2</td>
<td>61</td>
<td>56 not 60</td>
</tr>
<tr>
<td>31</td>
<td>3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29</td>
<td>62</td>
<td>32 and 61</td>
</tr>
</tbody>
</table>

Excluded full-texts with reasons:

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Title</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. B. McInnes, et al.</td>
<td>2017</td>
<td>Secukinumab sustains improvement in signs and symptoms of psoriatic arthritis: 2 year results from the phase 3 FUTURE 2 study</td>
<td>(no additional information, same study)</td>
</tr>
<tr>
<td>D. van der Heijde, et al.</td>
<td>2018</td>
<td>4-year results from the RAPID-PsA phase 3 randomised placebo-controlled trial of certolizumab pegol in psoriatic arthritis</td>
<td>(no additional information)</td>
</tr>
<tr>
<td>Authors</td>
<td>Year</td>
<td>Title</td>
<td>Details</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>------</td>
<td>----------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td>D. van der Heijde, et al.</td>
<td>2018</td>
<td>Efficacy and Safety of Ixekizumab in Patients with Active Psoriatic Arthritis: 52-week Results from a Phase III Study (SPIRIT-P1)</td>
<td>(no additional information)</td>
</tr>
<tr>
<td>J. A. Walsh, et al.</td>
<td>2018</td>
<td>Efficacy of certolizumab pegol with and without concomitant use of disease-modifying anti-rheumatic drugs over 4 years in psoriatic arthritis patients: results from the RAPID-PsA randomized controlled trial</td>
<td>(long term data study already included by dressler)</td>
</tr>
<tr>
<td>L. C. Coates, et al.</td>
<td>2018</td>
<td>Secukinumab provides sustained PASDAS-defined remission in psoriatic arthritis and improves health-related quality of life in patients achieving remission: 2-year results from the phase III FUTURE 2 study</td>
<td>(no additional information)</td>
</tr>
<tr>
<td>S. Cohen, et al.</td>
<td>2019</td>
<td>Decreased Injection Site Pain Associated with Phosphate-Free Etanercept Formulation in Rheumatoid Arthritis or Psoriatic Arthritis Patients: A Randomized Controlled Trial</td>
<td>(no ACR20 outcome)</td>
</tr>
<tr>
<td>S. Dauth, et al.</td>
<td>2018</td>
<td>Value of combining biologics with methotrexate for treatment of psoriatic arthritis-questions remain</td>
<td>(no RCT)</td>
</tr>
<tr>
<td>H. M. Y. de Jong, et al.</td>
<td>2019</td>
<td>Sustained remission with methotrexate monotherapy after 22-week induction treatment with TNF-alpha inhibitor and methotrexate in early psoriatic arthritis: an open-label extension of a randomized placebo-controlled trial</td>
<td>(no ACR20 outcome)</td>
</tr>
<tr>
<td>A. Deodhar, et al.</td>
<td>2018</td>
<td>Efficacy and safety of guselkumab in patients with active psoriatic arthritis: a randomised, double-blind, placebo-controlled, phase 2 study</td>
<td>(not approved by EMA for PsA)</td>
</tr>
<tr>
<td>M. C. Genovese, et al.</td>
<td>2018</td>
<td>Safety and efficacy of ixekizumab in patients with PsA and previous inadequate response to TNF inhibitors: week 52 results from SPIRIT-P2</td>
<td>(no additional information)</td>
</tr>
<tr>
<td>S. Glatt, et al.</td>
<td>2018</td>
<td>Dual IL-17A and IL-17F neutralisation by bimekizumab in psoriatic arthritis: evidence from preclinical experiments and a randomised placebo-controlled clinical trial that IL-17F contributes to human chronic tissue inflammation</td>
<td>(not approved by EMA for PsA)</td>
</tr>
<tr>
<td>A. B. Gottlieb, et al.</td>
<td>2018</td>
<td>Ixekizumab improves patient-reported outcomes up to 52 weeks in bDMARD-naive patients with active psoriatic arthritis (SPIRIT-P1)</td>
<td>(no additional info)</td>
</tr>
<tr>
<td>M. Haroon, et al.</td>
<td>2018</td>
<td>Inflammatory back pain in psoriatic arthritis is significantly more responsive to corticosteroids compared to back pain in ankylosing spondylitis: a prospective, open-labelled, controlled pilot study</td>
<td>(no ACR20 outcome, pilot study)</td>
</tr>
<tr>
<td>A. Kavanaugh, et al.</td>
<td>2019</td>
<td>Radiographic Progression Inhibition with Intravenous Golimumab in Psoriatic Arthritis: Week 24 Results of a Phase III, Randomized, Double-blind, Placebo-controlled Trial</td>
<td>(no additional info)</td>
</tr>
<tr>
<td>A. Kavanaugh, et al.</td>
<td>2019</td>
<td>Ixekizumab improves patient-reported outcomes in patients with active psoriatic arthritis and inadequate response to tumour necrosis factor inhibitors: SPIRIT-P2 results to 52 weeks</td>
<td>(no additional info SPIRIT p2)</td>
</tr>
<tr>
<td>Authors</td>
<td>Year</td>
<td>Title</td>
<td>Additional Info</td>
</tr>
<tr>
<td>---------</td>
<td>------</td>
<td>----------------------------------------------------------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>I. B. McInnes, et al.</td>
<td>2018</td>
<td>Secukinumab provides rapid and sustained pain relief in psoriatic arthritis over 2 years: results from the FUTURE 2 study</td>
<td>(no additional info)</td>
</tr>
<tr>
<td>M. Ohtsuki, et al.</td>
<td>2019</td>
<td>Efficacy and safety of risankizumab in Japanese patients with moderate to severe plaque psoriasis: Results from the SustalMM phase 2/3 trial</td>
<td>(Fewer than 20% of patients in any treatment group had psoriatic arthritis)</td>
</tr>
<tr>
<td>V. Strand, et al.</td>
<td>2019</td>
<td>Effect of tofacitinib on patient-reported outcomes in patients with active psoriatic arthritis and an inadequate response to tumour necrosis factor inhibitors in the phase III, randomised controlled trial: OPAL Beyond</td>
<td>(a same trial opal beyond data in ANN no outcome of interest)</td>
</tr>
<tr>
<td>V. Strand, et al.</td>
<td>2019</td>
<td>Tofacitinib or adalimumab versus placebo: patient-reported outcomes from OPAL Broaden-a phase III study of active psoriatic arthritis in patients with an inadequate response to conventional synthetic disease-modifying antirheumatic drugs</td>
<td>(no additional info same trial OPAL Broaden ANN)</td>
</tr>
<tr>
<td>D. van der Heijde, et al.</td>
<td>2019</td>
<td>Secukinumab provides sustained low rates of radiographic progression in psoriatic arthritis: 52-week results from a phase 3 study, FUTURE 5</td>
<td>(long term outcomes)</td>
</tr>
</tbody>
</table>
Appendix 5 Diabetes Mellitus

Diabetes mellitus: Systematic review of the evidence on psoriasis treatment and diabetes mellitus

We conducted a “Systematic review of the efficacy, effectiveness and safety of topical and systemic treatments for psoriasis in patients with diabetes mellitus”, for which a protocol was published on PROSPERO (CRD42018087908). The work was conducted as part of a doctoral thesis by Rhea Jakubzyk, who gave permission to print her work here. Passages here may be identical to her thesis.

For the guideline, the recommendations focus on the systemic treatment options licensed for plaque type psoriasis.

Eligibility criteria

We included all studies on adult patients with a clinical diagnosis of psoriasis and a concomitant diabetes mellitus of any type being treated for psoriasis.

The interventions were specified to be topical treatment (urea, salicylic acid, calcineurin-inhibitors (pimecrolimus, tacrolimus), dithranol, corticosteroids (betamethasone, mometasonfuroat), tazaroten, coal tar, vitamin D3 derivate (calcipotriol, tacalcitol, calcitriol, calcipotriol and betamethasone) or systemic treatment (aciretin, ciclosporin, fumarates, methotrexate, apremilast) for psoriasis including biologicals (Anti TNF-alpha: etanercept, infliximab, adalimumab; anti-IL12/23: ustekinumab; Anti-IL17: secukinumab, ixekizumab, brodalumab; Anti-IL23). We included studies comparing the intervention to placebo or another treatment and those without comparator.

The following outcomes were of interest:

- Change in skin lesions based on PASI (Psoriasis Area Severity Index) or PGA (Physician Global Assessment) or another study specific assessment.
- Fasting plasma glucose, HbA1c or insulin sensitivity measured by HOMA (Homeostasis Modell Assessment) or other study specific outcomes
- Type and proportion of other adverse events
- Quality of life based on SF-36 (The Short Form (36) Health Survey), DLQI (Dermatology Life Quality Index) or another study specific assessment.

Wherever possible, we evaluated the outcomes at different timings, based on what was reported in the publications (e.g. short-term, long-term).

Included were randomized controlled trials, clinical trials (with and without comparison group), cohort studies, case control studies and cross sectional studies. We used a step-wise approach for including studies (for each study drug and comparator) following the hierarchy of evidence (Murad et al., 2016).

We excluded studies on patients with psoriatic arthritis only because of the different pathophysiology and treatment options. We also excluded studies with less than 100 patients to minimize bias.

Information sources
Three databases were searched systematically (MEDLINE Ovid from 1946, Embase Ovid from 1974 and The Cochrane Central Register of Controlled Trials (CENTRAL); updated last in September 2019. Furthermore, we examined the reference lists of included studies to identify references to relevant trials. The full search strategy is shown below.

**Study selection**

We screened all identified abstracts/titles for eligibility. Included title/abstracts were then screened as full texts based on the above listed eligibility criteria.

**Data collection and reporting**

Endnote was used to manage all records. One reviewer performed the screening and did the data extraction using a standardized form. A second reviewer checked the screening. We recorded all full-texts excluded and the primary reason for exclusion (see below).

The following items were extracted: Author, year of publication, country in which the study took place, study design, inclusion and exclusion criteria, baseline characteristics of the included patients, details of the interventions, details of any co-interventions, number and reasons for drop-out, type of adverse events and proportion of patients experiencing adverse events and serious adverse events, proportion of patients who experienced worsening of diabetes parameters, proportion of patients who showed an improvement in skin lesions, proportion of patients who showed an improvement in quality of life, time of assessment of endpoints and number/rate of patients assessed.

**Methodological quality assessment/ Risk of bias assessment**

We assigned Levels of Evidence for all studies included using the Center of Evidence Based Medicine Oxford recommendations (OCEBM Levels of Evidence Working Group and *OCEBM Levels of Evidence Working Group = Jeremy Howick, 2011). We assigned Levels of Evidence for all studies using the Center of Evidence Based Medicine Oxford recommendations (OCEBM Levels of Evidence Working Group and *OCEBM Levels of Evidence Working Group = Jeremy Howick, 2011). To assess risk of bias in randomized trials we additionally used the RoB 2.0 tool (Higgins JPT, 2016). We planned to use the ROBINS-I tool for controlled non-randomized studies of interventions but none of these type were included (Sterne et al., 2016).

**Summary measures**

Data was summarized and sorted by study type (see Table 2 and 3).

**Results**

Our search yielded 1404 citations, eight of which fulfilled the inclusion criteria (September 2019; see study selection flow chart). Four prospective studies (Pinter et al., 2019, Al-Mutairi and Shabaan, 2016, Koenig et al., 2011, Kimball et al., 2011), one study based on registry data (Kalb et al., 2015) and three retrospective studies (Hong et al., 2019, Wu et al., 2014, Wu et al., 2015) were included.

We did not find any studies on acitretin, apremilast, brodalumab, fumarates, guselkumab, ixekizumab, risankizumab, tildrakizumab that reported diabetes mellitus outcomes.
Based on the “Levels of Evidence - Center of Evidence Based Medicine Oxford recommendations” four prospective studies were categorized level 2 (18-21) and four retrospective studies level 3 (22-26). Results of the additional assessment for prospective randomized studies are shown in Table 1 (18-21, 27-31).
Data for overall 3503 patients with psoriasis and diabetes mellitus was extracted. Summarized results, sorted by study type are shown below.

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Original study</th>
<th>Randomization process</th>
<th>Deviations from the intended interventions</th>
<th>Missing outcome data</th>
<th>Measurement of the outcome</th>
<th>Selection of the reported result</th>
<th>Overall risk of bias</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Langley, R.G. e al. (2014)</td>
<td>?</td>
<td>⊝ ⊝ ⊝ ⊝ ⊝ ⊝</td>
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</tbody>
</table>

Abbreviation: ⊖ = high risk of bias, ⊕ = some concerns, ⊝ = low risk of bias.

**Table 1 Risk of Bias in Prospective Studies**
<table>
<thead>
<tr>
<th>Title</th>
<th>Author(s)</th>
<th>Original study</th>
<th>Intervention</th>
<th>Duration of treatment (M)</th>
<th>Patients (n)</th>
<th>Patients with diabetes (n)</th>
<th>Follow-up (M)</th>
<th>Age (Y) (р±SD)</th>
<th>Y(%)</th>
<th>Psoriasis score at baseline (р±SD)</th>
<th>Quality of life at baseline (р±SD)</th>
<th>Diabetes parameters at baseline (р±SD)</th>
<th>End of follow-up (M)</th>
<th>Psoriasis score e.g. PASI 75</th>
<th>Mean change of quality of life (р±SD)</th>
<th>Mean change of diabetes parameters (р±SD)</th>
<th>Outcomes</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy and safety of etanercept among patients with moderate to severe psoriasis with comorbidities: A randomized, double-blind, placebo-controlled, phase II trial</td>
<td>Einbiel, A. et al. (2011)</td>
<td>Memort, A. et al. (2008)</td>
<td>ADA (80mg/40mg)</td>
<td>4</td>
<td>814</td>
<td>74</td>
<td>47.4±12.4</td>
<td>39.1</td>
<td>PASI 10.6±7.2</td>
<td>/</td>
<td>/</td>
<td>4</td>
<td>PASI 75 =46.6±20.6</td>
<td>DLQI =7.1±6.3</td>
<td>Glucose (ммоль/л) =0.47</td>
<td>SAE not infected n=2 (2.7%)</td>
<td>SAE infections n=1 (1.4%)</td>
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<tr>
<td></td>
<td>Placebo</td>
<td>398</td>
<td>52</td>
<td>48.8±12.6</td>
<td>36</td>
<td>19.3±7.2</td>
<td>PASI 75 =2 (3.8%)</td>
<td>DLQI =1.3±5.8</td>
<td>Glucose (ммоль/л) =-0.65</td>
<td>SAE not infected n=2 (3.8%)</td>
<td>SAE infections n=0 (0%)</td>
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<td>Characterization of responder groups to secukinumab treatment in moderate to severe plaque psoriasis</td>
<td>Blauwet, A. et al. (2017)</td>
<td>Pitera, A. et al. (2014)</td>
<td>UST (40mg/60mg)</td>
<td>4</td>
<td>358</td>
<td>87.5</td>
<td>44.8</td>
<td>4</td>
<td>PASI 100 n=6.6/69 (9.6%)</td>
<td>PASI 75 n=50/69 (72.5%)</td>
<td>PASI 50 n=9.4/69 (13.6%)</td>
<td>PASI &lt;50 n=3/69 (4.3%)</td>
<td>PASI100 =-4.3/69 (5.4%)</td>
<td>PASI 75 =-0.4/69 (1.4%)</td>
<td>PASI 50 =-0.4/69 (0.6%)</td>
<td>PASI &lt;50 =-0.4/69 (0.6%)</td>
<td>SAE not infected n=3 (3.8%)</td>
<td>SAE infections n=2 (2.7%)</td>
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<td>ETA (50mg/100mg)</td>
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<td>20±5</td>
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<td>/</td>
<td>/</td>
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<td>Impact of interventional therapy on glycemic control in a cohort of patients with psoriatic arthritis: The pristine trial</td>
<td>Oelting, A. et al. (2013)</td>
<td>Strobl, R. et al. (2010)</td>
<td>ETA (30mg/300mg)</td>
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<td>Al-Aderi, N. et al. (2014)</td>
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<td>ADA (30mg)</td>
<td>6</td>
<td>36</td>
<td>35</td>
<td>34</td>
<td>43.7±11.6</td>
<td>52.8</td>
<td>PASI 50 =15/30 (50%)</td>
<td>PASI 75 =10/30 (33%)</td>
<td>FPG (ммоль/л) =-2.7±0.24</td>
<td>HbA1c (%) =-1.3</td>
<td>FPG (ммоль/л) =10.2±2.5</td>
<td>IS =-0.3 ±0.4</td>
<td>HbA1c (%) =0.3</td>
<td>ETA (%) =1.1</td>
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<td>Effects of tumor necrosis factor alpha inhibitors on insulin sensitivity in psoriasis patients with type 2 diabetes mellitus</td>
<td>Al-Aderi, N. et al. (2014)</td>
<td></td>
<td>Topical corticosteroids, calcipotriol (n=8) MMF (n=7) MTX (n=9)</td>
<td>6</td>
<td>51</td>
<td>49</td>
<td>29</td>
<td>47.6±14.3</td>
<td>51.7</td>
<td>PASI 50 =10/30 (33%)</td>
<td>PASI 75 =5/30 (16.6%)</td>
<td>FPG (ммоль/л) =10.2±2.5</td>
<td>HbA1c (%) =0.3</td>
<td>FPG (ммоль/л) =0.0±0.16</td>
<td>IS =-0.3 ±0.4</td>
<td>HbA1c (%) =0.3</td>
<td>ETA (%) =1.1</td>
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</table>

<table>
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<th>Topic</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Corticosteroids, calcipotriol</td>
<td>Langley, R.G. et al. (2014)</td>
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<td>CsA, MTX</td>
<td>FPG (ммоль/л) =-2.7±0.24</td>
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<tr>
<td>ADA (n=14)</td>
<td>ADA (n=14)</td>
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<tr>
<td>IFX (n=12)</td>
<td>IFX (n=12)</td>
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<tr>
<td>ETA (n=8)</td>
<td>ETA (n=8)</td>
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</table>
### Risk of Serious Infection With Biological and Systemic Treatment of Psoriasis: Results from the Psoriasis Longitudinal Assessment and Registry (PSOLAR)

<table>
<thead>
<tr>
<th>Author</th>
<th>Intervention</th>
<th>Duration of treatment (M)</th>
<th>Patients with diabetes (n)</th>
<th>Psoriasis-score at baseline (1/310)</th>
<th>Quality of life at baseline (1/310)</th>
<th>Diabetes parameters at baseline (1/310)</th>
<th>Mean change of quality of life (рSD)</th>
<th>Mean change of diabetes parameters (рSD)</th>
<th>Adverse events</th>
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<tbody>
<tr>
<td>Kahl, R. E. et al. (2015)</td>
<td>ADA (n=183)</td>
<td>21</td>
<td>11461</td>
<td>493 (42.9%)</td>
<td>44.9%</td>
<td>PASI 75</td>
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<tr>
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<td>ETA (n=221)</td>
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<td>493 (42.9%)</td>
<td>44.9%</td>
<td>PASI 75</td>
<td>/</td>
<td>/</td>
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</tr>
<tr>
<td></td>
<td>UST (n=440)</td>
<td>21</td>
<td>11461</td>
<td>493 (42.9%)</td>
<td>44.9%</td>
<td>PASI 75</td>
<td>/</td>
<td>/</td>
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</tr>
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</table>

**End of follow-up**

- **Psoriasis score e.g. PASI 75**
- **Mean change of quality of life (рSD)**
- **Mean change of diabetes parameters (рSD)**

**Adverse events**

- "presence of diabetes mellitus was found to be a significant predictor of serious infection" (HR, 1.7; 95% CI, 1.25-2.23; p < 0.001)

### Risk factors for increased serum creatinine level in patients with psoriasis treated with cyclosporine in a real-world practice

<table>
<thead>
<tr>
<th>Author</th>
<th>Intervention</th>
<th>Duration of treatment (M)</th>
<th>Patients with diabetes (n)</th>
<th>Psoriasis-score at baseline (1/310)</th>
<th>Quality of life at baseline (1/310)</th>
<th>Diabetes parameters at baseline (1/310)</th>
<th>Mean change of quality of life (рSD)</th>
<th>Mean change of diabetes parameters (рSD)</th>
<th>Adverse events</th>
</tr>
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<tbody>
<tr>
<td>Hong, J. R. et al. (2019)</td>
<td>CsA</td>
<td>3</td>
<td>398</td>
<td>37 (9.3%)</td>
<td>45.3±15.6</td>
<td>HbA1c (%)</td>
<td>44.2%</td>
<td>45.3±15.6</td>
<td>1-12</td>
</tr>
</tbody>
</table>

**Diabetes parameters at baseline**

- **Mean change of diabetes parameters (рSD)**

**Adverse events**

- "relative risk of a greater than 10% increase in serum creatinine levels was increased in diabetic patients" (HR 2.34; 95% CI, 1.59–3.45; p <0 .001)
Search strategy for the review on psoriasis and diabetes mellitus (Embase via Ovid)

<p>| 1. exp Psoriasis/ or Psoria*.mp. | 34. narrow band uvb.mp. |
| 2. pustulosis palmaris et plantaris.ti,ab. | 35. narrow band ultraviolet.mp. |
| 3. (pustulosis and palm and soles).ti,ab. | 36. psoralen ultraviolet a.mp. |
| 4. palmoplantar* pustulosis.ti,ab. | 37. psoralen uva.mp. |
| 5. 1 or 2 or 3 or 4 | 38. Laser therap*.mp. or Laser Therapy/ |
| 6. Urea/ or Urea*.mp. | 39. Ciclosporo*.mp. or Cyclosporine/ |
| 7. uric acid.mp. or Uric Acid/ | 40. cyclospor*.mp. |
| 8. salicyl* acid.mp. or Salicylic Acid/ | 41. fumar*.mp. or exp Fumarates/ |
| 9. Calcineu* inhibito*.mp. or Calcineurin Inhibitors/ | 42. fumaderm.mp. |
| 10. Tacrolimus/ or Pimecrolim*.mp. | 43. dimethylfumara*.mp. |
| 11. dithranol*.mp. or Anthralin/ | 44. fae.ti,ab. |
| 12. Cortisone/ or cortiso*.mp. | 45. dmf.ti,ab. |
| 13. Betamethasone/ or Betametha*.mp. | 46. exp Methotrexate/ or MTX.mp. |
| 14. mometaso*.mp. or Glucocorticoids/ or Mometasone Furoate/ | 47. methotrexxa*.mp. |
| 15. Retinoids/ or tazarot*.mp. | 48. amethopterin.mp. |
| 16. coal tar.mp. or Coal Tar/ | 49. mexate.mp. |
| 17. vit d3.mp or Cholecalciferol/ | 50. acitretin.mp. or Acitretin/ |
| 18. calcipotrio*.mp. | 51. Retinoids/ |
| 19. tacalcito*.mp. | 52. Phosphodiesterase 4 Inhibitors/ or apremilast.mp. |
| 20. Calcitriol/ or calcitrio*.mp. | 53. cdp571.mp. |
| 21. phototherap*.mp. or exp Phototherapy/ | 54. (etanercep* or enbrel).mp. or Etanercept/ |
| 22. PUVA Therapy/ or Photochemotherapy/ or PUVA.mp. | 55. (Infliximab* or remicade).mp. or Infliximab/ |
| 23. exp Ultraviolet Therapy/ or UV-B therap*.mp. | 56. ustekinumab.mp. or Ustekinumab/ |
| 24. photodynamic therap*.mp. | 57. (briakinumab or ABT-874).mp. |
| 25. photochemotherap*.mp. | 58. CNTO 1275.mp. |
| 27. photoradiation therap*.mp. | 60. secukinumab.mp. |
| 28. BBUVB.mp. | 61. guselkumab.mp. |
| 29. NBUVB.mp. | 62. adalimumab*.mp. or Adalimumab/ |
| 30. BB-UVB.mp. | 63. (d2e7 or humira).mp. |
| 31. NB-UVB.mp. | 64. exp Antibodies, Monoclonal/ |
| 32. broad band uvb.mp. | 65. monoclonal antibod*.mp. |
| 33. broad band ultraviolet.mp. | 66. monoclonal antibod*.mp. |</p>
<table>
<thead>
<tr>
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<th></th>
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<tbody>
<tr>
<td>66.</td>
<td>exp Interleukin-23/ or exp Interleukin-12/</td>
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<td>67.</td>
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<tr>
<td>68.</td>
<td>ixekizumab.mp.</td>
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<td>69.</td>
<td>(tumor necrosis factor-alpha or tumour necrosis factor-alpha).mp.</td>
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<td>70.</td>
<td>anti tnf.mp.</td>
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<tr>
<td>71.</td>
<td>(tumor necrosis factor antibod* or tumour necrosis factor antibod*).mp.</td>
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<tr>
<td>72.</td>
<td>(antitumor necrosis factor or antitumour necrosis factor).mp.</td>
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<tr>
<td>73.</td>
<td>(anti tumor necrosis factor or anti tumour necrosis factor).mp.</td>
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<tr>
<td>74.</td>
<td>(tnf antibod* or tnf alpha antibod*).mp.</td>
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<tr>
<td>75.</td>
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<td>76.</td>
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<td>exp Tumor Necrosis Factor-alpha/</td>
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<td>78.</td>
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<td>K. Abuabara                                                                    K. Abuabara</td>
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<td>J. Alcantara-Gonzalez                                                           J. Alcantara-Gonzalez</td>
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<td>N. Al-Mutairi                                                                  N. Al-Mutairi</td>
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<td>A. Armstrong and E. Levi                                                        A. Armstrong and E. Levi</td>
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<td>H. H. Chen</td>
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<td>Y. J. Chen</td>
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**Arthritis and Rheumatism. Conference: Annual Scientific Meeting of the American College of Rheumatology and Association of Rheumatology Health Professionals, 63.**


Appendix 7 Viral Hepatitis

Hepatitis: Systematic review of the evidence on psoriasis treatment and viral hepatitis

The work was conducted as part of a doctoral thesis by Rhea Jakubzyk, who gave permission to print the work here. Passages here may be identical to her thesis.

Eligibility criteria

We included all studies on adult patients with a clinical diagnosis of psoriasis and a concomitant hepatitis B or C being treated for psoriasis. Viral hepatitis was defined as positive serological or virological marker for hepatitis B virus (HBV) or hepatitis C virus (HCV) before onset of the psoriasis treatment.

The interventions were specified to be topical treatment (urea, salicylic acid, calcineurin-inhibitors (pimecrolimus, tacrolimus), dithranol, corticosteroids (betamethasone, mometasonfuroat), tazarotene, coal tar, vitamin D3 derivate (calcipotriol, tacalcitrol, calcipotriol and betamethasone) or systemic treatment (aciretin, ciclosporin, fumarates, methotrexate, apremilast) for psoriasis including biologicals (Anti TNF-alpha: etanercept, infliximab, adalimumab; Anti-IL12/23: ustekinumab; Anti-IL17: secukinumab, ixekizumab, brodalumab; Anti-IL23). We included studies comparing the intervention to placebo or another treatment and those without comparator.

The following outcomes were of interest:

- Change in skin lesions based on PASI (Psoriasis Area Severity Index) or PGA (Physician Global Assessment) or another study specific assessment.
- Transaminases, viral load or other study specific outcomes
- Type and proportion of other adverse events
- Quality of life based on SF-36 (The Short Form (36) Health Survey), DLQI (Dermatology Life Quality Index) or another study specific assessment.

When possible, we evaluated the outcomes at different timings, based on what was reported in the publications (e.g. short-term, long-term).

Included were randomized controlled trials, clinical trials (with and without comparison group), cohort studies, case control studies and cross sectional studies. We used a step-wise approach for including studies (for each study drug and comparator) following the hierarchy of evidence (Murad et al., 2016).

We excluded studies on patients with psoriatic arthritis because of the different pathophysiology and treatment options.

Information sources

Three databases were searched systematically (MEDLINE Ovid from 1946, Embase Ovid from 1974 and The Cochrane Central Register of Controlled Trials (CENTRAL); updated last in January 2019). Furthermore, we examined the reference lists of included studies to identify references to relevant trials. The full search strategy is shown below.

Study selection
We screened all identified abstracts/titles for eligibility. Included titles/abstracts were then screened as full texts based on the above listed eligibility criteria.

Data collection and reporting

Endnote was used to manage all records. One reviewer performed the screening and did the data extraction using a standardized form. A second reviewer checked 50% of the data with high agreement. We recorded all full-texts excluded and the primary reason for exclusion (see below).

Data Items

The following items were extracted: Author, year of publication, country in which the study took place, study design, inclusion and exclusion criteria, baseline characteristics of the included patients, details of the interventions, details of any co-interventions, number and reasons for drop-out, type of adverse events and proportion of patients experiencing adverse events and serious adverse events, proportion of patients who experienced worsening of liver function, proportion of patients who showed an improvement in skin lesions, proportion of patients who showed an improvement in quality of life, time of assessment of endpoints and number/rate of patients assessed.

Risk of bias assessment

We assigned Levels of Evidence for all studies included using the Center of Evidence Based Medicine Oxford recommendations (OCEBM Levels of Evidence Working Group and * OCEBM Levels of Evidence Working Group = Jeremy Howick, 2011). To assess risk of bias in randomized trials we additionally used the RoB 2.0 tool (Higgins JPT, 2016). We planned to use the ROBINS-I tool for controlled, non-randomized studies of interventions but none of these type were included (Sterne et al., 2016).

Summary measures

Data was summarized and sorted by the medication used (see Table 4 and 5). We counted the number of patients across studies reported to have liver dysfunction or HBV/HCV-reactivation during follow-up and improvement in psoriasis to provide a pragmatic overview. We summarized the results - see Table 2 and 3 - with focus on clinically relevant information (e.g. liver dysfunction or HBV/HCV-reactivation).

Results

Our search yielded 1596 citations, 22 of which fulfilled the inclusion criteria (January 2019; see study selection flow chart). Three prospective studies (Ting et al., 2018, Chiu et al., 2018, AlMutairi and Abouzaid, 2018), two studies based on registry data (Sanz-Bueno et al., 2015, Tang et al., 2018) and 17 retrospective studies (Cho et al., 2012, Nosotti et al., 2010, Cassano et al., 2011, Hsieh et al., 2018, Pereira et al., 2018, Siegel et al., 2017, Piaserico et al., 2017a, Chiu et al., 2013, Fotiadou et al., 2011, Garavaglia and Altomare, 2010, Morisco et al., 2014, Navarro et al., 2013, Piaserico et al., 2017b, Snast et al., 2017, Navarro et al., 2014, Prignano et al., 2011, Di Nuzzo et al., 2013) were included.

No studies on acitretin, apremilast, brodalumab, ciclosporin, fumarates, guselkumab, ixekizumab, risankizumab and tildrakizumab were identified that reported outcomes for viral hepatitis.
Based on the Center of Evidence Based Medicine Oxford recommendations all references included were rated level 3 (Ting et al., 2018, Chiu et al., 2018, AlMutairi and Abouzaid, 2018, Cho et al., 2012, Nosotti et al., 2010, Cassano et al., 2011, Hsieh et al., 2018, Pereira et al., 2018, Siegel et al., 2017, Piaserico et al., 2017a, Chiu et al., 2013, Fotiadou et al., 2011, Garavaglia and Altomare, 2010, Morisco et al., 2014, Navarro et al., 2013, Piaserico et al., 2017b, Snast et al., 2017, Navarro et al., 2014, Prignano et al., 2011, Di Nuzzo et al., 2013, Sanz-Bueno et al., 2015, Tang et al., 2018, OCEBM Levels of Evidence Working Group and * OCEBM Levels of Evidence Working Group = Jeremy Howick, 2011). Results of the additional assignment for prospective randomized studies are shown in Table 1 (Chiu et al., 2018, AlMutairi and Abouzaid, 2018, Higgins JPT, 2016).
Data for overall 1128 patients with psoriasis and viral hepatitis was extracted. Of those, 854 patients suffered from hepatitis B infection and 274 from hepatitis C infection. Most of the included studies reported individual patient data. The tables below are providing detailed information, sorted by medication used.

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Abbreviation:
⊕ = high risk of bias
? = unknown risk of bias
⊙ = low risk of bias
### Hepatitis B

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**Abbreviation:**
- I = before treatment; 2 = while treatment; 3 = no difference in the occurrence of liver cirrhosis between MTX-users and a second cohort without MTX; 4 = as defined in the study at end of follow
- I * prospective study; II = retrospective study
- ** mean (SD not applicable or reported); *** as defined by threefold increase in transaminases or 10-fold increase in viral load; **** as defined in the study at end of follow
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## Hepatitis B

<table>
<thead>
<tr>
<th>Author [Y]</th>
<th>Place</th>
<th>Patients (n)</th>
<th>Drug</th>
<th>Duration of treatment (M) mean±SD</th>
<th>Age (Y) mean±SD</th>
<th>Baseline e.g. PASI-75 mean±SD</th>
<th>Baseline</th>
<th>Eof</th>
<th>Baseline</th>
<th>Eof</th>
<th>Baseline</th>
<th>Eof</th>
<th>Baseline</th>
<th>Eof</th>
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<th>HBV reactivation (n)</th>
<th>Other adverse events</th>
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### Abbreviation:
- I = before treatment; 2 = while treatment; 3 = no difference in the occurrence of liver cirrhosis between MTX-users and a second cohort without MTX; 4 = as defined in the study at end of follow
- * = prospective study; II = retrospective study
- AST = Alanine Aminotransferase; ALT = Aspartate Aminotransferase; AM: Body Surface Area; CsA = Cyclosporine A; CsA = Cyclosporine A; Eot = End of treatment; ENt = Entecavir; ETA = Etanercept; eod = end of follow-up; GOL = Golimumab; HCC = Hepatocellular Carcinoma; HBV = Hepatitis B Virus; IFN = Interferon; IFX = Infliximab; LAM = Lamivudine; MTX = Methotrexate; PASI = Psoriasis Area Severity Index; SEC = Secukinumab; UST = Ustekinumab

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64
### Hepatitis B

<table>
<thead>
<tr>
<th>Author</th>
<th>Place</th>
<th>Patients (n)</th>
<th>Drug</th>
<th>Duration of treatment (M) mean±SD</th>
<th>Age (Y) mean±SD</th>
<th>9 (%)</th>
<th>Eof (M) mean±SD</th>
<th>Baseline mean±SD</th>
<th>e.g. PASI-75 response eof (n)</th>
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<th>Eof</th>
<th>Baseline</th>
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<th>Eof (n)</th>
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</table>

**MTX**

| Tang, K. T. et al. (2018) | Taiwan | 370 | MTX | / | 42.6±13.2 | 28 | 50.4±38.4 | / | / | / | / | 48/370 | / | Liver cirrhosis (15/370) |
| Chiu H. Y. et al. (2018) | Taiwan | 25 | SEC | 7.7±3.8 | 49.7±8.6 | 16 | 9.1±3.9 | 13.4±8.2 | / | / | 43.7±42.2 | / | 3/25 | 6/25 | Hepatic cancer |
| Chiu H. Y. et al. (2018) | Taiwan | 24 | SEC | 8.7±3.7 | 54.7±13.4 | 25 | 9.2±3.7 | 20.1±8.3 | / | / | 41.1±28.0 | / | 11/24 | 1/24 | |

**UST**

| Ting, S. W. et al. (2018) | Taiwan | 54 | UST | / | 47±16.7 | 24 | /*none had liver failure*/ | / | / | / | / | / | / | 3/48 | / |
| Hsieh, T. Y. et al. (2018) | Taiwan | 75 | UST | / | / | 24.7 | / | / | / | / | / | / | unknown (2/75) | 2/75 | / |
| Chiu, H.Y. et al. (2013) | Taiwan | 14 | UST | 9.4±9 | 45.5±7.6 | 28.6 | 10.4 | / | 5/14 | unchanged | / | / | ENT (1/4) | LAM (1/54) | 2/14 | / |
| Piaserico, S. et al. (2017) | Italian | 5 | UST | 57.2±13.9 | 55.4±16.5 | 20 | 57 | / | 28.8±11.6 | 31.8±7.9 | 31.2±16.2 | 41.8±13.6 | 0 | 0 | LAM (4/5) | 0 | / |
| Navarro, R. et al. (2013) | Spain | 1 | UST | 7 | 56 | 0 | 25 | / | 17.6 | 1/1 PASI50 | 32 | 16 | 35 | 15 | / | / | ENT | 0 | none |

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I = prospective study; II = retrospective study

* = mean (SD not applicable or reported); ** = as defined by threefold increase in transaminases or 10-fold increase in viral load; *** = HCV reactivation 6 month prior antiviral therapy reported

ADA = Adalimumab; ADE = Adefovir; ALT = Alanine Aminotransferase; AST = Aspartate Aminotransferase; BSA = Body Surface Area; CSA = Cyclosporine A; ENT = Entecavir; ETA = Etanercept; eof = end of follow-up; GOL = Golimumab; HCC = Hepatocellular Carcinoma; HBV = Hepatitis B Virus; IFN = Interferon; IFX = Infliximab; LAM = Lamivudine; MTX = Methotrexate; PASI = Psoriasis Area Severity Index; SEC = Secukinumab; UST = Ustekinumab
<table>
<thead>
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<th>Author (Y)</th>
<th>Place</th>
<th>Patients (n)</th>
<th>Drug</th>
<th>Duration of treatment (M) mean±SD</th>
<th>Age (Y) mean±SD</th>
<th>%</th>
<th>Eof (M) mean±SD</th>
<th>Baseline mean±SD</th>
<th>e.g. PASI-75 response</th>
<th>Baseline</th>
<th>Eof</th>
<th>Baseline</th>
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<th>Eof (n)</th>
<th>Antiviral therapy</th>
<th>HBV reactivation (n)</th>
<th>Other adverse events</th>
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1 = before treatment; 2 = while treatment; 3 = no difference in the occurrence of liver cirrhosis between MTX-users and a second cohort without MTX; 4 = as defined in the study at end of follow-up

I = prospective study; II = retrospective study

* = mean (SD not applicable or reported); ** = as defined by threefold increase in transaminases or 10-fold increase in viral load; *** = HCV-reactivation 6 month prior antiviral therapy reported

ADA = Adalimumab; ADE = Adefovir; ALT = Alanine Aminotransferase; AST = Aspartate Aminotransferase; BSA = Body Surface Area; CsA = Cyclosporine A; ENT = Entecavir; ETA = Etanercept; e.g. = end of follow-up; GOL = Golimumab; HCC = Hepatocellular Carcinoma; HBV = Hepatitis B Virus; IFN = Interferon; IFX = Infliximab; LAM = Lamivudine; MTX = Methotrexate; PASI = Psoriasis Area Severity Index; SEC = Secukinumab; UST = Ustekinumab

Transaminases

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<th>AST mean±SD</th>
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<tr>
<td>&gt; 2000 IU/ml</td>
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Viral load

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Severity score (e.g. PASI)

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Respiratory infection (1/16), myocardial infarction (1/16), erythema (2/16)
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<th>Author (Year)</th>
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<th>Patients (n)</th>
<th>Drug</th>
<th>Duration of treatment (M) measured</th>
<th>Age (Y) mean±SD ♀ (%</th>
<th>Severity Score (e.g. PASI)</th>
<th>% (n)</th>
<th>Baseline</th>
<th>Ref</th>
<th>Baseline</th>
<th>Ref</th>
<th>Baseline</th>
<th>Ref</th>
<th>Baseline detectable (%)</th>
<th>Change at eof (%)</th>
<th>Antiviral therapy (n)</th>
<th>HIV reactivation (n)</th>
<th>Adverse event (n)</th>
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**Abbreviations:**
- ADA = Adalimumab
- ETN = Etanercept
- INF = Interferon
- IFX = Infliximab
- RIB = Ribavirin
- AUG = Augmentin
- PASI = Psoriasis Area Severity Index
- BSA = Body Surface Area
- DAA = Direct Acting Antiviral
- SEC = Secukinumab
- UST = Ustekinumab

* = mean (SD not applicable or reported); ** = as defined in the study at end of follow-up; "unchanged"
Search strategy for the review on psoriasis and viral hepatitis (Embase Ovid)

1. exp Psoriasis/ or Psoria*.mp.
2. pustulosis palmaris et plantaris.ti,ab.
3. (pustulosis and palm and soles).ti,ab.
4. palmoplantar* pustulosis.ti,ab.
5. 1 or 2 or 3 or 4
6. Urea/ or Urea*.mp.
7. uric acid.mp. or Uric Acid/
8. salicyl* acid.mp. or Salicylic Acid/
9. Calcineu* inhibitio*.mp. or Calcineurin Inhibitors/
10. Tacrolimus/ or Pimecrolim*.mp.
11. dithranol*.mp. or Anthralin/
12. Cortisone/ or cortiso*.mp.
13. Betamethasone/ or Betametha*.mp.
14. mometaso*.mp. or Glucocorticoids/ or Mometasone Furoate/
15. Retinoids/ or tazarot*.mp.
16. coal tar.mp. or Coal Tar/
17. vit d3.mp or Cholecalciferol/
18. calcipotrio*.mp.
19. tacalcito*.mp.
20. Calcitriol/ or calcitrio*.mp.
21. phototherap*.mp. or exp Phototherapy/
22. PUVA Therapy/ or Photochemotherapy/ or PUVA.mp.
23. exp Ultraviolet Therapy/ or UV-B therap*.mp.
24. photodynamic therap*.mp.
25. photochemotherap*.mp.
27. photoradiation therap*.mp.
28. BBUVB.mp.
29. NBUVB.mp.
30. BB-UVB.mp.
31. NB-UVB.mp.
32. broad band uvb.mp.
33. broad band ultraviolet.mp.
34. narrow band uvb.mp.
35. narrow band ultraviolet.mp.
36. psoralen ultraviolet a.mp.
37. psoralen uva.mp.
38. Laser therap*.mp. or Laser Therapy/
39. Ciclospori*.mp. or Cyclosporine/
40. cyclospor*.mp.
41. fumar*.mp. or exp Fumarates/
42. fumaderm.mp.
43. dimethylfumara*.mp.
44. fae.ti,ab.
45. dmf.ti,ab.
46. exp Methotrexate/ or MTX.mp.
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49. mexate.mp.
50. acitretin.mp. or Acitretin/
51. Retinoids/
52. Phosphodiesterase 4 Inhibitors/ or apremilast.mp.
53. cdp571.mp.
54. (etanerclep* or enbrel).mp. or Etanerccept/
55. (Infliximab* or remicade).mp. or Infliximab/
56. ustekinumab.mp. or Ustekinumab/
57. (briakinumab or ABT-874).mp.
58. CNTO 1275.mp.
59. stelara.mp.
60. secukinumab.mp.
61. guselkumab.mp.
62. adalimumab*.mp. or Adalimumab/
63. (d2e7 or humira).mp.
64. exp Antibodies, Monoclonal/
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66. exp Interleukin-23/ or exp Interleukin-12/
67. brodalumab.mp.
68. ixekizumab.mp.
69. (tumor necrosis factor-alpha or tumour necrosis factor-alpha).mp.
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74. (tnf antibod* or tnf alpha antibod*).mp.
75. climate therap*.mp. or Climatotherapy/
76. Psychotherapy/ or psychosocial therap*.mp.
77. exp Tumor Necrosis Factor-alpha/
78. 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77
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80. exp Hepatitis/ or Hepatit*.mp.
81. chronic hepatit*.mp. or exp Hepatitis, Chronic/
82. Hepatitis B/ or hepatit* b.mp.
83. HBV.ti,ab.
84. Hepatitis C, Chronic/ or Hepatitis C/ or hepatit* c.mp.
85. non a non b hepatit*.mp.
86. HCV.ti,ab.
87. hepati* d.mp.
88. Hepatitis A/ or hepatit* infection.mp.
89. HAV.ti,ab.
90. 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89
91. 79 and 90

Excluded full-texts for the review on psoriasis and viral hepatitis

A. Abuchar 2013 study design
A. J. Alcaide 2008 study design
N. AlMutairi and H. A. Abouzaid 2018 double
Anonymous 2003 off-topic
Anonymous 2016 double
E. A. Antoniou 2016 off-topic
M. Armengot-Carbo 2013 off-topic
S. Ashraf 2013 off-topic
S. Aslanidis 2007 off-topic
G. Babino 2013 study design
F. Bartalesi 2010 study design
S. E. Behnam 1970 off-topic
G. Berge 2018 study design
S. L. Bevans 2018 study design
S. L. Bevans 2015 off-topic
E. Bjorssson 1995 off-topic
M. J. Boffa 2011 study design
L. Bomm 2016 study design
C. Bonifati 1990 study design
W. W. Bottomley 2010 no relevant outcomes
D. E. Branisteanu 2012 off-topic
V. Brazzelli 1995 off-topic
N. P. Burrows 2017 study design
M. V. Cannizzaro 2008 off-topic
S. C. Carneiro 2008 off-topic
N. Cassano and G. A. Vena 2006 study design
I. Cavazzana 2015 off-topic
R. Cecchi and L. Bartoli 2018 off-topic
A. Chiricozzi 2018 off-topic
Y. Chiu 2018 no relevant outcomes
Y. M. Chiu 2018 no relevant outcomes
Y. M. Chiu 2017 no relevant outcomes
Y. M. Chiu 2017 off-topic
E. Chouela 1996 off-topic
C. H. Chu and C. Davis 2017 study design
W. T. Clarke 2018 off-topic
M. H. Collazo 2008 study design
A. Conde-Taboada 2009 study design
S. Couderc 2015 off-topic
M. S. Dag 2013 off-topic
B. Dahmani and O. Boudghene Stambouli 2013 off-topic
L. J. Dang 2014 off-topic
C. De Simone 2006 study design
V. Di Lernia and E. Guareschi 2010 off-topic
V. Di Lernia 2013 study design
S. Di Nuzzo 2016 study design
A. M. Downs and M. G. Dunnill 2000 off-topic
H. V. Dublin and E. R. Harrell 1970 off-topic
C. Efe 2010 off-topic
K. Eisendle and P. Fritsch 2005 study design
A. A. Elfert 2017 off-topic
M. Enomoto 2018 off-topic
M. Enomoto 2018 off-topic
E. Erkek 2000 study design
M. Esposito 2017 off-topic
D. A. Fairhurst and R. Sheehan-Dare 2009 off-topic
B. Feaster 2018 study design
D. J. Filip 1971 off-topic
A. Finet 2016 off-topic
B. Foroncewicz 2014 off-topic
C. Fotiadou 2018 study design
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References (EtD framework AND methods & evidence report)


Arthritis and Rheumatism Conference: Annual Scientific Meeting of the American College of Rheumatology and Association of Rheumatology Health Professionals. 2011;63(10 SUPPL. 1).


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