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S3-Leitlinie

Therapie der Psoriasis vulgaris

Evidenzbericht

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Leitlinienkoordination:	Prof. Dr. Alexander Nast

DDG Deutsche Dermatologische Gesellschaft BVDD

Inhaltsverzeichnis

Hinweise zur Anwendung / Haftungsausschluss

Die in dieser Leitlinie enthaltenen Empfehlungen dienen als Hilfestellung für Entscheidungen in der medizinischen Versorgung.

Die Anwender*innen der Leitlinie bleiben verantwortlich für jede diagnostische und therapeutische Applikation, Medikation und Dosierung. Die individuelle Aufklärung, unter anderem über unerwünschte Wirkungen von Arzneimitteln, eine Off-label-Verordnung und die Prüfung auf das Vorliegen von Kontraindikationen obliegt der verordnenden Ärztin bzw. dem verordnenden Arzt.

Empfehlungen in der Leitlinie beziehen sich in der Regel auf standardisierte klinische Situationen. Daher kann und muss unter Umständen von den ausgesprochenen Empfehlungen abgewichen werden. Entscheidungen über die Versorgung müssen unter Berücksichtigung aller individuell relevanten Gegebenheiten getroffen werden.

Anwender*innen müssen die Informationen in dieser Leitlinie unter Rückgriff auf die entsprechenden Fachinformationen sorgfältig überprüfen, zum Beispiel ob die Empfehlungen in Bezug auf Dosierung, Dosierungsschemata, unerwünschte Wirkungen, Kontraindikationen und Arzneimittelwechselwirkungen vollständig, korrekt, aktuell und angemessen sind. Dies gilt auch für Dosisadaptation entsprechend des Alters, des Körpergewichts oder bei Komorbidität. Im Zweifelsfall sind entsprechende Fachleute zu konsultieren.

In dieser Leitlinie enthaltene Angaben zur Dosierung von Medikamenten reflektieren die Meinung der Leitliniengruppe. Es handelt sich zum Teil um Indikationen und/oder Dosierungen, die gemäß den Angaben in den Fachinformationen nicht zugelassen sind (off-label-use).

In Hinblick auf die Sicherheit der thematisierten Interventionen beschränkt sich die Leitlinie auf die von der Leitlinienkommission priorisierten Aspekte. Eine umfassende Bewertung aller verfügbaren Sicherheitsinformationen für die thematisierten Interventionen wurde nicht vorgenommen.

Sollten Unstimmigkeiten oder andere Aspekte auffallen, sollen diese im allgemeinen Interesse der Leitlinienredaktion gemeldet werden.

Bei dieser Leitlinie handelte es sich um eine Adaption der EUROGUIDERM GUIDELINE ON THE SYSTEMIC TREATMENT OF PSORIASIS von Nast A et al., deren finale Fassung auf der Webseite des European Dermatology Forum (https://www.guidelines.edf.one/guidelines/psoriasis-guideline) zur Verfügung steht (lizen-ziert unter CC BY NC 4.0, https://creativecommons.org/licenses/by-nc/4.0/).

Die Autoren haben die EuroGuiDerm-Leitlinie sorgfältig überprüft und kommentiert, Teile der Leitlinie an die Versorgungsituation in Deutschland angepasst und über alle Abschnitte, in denen Empfehlungen ausgesprochen werden, abgestimmt. Für weitere Informationen, auch bezüglich des Konsensverfahrens gemäß dem AWMF-Regelwerk, siehe Abschnitt Methodik unten sowie den separat veröffentlichten Leitlinienreport.

Die EuroGuiDerm Guideline on the Systemic Treatment of Psoriasis vulgaris wurde gemäß dem EuroGuiDerm Methods Manual v1.3 entwickelt, welches auf der Webseite der European Dermatology Forum (EDF) im Unterabschnitt „EuroGuiDerm/EDF Guidelines“ zu finden ist: https://www.guidelines.edf.one/guideline-methods.

Neben der aktualisierten Fassung der europäischen Psoriasisleitlinie diente auch der Text der vorherigen Version der deutschen Psoriasis Leitlinie als Grundlage. Abschnitte, in denen keine Aktualsierungen durchgeführt wurden, sind daher unverändet übernommen worden. Autor*Innen, die aus dem Gremium ausgeschieden sind, wurden als Autor*innen nicht erneut aufgenommen.

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Vorbemerkungen zur Quellleitlinie

Die hier enthaltenen Evidenzberichte sind teilweise aus der EUROGUIDERM GUIDELINE ON THE SYSTEMIC TREATMENT OF PSORIASIS VULGARIS übernommen. Die vollständige EuroGuiDerm-Leitlinie, inklusive Methodenbericht und Evidenzdarstellung in den Einzelkapiteln finden Sie unter https://www.guidelines.edf.one/guidelines/psoriasis-guideline. Die Verwertungsrechte für diese Inhalte liegen beim European Dermatology Forum. Die Verwertungsrechte für die neu generierten Abschnitte liegen bei der Deutschen Dermatologischen Gesellschaft.

Ergebnis der AGREE-II-Bewertung der Quellleitlinie

Table 1: AGREE-II appraisal

Items aus AGREE II	Bewertung	Begründung
Domäne 3		
Es wurde systematisch nach Evidenz gesucht.	5	Für die als evidenzbasiert gekennzeichneten Empfehlungen/Kapitel (Hepatitis, Diabetes, Psoriasisarthritis) wurde in 2 Datenbanken recherchiert, Suchbegriffe und -Datum dokumentiert Da der Cochrane-Review zur Systemtherapie bei Psoriasis in Kooperation mit der Arbeitsgruppe entstand, war er bekannt. Er wurde als methodisch hochwertig bewertet (AMSTAR-II), es wurde daher nicht nach weiteren systematischen Reviews recherchiert.
Die Kriterien für die Auswahl der Evidenz sind eindeutig beschrieben.	7	PICO für jede Fragestellung dargestellt
Die Stärken und die Schwächen der Evidenz sind eindeutig beschrieben.	5	Cochrane Review: mit AMSTAR-II bewertet, die darin eingeschlossen Studien wurden von Cochrane-Autoren bewertet, certainty of the evidence wurde evaluiert Für die Recherchen zu den Kapiteln: Hepatitis, Diabetes, Psoriasisarthritis wurde die eingeschlossene Evidenz je nach Studientyp bewertet (RoB 2.0, für ‚uncontrolled prospective cohort studies‘ IHE checklist, OCEBM zur Erhebung des Levels of evidence), keine Bewertung von Fallberichten. Keine narrative Beschreibung der Evidenzqualität in den Hintergrundtexten. Auffindbarkeit in den Evidenzberichten in den Kapitel-PDF.
Das methodische Vorgehen bei der Formulierung der Empfehlungen ist eindeutig beschrieben.	6	Verfahren in ‚Methods section‘ der Langfassung kurz beschrieben mit Verweis auf Methodenreport und ausführlicher Darstellung dort in Kapitel 7
Der gesundheitliche Nutzen, Nebenwirkungen und Risiken wurden bei der Formulierung der Empfehlungen berücksichtigt.	5	Evidence to decision framework für den Cochrane Review vorhanden Narrative Darstellung im Evidenzbericht für die Kapitel Hepatitis, Diabetes, Psoriasisarthritis. Schadensaspekte wurden als Endpunkte evaluiert und in die Entscheidungsfindung einbezogen.
Die zugrunde liegende Evidenz kann den Empfehlungen eindeutig zugeordnet werden.	5	In Evidenzbasierten Kapiteln befindet sich ein Hinweis auf die Evidenzsynthese, die sich jeweils im Appendix der Einzel-PDF befindet.
Die Leitlinie ist vor ihrer Veröffentlichung durch externe Experten begutachtet worden.	7	Ein externer Review hat stattgefunden
Es existiert ein Verfahren zur Aktualisierung der Leitlinie.	4	Info im Methods report, S. 30 unten

Items aus AGREE II	Bewertung	Begründung
Domäne 6		
Die finanzierende Organisation hat keinen Einfluss auf die Inhalte der Leitlinie genommen.	5	The EuroGuiDerm Team is not involved in fundraising or in the decision making on which guideline (GL) or consensus statement (CS) development is funded. The decisions on which GL/CS is funded are made by the EuroGuiDerm Board of Directors independently. The EDF or any other body supporting the EuroGuiDerm is never involved in the guideline development and had no say on the content or focus of the guideline.
Interessenkonflikte der Mitglieder der Entwicklergruppe der Leitlinie wurden dokumentiert und bei der Leitlinienerstellung berücksichtigt.	7	Ja, siehe Tabelle 1 Methods report

1 Cochrane Review

1.1 Vorbemerkung

Der Cochrane Review von Sbidian et al. [1] bildet die Evidenzgrundlage für die Abbildung „Übersicht der Therapieoptionen“ und die Allgemeinen Empfehlungen des Kapitels IX der Langfassung der Leitlinie.

Für die Informationen in den Wirkstoffkapiteln wurden darüber hinaus die Fachinformationen sowie Publikationen herangezogen, die Sicherheits- oder Anwendungsaspekte adressierten.

1.2 Evidenztabelle

Table 2 Evidence table (Cochrane Review)

Reference	Charakteristics	Key results	Comment

Sbidian E. Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis. Cochrane Database of Systematic Reviews 2023, Issue 7. Art. No.: CD011535. [1]	**Aim:** compare the benefits and harms of non-biological systemic agents, small molecules, and biologics for people with moderate-to-severe psoriasis using a network meta-analysis, and to provide a ranking of these treatments according to their benefits and harms.
	Search date: October 2022
	Population:
	- Adults (>18y)
	- moderate-to-severe plaque psoriasis at
	Intervention:
	- non-biological systemic agents, small molecules, and biologics
	- at any stage of treatment with
	Comparison:
	- placebo
	- another active agent
	Outcomes:
	- proportion of participants who achieved clear or almost clear skin (at least Psoriasis Area and Severity Index (PASI) 90)
	- proportion of participants with serious adverse events (SAEs)
		Baseline results:
		- 12 new studies identified
		- total number of included studies: 179
		- number of randomised participants: 62,339
		- 67.1% men
		- mainly recruited from hospitals
		- Average age was 44.6 years,
		- mean PASI at baseline: 20.4 (range: 9.5-39)
		- placebo-controlled studies: 56%
		- 20 treatments assessed
		- multicentric: n= 152 (2-231 centres)
		- risk of bias:
		  ○ high: n= 65/179
		  ○ unclear: n= 24/179
		  ○ low: n= 90/179.
		- funding by pharmaceutical company: 138/179
		- 24 studies did not report a funding source
		Network meta-analysis at class level:
		- all interventions (non-biological systemic agents, small molecules, and biological treatments) showed a higher proportion of patients reaching PASI 90 than placebo.
		- Anti-IL17 treatment showed a higher proportion of patients reaching PASI 90 compared to all the interventions.
		- Biologic treatments anti-IL17, anti-IL12/23, anti-IL23, and anti-TNF alpha showed a higher proportion of patients reaching PASI 90 than the non-biological systemic agents.
			Methodological quality (AMSTAR-2): high

Reference	Charakteristics	Key results	Comment
	- at induction phase (8 to 24 weeks after randomisation) **Study design:** - RCTs	- For reaching PASI 90, the most effective drugs when compared to placebo were (SUCRA rank order, all high-certainty evidence): o infliximab (RR 49.16, 95% CI 20.49 to 117.95), o bimekizumab (RR 27.86, 95% CI 23.56 to 32.94), o ixekizumab (RR 27.35, 95% CI 23.15 to 32.29), o risankizumab (RR 26.16, 95% CI 22.03 to 31.07). - Clinical effectiveness of these drugs was similar when compared against each other. o Bimekizumab and ixekizumab were significantly more likely to reach PASI 90 than secukinumab. o Bimekizumab, ixekizumab, and risankizumab were significantly more likely to reach PASI 90 than brodalumab and guselkumab. o Infliximab, anti-IL17 drugs (bimekizumab, ixekizumab, secukinumab, and brodalumab), and anti-IL23 drugs except tildrakizumab were significantly more likely to reach PASI 90 than ustekinumab, three anti-TNF alpha agents, and deucravacitinib. o Ustekinumab was superior to certolizumab. o Adalimumab, tildrakizumab, and ustekinumab were superior to etanercept. o No significant difference was shown between apremilast and 2 non-biological drugs: ciclosporin and methotrexate. - no significant difference between any of the interventions and placebo for the risk of SAEs. - risk of SAEs was significantly lower for participants on methotrexate compared with most of the interventions. - SAE analyses were based on a very low number of events with very low- to moderate-certainty evidence for all the comparisons. - The findings therefore have to be viewed with caution. - For other efficacy outcomes (PASI 75 and Physician Global Assessment (PGA) 0/1), the results were similar to the results for PASI 90. Information on quality of life was often poorly reported and was absent for several of the interventions.	

1.3 League Table

Relative effects of the intervention as estimated from the network meta-analysis model for Psoriasis Area and Severity Index (PASI) 90 and serious adverse events (SAEs) Outcomes were all measured at the induction phase (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) of the intervention in the respective column versus the comparator in the respective row. RRs larger than 1 for the lower triangle and smaller than 1 for the upper triangle favour the treatment on the left. Certainty of evidence was assessed for each comparison using CINeMA and classified as high (highlighted in green), moderate (in blue), low (in yellow), and very low (in red). Significant results are highlighted in bold. The anticipated absolute effects were calculated from multiplication of the NMA-derived relative effects estimates (using a random-effects model within a frequentist approach) by an assumed control risk based on the weighted control event rate across all studies. ACI: acitretin; ADA: adalimumab; APRE: apremilast; BIME: bimekizumab; BRODA: brodalumab; CERTO: certolizumab; CICLO: ciclosporin; DEUCRAVA: deucravacitinib; ETA: etanercept; FUM: fumaric acid; IFX: infliximab; IXE: ixekizumab; GUSEL: guselkumab; MTX: methotrexate; NETA: netakimab; PBO: placebo; RISAN: risankizumab; SECU: secukinumab; SONELO: sonelokimab; TILDRA: tildrakizumab; USK: ustekinumab [1]

Number of participants (studies)	1693 (6)	1730 (4)	5775 (7)	3078 (10)	8459 (20)	313 (1)	4722 (5)	4467 (7)	11342 (16)	2217 (3)	5440 (11)	2173 (4)	1323 (5)	218 (2)	8464 (14)	4362 (9)	127 (1)	213 (1)	1130 (2)	-	
1693 (6)	IFX	2.28 (0.81, 6.37)	1.31 (0.57, 2.98)	1.72 (0.74, 3.99)	1.12 (0.51, 2.47)	0.96 (0.17, 5.55)	1.12 (0.46, 2.71)	1.32 (0.58, 2.98)	1.24 (0.56, 2.74)	1.49 (0.52, 4.3)	1.19 (0.52, 2.7)	1.51 (0.56, 4.02)	1.69 (0.57, 5.01)	3.09 (0.65, 14.66)	1.5 (0.67, 3.36)	1.6 (0.67, 3.81)	0.21 (0.01, 4.02)	1.5 (0.06, 39.18)	1.35 (0.45, 4.06)	1.18 (0.57, 2.43)	24 per 1000 (11 to 49)
2473 (5)	1.76 (0.73, 4.28)	BIME	0.57 (0.25, 1.31)	0.76 (0.33, 1.71)	0.49 (0.23, 1.07)	0.42 (0.07, 2.44)	0.49 (0.2, 1.18)	0.58 (0.26, 1.29)	0.54 (0.25, 1.16)	0.66 (0.23, 1.91)	0.52 (0.24, 1.11)	0.66 (0.25, 1.78)	0.74 (0.25, 2.22)	1.36 (0.29, 6.4)	0.66 (0.29, 1.5)	0.7 (0.29, 1.69)	0.09 (0.0, 1.77)	0.66 (0.03, 17.24)	0.59 (0.2, 1.8)	0.52 (0.25, 1.08)	10 per 1000 (5 to 22)
5875 (8)	1.8 (0.74, 4.36)	1.02 (0.92, 1.13)	IXE	1.32 (0.75, 2.32)	0.86 (0.54, 1.37)	0.73 (0.14, 3.8)	0.85 (0.45, 1.62)	1.01 (0.64, 1.58)	0.94 (0.58, 1.54)	1.14 (0.49, 2.67)	0.91 (0.53, 1.55)	1.15 (0.53, 2.5)	1.29 (0.52, 3.19)	2.36 (0.56, 9.89)	1.14 (0.71, 1.83)	1.22 (0.65, 2.28)	0.16 (0.01, 2.89)	1.14 (0.05, 28.33)	1.03 (0.41, 2.6)	0.9 (0.6, 1.35)	18 per 1000 (12 to 27)
3078 (10)	1.88 (0.77, 4.56)	1.06 (0.96, 1.18)	1.05 (0.94, 1.17)	RISAN	0.65 (0.4, 1.05)	0.56 (0.11, 2.9)	0.65 (0.34, 1.24)	0.76 (0.45, 1.3)	0.72 (0.45, 1.13)	0.87 (0.36, 2.1)	0.69 (0.41, 1.15)	0.88 (0.4, 1.93)	0.98 (0.39, 2.46)	1.79 (0.46, 7.03)	0.87 (0.49, 1.53)	0.93 (0.49, 1.77)	0.12 (0.01, 2.21)	0.87 (0.03, 21.59)	0.78 (0.31, 2.0)	0.68 (0.45, 1.05)	14 per 1000 (9 to 21)
9202(21)	2.04 (0.84, 4.94)	**1.15 (1.08, 1.23)**	**1.13 (1.04, 1.23)**	1.08 (0.99, 1.19)	SECU	0.85 (0.17, 4.3)	1.0 (0.55, 1.79)	1.17 (0.82, 1.69)	1.1 (0.75, 1.62)	1.33 (0.58, 3.07)	1.06 (0.66, 1.69)	1.34 (0.64, 2.81)	1.51 (0.63, 3.61)	2.75 (0.68, 11.21)	1.33 (0.83, 2.15)	1.42 (0.8, 2.55)	0.19 (0.01, 3.34)	1.33 (0.05, 32.75)	1.2 (0.49, 2.94)	1.05 (0.76, 1.45)	21 per 1000 (15 to 29)
313 (1)	2.1 (0.84, 5.24)	1.19 (0.94, 1.51)	1.17 (0.92, 1.49)	1.12 (0.88, 1.43)	1.03 (0.82, 1.29)	SONELO	1.17 (0.22, 6.25)	1.37 (0.27, 7.06)	1.29 (0.25, 6.59)	1.56 (0.26, 9.24)	1.24 (0.24, 6.42)	1.57 (0.28, 8.9)	1.76 (0.29, 10.62)	3.23 (0.39, 26.62)	1.56 (0.3, 8.1)	1.67 (0.31, 8.88)	0.22 (0.01, 5.82)	1.56 (0.04, 55.13)	1.41 (0.23, 8.55)	1.23 (0.25, 6.1)	25 per 1000 (5 to 122)
4722 (5)	2.22 (0.91, 5.4)	**1.26 (1.12, 1.41)**	**1.23 (1.09, 1.4)**	**1.18 (1.04, 1.34)**	1.09 (0.98, 1.21)	1.05 (0.82, 1.35)	BRODA	1.18 (0.63, 2.2)	1.11 (0.63, 1.93)	1.33 (0.53, 3.38)	1.06 (0.56, 2.01)	1.35 (0.58, 3.11)	1.51 (0.58, 3.95)	2.76 (0.64, 11.97)	1.34 (0.71, 2.53)	1.43 (0.71, 2.89)	0.19 (0.01, 3.44)	1.34 (0.05, 33.65)	1.21 (0.45, 3.2)	1.05 (0.63, 1.75)	21 per 1000 (13 to 35)
4467 (7)	2.22 (0.92, 5.38)	**1.26 (1.16, 1.37)**	**1.23 (1.15, 1.33)**	**1.18 (1.07, 1.3)**	**1.09 (1.02, 1.16)**	1.05 (0.84, 1.33)	1.0 (0.89, 1.12)	GUSEL	0.94 (0.59, 1.49)	1.13 (0.48, 2.67)	0.9 (0.56, 1.45)	1.15 (0.53, 2.46)	1.28 (0.52, 3.15)	2.35 (0.57, 9.72)	1.14 (0.68, 1.9)	1.21 (0.66, 2.25)	0.16 (0.01, 2.87)	1.14 (0.05, 28.09)	1.02 (0.41, 2.56)	0.9 (0.61, 1.31)	18 per 1000 (12 to 26)
11063 (16)	**2.84 (1.17, 6.87)**	**1.61 (1.49, 1.74)**	**1.58 (1.45, 1.72)**	**1.51 (1.38, 1.66)**	**1.39 (1.31, 1.47)**	**1.35 (1.07, 1.7)**	**1.28 (1.17, 1.4)**	**1.28 (1.18, 1.38)**	USK	1.21 (0.52, 2.79)	0.96 (0.59, 1.56)	1.22 (0.58, 2.57)	1.37 (0.57, 3.29)	2.5 (0.62, 10.14)	1.21 (0.75, 1.96)	1.29 (0.72, 2.33)	0.17 (0.01, 3.03)	1.21 (0.05, 29.74)	1.09 (0.44, 2.68)	0.95 (0.68, 1.34)	19 per 1000 (14 to 27)
2217 (3)	**2.89 (1.16, 7.2)**	**1.64 (1.27, 2.11)**	**1.61 (1.26, 2.06)**	**1.54 (1.19, 2.0)**	**1.42 (1.11, 1.82)**	1.37 (0.98, 1.92)	**1.3 (1.0, 1.7)**	**1.3 (1.02, 1.67)**	1.02 (0.8, 1.31)	TILDRA	0.8 (0.33, 1.9)	1.01 (0.36, 2.81)	1.13 (0.37, 3.48)	2.07 (0.42, 10.09)	1.0 (0.46, 2.19)	1.07 (0.43, 2.67)	0.14 (0.01, 2.74)	1.0 (0.04, 26.61)	0.9 (0.29, 2.83)	0.79 (0.36, 1.73)	16 per 1000 (7 to 35)
5476 (11)	**3.05 (1.26, 7.4)**	**1.73 (1.58, 1.89)**	**1.7 (1.54, 1.87)**	**1.62 (1.47, 1.79)**	**1.5 (1.38, 1.62)**	**1.45 (1.14, 1.84)**	**1.37 (1.21, 1.56)**	**1.37 (1.28, 1.48)**	1.07 (0.98, 1.18)	1.05 (0.82, 1.36)	ADA	1.27 (0.59, 2.75)	1.42 (0.58, 3.52)	2.6 (0.63, 10.75)	1.26 (0.73, 2.18)	1.35 (0.72, 2.52)	0.18 (0.01, 3.19)	1.26 (0.05, 31.2)	1.14 (0.45, 2.86)	0.99 (0.67, 1.47)	20 per 1000 (13 to 29)
2173 (4)	**3.52 (1.4, 8.87)**	**2.0 (1.46, 2.73)**	**1.96 (1.44, 2.67)**	**1.87 (1.37, 2.57)**	**1.73 (1.27, 2.35)**	**1.67 (1.14, 2.45)**	**1.59 (1.15, 2.18)**	**1.59 (1.16, 2.16)**	1.24 (0.91, 1.69)	1.22 (0.84, 1.77)	1.16 (0.85, 1.58)	DEUCRAVA	1.12 (0.39, 3.2)	2.05 (0.44, 9.48)	0.99 (0.46, 2.14)	1.06 (0.5, 2.25)	0.14 (0.01, 2.63)	0.99 (0.04, 25.68)	0.89 (0.31, 2.6)	0.78 (0.4, 1.52)	16 per 1000 (8 to 30)
1323 (5)	**4.04 (1.6, 10.19)**	**2.29 (1.7, 3.09)**	**2.25 (1.68, 3.02)**	**2.15 (1.59, 2.92)**	**1.98 (1.48, 2.66)**	**1.92 (1.33, 2.78)**	**1.82 (1.34, 2.48)**	**1.82 (1.35, 2.45)**	**1.43 (1.06, 1.91)**	1.4 (0.98, 1.99)	1.33 (0.98, 1.79)	1.15 (0.77, 1.72)	CERTO	1.83 (0.37, 9.08)	0.89 (0.36, 2.16)	0.95 (0.37, 2.44)	0.12 (0.01, 2.44)	0.89 (0.03, 23.71)	0.8 (0.25, 2.56)	0.7 (0.31, 1.58)	14 per 1000 (6 to 32)
486 (6)	**5.03 (1.96, 12.9)**	**2.85 (2.03, 4.0)**	**2.8 (1.99, 3.93)**	**2.68 (1.92, 3.72)**	**2.47 (1.76, 3.45)**	**2.39 (1.6, 3.58)**	**2.27 (1.6, 3.21)**	**2.27 (1.62, 3.18)**	**1.77 (1.27, 2.48)**	**1.74 (1.16, 2.61)**	**1.65 (1.18, 2.32)**	1.43 (0.93, 2.19)	1.24 (0.8, 1.93)	MTX	0.48 (0.12, 2.03)	0.52 (0.12, 2.23)	0.07 (0.0, 1.63)	0.48 (0.02, 15.57)	0.44 (0.09, 2.19)	0.38 (0.1, 1.52)	8 per 1000 (2 to 30)
10021 (18)	**5.09 (2.1, 12.33)**	**2.88 (2.55, 3.26)**	**2.83 (2.54, 3.15)**	**2.71 (2.37, 3.09)**	**2.5 (2.23, 2.79)**	**2.42 (1.88, 3.11)**	**2.29 (1.99, 2.64)**	**2.29 (2.04, 2.57)**	**1.79 (1.6, 2.01)**	**1.76 (1.4, 2.2)**	**1.67 (1.47, 1.89)**	**1.44 (1.07, 1.95)**	1.26 (0.95, 1.66)	1.01 (0.72, 1.42)	ETA	1.07 (0.58, 1.95)	0.14 (0.01, 2.53)	1.0 (0.04, 24.73)	0.9 (0.36, 2.26)	0.79 (0.53, 1.17)	16 per 1000 (11 to 23)
3949 (8)	**5.41 (2.18, 13.44)**	**3.06 (2.36, 3.98)**	**3.01 (2.32, 3.89)**	**2.88 (2.21, 3.75)**	**2.65 (2.05, 3.43)**	**2.57 (1.83, 3.61)**	**2.44 (1.86, 3.19)**	**2.44 (1.88, 3.15)**	**1.91 (1.47, 2.47)**	**1.87 (1.34, 2.6)**	**1.77 (1.36, 2.31)**	**1.54 (1.24, 1.9)**	1.34 (0.93, 1.93)	1.07 (0.73, 1.58)	1.06 (0.83, 1.36)	APRE	0.13 (0.01, 2.4)	0.94 (0.04, 23.46)	0.84 (0.32, 2.21)	0.74 (0.45, 1.2)	15 per 1000 (9 to 24)
322 (3)	**5.8 (2.29, 14.7)**	**3.29 (2.39, 4.51)**	**3.22 (2.36, 4.41)**	**3.09 (2.25, 4.23)**	**2.84 (2.08, 3.89)**	**2.75 (1.87, 4.05)**	**2.61 (1.89, 3.61)**	**2.61 (1.91, 3.57)**	**2.04 (1.49, 2.79)**	**2.0 (1.37, 2.92)**	**1.9 (1.39, 2.61)**	**1.65 (1.15, 2.37)**	1.43 (0.95, 2.16)	1.15 (0.8, 1.66)	1.14 (0.84, 1.54)	1.07 (0.79, 1.46)	CICLO	7.19 (0.1, 523.33)	6.47 (0.33, 128.8)	5.66 (0.32, 100.06)	113 per 1000 (6 to 1000)
333 (2)	**10.95 (3.4, 35.27)**	**6.21 (2.81, 13.73)**	**6.09 (2.76, 13.47)**	**5.83 (2.63, 12.9)**	**5.37 (2.43, 11.86)**	**5.2 (2.28, 11.85)**	**4.94 (2.23, 10.94)**	**4.93 (2.23, 10.9)**	**3.86 (1.75, 8.53)**	**3.79 (1.66, 8.62)**	**3.59 (1.63, 7.95)**	**3.11 (1.35, 7.17)**	**2.71 (1.17, 6.26)**	2.18 (0.93, 5.12)	2.15 (0.97, 4.77)	2.03 (0.89, 4.6)	1.89 (0.81, 4.39)	NETA	0.9 (0.03, 24.19)	0.79 (0.03, 19.01)	16 per 1000 (1 to 380)
1190 (3)	**12.81 (4.55, 36.09)**	**7.26 (4.08, 12.93)**	**7.13 (4.0, 12.68)**	**6.82 (3.82, 12.15)**	**6.28 (3.54, 11.17)**	**6.09 (3.28, 11.28)**	**5.77 (3.23, 10.32)**	**5.77 (3.24, 10.26)**	**4.52 (2.54, 8.03)**	**4.43 (2.39, 8.2)**	**4.2 (2.36, 7.48)**	**3.64 (1.93, 6.85)**	**3.17 (1.68, 5.99)**	**2.55 (1.33, 4.87)**	**2.52 (1.41, 4.49)**	**2.37 (1.28, 4.37)**	**2.21 (1.16, 4.19)**	1.17 (0.45, 3.03)	FUM	0.87 (0.38, 2.01)	17 per 1000 (8 to 40)
-	**49.16 (20.49, 117.96)**	**27.86 (23.56, 32.94)**	**27.35 (23.16, 32.29)**	**26.16 (22.03, 31.07)**	**24.12 (20.57, 28.28)**	**23.36 (17.74, 30.75)**	**22.16 (18.54, 26.48)**	**22.14 (18.83, 26.05)**	**17.33 (14.76, 20.35)**	**16.99 (12.92, 22.35)**	**16.13 (13.65, 19.06)**	**13.96 (10.26, 19.0)**	**12.16 (8.87, 16.68)**	**9.77 (6.83, 13.99)**	**9.66 (8.14, 11.48)**	**9.09 (6.97, 11.86)**	**8.48 (6.09, 11.8)**	**4.49 (2.07, 9.75)**	**3.84 (2.2, 6.68)**	PBO	20 per 1000
	934 per 1000 (389 to 1000)	529 per 1000 (448 to 626)	520 per 1000 (440 to 614)	497 per 1000 (419 to 590)	458 per 1000 (391 to 537)	444 per 1000 (337 to 584)	421 per 1000 (352 to 503)	421 per 1000 (358 to 495)	329 per 1000 (280 to 387)	323 per 1000 (245 to 425)	306 per 1000 (259 to 362)	265 per 1000 (195 to 361)	231 per 1000 (169 to 317)	186 per 1000 (130 to 266)	184 per 1000 (155 to 218)	173 per 1000 (132 to 225)	161 per 1000 (116 to 224)	85 per 1000 (39 to 185)	73 per 1000 (42 to 127)	19 per 1000	**Anticipated absolute effects**

1.4 Evidence to decision framework

Table 3 Evidence to decision framework (Cochrane Review)[1]

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

POPULATION: Patients with moderate to severe psoriasis vulgaris

INTERVENTION: Systemic treatments

Systemic conventional treatments	Small molecules	Tnf inhibitors	Anti-IL12/23	Anti-IL17	Anti-IL23
Acitretin	Apremilast	Adalimumab	Ustekinumab	Brodalumab	Guselkumab
Ciclosporin	Deucravacitinib	Certolizumab		Ixekizumab	Rizankizumab
FAEs		Etanercept		Secukinumab	Tildrakizumab
Methotrexate		Infliximab		Bimekizumab	

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)
- At induction phase (8 to 24 weeks after randomisation)

SETTING:
- Region: Germany (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
- Many psoriasis patients have significant comorbidity and specific advice is necessary to treat these patients
- Hence, the objectives of the guideline are to:
  - Include new treatments and the evidence that has become available
  - Develop a treatment algorithm including biologic and nonbiologic systemic treatment options

Evidence synthesis by:
Sbidian E, Chaimani A, Guelimi R, et al. Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis. Cochrane Database of Systematic Reviews. 2023;(7)doi:10.1002/14651858.CD011535.pub6 [1]

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

For the Cochrane Review author groups’ declaration of interests, see page 805 of the review.

Values

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

Previously, a PASI 75 has been defined as suitable treatment outcome. [2,3] Considerable process has been made concerning the development of new treatment options for psoriasis.

Currently, higher **treatment goals** (e.g. PASI 90) are aimed for and the traditional 75% rule is considered a minimal treatment goal. 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 [4].

- It has been shown that patients are first interested in safety followed by efficacy of biologic treatment, with some variations [5]
- 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?

see League table (chapter 1.3)

Equity

What would be the impact on health equity?

RESEARCH EVIDENCE

- Costs remain barrier to prescribing biologics [6]
- Reimbursement regulations and the ‘Wirtschaftlichkeitsgebot’, “Budget” restrictions and risk of ‘Regress’ influence treatment choices.

Acceptability

Is the intervention acceptable to key stakeholders?

RESEARCH EVIDENCE

- Patients are first interested in safety followed by efficacy of treatment, with some variations [5]
- 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.

Differences in efficacy or safety between the systemic treatment options identified in the network meta-analysis [1] were not doomed sufficiently relevant to establish a clear ranking as the analysis covers only the induction therapy. In addition, many more aspects need to be taken into consideration when choosing a systemic treatment.

Recommendations were also drafted along the line of drug licensing, taking practical aspect of reimbursement into account.

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 limitation to drug reimbursement, making the prescription of costly treatments such as the biologics and small molecules difficult.

Monitoring and evaluation

An evaluation of the guideline can be done by looking at:

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

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?
- What is the role of dose reduction or interval prolongation in maintenance treatment?
- What is the most suitable treatment option in given comorbid situations?
- What is the risk of reactivation of latent TB in patients receiving systemic treatment (especially in Il 12-23 inhibitors)?
- What kind of lab monitoring is really necessary during long termin systemic treatment?

2 Diabetes

2.1 History

Table 4 History (Diabetes)

Version	Search Date	Number of new studies	Additional information added	Implications for conclusions
Update 2	October 2022	4 (5 citations)	See below	See below
Update 1	June 2021	1	See below	See below
Original	September 2019	8	/	/

2.2 Summary of methods and results (2022/2023)

Authors: A. Pennitz and I. Vader (Update 2), M. Kinberger (Update 1), R. Jakubzyk (Original version)

Update 2 – 2022/2023 (blue = new data)

What was the aim of this systematic review?

The aim of this review update was to continuously inform the guideline development group of new evidence on patients with psoriasis vulgaris and concomitant diabetes mellitus.
Many patients suffering from psoriasis also have concomitant diabetes mellitus. In this systematic review, we investigated whether diabetes mellitus affects the efficacy and safety of psoriasis therapy. We also investigated whether psoriasis therapy had an impact on fasting blood glucose levels, long-term blood glucose and insulin resistance in diabetic patients.

What did we do?

We systematically searched in two medical databases. We only included studies with patients treated with systemic psoriasis vulgaris therapies who also had diabetes mellitus. We assigned Levels of Evidence for all studies included using the Center of Evidence Based Medicine Oxford recommendations [7] and used the risk of bias 2.0 for the randomized trials [8] and the IHE checklist for uncontrolled prospective cohort studies [9]. Effect measures were calculated where possible. For details, see Methods Report.

What are the main results of the review?

We found 6 prospective (1 study with 2 citations) [10-16] and 7 retrospective studies [17-23].

Change in psoriasis parameters (only prospective data available)

- Kimball et al. [12] conducted a subgroup analysis of an RCT comparing adalimumab against placebo in patients with diabetes mellitus. After 4 months, 46 of 73 (63%) participants in the adalimumab arm showed a PASI75 response compared to 2 of 52 in the placebo arm (PASI75 RR 16.4; 95% CI 4.16 to 64.5). The mean change in the DLQI score was -7.1±6.3 in the adalimumab arm compared to -1.3±5.8 in the placebo group (DLQI MD -5.8; 95% CI -7.94; -3.66) (risk of bias low).
- Pinter et al. [24] pooled data from three RCTs and evaluated secukinumab, ustekinumab and etanercept. After four weeks, a PASI75 response was described for 16 of 27 (59.3%) patients in the etanercept group, for 56.6 of 69 (82.1%) in the secukinumab group and for 80.5 of 97.5 (82.6%) patients in the ustekinumab group (risk of bias unclear).
- Lin et al. [14] compared treatment with liraglutide alone (study arm not included here) with a treatment regime of acitretin, calcipotriol ointment and oral antidiabetics in patients with psoriasis and coexisting diabetes mellitus type 2. A PASI75 response after 12 weeks was seen in 1 of 13 (7.69%) participants in the acitretin and calcipotriol ointment group. The mean change in the DLQI score was -8.54±5.33 in this group (risk of bias unclear).
- By analysing data from the CorEvitas Psoriasis Registry, Enos et al. [11] investigated whether diabetes affected the response to newly initiated tumour necrosis factor inhibitors (TNFi), interleukin (IL)-17i, IL-12/23i, or IL-23i in patients with psoriasis. Patients with diabetes, receiving IL-17i, achieved PASI75 and PASI90 less often than those without diabetes 47.5% (104/219) vs. 60.6% (613/1011), aOR 0.61 (95% CI 0.45, 0.85) and 33.8% (74/219) vs. 44.4% (449/1011), aOR 0.69 (95% CI 0.49, 0.96), respectively. The odds ratio was adjusted for age, sex, race, smoking, education, duration of psoriasis, psoriatic arthritis, number of prior biologics, and obesity.

Change in diabetes mellitus parameters

Fasting plasma glucose (prospective study data, 76 patients)

- Al-Mutairi and Shabaan [15] compared TNFi (ADA, ETA, IFX) with conventional treatments (topical corticosteroids, calcipotriol, CsA, MTX) in patients with diabetes mellitus and psoriasis. In the TNFi group a mean change in the fasting plasma glucose of -2.74±0.34 vs -0.02±0.16 mmol/L in the conventional group after six months was described (MD -2.72; 95% CI -2.85; -2.59) (risk of bias high).
- Lin et al. [14] described a mean change of -0.20±1.49 in fasting plasma glucose in 13 patients treated with acitretin, calcipotriol ointment and oral antidiabetics after three month (risk of bias unclear).

Fasting plasma glucose (retrospective study data)

- In two retrospective analyses, Wu et al. [19,20] investigated changes in diabetic parameters in patients with diabetes and psoriasis receiving MTX, MTX and TNFi or TNFi alone. One study reported a mean change of 3.7±18.6 in FPG with combined therapy (n=34) vs. 1.3±24.5 with MTX therapy alone (n=92). In the other study, no significant difference between TNFi (mean change 1.5±40.7) and MTX (mean change -15.6±54) was found (MD 17.1; 95% CI -3.93; 28.13). The Oxford level of evidence was 3 in both studies.

HbA1c (prospective study data)

- Koenig et al. [16] described a mean reduction in HbA1c of -0.3% in 35 patients treated with etanercept treatment after three months (risk of bias unclear).

- Al-Mutairi and Shabaan [15] found a mean change in the HbA1c of -1.3% vs. 0.2% in 34 patients treated with TNFi compared to 29 patients treated with conventional treatment, respectively after six month (risk of bias high).
- A mean reduction of -0.82%±0.73% in HbA1c was reported in the acitretin, calcipotriol ointment and oral antidiabetics group by Lin et al. [14] (risk of bias unclear).

HbA1c (retrospective study data)

- No relevant changes of HbA1c were reported by Wu et al. [20] comparing MTX with an additional TNFi (-0.1%±1.0%) and MTX alone (0.0%±0.8%).

HOMA-Index (only prospective data available)

- Al-Mutairi and Shabaan [15] described a mean change in HOMA-Index of 1.2±0.4 in 34 patients treated with TNFi vs -0.3±0.12 in the conventional treatment group (n=29) after 6 month.
- Lin et al. [14] reported a mean change of 0.37±2.09 in HOMA-Index after treatment with acitretin, calcipotriol ointment and oral antidiabetics combined for 3 months.

Safety (prospective study data)

- In the subgroup analysis by Kimball et al. [12] 3 of 73 (4.1%) patients treated with adalimumab and 2 of 52 (3.8%) patients in the placebo group reported severe adverse events.
- Enos et al. [10] conducted another analysis of the CorEvitas Psoriasis Registry. They explored, whether patients with psoriasis discontinued their newly implemented therapy with TNFi, IL-17i, IL-12/23i, or IL-23i more often if they had comorbidities. Discontinuations within 6 months occurred more frequently in patients with diabetes than in those without, if they received TNFi (33/96 (34.4%) vs. 111/455 (24.4%); $p < 0.05$) or IL-23i or IL-12/23i (25/192 (13%) vs 78/950 (8.2%); $p < 0.05$).

Safety (retrospective study data)

- In a retrospective registry study, Kalb et al. [17] described that the presence of diabetes mellitus is a significant predictor of serious infection in patients treated with adalimumab, etanercept or ustekinumab (HR, 1.7; 95% CI, 1.25-2.23; $p < 0.001$, n= 1459 with diabetes).
- In another retrospective analysis by Hong et al. [18], diabetic patients receiving ciclosporin seemed to have a higher risk for a greater than 10% increase in serum creatinine levels compared to non-diabetes patients (HR 2.34; 95% CI, 1.59–3.45; $p <0 .001$, n= 37).
- Rattanakaemakorn et al. [22] performed a retrospective cohort study in patients with psoriasis, treated with methotrexate or with a combination of methotrexate and acitretin. A multivariate regression indicated, that the risk of developing a hepatic fibroses was associated with a comorbid diabetes, no matter how high the cumulative MTX dose was (adjusted HR 2.40 (95% CI: 1.05–5.51)). There could be no information identified, what the regression model was adjusted for.
- Drug persistence at 104 weeks in patients (n= 302) treated with secukinumab was retrospectively analysed by Mendes-Bastos et al. [21]. In total, 84 patients with psoriasis discontinued therapy. Exploratory univariable analysis indicated that patients with diabetes had a higher drug persistence than those without diabetes. Results were only presented graphically and without details on effect size and confidence intervals.
- Van Muijen et al. [23] applied prospective and retrospective data to analyse drug survival rates in patients with psoriasis receiving guselkumab. A multivariate cox regression model suggested an association between a shorter drug survival due to ineffectiveness and comorbid diabetes mellitus type 2 (HR 3.69 (95% CI 1.14–11.98). The association between discontinuation due to side effects and diabetes mellitus type 2 was analysed in a univariate analysis HR 0.605 (95%CI 0.079–4.654).

Key message

Neither treatment with TNFi (n=484), MTX (n=635) nor acitretin (n=13) led to an increase in HbA1c or fasting glucose in patients with psoriasis vulgaris and concomitant diabetes mellitus. The methodological quality of the data varies. For MTX, only retrospective data was available. A total of 2 studies with 76 patients reported no or only small changes in HOMA-Index in patients with psoriasis vulgaris and diabetes mellitus treated with systemic psoriasis therapy.

Data from the CorEvitas Psoriasis Registry indicates a weaker treatment response[11] or shorter drug survival[10] to psoriasis treatments in diabetic patients with newly initiated tumour necrosis factor inhibitors (TNFi)[10], interleukin (IL)-17i[11], IL-12/23i[10], or IL-23i[10] than in non-diabetic patients.

How up-to-date is this review?

We searched for studies that have been published up to 26 October 2022

2.3 Methods

2.3.1 Inclusion criteria

Apart from the newly included drug, deucravacitinib we did not change the search strategy and the inclusion criteria of the previous version.

Table 5 Eligibility criteria for the review update on psoriasis and diabetes mellitus

	Criteria
Patients	Inclusion: adult patients with a clinical diagnosis of psoriasis and a concomitant diabetes mellitus of any type being treated for psoriasis Exclusion: patients with psoriatic arthritis only
Intervention	acitretin, apremilast, ciclosporin, fumarates, methotrexate TNFi: adalimumab, etanercept, certolizumab pegol, infliximab; anti-IL12/23: ustekinumab; anti-IL17: bimekizumab, brodalumab, ixekizumab, secukinumab; anti-IL23: guselkumab, risankizumab, tildrakizumab; tyrosine kinase 2 (TYK2) inhibitor: deucravacitinib (new)
Comparator	Comparisons with another included drug and/or placebo
Outcomes	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.
Study Design	Inclusion: randomized controlled trials, clinical trials (with and without comparison group), cohort studies, case control studies and cross-sectional studies Exclusion: case series, case reports, retrospective studies with less than 100 patients

2.3.2 Information source

The search strategy was updated and the databases MEDLINE Ovid from 1946 and Embase Ovid from 1947 were searched for the period June 2021 to 27 October 2022. The full search strategy is shown below (see Table 9). We screened all identified abstracts/titles for eligibility. Included title/abstracts were then screened as full texts based on the above listed eligibility criteria.

2.3.3 Data collection, statistical analysis and evaluation

We performed the screening and did the data extraction using a standardized form. We recorded all full-texts excluded and the primary reason for exclusion (see Table 10).

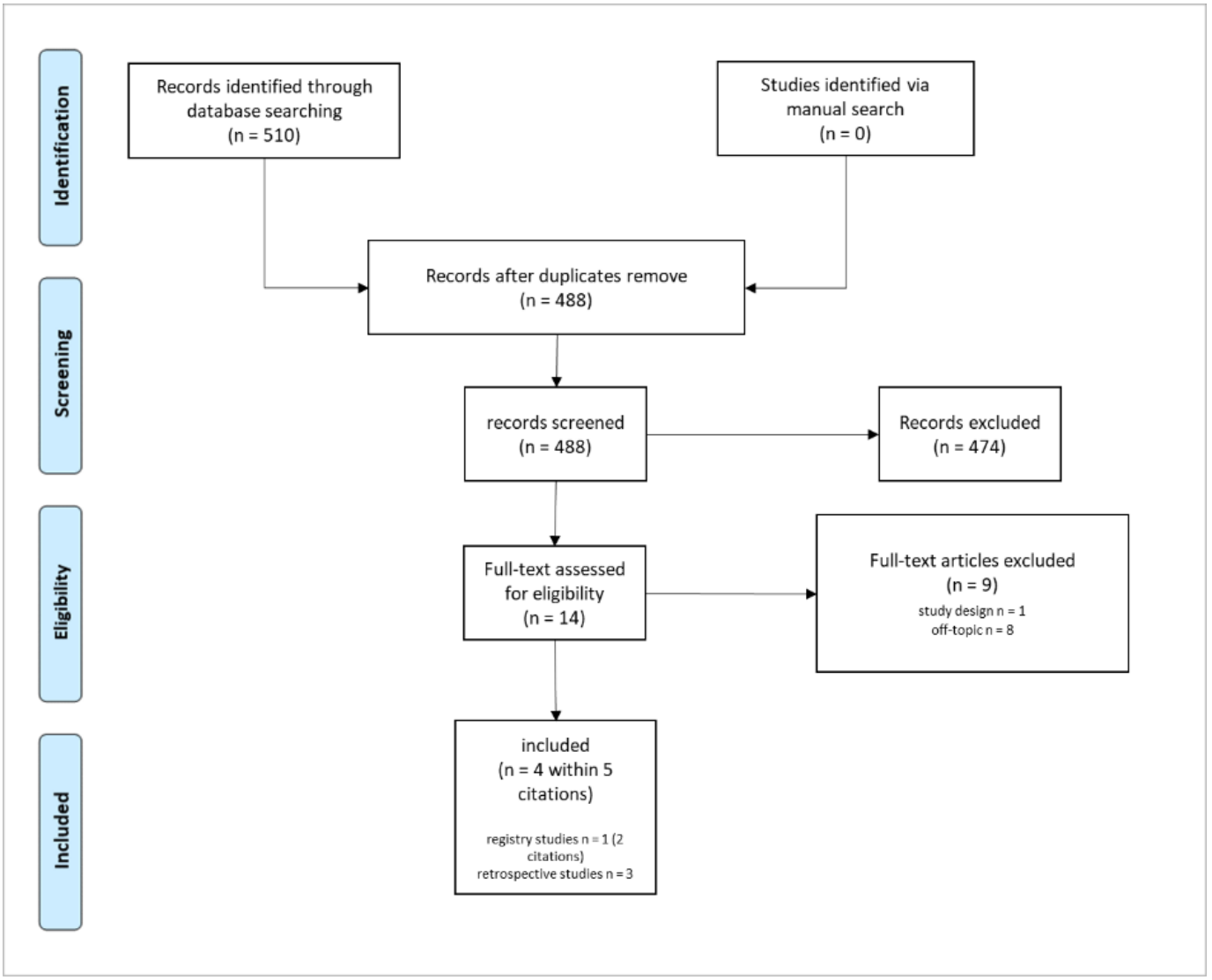
2.3.4 Methodological quality assessment/ Risk of bias assessment

We assigned Levels of Evidence for all studies included using the Center of Evidence Based Medicine Oxford recommendations. To assess risk of bias in uncontrolled prospective cohort studies, we applied and modified the IHE checklist [9]. We extended the possible answers in Item 13 by “not applicable” and in Item 10, 12 by “unclear”.

2.4 Results

Our update search yielded 510 citations, 5 citations (4 studies) fulfilled the inclusion criteria [10,11,21-23] (see Figure 1).

Figure 1 Flow chart (diabetes mellitus)



Based on the “Levels of Evidence - Center of Evidence Based Medicine Oxford recommendations” 5 prospective studies [14-16,23,24] were categorized level 2, 1 prospective study (2 citations) was categorized as level 3 [10,11] and the retrospective studies [17-23] as level 3. Results of the additional assessment for prospective randomized studies with the Risk of Bias Tool 2 (RoB 2) and with the IHE checklist are shown in Figure 2 and Table 6, respectively.

Table 6 uncontrolled prospective cohort studies - results of the IHE checklist

reference	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	Col/ Funding
Enos C. W., et al. Proportions of Biologic Discontinuation Among Psoriasis Patients With Metabolic Comorbidities. Journal of Psoriasis and Psoriatic Arthritis. 2022.	Y	Y	Y	N	Y	Y (Stroberet al.)	U	P	N	U	U	U	n.a.	U	Y	N	N	Y	P/Y	Y	funded by CorEvitas LLC CorEvitas has been supported through contracted subscriptions in the last two years by AbbVie, Amgen, Arena, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Chugai, Eli Lilly and Company, Genentech, Gilead, GSK, Janssen, LEO, Novartis, Ortho Dermatologics, Pfizer Inc., Regeneron, Sanofi,Sun and UCB
Enos C. W., et al. Comorbid obesity and history of diabetes are independently associated with poorer treatment response to biologics at 6 months: A prospective analysis in Corrona Psoriasis Registry. Journal of the American Academy of Dermatology. 2022	Y	Y	Y	N	Y	Y (Stroberet al.)	U	P	N	U	U	U	Y	U	Y	N	Y	N	Y	Y	Sponsored by CorEvitas (formerly Corrona) LLC CorEvitas has been supported through contracted subscriptions in the last 2 years by AbbVie, Amgen, ARENA, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Chugai, Eli Lilly and Company, Genentech, Gilead, GSK, Janssen, LEO, Novartis, Ortho Dermatologics, Pfizer Inc, Regeneron, Sanofi, SUN, and UCB. This study was supported through a partnership between CorEvitas and the National Psoriasis Foundation.
																					Y = Yes; N = No; P = Partial; U = Unclear; n.a. = not applicable

To appraise Item 6 of the IHE checklist [9] we identified a previous publication [25] via hand searching, in which the inclusion criteria are described more precisely.

Figure 2 Risk of bias in prospective studies (diabetes)

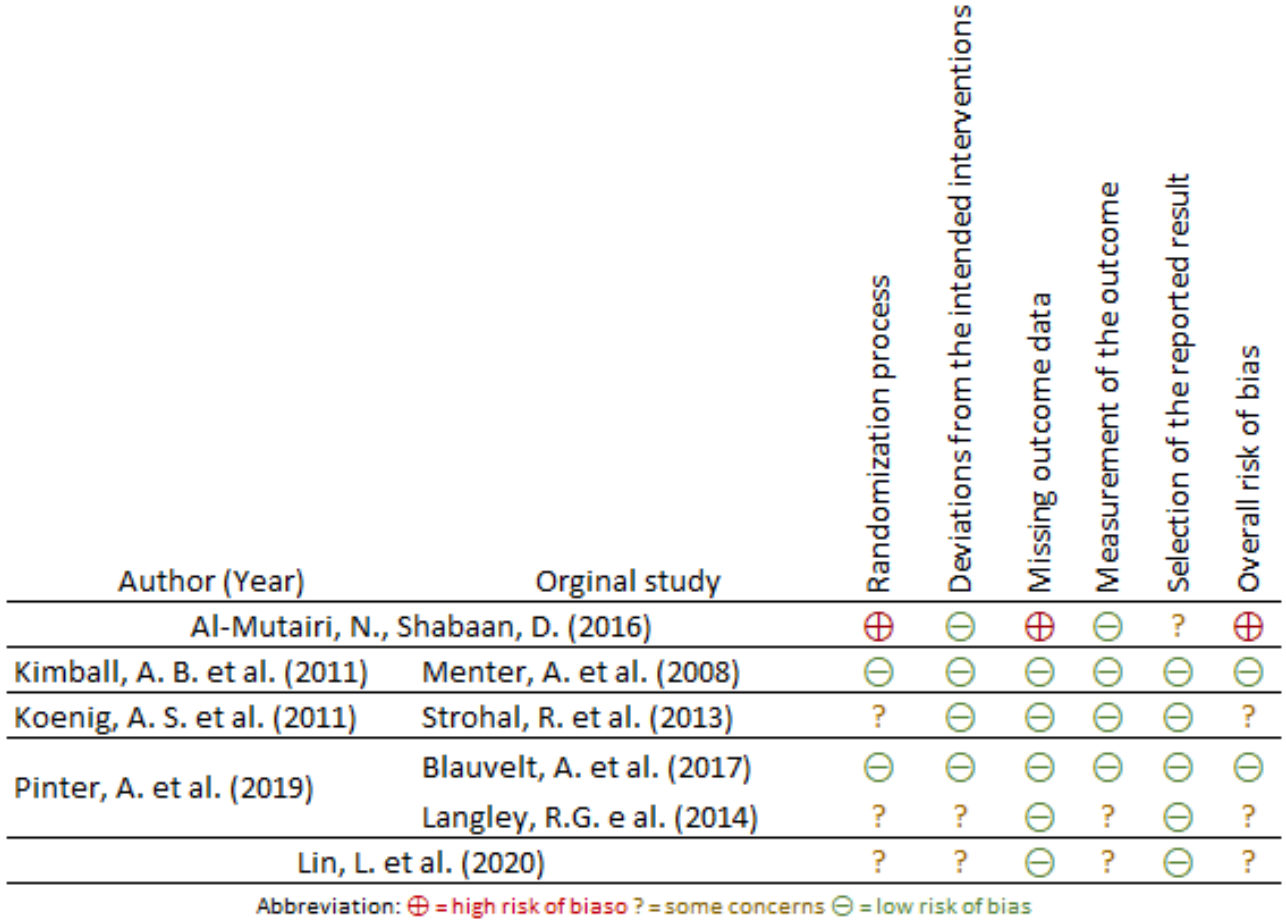


Table 7 Prospective data from the included studies for the systematic review of the evidence on psoriasis treatment and diabetes mellitus (Update 2)

Titel	Author (Y)	Original study	Intervention	Duration of treatment (M)	Patients (n)	Patients with diabetes (n)	Follow up (M)	Age (Y) (Ø±SD)	♀ (%)	Poriasis-score at baseline (Ø±SD)	Qualtity of life at baseline (Ø±SD)	Diabetes parameters at baseline (Ø±SD)	Outcomes					overall RoB
													End of dollow up (M)	Psorias-Score e.g. PASI 75	Mean change of quality of life (Ø±SD)	Mean change of diabetes parameters (Ø±SD)	Adverse events	
Efficacy and safety of adalimumab among patients with moderate to severe psoriasis with co-morbidities: Subanalysis of results from a randomized, double-blind, placebo-controlled, phase III trial	Kimball, A. B. et al. (2011) [12]	Menter, A. et al. (2008)	ADA (80mg/40mg)	4	814	73	13	47.2±12.4[1]	35%[1]	PASI 19.3±7.2	/	/	4	PASI 75 n=46 (63%)	DLQI -7.1±6.3	Glucose (mmol/L) -0.47	SAE not infectios n=2 (2.7%) SAE infectios n= 1 (1.4%) Dropout because of AE n=1 (1.4%)	low
			Placebo		398	52		48.8±12.6[1]	36%[1]	PASI 19.1±7.6				PASI 75 n=2 (3.8%)	DLQI -1.3±5.8	Glucose (mmol/L) -0.65	SAE not infectios n=2 (3.8%) SAE infectios n=0 (0%) Dropout because of AE n=2 (3.8%)	
Characterization of responder groups to secukinumab treatment in moderate to severe plaque psoriasis	Pinter, A. et al. (2019) [24]	Blauvelt, A. et al. (2017) [13] Langley, R.G. et al. (2014)	ETA (50mg)	4	298	27	4	43.6[1]	/	/			4	PASI100 n=1/27 (3.7%) PASI75 n=15/27 (55.6%) PASI50 n=8/27 (29.6%) <PASI50 n=3/27 (11.1%)	/	/	Blauvelt: low Langley: unclear
			SEC (300mg)		867	69		44.8[1]						PASI100 n=6.6/69 (9.6%) PASI75 n=50/69 (72.5%) PASI50 n=9.4/69 (13.6%) <PASI50 n=3/69 (4.3%)				

Titel	Author (Y)	Original study	Intervention	Duration of treatment (M)	Patients (n)	Patients with diabetes (n)	Follow up (M)	Age (Y) (Ø±SD)	♀ (%)	Poriasis-score at baseline (Ø±SD)	Qualtity of life at baseline (Ø±SD)	Diabetes parameters at baseline (Ø±SD)	Outcomes					overall RoB
													End of dollow up (M)	Psorias-Score e.g. PASI 75	Mean change of quality of life (Ø±SD)	Mean change of diabetes parameters (Ø±SD)	Adverse events	
			UST (45/90mg)		318	97.5		44.8[1]						PASI100 n=23.5/97.5 (24.1%) PASI75 n=57/97.5 (58.5%) PASI50 n=9/97.5 (9.2%) <PASI50 n=8/97.5 (8.2%)				
Impact of etanercept therapy on glycemic control in a cohort of psoriatic patients: The pristine trial	Koenig, A.S. et al. (2011) [16]	Strohal, R. et al. (2013, Studienende 2010)	ETA (50mg/100mg)	3	273	35	3	44[1]	30[1]	21[1]	/	HbA1c (%) 7.0 FPG (mmol/l) 6.8 IS 5.3 PI (mcU/mL) 14.0	3	/	/	HbA1c (%) -0.3 FPG (mmol/l) 0.1 IS 1.1 PI (mcU/mL) 3.0	/	unclear
Effects of tumor necrosis factor alpha inhibitors extend beyond psoriasis: insulin sensitivity in psoriasis patients with type 2 diabetes mellitus	Al-Mutairi, N., Shabaan, D. (2016) [15]		ADA (n=14) ETA (n=8) IFX (n=12)	6	34 (35 randomised)	34 (35 randomised)	6	43.7±21.6	52.9% (18/34)	/	/	HbA1c (%) 8.4±0.38 FPG (mmol/L) 10±25 IS 5.9±0.52	6	/	/	HbA1c (%) -1.3 FPG (mmol/L) -2.74±0.34 IS 1.2±0.4	/	high
			Topic corticosteroids, calcipotriol (n=8) CsA (n=7) MTX (n=14)		29 (35 randomisedt)	29 (35 randomised)		47.7±14.2	51.7% (15/29)			HbA1c (%) 8.1±0.21 FPG (mmol/L) 11±0.4 IS 5.4±0.31				HbA1c (%) 0.2 FPG (mmol/L) -0.02±0.16 IS -0.3±0.12		
Glucagon-like peptide-1 receptor agonist liraglutide therapy for psoriasis patients with type 2 diabetes: a randomized-controlled trial	Lin, L. et al. (2020) [14]		liraglutide 0.6mg - 1.8mg		11 (12 randomised)	11 (12 randomised)	12	56.73±8.27	9.1% (1/11)	PASI 14.02±10.67	DLQI 22.00±5.85	HbA1c (%) 7.80±2.55 FPG (mmol/l) 6.28±1.48 Fasting insulin (ug/ml) 10.61±4.39	3	PASI-Change -12.32±10.05 PASI50 90.91% (10/11) PASI75 72.73% (8/11)	DLQI-Change -18.18±5.86	HbA1c (%) -1.07±1.75 FPG (mmol/l) -0.55±1.50 Fasting insulin (ug/ml) -2.92±5.03	no SAE n = 1 nosebleed n = 6 gastrointestinal AE n=1 withdrawal due to adverse events	

Titel	Author (Y)	Original study	Intervention	Duration of treatment (M)	Patients (n)	Patients with diabetes (n)	Follow up (M)	Age (Y) (Ø±SD)	♀ (%)	Poriasis-score at baseline (Ø±SD)	Qualtity of life at baseline (Ø±SD)	Diabetes parameters at baseline (Ø±SD)	Outcomes					overall RoB
													End of dollow up (M)	Psorias-Score e.g. PASI 75	Mean change of quality of life (Ø±SD)	Mean change of diabetes parameters (Ø±SD)	Adverse events	
												Fasting C-peptide (ng/mL) 1.50±0.94 IR 2.96±1.35				Fasting C-peptide (ng/mL) 0.43±0.38 IS - 0.94±1.06		
			acitretin 30-50mg/d + calcipotriol ointment + metformin alone or + glimepirid or sitagliptin		13	13		55.23±7.84	15.4% (2/13)	PASI 13.57±5.49	DLQI 18.23±5.17	HbA1c (%) 7.30±1.88 FPG (mmol/l) 6.29±1.89 Fasting insulin (ug/ml) 11.79±7.84 Fasting C-peptide (ng/mL) 1.47±1.05 IP 3.69±3.20		PASI-Change -6.15±3.43 PASI50 38.46% (5/13) PASI75 7.69 (1/13)	DLQI-Change -8.54±5.33	HbA1c (%) - 0.82±0.73 FPG (mmol/l) - 0.20±1.49 Fasting insulin (ug/ml) 0.86±4.81 Fasting C-peptide (ng/mL)- 0.06±0.37 IS 0.37±2.09	no SAE no AW	unclear
Proportions of Biologic Discontinuation Among Psoriasis Patients With Metabolic Comorbidities. Journal of Psoriasis and Psoriatic Arthritis.	Enos C. W., et al. (2022) [10]		TNF-α inhibitors	initiation in the past 12 months	2924	96	6	56.9 ± 11,9[3]	252/507 (49.7)[3]	PASI 9.1 ± 7.2 [3]	/	/	6	/	/	/	discontinuation of therapy patients with diabetes: n= 33/96 (34.4%) patients without diabetes: n= 111/455 (24.4%)	See table 5
			IL-17 inhibitors			219											discontinuation of therapy patients with diabetes: n= 44/219 (20.1%) patients without diabetes: n= 155/1011 (15.3%)	
			IL-23 / IL-12/23 inhibitors			192											discontinuation of therapy patients with diabetes: n= 25/192 (13.0%) patients without diabetes: n= 78/950 (8.2%)	

Titel	Author (Y)	Original study	Intervention	Duration of treatment (M)	Patients (n)	Patients with diabetes (n)	Follow up (M)	Age (Y) (Ø±SD)	♀ (%)	Poriasis-score at baseline (Ø±SD)	Qualtity of life at baseline (Ø±SD)	Diabetes parameters at baseline (Ø±SD)	Outcomes					overall RoB
													End of dollow up (M)	Psorias-Score e.g. PASI 75	Mean change of quality of life (Ø±SD)	Mean change of diabetes parameters (Ø±SD)	Adverse events	
Comorbid obesity and history of diabetes are independently associated with poorer treatment response to biologics at 6 months: A prospective analysis in Corrona Psoriasis Registry. Journal of the American Academy of Dermatology.	Enos C. W., et al. (2022) [11]		TNF-α inhibitors	initiation in the past 12 months	2924	96	6	50.0 ± 14.4[2]	268 (48.6) [2]	PASI 7.8 ± 6.9 [2]	/	/	6	**achieving PASI75** (patients with vs. without diabetes) 43.8% (42/96) vs. 53.0% (241/455) aOR 0.72 (95%CI 0.44, 1.18) [§] **achieving PASI90** (patients with vs. without diabetes) 29.2% (28/96) vs. 36.5% (166/455) aOR 0.81 (95%CI 0.47, 1.38) [§]	/	/	/	See table 5
			IL-17 inhibitors			219		51.2 ± 13.8[2]	576 (46.8) [2]	PASI 8.4 ± 7.7 [2]				**achieving PASI75** (patients with vs. without diabetes) 47.5% (104/219) vs. 60.6% (613/1011) aOR 0.61 (95%CI 0.45, 0.85) [§] **achieving PASI90** (patients with vs. without diabetes) 33.8% (74/219) vs. 44.4% (449/1011) aOR 0.69 (95% CI 0.49, 0.96) [§]				
			IL-23 / IL-12/23 inhibitors			192		49.8 ± 15.0[2]	534 (46.8) [2]	PASI 8.9 ± 7.5 [2]				**achieving PASI75** (patients				

Titel	Author (Y)	Original study	Intervention	Duration of treatment (M)	Patients (n)	Patients with diabetes (n)	Follow up (M)	Age (Y) (Ø±SD)	♀ (%)	Poriasis-score at baseline (Ø±SD)	Qualtity of life at baseline (Ø±SD)	Diabetes parameters at baseline (Ø±SD)	Outcomes					overall RoB
													End of dollow up (M)	Psorias-Score e.g. PASI 75	Mean change of quality of life (Ø±SD)	Mean change of diabetes parameters (Ø±SD)	Adverse events	
														with vs. without diabetes) 52.6% (101/192) vs. 62.3% (592/950) aOR 0.77 (95%CI 0.55, 1.09) § **achieving PASI90** (patients with vs. without diabetes) 39.1% (75/192) vs. 45.6% (433/950) aOR 0.92 (95%CI 0.65, 1.30) §				

Abbreviation:
1 = refers to all patients; 2 = refers to all patients in the subgroup; 3= refers to all patients with diabetes; a = adjusted; ADA = Adalimumab; AE = Adverse Event; APR = Apremilast; BSA = body surface area (%); CI = Confidence intervall; CsA = Cyclosporine A; DLQI = Dermatology Life Qulity Index; ETA = Etanercept; FPG = Fasting Plasma Glucose; GOL = Golimumab; HbA1c = Haemoglobin A1c; IFX = Infliximab; IS = Insuline Sensitivity measured by HOMA (Homeostasis Modell Assessment); M = Month; MTX = Methotrexate; Ø±SD = Mean ± standard deviation; OR = Odds ratio; PASI = Psoriasis area severity index; PASI100/90/75/50 = 100%/90%/75%/50% improvement in PASI; PI = Plasma Insuline; SAE = Severe Adverse Event; SEC = Secukinumab; TNFi = Tumour Necrosis Factor inhibitor; UST = Ustekinumab; Y = Year; blue = new studies update 2022; § = Odds ratio adjusted for: age, sex, race, smoking, education, duration of psoriasis, psoriatic arthritis, number of prior biologics, and obesity

Table 8 Retrospective data from the included studies for the systematic review of the evidence on psoriasis treatment and diabetes mellitus (Update 2)

Titel	Author (Y)	Intervention	Duration of treatment (M)	Patients (n)	Patients with diabetes (n)	Age (Y) (Ø±SD)	♀ (%)	Poriasis-score at baseline (Ø±SD)	Qualtity of life at baseline (Ø±SD)	Diabetes parameters at baseline (Ø±SD)	Outcomes					Oxford Levels of Evidence
											End of dollow up (M)	Psorias-score e.g. PASI 75	Mean change of quality of life (Ø±SD)	Mean change of diabetes parameters (Ø±SD)	Adverse events	
Risk of Serious Infection With Biologic and Systemic Treatment of Psoriasis: Results From the Psoriasis Longitudinal Assessment and Registry (PSOLAR)	Kalb, R. E. et al. (2015) [17]	ADA (n=331) ETA (n=221) IFX (n=161) UST (n=440)	21[1]	11461	1459 (12.7%[1])	48.5±13.8[1]	44.9%[1]	/	/	/	/	/	/	/	"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)	3
		Non-MTX/Non-biologics (n=204)													/	
Risk factors for increased serum creatinine level in patients with psoriasis treated with cyclosporine in a real-world practice	Hong, J. R. et al. (2019) [18]	CsA	3	398	37 (9.3%)	45.3±15.6[1]	44.2%[1] (176/398)	PASI 11.5[1]	/	/	/	/	/	/	"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)	3

Titel	Author (Y)	Intervention	Duration of treatment (M)	Patients (n)	Patients with diabetes (n)	Age (Y) (Ø±SD)	♀ (%)	Poriasis-score at baseline (Ø±SD)	Qualtity of life at baseline (Ø±SD)	Diabetes parameters at baseline (Ø±SD)	Outcomes					Oxford Levels of Evidence
											End of dollow up (M)	Psorias-score e.g. PASI 75	Mean change of quality of life (Ø±SD)	Mean change of diabetes parameters (Ø±SD)	Adverse events	
No association between TNF inhibitor and methotrexate therapy versus methotrexate in changes in hemoglobin A1C and fasting glucose among psoriasis, psoriatic arthritis, and rheumatoid arthritis patients	Wu, J. J. et al. (2015) [20]	MTX + TNFi (ADA/ ETA/IFX)/GoI	12	118	99 (83.9%[2])	59.4±9.43[2]	70.3%[2] (83/118)	/	/	HbA1c (%) 6.9±1.7	1 - 12	/	/	HbA1c (%) -0.1±1.0	/	3
				121	34 (28.1%[2])	57.7±9.78[2]	73.9%[2] (86/121)			FPG (mg/dl) 102.5±22.1				FPG (mg/dl) 3.7±18.6		
		MTX		344	247 (71.8%[2])	64.7±10.36[2]	67.2%[2] (231/344)	/	/	HbA1c (%) 6.7±1.2				HbA1c (%) 0.0±0.8		
				524	92 (17.6%[2])	64.7±11.16[2]	73.9%[2] (387/524)			FPG (mg/dl) 104.1±28.1				FPG (mg/dl) 1.3±24.5		
Initiation of TNF inhibitor therapy and change in physiologic measures in psoriasis	Wu, J. J. et al. (2014) [19]	TNFi	12	1274	209/1274 (16.4%[2])	46.7±13.8[2]	48.5%[2] (618/1274)	/	/	/	6	/	/	FPG (mg/dl; n=35 diabetes patients) 1.5±40.7	/	3
		MTX		979	163/979 (16.7%[2])	50.9±14.4[2]	52.3%[2] (512/979)							FPG (mg/dl; n=43 diabetes patients) -15.6±54		
		Photo-therapy		4309	711/4309 (16.5%[2])	52±15.9[2]	47.1%[2] (2029/4309)							/		
Persistence, effectiveness, and real-world outcomes in psoriasis patients treated with secukinumab in Portugal.	Mendes-Bastos P., et al. (2022) [21]	SEC	> 3	302	24/302 (7.9%[1])	48.4 ± 13.4[1]	41.7%[1] (126/302)	PASI Median (IQR) 16.6[1] (11.8; 24.0)	DLQI score Median (IQR) 16.0[1] (12.0; 20.5)	/	104 weeks	/	/	/	Drug persistence (= time since initiation until its discontinuation or last medical contact) "diabetes mellitus patients presented a significantly higher persistence in secukinumab than patients who were not diabetic (p = 0.007)"	3
Incidence and Risk Factors of Hepatic Fibrosis in Psoriatic Patients Receiving Methotrexate with Concomitant Acitretin Therapy and Methotrexate Monotherapy.	Rattanakaemakorn P., et al. (2021) [22]	MTX	/	128	25/128 (19.5%[2])	age of disease onset: Median (IQR) 33.0[2] (28–81)	50.8%[2] (65/128)	8.5[2] (6.3)	/	/	1604.37 person-years	/	/	/	Hepatic Fibrosis "Cumulative incidence of hepatic fibrosis at 5 years was estimated to be 16% in the MTX-ACI group and 17% in the MTX group." "multivariate regression analysis showed that T2DM (aHR = 2.40, 95% CI: 1.05–5.51; p = 0.04) and [..] increased the probability of developing hepatic fibrosis" no information identified, what the HR is adjusted for	3
		MTX-ACI		32	8/32 (25.0%[2])	age of disease onset: Median (IQR) 26.0[2] (23–78)	40.6%[2] (13/32)	8.9[2] (6.1)			108.65 person-years					

Titel	Author (Y)	Intervention	Duration of treatment (M)	Patients (n)	Patients with diabetes (n)	Age (Y) (Ø±SD)	♀ (%)	Poriasis-score at baseline (Ø±SD)	Qualtity of life at baseline (Ø±SD)	Diabetes parameters at baseline (Ø±SD)	Outcomes					Oxford Levels of Evidence
											End of dollow up (M)	Psorias-score e.g. PASI 75	Mean change of quality of life (Ø±SD)	Mean change of diabetes parameters (Ø±SD)	Adverse events	
Real-world Data Reveal Long Drug Survival for Guselkumab in Patients with Plaque Psoriasis.	Van Muijen M. E., et al. (2022) [23]	GUS	Inclusion was allowed during the entire study period, leading to various lengths in follow-up duration	195	26/195 (13.3%[1])	at GUS initiation 49.4[1] ± 14.2 (missing values: n= 31)	43.6%[1] (85/195)	Psoriasis Area and Severity Index Median (IQR) 9.2[1] (9.3) (missing values: n= 71)	Dermatology Life Quality Index 14.3[1] ± 8.0 (missing values: n= 148)	/	various lengths in follow-up duration; ≥ 1 follow-up visit after GUS initiation	/	/	/	Drug survival[5] "The multivariable model showed a significant association between diabetes mellitus type 2 (T2DM) and a shorter drug survival (HR 3.69 (95% CI 1.14–11.98) (p = 0.030) due to ineffectiveness."	3

Abbreviation:
1 = refers to all patients; 2 = refers to all patients in the subgroup; a = adjusted; ACI = Acitrtin; ADA = Adalimumab; AE = Adverse Event; CsA = Cyclosporine A; DLQI = Dermatology Life Qulity Index; ETA = Etanercept; FPG = Fasting Plasma Glucose; GOL = Golimumab; GUS = Guselkumab; HbA1c = Haemoglobin A1c; IFX = Infliximab; IS = Insuline Sensitivity measured by HOMA (Homeostasis Modell Assessment); HR = Hazard ratio; M = Month; MTX = Methotrexate; Ø±SD = Mean ± standard deviation; PASI = Psoriasis area severity index; PASI100/90/75/50 = 100%/90%/75%/50% improvement in PASI; PI = Plasma Insuline; SAE = Severe Adverse Event; SEC = Secukinumab; T2DM = Diabetes mellitus, type 2; TNFi = Tumour Necrosis Factor Inhibitor; UST = Ustekinumab; Y = Year; $ = "Temporary treatment interruptions for any reason were allowed if <90 days. This 90day gap was prolonged up to 1 year if patients discontinued due to fear of COVID19 or due to remission"
blue = new study update 2022

2.5 Appendix: Search strategy

Databases: Embase Classic+Embase 1947 to 2022 October 26

Ovid MEDLINE(R) ALL 1946 to October 26, 2022

Search date: October 27, 2022

Hits: 482 + 0 Deucra (Embase)

28 + 0 Deucra (MEDLINE)

Table 9 Search strategy for the review update 2 on psoriasis and diabetes mellitus (Embase via 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* inhibito*.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.
26.	light therap*.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.
47.	methotrexa*.mp.
48.	amethopterin.mp.
49.	mexate.mp.
50.	acitretin.mp. or Acitretin/

51.	Retinoids/
52.	Phosphodiesterase 4 Inhibitors/ or apremilast.mp.
53.	(etanercep* or enbrel).mp. or Etanercept/
54.	(Infliximab* or remicade).mp. or Infliximab/
55.	ustekinumab.mp. or Ustekinumab/
56.	CNTO 1275.mp.
57.	stelara.mp.
58.	secukinumab.mp.
59.	guselkumab.mp.
60.	adalimumab*.mp. or Adalimumab/
61.	(d2e7 or humira).mp.
62.	exp Antibodies, Monoclonal/
63.	monoclonal antibod*.mp.
64.	exp Interleukin-23/ or exp Interleukin-12/
65.	brodalumab.mp.
66.	ixekizumab.mp.
67.	bimekizumab.mp.
68.	(tumor necrosis factor-alpha or tumour necrosis factor-alpha).mp.
69.	certolizuma*.mp.
70.	risankizumab.mp.
71.	tildrakizumab.mp.
72.	anti tnf.mp.
73.	(tumor necrosis factor antibod* or tumour necrosis factor antibod*).mp.
74.	(antitumor necrosis factor or antitumour necrosis factor).mp.
75.	(anti tumor necrosis factor or anti tumour necrosis factor).mp.
76.	(tnf antibod* or tnf alpha antibod*).mp.
77.	climate therap*.mp. or Climatotherapy/
78.	Psychotherapy/ or psychosocial therap*.mp.
79.	exp Tumor Necrosis Factor-alpha/
80.	deucravacitinib.mp.
81.	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 or 78 or 78 or 79 or 80
82.	5 and 81
83.	Diabetes mellitus.mp. or Diabetes mellitus/
84.	Diabetes Mellitus, Type 1/ or Diabetes Mellitus, Type 2/ or diabetes mellitus type 1.mp.
85.	DM.ti,ab.
86.	(Type 1 diabetes mellitus or type 2 diabetes mellitus).ti,ab.
87.	(type 1 DM or type 2 DM).ti,ab.
88.	83 or 84 or 85 or 86 or 87
89.	82 and 88

Additional time-frame filters:

("202106*" or "202107*" or "202108*" or "202109*" or "202110*" or "202111*" or "202112*" or "2022*").dc. (Embase)

("202106*" or "202107*" or "202108*" or "202109*" or "202110*" or "202111*" or "202112*" or "2022*").dt. (Medline)

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.	deucravacitinib.mp.
7.	5 and 6
8.	Diabetes mellitus.mp. or Diabetes mellitus/
9.	Diabetes Mellitus, Type 1/ or Diabetes Mellitus, Type 2/ or diabetes mellitus type 1.mp.
10.	DM.ti,ab.
11.	(Type 1 diabetes mellitus or type 2 diabetes mellitus).ti,ab.
12.	(type 1 DM or type 2 DM).ti,ab.
13.	8 or 9 or 10 or 11 or 12

14.	7 and 13

Additional time-frame filters:

("202101*" or "202102*" or "202103*" or "202104*" or "202105*").dc. (Embase)
("202101*" or "202102*" or "202103*" or "202104*" or "202105*").dt. (Medline)

Table 10 Excluded full texts for the review update 2 on psoriasis and diabetes mellitus

Citation	Reason
Chen C. B., et al. Real-World Effects of Biologics on Renal Function in Psoriatic Patients: A Retrospective Study. BioDrugs. 2022.36(5):657-666.	off-topic
Enos C. W., et al. Cardiometabolic multimorbidity is common among patients with psoriasis and is associated with poorer outcomes compared to those without comorbidity. Journal of Dermatological Treatment. 2022.	off-topic
Fitzgerald T., et al. Characteristics of Patients Initiating Guselkumab for Plaque Psoriasis in the Symphony Health Claims Database. Journal of Drugs in Dermatology: JDD. 2021.20(10):1127-1131.	off-topic
Gottlieb A. B., et al. Clinical efficacy and safety of secukinumab in patients with psoriasis and comorbidities: pooled analysis of 4 phase 3 clinical trials. Journal of Dermatological Treatment. 2022.33(3):1482-1490.	off-topic
Liles J. E., et al. Association of IL-17 Inhibitor and SGLT2 Inhibitor with Candida Pyelonephritis. American Journal of Medicine. 2021.134(11):e561-e562.	case report
Nguyen H. T., et al. Secukinumab Demonstrated High Effectiveness in Vietnamese Patients with Moderate-To-Severe Plaque Psoriasis in a Real-World Clinical Setting: 16 Week Results from an Observational Study. Dermatology and Therapy. 2021.11(5):1613-1621.	off-topic
Setyawan J., et al. Risk of Thromboembolic Events and Associated Risk Factors, Including Treatments, in Patients with Immune-mediated Diseases. Clinical Therapeutics. 2021.43(8):1392-1407.e1.	off-topic
Tsuruta N., et al. Establishment of the Western Japan Psoriasis Registry and first cross-sectional analysis of registered patients. Journal of Dermatology. 2021.48(11):1709-1718.	off-topic
Zhou Y., et al. Anti-tumor Necrosis Factor-Alpha Therapy and Hypoglycemia: A Real-World Pharmacovigilance Analysis. Drug Safety. 2022.45(9):951-959.	off-topic

3 Virushepatitis

3.1 History

Table 11 History (Viral hepatitis)

Version	Search Date	Number of new studies	Additional information added	Implications for conclusions
Update 2	October 2022	5	See below	See below
Update 1	June 2021	6	See below	See below
Original	September 2019	22	n/a	n/a

3.2 Summary of methods and results (2022/2023)

Update 2 – December 2022 (blue = new study or additional data)

What was the aim of this systematic review?

The aim of this review update was to continuously inform the guideline development group of new evidence on patients with psoriasis vulgaris and coexisting viral hepatitis.
Many systemic psoriasis treatments modulate immune functions and can reactivate hepatitis, and are known to cause liver injury. However, patients with severe psoriasis and viral hepatitis still need systemic treatment. In this systematic review we investigated the safety and efficacy of systemic psoriasis treatment options for patients with concomitant viral hepatitis.

What did we do?

Two databases were searched systematically. We only included studies with patients treated with systemic psoriasis therapies who also had viral hepatitis B or C. We assigned Levels of Evidence for all studies included using the Center of Evidence Based Medicine Oxford recommendations [7] and RoB 2.0 tool [8] for the randomized trials.

What are the main results of the review?

We found 3 prospective studies [26-28], 2 register studies [29,30] and 28 retrospective studies [30-57] with 1758 patients with psoriasis vulgaris and coexisting viral hepatitis (hepatitis B n=1363; hepatitis C n=395).

Hepatitis B

- Prospective data
  - In a study by Chiu et al. 49 patients with psoriasis and hepatitis B were treated with secukinumab. A reactivation of hepatitis B was reported in 7 of 49 (14.3%) patients (risk of bias high) [27].
  - In a cohort study Ting et al. reported hepatitis B reactivation in 3 of 48 (6.3%) patients with isolated anti-HBc or resolved HBV infection treated with ustekinumab (Oxford Level of Evidence 3) [26].
  - Al Mutairi and Abouzaid reported that of 32 patients treated with biologics (ADA, ETA, UST), none suffered from hepatitis reactivation, an increase in transaminases or viral load. A PASI75 response was reported in all 32 patients (risk of bias high) [28].
- Retrospective data
  - Acitretin

- Chularojanamontri et al. reported that viral reactivation did not occur in 9 patients treated with acitretin [58].

- CsA
  - Chularojanamontri et al. reported that viral reactivation did not occur in 2 patients treated with ciclosporin [58].

- MTX
  - Tang et al. reported that 15 of 370 (4.1%) hepatitis B patients treated with MTX developed liver cirrhosis [29].
  - Chularojanamontri et al. reported that 2 of 6 (33.3%) patients treated with MTX suffered from viral reactivation [58].

- TNFi
  - ADA: A total of 8 studies with 38 patients reported no hepatitis B reactivation in patients treated with adalimumab [34,37,45,47-49,51,56]. A total of 3 studies with 29 patients reported a PASI75 response in 28 (96.6%) patients treated with adalimumab [37,45,51].
  - ETA: A total of 8 studies with 43 patients reported hepatitis B reactivation in 3 (7.0%) patients treated with etanercept [34,37,46-48,52,56,58]. A total of 3 studies with 14 patients reported at least a PASI50 response in 13 (92.9%) patients treated with etanercept [37,47,56].
  - IFX: A total of 5 studies with 13 patients reported a hepatitis B reactivation in 1 (7.7%) patient treated with infliximab [37,46,47,49,58]. A total of 2 studies with 2 patients reported a PASI75 response in 1 (50%) patient treated with infliximab [37,47].

- UST
  - A total of 7 studies with 111 patients reported a hepatitis B reactivation in 4 (3.6%) patients treated with Ustekinumab [32,41,42,47,49,54,57]. One study reported a PASI75 response in 5 of 14 (35.7%) patients 10 and one study reported a PASI50 response in 1 of 1 (100%) patient [47].

- SEC
  - A total of 5 studies with 60 patients reported a hepatitis B reactivation in 1 (1.7%) patient treated with secukinumab [38,43,49,53,55]. One study with 5 patients reported a “complete clearance” of psoriasis lesions in all 5 patients [38]. One study with 20 patients reported a PASI75 response in 100% (20/20) of patients, a PASI90 response in 90% (18/20) and a PASI100 response in 63% treated with secukinumab [53]. Qin et al. reported that 1 of 14 (10.9%) patients with resolved HBV infection treated with secukinumab developed hepatitis with negative HBV load [53].

- More than one treatment
  - A total of 8 studies with 217 patients treated with more than one drug (conventional and biologics) reported a hepatitis B reactivation in 1 (0.5%) patient [30,31,40,44,49,50,56,58]. One study with 359 patients reported a total of 561 treatment episodes with more than one drug (only biologics). A total of 88/561 (15.7%) HBV reactivations were reported [33]. Gargiulo et al. reported a PASI100 response in 12/17 (70.59%) and a PASI90 response in 15/17 (88.24%) patients treated with more than one treatment [40]. Chiu et al. reported a mean PASI improvement of 75.1% ± 21.6 in patients with chronic HBV infection, 76.2%

± 18.7 in patients with occult HBV infection and of 78.5% ± 18.5 in patients with resolved HBV infection [33].

Hepatitis C

- Prospective data
  - In a study by Chiu et al. 14 patients with psoriasis and hepatitis C were treated with secukinumab. A reactivation of hepatitis C was reported in 1 of 14 (7.1%) patients (risk of bias high) [27].
  - AlMutairi and Abouzaid reported that of 7 patients treated with TNFi (ADA, ETA), none sufferd from hepatitis reactivation, an increase in transaminases or viral load. A PASI75 response was reported in all 7 patients (risk of bias high) [15].
- Retrospective data
  - Acitretin
    - Chularojanamontri et al. reported “no worsening of HCV infection” during acitretin treatment in 1 patient with psoriasis vulgaris and hepatitis C [35].
  - CsA
    - Chularojanamontri et al. reported “no worsening of HCV infection” during ciclosporin treatment in 1 patient with psoriasis vulgaris and hepatitis C [35].
  - MTX
    - Tang et al. reported that 19 of 174 (10.9%) hepatitis C patients treated with MTX developed liver cirrhosis [29].
    - Chularojanamontri et al. reported “no worsening of HCV infection” during MTX treatment in 4 patients with psoriasis vulgaris and hepatitis C [35].
  - TNFi
    - ADA: A total of 3 studies with 27 patients reported no hepatitis C reactivation in patients treated with adalimumab [45,47,57]. In 20 of 27 (74.1%) patients, a PASI75 response was reported [45,47,57].
    - ETA: A total of 4 studies with 25 patients reported no hepatitis C reactivation in patients treated with etanercept [36,39,47,56]. A total of 3 studies with 20 patients reported a PASI75 response in 12 (60%) patients treated with etanercept [39,47,56].
  - UST
    - A total of 2 studies with 15 patients reported hepatitis C reactivation in 2 (13.3%) patients treated with ustekinumab [32,54].
  - SEC
    - A total of 2 studies with 33 patients reported 1 (3.0%) HCV reactivation in patients treated with secukinumab [43,55].
  - More than one treatment
    - A total of 6 studies with 33 patients reported zero cases of hepatitis C reactivation in patients treated with more than one systemic drug (conventional and biologics) [35,40,44,47,52,56]. One study with 61 patients reported a total of 112 treatment episodes with more than one drug (biologics). A total of 14/112 (12.5%) HCV

reactivations were reported 26. Gargiulo et al. reported a PASI100 response in 2/4 (50%) patients treated with more than one treatment [40]. Chiu et al. reported a mean PASI improvement of 75.2% ± 23.0 in patients treated with more than one treatment [33].

Key message

Hepatitis B reactivation was reported in 22 of 629 patients who received systemic psoriasis treatment. One study with 359 patients reported 561 treatment episodes with more than one drug and a total of 88/561 (15.7%) HBV reactivations.

Hepatitis C reactivation was reported in 4 of 130 patients who received systemic psoriasis treatment. One study with 61 patients reported 112 treatment episodes with more than one drug and a total of 14/112 (12.5%) HCV reactivations. Very few prospective studies and few retrospective studies are available. The reporting on whether patients have also received antiviral treatment during psoriasis therapy is inconsistent or incomplete. In addition, the antigen and antibody status of hepatitis B patients is reported inconsistently, hence further differentiation by status is not possible. Transaminases levels almost remained stable in the reported studies.

In 64 of 81 (79.0%) patients with psoriasis vulgaris and hepatitis B or C treated with TNFi a PASI75 response was reported in retrospective studies. Prospective data was only in one study available in which all patients (n=32) with psoriasis vulgaris and hepatitis B showed a PASI75 response after a treatment with ADA, ETA or UST (risk of bias high). However, a direct comparison with non-hepatitis patients is missing.

How up-to-date is this review?

We searched for studies that have been published up to 27 October 2022.

3.3 Methods

3.3.1 Inclusion criteria

Apart from the newly included drug deucravacitinib we did not change the search strategy and the inclusion criteria of the previous version.

Table 12 Eligibility criteria for the review update on psoriasis and viral hepatitis

	Criteria
Patients	Inclusion: only adult patients with a clinical diagnosis of psoriasis and a concomitant hepatitis B or C being treated for psoriasis Exclusion: patients with psoriatic arthritis only
Intervention	acitretin, apremilast, ciclosporin, fumarates, methotrexate TNFi: adalimumab, etanercept, certolizumab pegol, infliximab; anti-IL12/23: ustekinumab; anti-IL17: bimekizumab, brodalumab, ixekizumab, secukinumab; anti-IL23: guselkumab, risankizumab, tildrakizumab; tyrosinkinase-2-inhibitor: deucravacitinib (new))
Comparator	Comparisons with another included drug and/or placebo
Outcomes	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.
Study Design	Inclusion: randomized controlled trials, clinical trials (with and without comparison group), cohort studies, case control studies, cross sectional studies and case series Exclusion:

	Criteria
	case reports

3.3.2 Information sources

The search strategy was updated and the databases MEDLINE Ovid from 1946 and Embase Ovid from 1974 were searched for the period June 2021 to 27 October 2022. The newly included drug deucravacitinib was searched for the period January 2021 to 27 October 2022. The full search strategy is shown in the Appendix (Table 16 and Table 17) below. We screened all identified abstracts/titles for eligibility. Included titles/abstracts were then screened as full texts based on the above listed eligibility criteria (see Table 12).

3.3.3 Data collection, statistical analysis and evaluation

We performed the screening and did the data extraction using a standardized form. We recorded all full-texts excluded and the primary reason for exclusion (see below).

3.3.4 Methodological quality assessment/ Risk of bias assessment

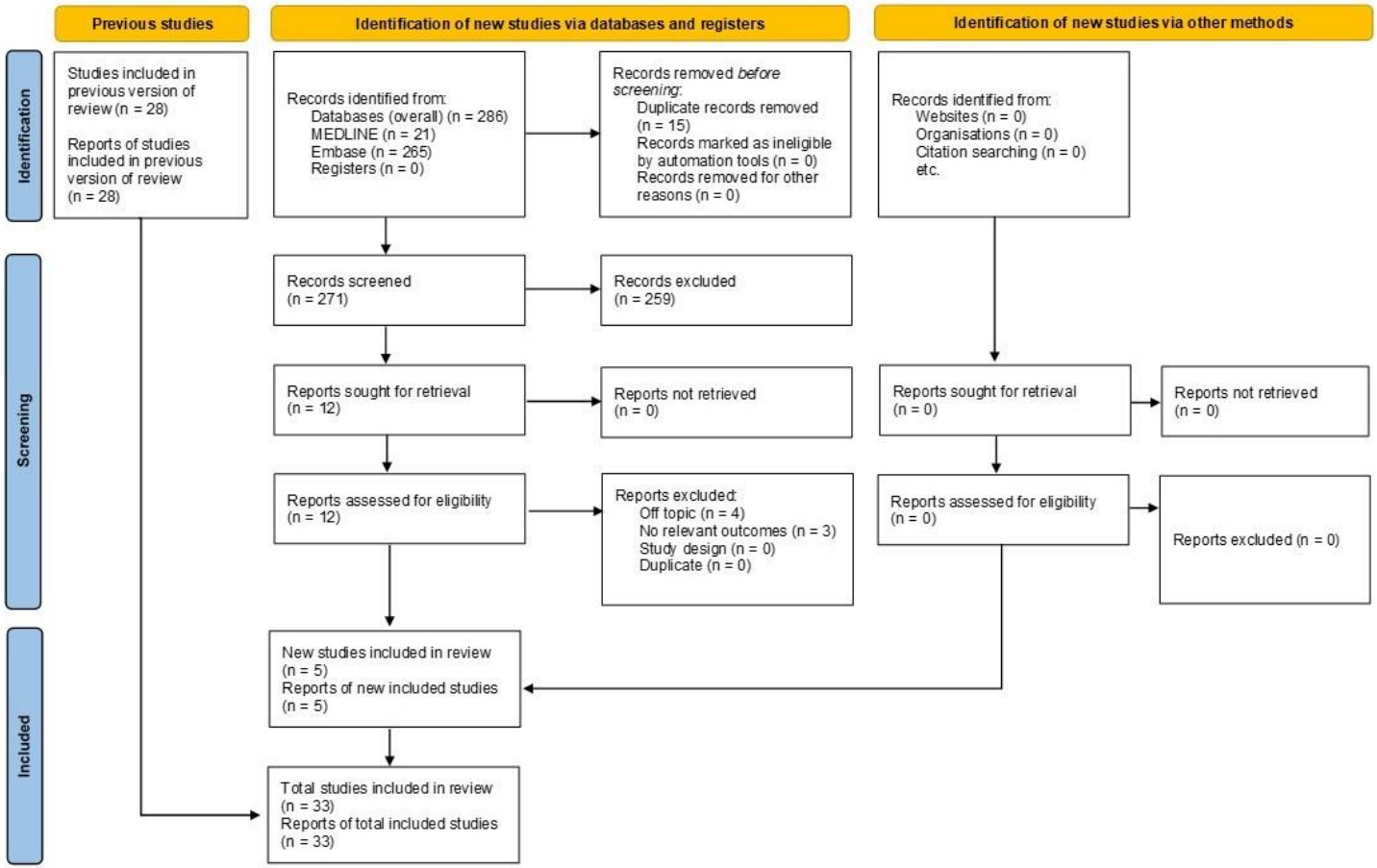
We assigned Levels of Evidence for all studies included using the Center of Evidence Based Medicine Oxford recommendations [7] . To assess risk of bias in randomized trials we additionally used the RoB 2.0 tool [8].

3.4 Results

Our update search yielded 286 citations, 5 of which fulfilled the inclusion criteria [33,40,42,43,53] (see study selection flow chart, Figure 3).

No studies on systemic treatment with apremilast, bimekizumab, certolizumab pegol, fumarates, deucravacitinib and guselkumab were identified that reported outcomes for viral hepatitis neither in the original search nor in the update.

Figure 3 Flow chart (viral hepatitis)



Based on the ‘Levels of Evidence - Center of Evidence Based Medicine Oxford recommendations’ all retrospective studies were categorized level 3. Results of the additional assessment for prospective randomized studies with Risk of Bias Tool 2 (RoB 2) [8] are shown in Table 13. In the update, no further prospective randomized studies were found.

Table 13 Risk of bias in prospective studies (no new data since 2019)

Abbreviation: ⊕ = high risk of bias ? = unknown risk of bias ⊖ = low risk of bias	Randomization process	Deviations from the intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall risk of bias
Author (Year)						
Al Mutairi, N. and Abouzaid, H.A. (2018)	⊕	⊕	⊕	⊖	⊖	⊕
Chiu H. Y. et al. (2018)I	⊕	⊕	⊕	⊖	⊖	⊕

Risk of bias – prospective randomized studies

Data for overall 1758 patients with psoriasis and viral hepatitis was extracted. Of those, 1363 patients suffered from hepatitis B infection and 395 from hepatitis C infection. The tables (Table 14 and Table 15 Hepatitis C) below are providing detailed information, sorted by medication used.

Table 14 Hepatitis B

								Severity score (e.g. PASI)		Transaminasis				Viral load					
										AST mean±SD		ALT mean±SD							
Author (Y)	Place	Patients (n)	Drug	Duration of treatment (M) mean± SD	Age (Y) mean± SD	♀ (%)	Eof (M) mean± SD	Baseline mean±SD	e.g. PASI-75 response eof (n)	Baseline	Eof	Baseline	Eof	Baseline (n)	Eof (n)	Antiviral therapy	HBV reactivation (n)[4]	other adverse events	Oxford Level of Evidence
	Acitretin																		
Chularojanamontri, L. et al.[58] (2020)[II]	Thailand	9	Acitretin	20.4 ±25.8	55.8±9.0	11.1	/	/	/	/	/	/	/	5/11	2/11 / = 1/11	none (4/11) LAM/TEN/EFA[2] (1/11) LAM/TEN[2] (1/11) TEN/LAM[2] (1/11) LAM[2] (1/11) LAM/ENT[2] (1/11)	0	/	3
	ADA																		
Piaserico, S et al.[51] (2017)[II]	Italy	17	ADA	27*	50.8±12.5	35.3	/	21.2±6.9	16/17	39±25.4	40.4±25	39.7±27.8	44.9±30.4	0	0	LAM[1] (8/17) LAM/ENT[1] (1/17)	0	/	3
Fotiadou, C. et al. [37] (2011)[II]	Greece	3	ADA	12±3	53.7±10.6	33.3	6-24	14.1±2	3/3	19.3±2.1	20.7±1.2	21±2.6	21.3±2.5	0	0	none	0	/	3
Nosotti, L. et al. [48] (2010)[II]	Italy	3	ADA	9.1±3.7	54±7.2	33.3	/	12.1±13.7	/	13±1.7	18.7±4.2	"unchanged"	"unchanged"	0	0	none	0	/	3
Navarro, R. et al. [46] (2014)[II]	Spain	2	ADA	11 26	74 68	50	/	/		17 9	19 21	20 14	20 43	/		none	0	/	3
Snast, I. et al. [56] (2017)[II]	Israel	2	ADA	12 72	55 69	0	63.7*	26.1 BSA 50	2/2 PASI50	35 19	29 34	34 24	42 14	0	0	none	0	Pneumonia (1/2)	3
Cho, Y.T. et al. [34] (2012)[II]	Taiwan	1	ADA	27	44	0	14	/		15	46	22	34	0	0	none	0	none	3

								Severity score (e.g. PASI)		Transaminasis				Viral load					
										AST mean±SD		ALT mean±SD							
Author (Y)	Place	Patients (n)	Drug	Duration of treatment (M) mean± SD	Age (Y) mean± SD	♀ (%)	Eof (M) mean± SD	Baseline mean±SD	e.g. PASI-75 response eof (n)	Baseline	Eof	Baseline	Eof	Baseline (n)	Eof (n)	Antiviral therapy	HBV reactivation (n)[4]	other adverse events	Oxford Level of Evidence
Ozcelik, S. et al. [49] (2020)[II]	Turkey	1	ADA	48	55	0	/	/	/	29	22	26	16	0	0	none	0	/	3
Narcisi, A. et al. [45] (2020)[II]	Italy	9	ADA	20±5.2	59±9.4	44.4	/	18.44±4.14	PASI100 7/9 PASI75 2/9	32.1±16.8	"no worsening"	23.6±19.4	"no worsening"	2/9	"no worsening"	TEN (2/9) LAM (2/9) none (5/9)	0	no SAE	3
	CSA																		
Chularojanamontri, L. et al. [58] (2020)[II]	Thailand	2	CsA	21.5±10.6	43.5±2.1	0	/	/	/	/	/	/	/	2/2	/ = 1/2	LAM[2] (1/2) TEN[2] (1/2)	0	/	3
	ETA																		
Prignano, F. et al. [52] (2011)[II]	Italy	11	ETA	8.6*	61.4*	27.3	7.3	/		"unchanged"				0	0	none	0	/	3
Snast, I. et al. [56] (2017)[II]	Israel	8	ETA	55.2±46.3	57.3±12.2	37.5	63.7*	19.8±2.7 BSA 50 (4/8)	8/8 PASI50	27.6±16.8	22.2±7.2	24±9.2	19.5±8.5	0	0	LAM[2] (1/8)	0	none	3
Navarro, R. et al. [46] (2014)[II]	Spain	7	ETA	28.7±20.7	60.6±15.4	28.6	/	/		34.9±14.9	34.7±21.4	44±23.4	32.6±19.6	/		none	0	/	3
Cho, Y.T. et al. [34] (2012)[II]	Taiwan	6	ETA	24.8±12.7	42.6±4.1	16.7	31.3±13	/		34.5±26.7	35.5±8.2	33.3±24.6	47±28.9	2	2	LAM[2] (1/6) LAM/ENT[2] (1/6)	3/6	none	3
Nosotti, L. et al. [48] (2010)[II]	Italy	4	ETA	10.5±5.7	51.3±5.7	0	/	7.4±4.6	/	23.5±3.1	28.3±5.7	"unchanged"	"unchanged"	0	0	LAM[2] (1/4)	0	/	3
Fotiadou, C. et al. [37] (2011)[II]	Greece	3	ETA	12.1±5.9	49.7±14	66.7	6-24	12.1±2.2	3/3	17.3±1.5	18.3±1.5	20.3±3.1	22.7±3.2	0	0	LAM[2] (1/3)	0	/	3

								Severity score (e.g. PASI)		Transaminasis				Viral load					
										AST mean±SD		ALT mean±SD							
Author (Y)	Place	Patients (n)	Drug	Duration of treatment (M) mean± SD	Age (Y) mean± SD	♀ (%)	Eof (M) mean± SD	Baseline mean±SD	e.g. PASI-75 response eof (n)	Baseline	Eof	Baseline	Eof	Baseline (n)	Eof (n)	Antiviral therapy	HBV reactivation (n)[4]	other adverse events	Oxford Level of Evidence
Navarro, R. et al. [47] (2013)[II]	Spain	3	ETA	27±19	43.7±13	33.3	25*	19.7±4.8	2/3 PASI50	28.3±4	44.3±14.6	46.3±3	45.7±13.7	1	0	ADE/ENT[2] (1/3) LAM[2] (2/3)	0	none	3
Chularojanamontri, L. et al. [58] (2020)[II]	Thailand	1	ETA	1	70	0	/	/	/	/	/	/	/	/	/	none	0	/	3
	IFX																		
Navarro, R. et al. [46] (2014)[II]	Spain	4	IFX	25.5±10.3	60.5±10	25	/	/		28.5±8.3	30.8± 15.2	30.3± 14.8	19.8± 8.7	/		none	0	/	3
Fotiadou, C. et al. [37] (2011)[II]	Greece	1	IFX	10	48	100	6-24	20.2	1/1	25	30	31	40	0	0	none	0	/	3
Navarro, R. et al. [47] (2013)[II]	Spain	1	IFX	37	36	100	25*	22.2	0	42	52	64	62	0	0	LAM[2]	0	none	3
Ozcelik, S. et al. [49] (2020)[II]	Türkei	6	IFX	24±10.7	58.2±10.8	33.3	/	/	/	22.3±4.8	23.3±3.1	24.6±10.6	23±10.5	0	1	LAM[1] (1/6) none (5/6)	1/6	/	3
Chularojanamontri, L. et al. [58] (2020)[II]	Thailand	1	IFX	3	57	0	/	/	/	/	/	/	/	0	0	none	0	/	3
	MTX																		
Tang, K. T. et al. [29] (2018)[II]	Taiwan	370	MTX	/	42.6±13.2	28	50.4 ±38.4	/		/				/		48/370	/	Liver cirrhosis (15/370) [3]	3
Chularojanamontri, L. et al. [58] (2020)[II]	Thailand	6	MTX	27±30.1 / = 1/6	56±8.2	66.7	/	/	/	/	/	/	/	3/6 / = 2/6	2/6 / = 1/6	LAM[1](3/6) none (3/6)	2/6 / = 1/6	/	3

								Severity score (e.g. PASI)		Transaminasis				Viral load					
										AST mean±SD		ALT mean±SD							
Author (Y)	Place	Patients (n)	Drug	Duration of treatment (M) mean± SD	Age (Y) mean± SD	♀ (%)	Eof (M) mean± SD	Baseline mean±SD	e.g. PASI-75 response eof (n)	Baseline	Eof	Baseline	Eof	Baseline (n)	Eof (n)	Antiviral therapy	HBV reactivation (n)[4]	other adverse events	Oxford Level of Evidence
	SEC																		
Chiu H. Y. et al. [27] (2018)[I]	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[1]	6/25	Hepatic cancer	2; RoB high
		24		8.7 ± 3.7	54.7 ± 13.4	25	9.2 ± 3.7	20.1 ± 8.3				41.1 ± 28.0				11/24[1]	1/24	/	
Siegel, S. A. R. et al. [59] (2017)[II]	USA	2	SEC	/	/	/	/	/		/				/		2	0	/	3
Ozcelik, S. et al. [49] (2020)[II]	Turkey	1	SEC	12	45	0	/	/	/	37	25	26	28	0	0	none	0	/	3
Galluzzo, M. et al. [38] (2019)[II]	Italy	5	SEC	at least 3.5	/	/	/	/	"complete clearance" 5/5	/	/	/	/	/	"no loger detectable"	2/5[1]	0	/	3
Megna et al. [43] (2022)[II]	Italy	13 HBsAg positive	SEC	53.5 ± 37.5 weeks, Range: 16–240 weeks	59.3 ± 9.1[$]	25/60 (41.7 %)[$]	/	/	/	31.4 ± 15.8 (IU/L)[$]	/	27.9 ± 18.6 (IU/L)[$]	/	/	/	LAM (12) ENT (1)	0	/	3
		19 HBcAb positive														LAM (1) ENT (1)	1		

								Severity score (e.g. PASI)		Transaminasis				Viral load					
										AST mean±SD		ALT mean±SD							
Author (Y)	Place	Patients (n)	Drug	Duration of treatment (M) mean± SD	Age (Y) mean± SD	♀ (%)	Eof (M) mean± SD	Baseline mean±SD	e.g. PASI-75 response eof (n)	Baseline	Eof	Baseline	Eof	Baseline (n)	Eof (n)	Antiviral therapy	HBV reactivation (n)[4]	other adverse events	Oxford Level of Evidence
Qin et al. [53] (2022)[II]	China	4 with chronic inactive HBV infetion [HBsAg (+), HBeAg (-)]	SEC	≥24 weeks	43.7 ± 13.5	30	24 weeks	IGA: - clear / almost clear: 5% - mild: 25% - moderate / severe: 70% DLQI: - none: 0% - small: 10% - moderate / very large / extremely large: 90%	PASI-75: 100% PASI-90: 90% PASI-100: 63% IGA: - clear / almost clear: 90% - mild: 10% - moderate / severe: 0% DLQI: - none: 75% - small: 20% - moderate / very large / extremely large:	32.3 ± 20.7 (IU/L)	23 ± 1.2 (IU/L)	41 ± 29.7 (IU/L)	29.3 ± 6.4 (IU/L)	<500 IU/mL	/	ENT (2) none (2)	0	/	3
		2 with occult HBV infection [HBsAg (-), HBsAb (-), HBcAb (+)]								31 ± 7 (IU/L)	30 ± 5 (IU/L)	41.5 ± 1.5 (IU/L)	44 ± 1 (IU/L)	<500 IU/mL	/	ENT (1) none (1)	0	/	

								Severity score (e.g. PASI)		Transaminasis				Viral load					
										AST mean±SD		ALT mean±SD							
Author (Y)	Place	Patients (n)	Drug	Duration of treatment (M) mean± SD	Age (Y) mean± SD	♀ (%)	Eof (M) mean± SD	Baseline mean±SD	e.g. PASI-75 response eof (n)	Baseline	Eof	Baseline	Eof	Baseline (n)	Eof (n)	Antiviral therapy	HBV reactivation (n)[4]	other adverse events	Oxford Level of Evidence
		14 with resolved HBV infection [HBsAg (-), HBsAb (+), HBcAb (+)]							5% Mean improvement of: PASI: −13.35 ± 7.41 % BSA affected: −17.11 ± 17 IGA: −2.55 ± 0.94 DLQI: −12.3 ± 7.39 Nota bene: different numbers reported in the text and in Fig. 3 for mean improvement in DLQI	21.6 ± 7.8 (IU/L)	22.9 ± 13.7 (IU/L)	27.4 ± 22.5 (IU/L)	29.4 ± 38.6 (IU/L)	<500 IU/mL (10) <20 IU/mL (4)	/	none	0	hepatitis (1)	
	UST																		
Ting, S. W. et al.[26] (2018)[l]	Taiwan	54	UST	/	47*	16.7	24*	/		"none had liver failure"						ENT[1] (1/54)	3/48	/	3

								Severity score (e.g. PASI)		Transaminasis				Viral load					
										AST mean±SD		ALT mean±SD							
Author (Y)	Place	Patients (n)	Drug	Duration of treatment (M) mean± SD	Age (Y) mean± SD	♀ (%)	Eof (M) mean± SD	Baseline mean±SD	e.g. PASI-75 response eof (n)	Baseline	Eof	Baseline	Eof	Baseline (n)	Eof (n)	Antiviral therapy	HBV reactivation (n)[4]	other adverse events	Oxford Level of Evidence
																LAM[2] (1/54)			
Hsieh, T. Y. et al. [41] (2018)[II]	Taiwan	75	UST	/	/	/	24.7*	/		/				/		unknown[2] (2/75)	2/75	/	3
Chiu, H.Y. et al. [32] (2013)[II]	Taiwan	14	UST	9.4±9	45.5±7.6	28.6	10.4*	/	5/14	"unchanged"				/	"increased" (4/14)	ENT[2] (4/14)	2/14	/	3
Piaserico, S. et al. [51] (2017)[II]	Italy	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±19	0	0	LAM[1] (4/5)	0	/	3
Navarro, R. et al. [47] (2013)[II]	Spain	1	UST	7	56	0	25*	17.6	1/1 PASI50	32	16	35	15	1/1	0	ENT[2]	0	none	3
Ozcelik, S. et al. [49] (2020)[II]	Turkey	1	UST	24	43	0	/	/	/	18	21	37	27	0	0	LAM[1]	0	/	3
Siegel, S. A. R. et al. [54] (2019)[II]	USA	10	UST	/	47.7±13.5	30	/	BSA 20.1±16.6	BSA 3.2±4.2	/	/	/	"no significant elevation" **	5/10 / = 5/10	3/10 / = 7/10	/	0	/	3
Klujszo et al. [42] (2022)[II]	Poland	5	UST	82.4 (28, 96) weeks[$]	n.r., Range: 54-75	60	75.2 (31, 176) weeks [$]	n.r., Range: 18.4-24	/	/	/	/	/	undetectable	undetectable	/	0	/	3
	> than one treatment																		

								Severity score (e.g. PASI)		Transaminasis				Viral load					
										AST mean±SD		ALT mean±SD							
Author (Y)	Place	Patients (n)	Drug	Duration of treatment (M) mean± SD	Age (Y) mean± SD	♀ (%)	Eof (M) mean± SD	Baseline mean±SD	e.g. PASI-75 response eof (n)	Baseline	Eof	Baseline	Eof	Baseline (n)	Eof (n)	Antiviral therapy	HBV reactivation (n)[4]	other adverse events	Oxford Level of Evidence
Cassano N. et al. [31] (2010)[II]	Italy	62	ETA (44) ADA (10) IFX (8)	27.8* 19* 28.8*	54*	32.3	55	15.3 (10.2-39.9)	/	"normal value"				"undetectable"		LAM[2] (1/62)	0	/	3
Morisco, F. et al. [60] (2014)[II]	Italy	23	ADA, ETA, UST, IFX, MTX, CsA	/	66±10.6	56.5	/	/	/	/	"unchanged"	27±2.3	"unchanged"	0	0	none	0	/	3
		36			52±12.4	25						24±3.2							
Al Mutairi, N. and Abouzaid, H.A. [28] (2018)[I]	Kuwait	28	ADA (11) ETA (10) UST (8)	14.7±12.3 21.7±25.3 30±14.7	51±13.2	10.7	41.4 ±21.4	14.2±1.5	28/28	22 (17–25.8)	23 (12.3–28.8)	21 (17.1–26.4)	23 (14.7–25.3)	0		none	0	none	2; RoB high
		4	ADA (3) ETA (4) UST (1)	15.4±11.7 18.5±23.6 28±11.9	49±15.6	25			4/4							LAM[2] (4/4)			
Pereira, R.et al. [50] (2018)[II]	Portugal	26	ETA (12) ADA (8) IFX (6)	37.2 50.4 58.8 /	52.7±14.1	38.5	43.6 ±28.7	/		/				"undetectable"		/	0	/	3

								Severity score (e.g. PASI)		Transaminasis				Viral load					
										AST mean±SD		ALT mean±SD							
Author (Y)	Place	Patients (n)	Drug	Duration of treatment (M) mean± SD	Age (Y) mean± SD	♀ (%)	Eof (M) mean± SD	Baseline mean±SD	e.g. PASI-75 response eof (n)	Baseline	Eof	Baseline	Eof	Baseline (n)	Eof (n)	Antiviral therapy	HBV reactivation (n)[4]	other adverse events	Oxford Level of Evidence
			> 1 (13)																
Sanz-Bueno, J. et al. [30] (2015)[II]	Spain	20	ADA (13) ETA (7) UST (6) IFX (7)	13 16 18 22	/	25	40*	/		"unchanged"				0	0	none	0	/	3
Snast, I. et al. [56] (2017)[II]	Israel	16	ETA (16), ADA (14), IFX (5), UST (12), SEC (3), GOL (1), ALE (1)	70.8±32.4	55.2±11.4	31.3	63.7*	23.3±8.6 BSA 50 (5/16) BSA 70 (1/16)	9/16 PASI50	22.7±5.6	21.9±8.3	21.5±7	19.3±10.7	0	0	LAM[2] (1/16)	0	respiratory infection (1/16), myocardial infarction (1/16) erythema (2/16)	3

								Severity score (e.g. PASI)		Transaminasis				Viral load					
										AST mean±SD		ALT mean±SD							
Author (Y)	Place	Patients (n)	Drug	Duration of treatment (M) mean± SD	Age (Y) mean± SD	♀ (%)	Eof (M) mean± SD	Baseline mean±SD	e.g. PASI-75 response eof (n)	Baseline	Eof	Baseline	Eof	Baseline (n)	Eof (n)	Antiviral therapy	HBV reactivation (n)[4]	other adverse events	Oxford Level of Evidence
Ozcelik, S. et al. [49] (2020)[II]	Turkey	7	ADA (5) ETA (2) IFX (7) SEC (3) UST (1)	65.7±38.2	57.3±12.4	42.9	/	/	/	23.1±6.8	32.9±21.1	24.4±14.9	30±20.4	0	0	LAM[1] (1/7) none (6/7)	0	/	3
Chularojanamontri, L. et al. [58] (2020)[II]	Thailand	10	Acitritin (8) CsA (8) ETA (3) IFX (3) MTX (6)	/	51.5±10.9	18.2	/	/	/	/	/	/	/	/	/	/	1/10 / = 4/10	/	3
Chiu, H.Y. et al. [33] (2021)[II]	Taiwan	359 n.r. for each heaptitis B infection	ADA ETA GOL SEC UST	number of treatment episodes: 210	47.6 ± 9.4	20.5	3012 person-months	PASI: 16.8 ± 8.9	Mean PASI improvement (%): 75.1 ± 21.6	/	/	42 ± 65 IU/L	/	99034.5 ± 564964.4 IU/mL	/	51 (24.2%) LAM 3/51 (5.8%) ENT 40/51 (78.4%) TELB 8/51 (15.6%) TEN 2/51 (3.9%)	Chronic HBV: 72/210 (34.3%)	/	3

								Severity score (e.g. PASI)		Transaminasis				Viral load					
										AST mean±SD		ALT mean±SD							
Author (Y)	Place	Patients (n)	Drug	Duration of treatment (M) mean± SD	Age (Y) mean± SD	♀ (%)	Eof (M) mean± SD	Baseline mean±SD	e.g. PASI-75 response eof (n)	Baseline	Eof	Baseline	Eof	Baseline (n)	Eof (n)	Antiviral therapy	HBV reactivation (n)[4]	other adverse events	Oxford Level of Evidence
				number of treatment episodes: 93	54.3 ± 10.5	24.7	1265 person-months	PASI: 19.2 ± 9.3	Mean PASI improvement (%): 76.2 ± 18.7			28 ± 20 IU/L		4.4 ± 8.2 IU/mL		0 (0%)	Occult HBV infection: 3/93 (3.2%)		
				number of treatment episodes: 258	50.6 ± 11.5	22.5	4532 person-months	PASI: 22.9 ±12.7	Mean PASI improvement (%): 78.5 ± 18.5			33 ± 25 IU/L		1.3 ± 5.8 IU/mL		0 (0%)	Resolved HBV: 13/258 (5.0%)		
Gargiulo et al.[40] (2022)[II]	Italy	17	ADA (1) BRO (1) ETA (1) IXE (2) RIS (10) SEC (2) TIL (2) UST (2)	/	Median: 57, Range: /	29.41	Mean: /, Range: 52-208 weeks	Median: 15, Range: 10-32	PASI-100: 12/17 (70.59%) PASI-90: 15/17 (88.24%)	/	/	/	/	undetectable	/	none	0	/	3

								Severity score (e.g. PASI)		Transaminasis				Viral load					
										AST mean±SD		ALT mean±SD							
Author (Y)	Place	Patients (n)	Drug	Duration of treatment (M) mean± SD	Age (Y) mean± SD	♀ (%)	Eof (M) mean± SD	Baseline mean±SD	e.g. PASI-75 response eof (n)	Baseline	Eof	Baseline	Eof	Baseline (n)	Eof (n)	Antiviral therapy	HBV reactivation (n)[4]	other adverse events	Oxford Level of Evidence
Abbreviation: / = data not applicable or reported 1 = before treatment; 2 = while treatment; 3 = no diffrence 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 = prospectice study; II = retrospective study * = mean (SD not applicable or reported); ** = as defined by threefold increase in transaminases or 10-fold increase in viral load; $ = refers to all patients in the study population ADA = Adalimumab; ADE = Adefovir; ALT = Alanine Aminotransferase; AST = Aspartate Aminotransferase; BRO = Brodalumab; BSA = Body Surface Area; CsA = Cyclosporine A; ENT = Entecavir; ETA = Etanercept; eof = end of follow-up; EFA = Efavirenz; GOL = Golimumab; HCC = Hepatocellular Carcinoma; HBV = Hepatitis B Virus; IFN = Interferon; IFX = Infliximab; IXE = Ixekizumab; LAM = Lamivudine; MTX = Methotrexate; TEN = Tenofovir; TELB / LTD = Telbivudine; PASI = Psoriasis Area Severity Index; RIB = Ribavirin; RIS = Risankizumab; SAE = Severe Adverse Event; SEC = Secukinumab; TIL = Tildrakizumab; UST = Ustekinumab yellow = new study updates 2021 and 2022																		

Table 15 Hepatitis C

								Severity score (e.g. PASI)		Transaminasis				Viral load					
										AST mean±SD		ALT mean±SD							
Author (Y)	Place	Patients (n)	Drug	Duration of treatment (M) mean± SD	Age (Y) mean± SD	♀ (%)	Eof (M) mean±SD	Baseline mean± SD	e.g. PASI-75 response eof (n)	Baseline	Eof	Baseline	Eof	Baseline (n)	Eof (n)	Antiviral therapy	HcV reactivation (n)[4]	other adverse events	Oxford level of evidence
Acitretin																			
Chularojanamontri, L. et al.[35] (2021)[II]	Thailand	1	Acitretin	3	44	0	/	/	/	65	177	91	301	/	/	0	no worsening of HCV infection during psoriasis treatment'	/	3
ADA																			

								Severity score (e.g. PASI)		Transaminasis				Viral load					
										AST mean±SD		ALT mean±SD							
Author (Y)	Place	Patients (n)	Drug	Duration of treatment (M) mean± SD	Age (Y) mean± SD	♀ (%)	Eof (M) mean±SD	Baseline mean± SD	e.g. PASI-75 response eof (n)	Baseline	Eof	Baseline	Eof	Baseline (n)	Eof (n)	Antiviral therapy	HcV reactivation (n)[4]	other adverse events	Oxford level of evidence
Piaserico, S et al.[51] (2017)[II]	Italy	20	ADA	40*	49.8±11.3	30	/	15.8±6.2	14/20	39.5±21.2	53.9±32.7	38±20.7	57.3±36.4	16/20	↓ 7/16 (0.7±0.3) ↑ 9/16 (8.8±17.1)	RIB[1] (1/20) IFN/RIB[1] (1/20)	0	/	3
Navarro, R. et al. [47] (2013)[II]	Spain	1	ADA	2	65	0	/	15.6	0/1	20	30	34	55	1/1	↑ (1.03)	none	0	Stroke (1/1)	3
Narcisi, A. et al. [45] (2020)[II]	Italy	6	ADA	17±59	58±5.0	50	/	17.5±6.75	PASI100 (5/6) PASI75(1/6)	63.8±17.6	"no worseneing"	57.5±16.0	"no worsening"	1/6	"no worsening"	0	0	no SAE	3
CsA																			
Chularojanamontri, L. et al. [35] (2021)[II]	Thailand	1	CsA	24	60	0	/	/	/	96	82	59	73	/	/	/	no worsening of HCV infection during psoriasis treatment'	/	3
ETA																			
Navarro, R. et al. [47] (2013)[II]	Spain	12	ETA	15.5±5.9	51.5±12.8	16.7	/	17.8±8.8	6/12	82.8±42.2	61.9±31	88.1±40.9	53.1±22.5	6/12	↓ 4/6 (0.04±0.08) ↑ 2/6 (8.2±12)	IFN/RIB[2] (3/12)	0	Respratory infection (1/12) HCC (2/12)	3

								Severity score (e.g. PASI)		Transaminasis				Viral load					
										AST mean±SD		ALT mean±SD							
Author (Y)	Place	Patients (n)	Drug	Duration of treatment (M) mean± SD	Age (Y) mean± SD	♀ (%)	Eof (M) mean±SD	Baseline mean± SD	e.g. PASI-75 response eof (n)	Baseline	Eof	Baseline	Eof	Baseline (n)	Eof (n)	Antiviral therapy	HcV reactivation (n)[4]	other adverse events	Oxford level of evidence
Garavaglia, M.C. et al. [39] (2010)[II]	Italy	5	ETA	15.6±7.1	59±10.7	20	7-24	22.9±3.2	4/5	42.8±14.1	43±23.6	49±10.5	52.4±37.7	4/5	↓ 3/4 (0.64±0.5) ↑ 1/4 (1.22)	IFN/RIB[2] (1/5)	0	/	3
Di Nuzzo, S. et al. [36] (2013)[II]	Italy	5	ETA	12*	60*	0	/	/		"increased" (2/5)				"unchanged"		/	0	HCC (1/5)	3
Snast, I. et al. [56] (2017)[II]	Israel	3	ETA	18±9.6	57±16.6	0	22.3 (8-36)	19.5±6.7	2/3	48.3±7.6	53.7±18.6	58.7±5.7	72.3±22.9	3/3	↓ 1/3 (0) ↑ 2/3 (1.93±0.93)	none	0	none	3
MTX																			
Tang, K. T. et al. [29] (2018)[II]	Taiwan	174	MTX	/	50.4±12.6	36	57.6±4.2	/		/		/		/		42/174	/	Liver cirrhosis (19/174)[3]	3
Chularojanamontri, L. et al. [35] (2021)[II]	Thailand	4	MTX	43±61.5	62.8±12.8	25	/	/	/	30.8±17.1	30.3±17.8	27.5±19.7	33±20.1	1/4 / = 3/4	/	pegIFN/RIB[2] (1/4) / = 3/4	no worsening of HCV infection during psoriasis treatment'	/	3
SEC																			

								Severity score (e.g. PASI)		Transaminasis				Viral load					
										AST mean±SD		ALT mean±SD							
Author (Y)	Place	Patients (n)	Drug	Duration of treatment (M) mean± SD	Age (Y) mean± SD	♀ (%)	Eof (M) mean±SD	Baseline mean± SD	e.g. PASI-75 response eof (n)	Baseline	Eof	Baseline	Eof	Baseline (n)	Eof (n)	Antiviral therapy	HcV reactivation (n)[4]	other adverse events	Oxford level of evidence
Chiu, H. Y. et al. [27] (2018)[I]	Taiwan	14	SEC	8.6 ± 3.4	53.9 ± 12.7	14.3	9.0 ± 3.9	/	"Improvement in PASI": 77.7 ± 18.5	/		48.4 ± 50.1	"no significant differences"	/	"no significant differences"	IFN/RIB[1] (4/14) DAA[2] (1/14)	1	HCC	2; RoB high
Siegel, S. A. R. et al. [55] (2017)[II]	USA	3	SEC	/	54-64	/	/	/		"no evidence of significant elevations"				/		/	0	/	3
Megna et al. [43] (2022)[II]	Italy	30	SEC	53.5 ± 37.5 weeks, Range: 16–240 weeks	59.3 ± 9.1 [$]	25/60 (41.7 %)[$]	/	/	/	31.4 ± 15.8[$]	/	27.9 ± 18.6 (IU/L)[$]	/	undetectable	1 2,000,000 copies/mL	none	1	/	3
UST																			
Chiu, H.Y. et al. [32] (2013)[II]	Taiwan	4	UST	8±2.6	64.8±12.1	0	9.5*	/	0/4	"slightly increased" (3/4)				/	"increased" (3/4)	none	1	HCC (1/4)	3

								Severity score (e.g. PASI)		Transaminasis				Viral load					
										AST mean±SD		ALT mean±SD							
Author (Y)	Place	Patients (n)	Drug	Duration of treatment (M) mean± SD	Age (Y) mean± SD	♀ (%)	Eof (M) mean±SD	Baseline mean± SD	e.g. PASI-75 response eof (n)	Baseline	Eof	Baseline	Eof	Baseline (n)	Eof (n)	Antiviral therapy	HcV reactivation (n)[4]	other adverse events	Oxford level of evidence
Siegel, S. A. R. et al. [54] (2019)[II]	USA	11	UST	/	54.3±5.8	27.3	/	BSA 36.5±20.3	BSA 10.8±9.6	/	/	/	no significant elevation ** 11/11	7/11 / = 4/11	no significant increase** / = 3/11	3/11[2]	1***	/	3
> than one treatment																			
Morisco, F. et al. [44] (2014)[II]	Italy	15	ADA, ETA, UST, IFX	/	62±11.8	20	48	/		/	/	25	"unchanged"	/	"unchanged"	none	0	/	3
Al Mutairi, N. and Abouzaid, H.A. [28] (2018)[I]	Kuwait	7	ADA (7) ETA (1)	13.7±10.4 20	54±12.9	40	41.4±21.4	/	7/7	22 (17–25.8)	21 (17.1–26.4)	23 (12.3–28.8)	23 (14.7–25.3)	"detectable level" (2/4)	"detectable level" (2/4)	/	0	none	2; RoB high
Prignano, F. et al.[52] (2011)[II]	Italy	5	ADA (2) ETA (3)	6 8.6	50.4*	25	7.3	/		"unchanged"				"unchanged"		none	0	/	3

								Severity score (e.g. PASI)		Transaminasis			Viral load						
										AST mean±SD		ALT mean±SD							
Author (Y)	Place	Patients (n)	Drug	Duration of treatment (M) mean± SD	Age (Y) mean± SD	♀ (%)	Eof (M) mean±SD	Baseline mean± SD	e.g. PASI-75 response eof (n)	Baseline	Eof	Baseline	Eof	Baseline (n)	Eof (n)	Antiviral therapy	HcV reactivation (n)[4]	other adverse events	Oxford level of evidence
Navarro, R. et al. [47] (2013)[II]	Spain	5	ADA (3) ETA (5) UST (1) IFX (1)	6.7±3.8 15.6±16.2 17 8	39.8±11.3	0	/	14.6±8.3	2/5	110±78.9	145±114.7	106.6±68.1	107.9±46.1	2/5	↓ 1/2 (0) ↑ 1/2 (1.57)	none	0	none	3
Snast, I. et al. [56] (2017)[II]	Israel	1	ETA ADA	36	78	0	22.3*	BSA 50	1/1	68	32	74	32	/		none	0	none	3
Chularojanamontri, L. et al. [35] (2021)[II]	Thailand	3	Acitretin (3) CsA (2) ETA (1) IFX (1) MTX (1)	/	52.7±6.4	33.3	/	/	/	46.6±27,8	27±21.7	43±30.6	14.7±4.9	1/3 / = 2/3	/	pegIFN/RIB[2] 1/3 / = 2/3	no worsening of HCV infection during psoriasis treatment'	/	3
Chiu, H.Y. et al. [33] (2021)[II]	Taiwan	61	ADA ETA GOL SEC UST	number of treatment episodes: 112	53.1 ± 11.9	17.9	1522 person-months	18.5 ± 7.6	Mean PASI improvement (%): 75.2 (± 23.0)	/	/	47 ± 44 (IU/L)	/	2660887.6 ± 7554939.7 (IU/mL)	/	14/112 (12.5%)[§]	14/112 (12.5%)	/	3
Gargiulo et al. [40] (2022)[II]	Italy	4	ADA (1) BRO (1) IXE (1) RIS (1) SEC	/	Median 54.5, Range: /	25	Mean / Range: 52-220 weeks	Mean / Range: 10-30	PASI-100: 2/4 (50%)	/	/	/	/	undetectable	/	/	0	/	3

								Severity score (e.g. PASI)		Transaminasis				Viral load					
										AST mean±SD		ALT mean±SD							
Author (Y)	Place	Patients (n)	Drug	Duration of treatment (M) mean± SD	Age (Y) mean± SD	♀ (%)	Eof (M) mean±SD	Baseline mean± SD	e.g. PASI-75 response eof (n)	Baseline	Eof	Baseline	Eof	Baseline (n)	Eof (n)	Antiviral therapy	HcV reactivation (n)[4]	other adverse events	Oxford level of evidence
			(1) UST (1)																

Abbreviation:
/ = data not applicable or reported
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
I = prospectice 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; § = Patients with HCV who had received antiviral drugs before or concurrently with biologics; $ = refers to all patients in the study population
ADA = Adalimumab; ADE = Adefovir; ALT = Alanine Aminotransferase; AST = Aspartate Aminotransferase; BSA = Body Surface Area; CsA = Cyclosporine A; DAA = Direct acting antivirals; ENT = Entecavir; ETA = Etanercept; eof = end of follow-up; EFA = Efavirenz; GOL = Golimumab; HCC = Hepatocellular Carcinoma; HCV = Hepatitis C Virus; IFN = Interferon; IFX = Infliximab; LAM = Lamivudine; MTX = Methotrexate; TEN = Tenofovir; PASI = Psoriasis Area Severity Index; PegIFN = Pegylated Interferon; RIB = Ribavirin; SAE = Severe Adverse Event; SEC = Secukinumab; UST = Ustekinumab
yellow = new study updates 2021 and 2022

3.5 Appendix: search strategy

Table 16 Search strategy for the review update on psoriasis and viral hepatitis

Databases: Embase Classic+Embase 1947 to 2022 October 26

Ovid MEDLINE(R) ALL 1946 to October 26, 2022

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* inhibito*.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.
26	light therap*.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.
47	methotrexa*.mp.
48	amethopterin.mp.
49	mexate.mp.
50	acitretin.mp. or acitretin/
51	retinoids/
52	phosphodiesterase 4 inhibitors/ or apremilast.mp.
53	(etanercep* or enbrel).mp. or etanercept/
54	(infliximab* or remicade).mp. or infliximab/
55	ustekinumab.mp. or ustekinumab/

56	cnto 1275.mp.
57	stelara.mp.
58	secukinumab.mp.
59	guselkumab.mp.
60	adalimumab*.mp. or adalimumab/
61	(d2e7 or humira).mp.
62	exp antibodies, monoclonal/
63	monoclonal antibod*.mp.
64	exp interleukin-23/ or exp interleukin-12/
65	brodalumab.mp.
66	ixekizumab.mp.
67	risankizumab.mp.
68	tildrakizumab.mp.
69	certolizumab.mp.
70	bimekizumab.mp.
71	deucravacitinib.mp.
72	(tumor necrosis factor-alpha or tumour necrosis factor-alpha).mp.
73	anti tnf.mp.
74	(tumor necrosis factor antibod* or tumour necrosis factor antibod*).mp.
75	(antitumor necrosis factor or antitumour necrosis factor).mp.
76	(anti tumor necrosis factor or anti tumour necrosis factor).mp.
77	(tnf antibod* or tnf alpha antibod*).mp.
78	climate therap*.mp. or climatotherapy/
79	psychotherapy/ or psychosocial therap*.mp.
80	exp tumor necrosis factor-alpha/
81	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 or 78 or 79 or 80
82	5 and 81
83	exp hepatitis/ or hepatit*.mp.
84	chronic hepatit*.mp. or exp hepatitis, chronic/
85	hepatitis b/ or hepatit* b.mp.
86	hbv.ti,ab.
87	hepatitis c, chronic/ or hepatitis c/ or hepatit* c.mp.
88	non a non b hepatit*.mp.
89	hcv.ti,ab.
90	hepati* d.mp.
91	hepatitis a/ or hepatit* infection.mp.
92	hav.ti,ab.
93	83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92
94	82 and 93

Additional time filters:

("202106*" or "202107*" or "202108*" or "202109*" or "202110*" or "202111*" or "202112*" or "2022*").dc. (Embase)

("202106*" or "202107*" or "202108*" or "202109*" or "202110*" or "202111*" or "202112*" or "2022*").dt. (Medline)

Table 17 Search strategy for the review update on psoriasis and viral hepatitis (Deucra)

Databases: Embase Classic+Embase 1947 to 2022 October 26

Ovid MEDLINE(R) ALL 1946 to October 26, 2022

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	deucravacitinib.mp.
7	5 and 6
8	exp hepatitis/ or hepatit*.mp.
9	chronic hepatit*.mp. or exp hepatitis, chronic/
10	hepatitis b/ or hepatit* b.mp.
11	hbv.ti,ab.
12	hepatitis c, chronic/ or hepatitis c/ or hepatit* c.mp.
13	non a non b hepatit*.mp.
14	hcv.ti,ab.
15	hepati* d.mp.
16	hepatitis a/ or hepatit* infection.mp.
17	hav.ti,ab.
18	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
19	7 and 18

Additional time filters:

("202101*" or "202102*" or "202103*" or "202104*" or "202105*").dc. (Embase)

("202101*" or "202102*" or "202103*" or "202104*" or "202105*").dt. (Medline)

Table 18 Excluded full-texts for the review update on psoriasis and viral hepatitis

Reference	**Reason for exclusion**
Babuna Kobaner G, Polat Ekinci A, Kutlay A. Long-term efficacy and safety of ustekinumab for moderate-to-severe psoriasis: A 9-year real-life experience from a tertiary referral center in Turkey. Dermatol Ther. 2021;34(4) (no pagination).	Off topic
Chularojanamontri L, Nimanong S, Wongpraparut C, Silpa-Archa N, Chaiyabutr C, Charoenpipatsin N. How do we treat psoriasis patients with hepatitis C infections in real-world situations? A retrospective analysis of 34 patients. Journal of Dermatological Treatment. 2021;32(3):321-7.	Off topic
Fidan S, Capkin E, Arica DA, Durak S, Okatan IE. Risk of hepatitis B reactivation in patients receiving anti-tumor necrosis factor-alpha therapy. International Journal of Rheumatic Diseases. 2021;24(2):254-9.	Off topic
Hung MH, Tien YC, Chiu YM. Risk factors for losing hepatitis B virus surface antibody in patients with HBV surface antigen negative/surface antibody positive serostatus receiving biologic disease-modifying anti-rheumatic drugs: a nested case-control study. Advances in Rheumatology. 2021;61(1) (no pagination).	No relevant outcomes
Munera-Campos M, Vilar-Alejo J, Rivera R, Carrascosa JM, Dauden E, Herrera-Acosta E, et al. The risk of hepatic adverse events of systemic medications for psoriasis: a prospective cohort study using the BIOBADADERM registry. Journal of Dermatological Treatment. 2022;33(4):2110-7.	No relevant outcomes
Nguyen HT, Pham NTU, Tran TNA, Nguyen NTT, Vu TTP. Secukinumab Demonstrated High Effectiveness in Vietnamese Patients with Moderate-To-Severe Plaque Psoriasis in a Real-World Clinical Setting: 16 Week Results from an Observational Study. Dermatol Ther (Heidelb). 2021;11(5):1613-21.	No relevant outcomes
Ozaki S, Ichiyama S, Ito M, Hoashi T, Kanda N, Saeki H. Real-world blood examination screening data before initiation of biologics for psoriasis patients. J Dermatol. 2022;49(5):534-8.	Off topic

4 Tuberkulose

4.1 Preliminary notes

The search process for the chapters on tuberculosis (Screening und Management) was iterative:

1. A search for systemtic reviews (SR) on the topic ‘Tuberculosis in Patients with systemic anti-inflammatory treatments’ was performed in one database (Medline via Ovid) for the update of the EuroGuiDerm-Guideline.
2. An update was carried out in two databases to investigate the risk of reactivation of latent tuberculosis infection (LTBI) when using systemic antiinflammatory therapies in patients that did not receive preventive antituberculous therapy. In this search, one SR published in 2024 was identified that was (due to its date of publication) not identified in the initial search. The SR was assessed as having sufficient methodological quality, and the information on preventive anti-tuberculous therapy not prioritised in the SR was re-extracted from the included primary studies.
3. The manufacturer of IL17, IL23 and IL12/23 inhibitors were asked for safety signals regarding reactivation of LTBI.
4. A non-representative online survey of German dermatologists and pulmonologists was conducted with regard to screening and prescribing behavior prior to the initiation of systemic therapies.

4.2 First step: Review of the evidence on psoriasis and tuberculosis in one database (2023)

What was the aim of this review?

The aim of this review was to inform the guideline development group about new evidence on the risk of tuberculosis (TB) in patients with psoriasis vulgaris who are about to be treated with a therapy other than TNFis. The goal was to potentially update the chapters on tuberculosis screening and tuberculosis management.

4.2.1 Research questions

Which antipsoriatic drugs (other than TNFi) are associated with a risk of activating latent tuberculosis?

4.2.2 Screening criteria

Table 19 Screening criteria (Tuberculosis)

	Inclusion criteria	Exclusion criteria
Patients	Adult patients (psoriasis, psoriasis arthritis, inflammatory bowel disease, ankylosing spondylitis, rheumatic disease, rheumatoid arthritis or autoimmune disease) with primarily positive Quantiferon test (or equivalent) or Tuberkulin skin test in screening prior to initiation of immunsuppressive therapy and consecutive exclusion of active TB	Children Animal studies
Intervention	**conventional systemic treatment:** acitretin, ciclosporin, fumarates, methotrexate **biologicals:** anti-IL12/23: ustekinumab anti-IL17: bimekizumab, brodalumab, ixekizumab, secukinumab	

	Inclusion criteria	Exclusion criteria
	anti-IL23: guselkumab, risankizumab, tildrakizumab **Small molecules:** PDE4i: apremilast tyrosine kinase 2 (TYK2) inhibitor: deucravacitinib (new))	
Comparator	For RCTs: another included drug and/or placebo If TNFi is comparator, include as single-arm study or case series	
Outcomes	Cases of activation of tuberculosis (symptoms, tests) with or without TB prophylaxis	
Study Design	Primary: Systematic reviews	non-systematic reviews in-vitro studies expert opinions without primary data letters (if of narrative character or expert opinion only) randomized controlled trials, clinical trials (with and without comparison group), cohort studies, case control studies and cross sectional studies, case series, case reports, retrospective studies, letters (if primary data is presented)

4.2.3 Information source and screening process

The search strategy was updated and the database MEDLINE via Ovid from 1946 was searched for all entries up until February 27, 2023. The full search strategy is shown below (see Table 20). Two methodologists conducted a topic specific screening of all identified systematic reviews (for filter see chapter “Search strategy”) independently. Included title/abstracts were then screened as full texts based on the above listed eligibility criteria by one methodologist and cross-checked by another one.

4.2.4 Methodological quality assessment

The AMSTAR-2-Tool was used for all systematic reviews, that were included following title and abstract screening and had a “prioritized study design” and an “adequate research question”.

4.2.5 Results

Our update search yielded 1612 citations. No systematic reviews fulfilled the inclusion criteria.

One non-systematic but structured review, conducted by Diel et al. [61] was identified and integrated in the background text of the German Guideline. The detailed findings are presented in the PRISMA diagram provided below:

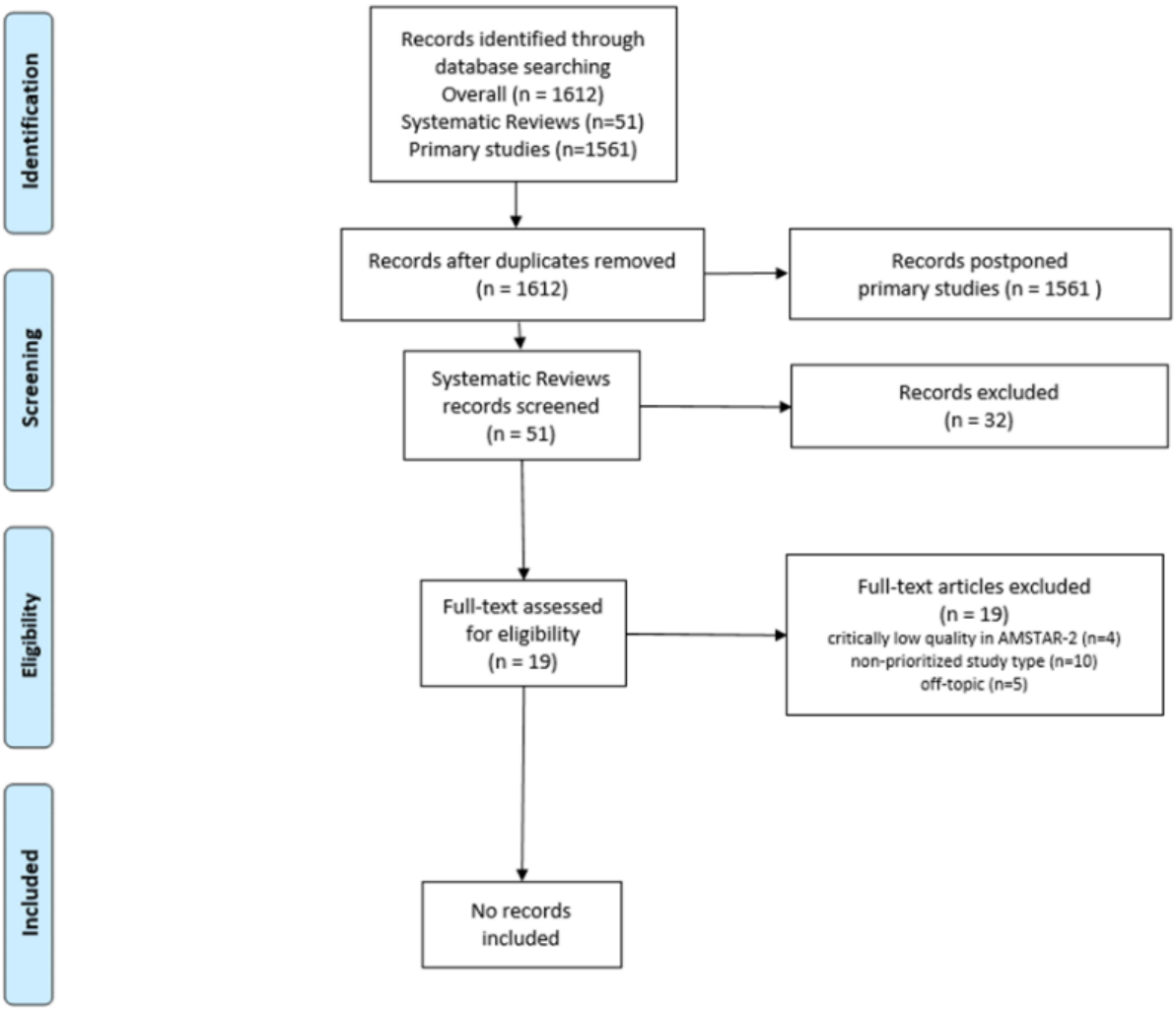


Figure 4 Flowchart (tuberculosis)

4.2.6 Appendix: Search strategy (28.02.2023)

Filter for identification of systematic reviews and meta-analysis: Wong SSL, Wilczynski NL, Haynes RB. Comparison of top-performing search strategies for detecting clinically sound treatment studies and systematic reviews in MEDLINE and EMBASE. J Med Libr Assoc 2006; 94(4): 451-455. (https://pubmed.ncbi.nlm.nih.gov/17082841/) (high specificity strategy)

Ressource: Ovid MEDLINE(R) ALL <1946 to February 27, 2023>

Table 20 Search strategy tuberculosis

No.	Search term	Result
1	exp Methotrexate/	40965
2	methotrexate$.mp.	59783
3	amethopterin.mp.	401
4	mtx.ti,ab.	14675
5	exp Fumarates/	5336
6	(fumar$ and esters).mp.	471
7	dimethylfumarate.mp.	207
8	fae.ti,ab.	1026
9	dmf.ti,ab.	9775

No.	Search term	Result
10	fumarate$1.mp.	20919
11	Acitretin/	1291
12	acitretin.mp.	2033
13	Ustekinumab.mp.	3013
14	secukinumab.mp.	1877
15	apremilast.mp.	1037
16	guselkumab.mp.	536
17	exp Interleukin-23/ or exp Interleukin-12/ or Interleukin-17/	30204
18	exp Interleukin-12 Subunit p40/ or p40 subunit.mp.	1902
19	Cyclosporine/	30502
20	(Ciclosporin* or cyclosporin*).mp.	61734
21	brodalumab.mp.	511
22	ixekizumab.mp.	949
23	tildrakizumab.mp.	249
24	bimekizumab.mp.	110
25	risankizumab.mp.	347
26	deucravacitinib.mp.	52
27	TYK2 Kinase/	615
28	(TYK2 or "tyrosine kinase 2").ti,ab.	2152
29	**or/1-28**	**188571**
30	exp Tuberculosis/	204867
31	Tuberculos*.ti,ab,kf.	234862
32	Mycobacterium tuberculosis/	56817
33	(TB or Tbc).ti,ab,kf.	72949
34	ltbi.ti,ab,kf.	2993
35	**or/30-34**	**300757**
36	cochrane database of systematic reviews.jn. or search.tw. or meta analysis.pt. or MEDLINE.tw. or systematic review.tw.	667197
37	exp animals/ not humans.sh.	5097167
38	29 and 35	2037
39	38 not 37	1612
40	**36 and 39**	**51**
41	**39 not 40**	**1561**

4.3 Second step: Review of the evidence on psoriasis and tuberculosis (update search)

What is the aim of this review?

The aim of this review is to inform the guideline development group about new evidence on the risk of tuberculosis in patients with psoriasis vulgaris that are about to be treated with a therapy other than TNFis, acitretin, apremilast, ciclosporin, fumarates or methotrexate.

The treatment of psoriasis often involves the use of immunosuppressive therapies that can increase the risk of developing infections, including tuberculosis (TB). While current guidelines recommend TB screening prior to initiating psoriasis therapy, it can be suggested that this risk is not identical for all immunosuppressive agents in use.

4.3.1 Research questions

A systematic review on which antipsoriatic drugs are associated with a risk of activating latent tuberculosis.

4.3.2 Screening criteria

Table 21 Screening criteria tuberculosis (primary studies)

	Inclusion criteria	Exclusion criteria
Patients	Patients with any disease for which the treatments below are being used (e.g. psoriasis, psoriasis arthritis, inflammatory bowel disease, ankylosing spondylitis, rheumatic disease, rheumatoid arthritis or autoimmune disease) with diagnosis of LTBI (as defined in the study, e.g. IGRA, TST) in screening prior to initiation of immunosuppressive or immune modulating therapy and consecutive exclusion of active TB: - without TB prophylaxis/ prevention (population of interest) - with TB prophylaxis/ prevention (postpone but do not exclude)	Animal studies
Intervention	IL12/23i: ustekinumab IL17i: bimekizumab, brodalumab, ixekizumab, secukinumab IL23i: guselkumab, risankizumab, tildrakizumab TYK2i: deucravacitinib	TNFi, acitretin, apremilast, ciclosporin, fumarates, methotrexate
Comparator	For RCTs: another included drug and/or placebo If TNFi, acitretin, apremilast, ciclosporin, fumarates, methotrexate is comparator, include as single-arm study or case series	
Outcomes	Cases of reactivation of tuberculosis (as defined in study, e.g. symptoms, tests, X-ray, PCR)	
Study Design	Systematic reviews RCTs, CCTs (with and without comparison group) with a LTBI-population, cohort studies, case control studies, cross sectional studies, case series, case reports, retrospective studies, letters (if primary data is presented)	RCTs or CCTs, that explore the efficacy and safety of the above-mentioned drugs in a non-LTBI-population non-systematic reviews in-vitro studies expert opinions or letters/ comments without primary data

4.3.3 Information source and screening process

The databases MEDLINE and Embase via Ovid were searched for all entries from inception up until current search date. The full search strategy is shown below (see Table 22 and Table 23). Two methodologists conducted the title and abstract and full text screening independently. One methodologist (re-)extracted relevant information and appraised the methodological quality of systematic reviews. The results were cross-checked by another methodologist.

4.3.4 Results

4.3.4.1 Results of the systematic search

Database	**Results**
Medline	1016
Embase	2033
Sum	**3049**
Excluded (duplicates)	706
Excluded (Not English or German)	187

Database	Results
To screen	**2156**
Included	**1**
Postponed	**2155**

The objective was to implement a stepwise approach with the screening of results, retrospectively from the most recent publication. The first systematic review [62] identified was from 2024, and it evaluated the risk of reactivations of latent tuberculosis infection (LTBI) in patients with antipsoriatic biologic therapy. Studies were included from a case number of 10. [62] The methodological quality of the publication [62] was assessed using the AMSTAR-2 tool and it deemed to be of sufficient methodological quality. Subsequent screening was then terminated, and the primary studies cited in the systematic review were examined in detail. The re-extraction process was then conducted to ascertain whether the subjects who exhibited reactivations of LTBI under systemic therapy had received preventive antituberculous therapy. The original extractions by Zhu et al. [62] are marked in the table in black, re-extractions in blue, and reactivations in red.

4.3.4.2 Extraktionstabelle (Zuh et al. [62])

Study	Year	Sample Size (positive at baseline)	Type of screening	Active TB excluded	Number of Patients with preventive therapy (PT) n (%)	Type(s) of PT	LTBI Reactivation (with PT) n/N (%)	Number of patients with un- or not fully treated LTBI n (%)	LTBI Reactivation (without PT) n/N (%)	Type of biologics	Study design	duration of biologic use	number of patients with previous biologic therapy	Geographic region	NOS score	Comment
Torres et al. [63]	2024	Secu: n= 121 Ixe: n= 61 Brod: n= 34 Risan: n= 101 Gusel: n= 58 Tildra: n= 30	TST and/ or IGRA	yes	Secu: n= 86 (71,1%) Ixe: n= 35 (57,4 %) Broda: n= 24 (70,6 %) Risan: n= 56 (55,5 %) Gusel: n= 39 (67,2 %) Tildra: n= 12 (40 %)	INH for 6 mo; RFP for 4 mo; INH + RFP for 3 mo	Secu: 0/86 Ixe: 0/35 Broda: 0/24 Risan: 0/56 Gusel: 0/39 Tildra: 0/12	Secu: n= 35 (28,9%) Ixe: n= 26 (42,6 %) Brod: n= 10 (29,4 %) Risan: n= 45 (44,5 %) Gusel: n= 19 (32,8 %) Tildra: n= 18 (60 %)	Secu: 0/35 **Ixe: 1/26 (3,8%)** Brod: 0/10 Risan: 0/45 Gusel: 0/19 Tildra: 0/18	IL-17 inhibitors IL-23 inhibitors	Retrospective	mean: 32.87 ± 20.95 months (range: 1.05–110.82 months)	n= 192 (47.4%)	Europe Brazil	8	Pts also included, if biologic was administered for 1 day only
Xiao et al. [64]	2023	62	IGRA	yes	n= 48	INH (300 mg/d); INH (300 mg/d) + RFP (450 mg/d); patients with old pulm. TB or suspicious chest CT: INH (300 mg/d) + RFP (450 mg/d) + ethambutol under guidance of infectious disease doctor	0/48	n= 14	0/14	Secukinumab	Retrospective	mean (SD): 23.37 (8.53)	n= 3 (4,84%)	China	8	
Manzanares et al. [65]	2023	Ixe: n=2 Secu: n= 1 Broda: n= 1 Risan: n= 21 Gusel: n= 5 Tildra: n= 5	n.r.	n.r.	0	n.a.	n.a. n.a.	Ixe: n=2 (100 %) Secu: n= 1 (100 %) Broda: n= 1 (100 %) Risan: n= 21 (100 %) Gusel: n= 5 (100 %) Tildra: n= 5 (100 %)	Ixe: 0/2 Secu: 0/1 Broda: 0/1 Risan: 0/21 Gusel: 0/5 Tildra: 0/5	IL-17 inhibitors IL-23 inhibitors	Retrospective	median: 24 months [6-100]	n= 10 (28,6%)	Spain	6	
Lupea-Chilom et al. [66]	2023	n= 30 (medication not specified)	Mantoux test + chest X-ray	yes	n= 30	INH 9 mo	0/30	0	n.a.	Mixed use	Retrospective	mean [min; max]: 6.9 y [1 y; 17 y]	not clearly reported	Romania	7	Seroconversions reported; Number of patients with Uste and IGRA + at baseline not reported
Mastorino et al. [67]	2022	Risan: n= 1 Secu: n= 4 Ixe: n= 3 Broda: n= 1 Uste: n= 1	**QTF**	yes	Risan: n= 0 Secu: n= 2 (50 %) Ixe: n= 3 (100 %) Broda: n= 0 Uste: n= 1 (100 %)	n.r.	Secu: 0/2 Ixe: 0/3 Uste: 0/1	Risan: n= 1 (100 %) Secu: n= 2 (50 %) Broda: n= 1 (100 %)	Risan: 0/1 Secu: 0/2 Broda: 0/1	Mixed use	Retrospective	Risan: 12 mo Secu: 18-32 mo Ixe: 14-30 mo Broda: 16 mo Uste: 30 mo	Risan: n= 0 Secu: n= 1 (25%) Ixe: n= 3 (100%) Broda: n= 0 Uste: n= 1 (100%)	Italy	8	
Koo et al. [68]	2022	n= 46 (medication not specified for IGRA+)	IGRA	yes	n= 41 (89,1 %)	INH 9 mo; INH + RFP 3 mo	Uste: n= 1 N not reported	n= 5 (10,9 %)	n= 0 (medication not specified)	Mixed use	Retrospective	n.r. for IGRA+ patients at baseline; duration in reactivation: 33 mo	n.r. for IGRA+ patients at baseline; note: pt. with reactivation was biologic naive	South Korea	7	
Megna et al. [69]	2022	n= 59	IGRA	yes	n= 49 (83,1%)	INH; INH + RFP; RFP	0	n= 10 (16,9%)	0/10	Secukinumab	Retrospective	mean (SD): 84 (± 62.4) weeks	n= 24 (40,7%)	Italy	8	

Study	Year	Sample Size (positive at baseline)	Type of screening	Active TB excluded	Number of Patients with preventive therapy (PT) n (%)	Type(s) of PT	LTBI Reactivation (with PT) n/N (%)	Number of patients with un- or not fully treated LTBI n (%)	LTBI Reactivation (without PT) n/N (%)	Type of biologics	Study design	duration of biologic use	number of patients with previous biologic therapy	Geographic region	NOS score	Comment
Elewski et al. [70]	2020	383	IGRA; purified protein derivative test; TST	yes	n= 383 (100 %)	according to local guidelines	0	0	n.a.	Secukinumab	Retrospective	16-260 wks	n.r.	n.r.	7	- pooled analysis of RCTs - pts. with at least 1 dose of included
Shu et al. [71]	2020	20	IGRA	yes	n= 1 (5%)	INH (≤300 mg/d) + (RFP) (≤600 mg/d) for 3 mo; INH (≤300 mg/d) for 6 or 9 mo	0/1	n= 19 (95 %)	0/19	Secukinumab	Prospective for 18 pts. Retrospective for 2 pts.	median (range) 43.0 (16-267) wks	infliximab: n= 3/20 (15%) etanercept: n=2/20 (10%) adalimumab: n=1/20	China	7	19 at baseline, 1 after 6 mo IGRA+
Narcisi et al. [45]	2020	11	IGRA	yes	n= 11 (100 %)	INH (300 mg/day) for 6 mo	0/11	0	n.a.	Adalimumab	Retrospective	median [range] 96 [48-96] wks	n.r. for IGRA+ patients at baseline	Italy	7	
Mrowietz et al. [72]	2020	Pso: n= 31 PsA: n= 8	IGRA	n.r.	Pso: n= 27 (87,1 %) PsA: n= 6 (75%)	INH; INH + RFP; RFP	0	Pso: n= 4 (12,9 %) PsA: n= 2 (25%)	0	Ixekizumab	Retrospective (pooled analysis of RCT)	212d - 1785d	n.r.	n.r.	6	- pooled analysis of RCTs; - pts. with at least 1 dose included - all LTBI+ were treatment emergent and not detected at baseline
Puig et al. [73]	2020	69	IGRA or Purified Protein Derivative testing	yes	n= 69 (100 %)	INH; RFP; Rifinah; Ethambutol; Nicovit; Pyrazinamide; Odinah; Rifabutin	0	0	n.a.	Guselkumab	Retrospective (pooled analysis of RCTs)	16 wks	30/69 (43,5%)	n.r.	7	data reported after cross over (from Ada to Guselkumab) up to 100 wks: 0/122 LTBi+ had active TB
		36			n= 36 (100 %)		0	0	n.a.	Adalimumab			2/36 (5,6%)			
Kaneko et al. [74]	2020	65 (medication not specified for IGRA+)	IGRA	yes	n= 64 (98,5 %)	INH, RFP	**Ada: n= 1** Number of patients with Ada at baseline not reported	n= 1 (1,5 %) (biological n.r.)	0/1	Mixed use	Retrospective	Adalimumab: 13 mo (in patient with reactiviation)	n.r.	Japan	7	

Study	Year	Sample Size (positive at baseline)	Type of screening	Active TB excluded	Number of Patients with preventive therapy (PT) n (%)	Type(s) of PT	LTBI Reactivation (with PT) n/N (%)	Number of patients with un- or not fully treated LTBI n (%)	LTBI Reactivation (without PT) n/N (%)	Type of biologics	Study design	duration of biologic use	number of patients with previous biologic therapy	Geographic region	NOS score	Comment
Blauvelt et al. [75]	2020	55	IGRA, PPD	yes	n= 24 (43,6 %)	n.r.	0/24	n= 31 (56,4 %)	0/31	Risankizumab	Prospective	up to 104 wks	n.r. for IGRA+ patients at baseline	Australia, Belgium, Canada, Czech Republic, France, Germany, Japan, South Korea, the US.	8	RCT
Wu et al. [76]	2019	18 (medication not specified for IGRA+)	IGRA	n.r.	n= 18 (100 %)	INH	0/18	0	n.a.	IL-17 inhibitors (Secu, Ixe)	Retrospective	n.r. for IGRA+ patients at baseline	n.r. for IGRA+ patients at baseline	Taiwan	7	
Ribero et al. [77]	2019	12	purified protein derivative skin test	n.r.	0	n.a.	n.a.	n= 12 (100 %)	0/12	Secukinumab	Retrospective	52 wks	n.r.	Italy	5	case series
Snast et al. [78]	2018	95 (medication not specified for IGRA+)	TST (with or without IGRA)	yes	n= 56 (58,9 %) (biological not specified for IGRA+)	INH (300 mg/d; 9 months); RFP (600 mg/d; 4 months)	0/56	n= 39 (41,1 %) Note: results do not total 100%, as some patients received >1 drug: Eta: n= 29 Ada: n= 26 Uste: n= 20 Sec: n= 9 Inf: n= 1	0 Note: results do not total 100%, as some patients received >1 drug: Eta: 0/29 Ada: 0/26 Uste: 0/20 Sec: 0/9 Inf: 0/1	Mixed use	Retrospective	- subgroup TST-positive: mean 45 ± 31 mo - subgroup with discordant tests who did not receive PT: mean 37 ± 30 mo	n.r.	Israel	8	treatment emergent LTBI+ (n= 17) also included in sample size (column D) distribution of medication among patients with positive TST: Etanercept: 83% Adalimumab: 66%, Ustekinumab 45%, Secukinumab 15%, Infliximab 11%, […]

Study	Year	Sample Size (positive at baseline)	Type of screening	Active TB excluded	Number of Patients with preventive therapy (PT) n (%)	Type(s) of PT	LTBI Reactivation (with PT) n/N (%)	Number of patients with un- or not fully treated LTBI n (%)	LTBI Reactivation (without PT) n/N (%)	Type of biologics	Study design	duration of biologic use	number of patients with previous biologic therapy	Geographic region	NOS score	Comment
Kammüller et al. [79]	2017	107								Secukinumab	Retrospective			n.r.	7	excluded: pooled analysis of RCTs, all already synthesised in Elewski ((ERASURE, FIXTURE, FEATURE, JUNCTURE, SCULPTURE)
Conti et al. [80]	2017	Eta: n= 19 ADA: n= 3 IFX: n= 15 EFA: n= 1 switch within TNFi: n= 15	TST and/ or QFT	yes	n= 56 (100 %)	INH 300mg/d for 9 mo (standard) rifampicin (10 mg/kg/die) for 4 months (rescue therapy in case of AE [n= 1])	**Eta: 1/19 (5,3%)** ADA: 0/3 IFX: 0/15 EFA: 0/1 switch within TNFi: 0/15	unclear (probably 0)	n.a.	TNF-α inhibitors	Retrospective	in mo, mean±SD Eta: 33.5 ± 21.6 ADA: 49.5 ± 8.5 IFX: 36.4 ± 22.5 EFA: 13.0 switch within TNFi: range of means: 39.0 - 64.7	n.r.	Italy	7	
		switch from TNFi to Uste: n= 2					switch from TNFi to Uste: 0/2			switch from TNFi to Uste		switch from TNFi to Uste: 73.0 ± 11.0				
		Uste: n= 1					Uste: 0/1			Ustekinumab		Uste: 2.0 mo				
Cataño et al. [81]	2016	Eta: n= 41 ADA: n= 38 IFX: n= 7	TST and fibrotic changes in chest x-ray	yes	n= 85 (85 %) (biological not reported)	INH 300mg/d for 9 mo; switch to RFP for 4 mo	**Eta: n= 2** **Ada: n= 1** IFX: n= 0 N not reported	n= 15 (15 %) (biological not specified)	0/15 (biological not specified)	TNF-α inhibitors	Prospective	only reported for active TB cases: Eta: 2 and 6 mo Ada: 8 mo	n.r.	Columbia	8	1 person from sample size was not TST positive
		Uste: n= 15					Uste: n= 0			Ustekinumab						

Abbreveiations: Ada Adalimumab; Broda Brodalumab; d day(s); Eta Etanercept; Gusel Guselkumab; Ifx Infliximab; IGRA Interferone-Gamma-Release-Assay; INH Isoniazid; Ixe Ixekizumab; LTBI latent tuberculosis infection; mg milligramm; mo month(s); n.a. not applicable; NOS: Newcastle Ottawa scale; n.r. not reported; PPD Purified Protein Derivative test; PT preventive therapy; RFP Rifampicin; Risan Risankizumab; SD standard deviation; Secu Secukinumab; TB, TuberculosisTildra Tildrakizumab; TST Tuberculin-Skin-Test; Uste Ustekinumab; wk week(s); y year(s)

Please note: The original extractions by Zhu et al. are marked in black, re-extractions in blue, and reactivations in red.

4.3.5 Appendix: Search strategy (12.08.2024)

Ovid MEDLINE(R) ALL <1946 to August 09, 2024>

Table 22 Search strategy tuberculosis (primary studies) - Medline

No.	Search term	Result
1	ustekinumab.mp.	3597
2	secukinumab.mp.	2303
3	guselkumab.mp.	762
4	brodalumab.mp.	605
5	ixekizumab.mp.	1183
6	tildrakizumab.mp.	322
7	bimekizumab.mp.	228
8	risankizumab.mp.	553
9	deucravacitinib.mp.	163
10	TYK2 Kinase/ or Tyrosine Kinase Inhibitors/	1385
11	(TYK2 or "tyrosine kinase 2").ti,ab,kf.	2531
12	exp Interleukin-23/ or exp Interleukin-12/ or Interleukin-17/	32046
13	(inhibit* or antagonist* or block*).ti,ab,kf.	3660828
14	12 and 13	10653
15	Interleukin Inhibitors/	84
16	((p40 or p19) adj1 subunit).ti,ab,kf.	767
17	((interleukin-12* or interleukin-17* or interleukin-23* or IL-12* or IL-17* or IL-23* or IL12* or IL17* or IL23*) adj3 (inhibit* or antagonist* or block*)).ti,ab,kf.	5658
18	Antibodies, Monoclonal/ae [Adverse Effects]	13740
19	Antibodies, Monoclonal, Humanized/ae [Adverse Effects]	8629
20	(monoclonal adj2 (antibody or antibodies)).ti,ab,kf.	215843
21	Biological Products/ae [Adverse Effects]	2402
22	Biological Therapy/ae, mo [Adverse Effects, Mortality]	445
23	Immunotherapy/ae, mo [Adverse Effects, Mortality]	3961
24	Immunosuppression Therapy/ae, mo [Adverse Effects, Mortality]	4858
25	Immunomodulating Agents/ae [Adverse Effects]	26
26	Immunosuppressive Agents/ae [Adverse Effects]	22309
27	(biologicals or biologics or ((biologic* or immunosupress* or immunomodulat*) adj2 (therap* or drug* or medication* or intervention* or agent*))).ti,ab,kf.	72352
28	or/1-11,14-27	343314
29	exp Tuberculosis/	210234
30	Mycobacterium tuberculosis/	59352
31	(Tuberculos* or TB or Tbc).ti,ab,kf.	276620
32	(reactiv* or conversion* or seroconversion* or latent*).ti,ab,kf.	1121925
33	(29 or 30 or 31) and 32	19418
34	Latent Tuberculosis/	4250
35	ltbi.ti,ab,kf.	3331
36	or/33-35	20178
37	exp animals/ not humans.sh.	5247600
38	28 and 36	1096
39	38 not 37	1016

Embase Classic+Embase <1947 to 2024 August 09>

Table 23 Search strategy tuberculosis (primary studies) - EMBASE

No.	Search term	Result
1	ustekinumab.mp.	15020
2	secukinumab.mp.	8463
3	guselkumab.mp.	2916
4	brodalumab.mp.	2307
5	ixekizumab.mp.	4321
6	tildrakizumab.mp.	1332
7	bimekizumab.mp.	714
8	risankizumab.mp.	2103
9	deucravacitinib.mp.	530
10	(TYK2 or "tyrosine kinase 2").ti,ab,kf.	3655
11	((p40 or p19) adj1 subunit).ti,ab,kf.	1315
12	((interleukin-12* or interleukin-17* or interleukin-23* or IL-12* or IL-17* or IL-23* or IL12* or IL17* or IL23*) adj3 (inhibit* or antagonist* or block*)).ti,ab,kf.	9162
13	protein kinase TYK2/	1399
14	protein tyrosine kinase inhibitor/	42186
15	cytokine receptor antagonist/	3131
16	interleukin 23/	21460
17	interleukin 12/	59718
18	interleukin 17/	74924
19	or/16-18	131982
20	(inhibit* or antagonist* or block*).ti,ab,kf.	4824459
21	19 and 20	39134
22	monoclonal antibody/	237631
23	human monoclonal antibody/ae, pv, tm [Adverse Drug Reaction, Special Situation for Pharmacovigilance, Unexpected Outcome of Drug Treatment]	100
24	biological product/ae, pv, tm [Adverse Drug Reaction, Special Situation for Pharmacovigilance, Unexpected Outcome of Drug Treatment]	2362
25	biological therapy/ae [Adverse Drug Reaction]	53
26	immunotherapy/ae [Adverse Drug Reaction]	153
27	immunosuppressive treatment/ae [Adverse Drug Reaction]	905
28	immunomodulating agent/ae, pv, tm [Adverse Drug Reaction, Special Situation for Pharmacovigilance, Unexpected Outcome of Drug Treatment]	3005
29	immunosuppressive agent/ae, pv, tm [Adverse Drug Reaction, Special Situation for Pharmacovigilance, Unexpected Outcome of Drug Treatment]	13509
30	(monoclonal adj2 (antibody or antibodies)).ti,ab,kf.	279638
31	(biologicals or biologics or ((biologic* or immunosupress* or immunomodulat*) adj2 (therap* or drug* or medication* or intervention* or agent*))).ti,ab,kf.	126621
32	or/1-15,21-31	585491
33	exp tuberculosis/	309903
34	Mycobacterium tuberculosis/	91972
35	(Tuberculos* or TB or Tbc).ti,ab,kf.	334202
36	(reactiv* or latent or conversion* or seroconversion*).ti,ab,kf.	1423569
37	(33 or 34 or 35) and 36	30208
38	latent tuberculosis/	8661
39	ltbi.ti,ab,kf.	4773
40	or/37-39	32182
41	32 and 40	2160
42	exp animal/ not exp human/	6093783
43	41 not 42	2033

4.4 Third step: Inquiry to the pharmaceutical companies

4.4.1 Questionnaire

The pharmaceutical companies that manufacture IL17, IL23 and IL12/23 inhibitors were asked the following questions:

Table 24 Inquiry regarding TB reactivations

Inquiry Regarding Tuberculosis (TB) Reactivations and New Infections During […] Antibody Therapy					
Name of Active Pharmaceutical Ingredient (API)					
Due to regional variations in TB incidence, it is essential to provide data broken down by regions. Please provide data both regionally and globally. If regional data is not available, please provide global data only.					
Sources can be: **Clinical Trial Data, Investigator-Initiated Trials (IIT), Registries and Other Sources.** If possible, please provide data source.					
1. Patient/ Drug Exposure					
	US	EU	Other	Globally/ Total	Comment
Date of market authorization					
Estimate of patient years on treatment					
Dosages prescribed [DDD or other]					
2. Reported Active TB Cases					
	US	EU	Other	Globally/ Total	Comment
Reported cases of **active TB** while on product (regardless of IGRA status)					
Manifestation/Location of TB					
Treatment success with standard treatment					
Treatment success with second line treatment					
Course of disease of individual cases					
Death					
Other					
Comment					
3. TB Seroconversion					
	US	EU	Other	Globally/ Total	Comment
Initally IGRA neg. patients with **seroconversion to TB infection** during treatment * seroconversion= IGRA becomes positive for the first time					
Thereof: Asymptomatic (latent TB/LTBI)					
Symptomatic (active TB)					
Treatment success with standard TB treatment					
Treatment success with second line TB treatment					
Death					
Other					
Comment					
4. TB Reactivation during Treatement without Chemoprevention (CP)					
	US	EU	Other	Globally/ Total	Comment
Number of IGRA pos. patients receiving antipsoriatic biological treatment without CP					
Thereof: Reported cases of TB reactivation					
Treatment success with standard treatment					
Treatment success with second line treatment					
Death					
Other					
Comment					

4.4.2 Results oft the inquiry

We received a response from UCB for Bimekizumab, Leo Pharma for Brodalumab, Eli Lilly for Ixekizumab, Janssen for Guselkumab and Ustekinumab, AbbVie for Risankizumab and Almirall for Tildrakizumab.

We reviewed all responses. None of the responses indicated a documented safety signal leading to a concern of increased TB reactivation during the use of these medications. The data was very limited and information if a reactivation occurred while on chemoprevention or not was mostly missing.

4.5 Fourth step: Health services research

For further Information please see ‘Current Standard of Care in Systemic Psoriasis Treatment with Regard to Latent Tuberculosis Screening and Chemoprevention: An Online Survey Assessment’ by Zeyen et al. [82].

5 Herzerkrankungen

5.1 Methods

5.1.1 Inclusion criteria

Table 25 Screening criteria (heart disease)

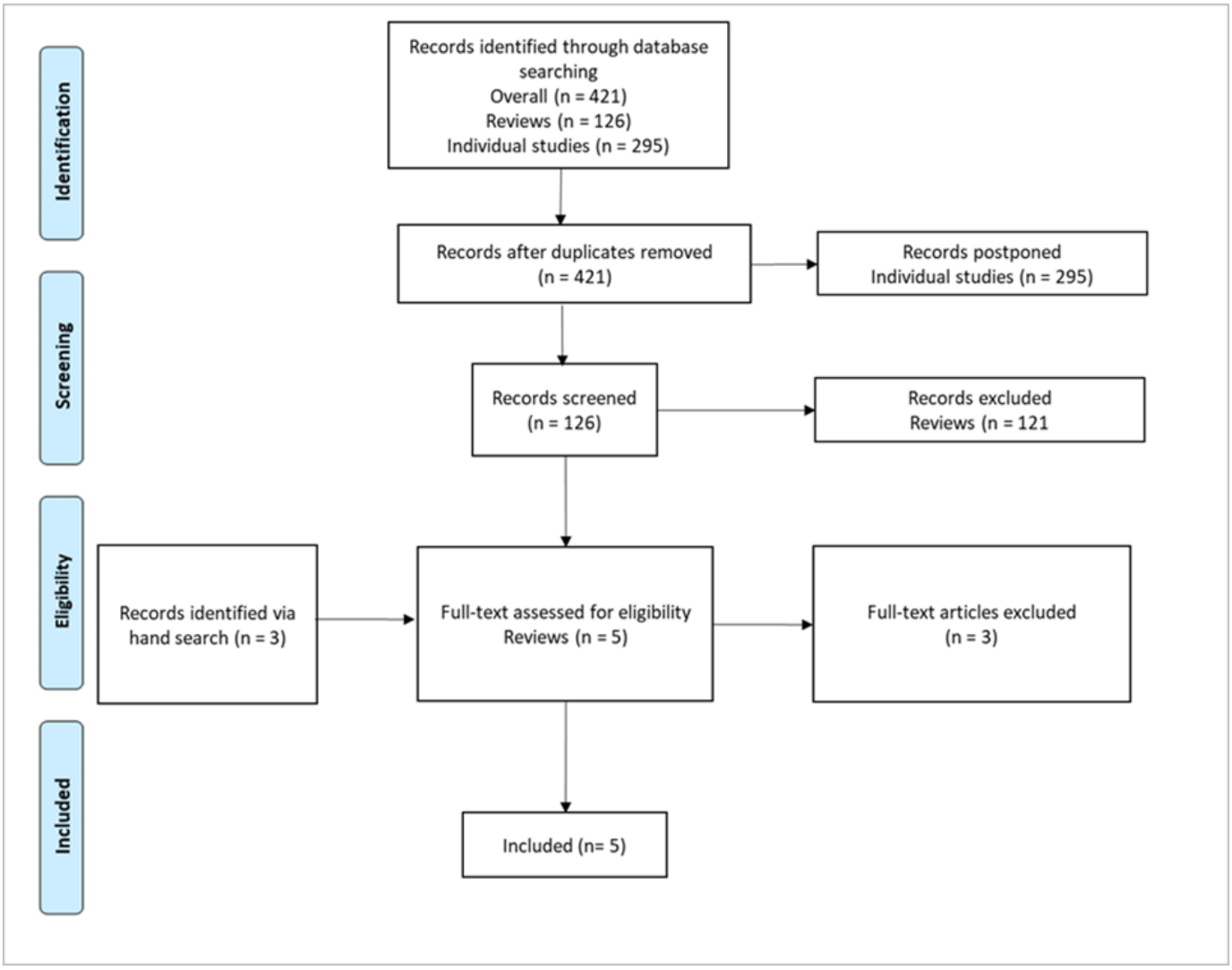
	Criteria
Patients	Inclusion: adult patients with a clinical diagnosis of psoriasis and heart diseases or cardiovascular risk factors
Intervention	acitretin, apremilast, ciclosporin, fumarates, methotrexate TNFi: adalimumab, etanercept, certolizumab pegol, infliximab; anti-IL12/23: ustekinumab; anti-IL17: bimekizumab, brodalumab, ixekizumab, secukinumab; anti-IL23: guselkumab, risankizumab, tildrakizumab; tyrosine kinase 2 (TYK2) inhibitor: deucravacitinib (new)
Comparator	Comparisons with another included drug and/or placebo
Outcomes	▪ risk for developing cardiovascular events ▪ influence on cardiovascular risk factors (weight, hypertension, dyslipidaemia)
Study Design	Inclusion: Primary: Systematic reviews Secondary: randomized controlled trials, clinical trials (with and without comparison group), cohort studies, case control studies and cross sectional studies, case series, case reports, retrospective studies Exclusion: non-systematic reviews, letter, comments, animal, in-vitro or in-silico studies

5.1.2 Information source and screening process

The search strategy was updated and the database MEDLINE via Ovid from 1946 was searched for the period October 2019 to 18 January 2023 (see Table 26). One methodologist conducted a topic specific but non-systematic screening. The authors of the chapter then screened included full texts based on the above listed eligibility criteria.

1.1. Results

Figure 5 Flow chart (heart disease)



1.2. Appendix: Search strategy

Filter for detecting systematic reviews: Wong SSL, Wilczynski NL, Haynes RB. Comparison of top-performing search strategies for detecting clinically sound treatment studies and systematic reviews in MEDLINE and EMBASE. J Med Libr Assoc 2006; 94(4): 451-455. https://pubmed.ncbi.nlm.nih.gov/17082841/ (Strategies minimizing difference between sensitivity and specificity)

Ressource: Ovid MEDLINE(R) ALL <1946 to January 17, 2023>

Table 26 search strategy (heart disease)

ID	Search term	Result
1	exp Methotrexate/	40879
2	methotrexate$.mp.	59566
3	amethopterin.mp.	401
4	mtx.ti,ab.	14592
5	exp Fumarates/	5316
6	(fumar$ and esters).mp.	468
7	dimethylfumarate.mp.	205
8	fae.ti,ab.	1021
9	dmf.ti,ab.	9700
10	fumarate$1.mp.	20781
11	Etretinate/	1352
12	Acitretin/	1286
13	((oral or orally or systemic) and retinoid$).ti,ab.	2931
14	Isotretinoin/	3942
15	isotretinoin.ti,ab.	3695
16	etretin$.mp.	1745
17	acitretin.mp.	2023
18	Retinoids/	6308
19	Ustekinumab.mp.	2952
20	secukinumab.mp.	1851
21	apremilast.mp.	1027
22	guselkumab.mp.	524
23	exp antibodies, monoclonal/	271864
24	monoclonal antibod$.mp.	204408
25	exp Interleukin-23/ or exp Interleukin-12/ or Interleukin-17/	30052
26	exp Interleukin-12 Subunit p40/ or p40 subunit.mp.	1901
27	exp Tumor Necrosis Factors/ or exp Tumor Necrosis Factor-alpha/ or exp Receptors, Tumor Necrosis Factor, Type II/ or exp Receptors, Tumor Necrosis Factor/ or exp Receptors, Tumor Necrosis Factor, Type I/ or exp TNF-Related Apoptosis-Inducing Ligand/	196082
28	(anti tumour necrosis factor or anti tumor necrosis factor).mp.	6177
29	(tumor necrosis factor-alpha or tumour necrosis factor-alpha).mp.	189039
30	anti tnf.mp.	12449
31	(tnf antibod$ or tnf alpha antibod$).mp.	2387
32	(tumour necrosis factor antibod$ or tumor necrosis factor antibod$).mp.	161
33	(antitumor necrosis factor or antitumour necrosis factor).mp.	918
34	exp Immunoglobulin Fab Fragments/	29391
35	(infliximab$ or monoclonal antibody cA2).mp.	17256
36	etanercept$.mp.	9583
37	adalimumab$.mp.	10560
38	Cyclosporine/	30456
39	(Ciclosporin or cyclosporine or cyclosporin).mp.	59498
40	brodalumab.mp.	498
41	ixekizumab.mp.	934

ID	Search term	Result
42	certolizumab.mp.	1554
43	Certolizumab Pegol/	726
44	tildrakizumab.mp.	243
45	bimekizumab.mp.	105
46	risankizumab.mp.	336
47	**or/1-46**	**777987**
48	deucravacitinib.mp.	45
49	TYK2 Kinase/	609
50	(TYK2 or tyrosine kinase 2).ti,ab.	2131
51	**or/48-50**	**2252**
52	psoria$.ti,ab.	57249
53	exp Psoriasis/	46876
54	palmoplantar$ pustulosis.ti,ab.	664
55	pustulosis palmaris et plantaris.ti,ab.	173
56	(pustulosis and palms and soles).ti,ab.	107
57	**or/52-56**	**63986**
58	exp Cardiovascular Diseases/	2676632
59	exp Coronary Artery Bypass/	56307
60	cardiometabolic risk factors/	941
61	exp Obesity/	253622
62	Metabolic Syndrome/	37466
63	exp Dyslipidemias/	86142
64	(hypercholesterol* or hypercholesterin* or hypertriglycerid* or dyslipid* or obesity or obese or hyperlipoprotein* or Dyslipoprotein*).ti,ab.	432416
65	(hypertens* or ((high or elevated) and blood pressure)).ti,ab.	549372
66	(myocard* or coronar* or ischemi* or ischaemi* or cardial* or cardiac* or cardio* or heart* or infarct* or STEMI or NSTEMI).ti,ab.	2452291
67	(Arteriosclero* or Atherosclero*).ti,ab.	183237
68	(metabolic adj6 (syndrom* or risk*)).ti,ab.	78073
69	**or/58-68**	**4320576**
70	47 and 57 and 69	1583
71	("201910*" or "201911*" or "201912*" or "2020*" or "2021*" or "2022*" or "2023*").dt.	5035956
72	70 and 71	417
73	51 and 57 and 69	8
74	72 or 73	421
75	meta analysis.mp,pt. or review.pt. or search:.tw.	3569837
76	**74 and 75**	**126**
77	**74 not 76**	**295**

6 Depressionen

6.1 Methods

6.1.1 Inclusion criteria

Table 27 Screening criteria (depression)

	Criteria
Patients	adult patients with a clinical diagnosis of psoriasis and depression
Intervention	acitretin, apremilast, ciclosporin, fumarates, methotrexate TNFi: adalimumab, etanercept, certolizumab pegol, infliximab; anti-IL12/23: ustekinumab; anti-IL17: bimekizumab, brodalumab, ixekizumab, secukinumab; anti-IL23: guselkumab, risankizumab, tildrakizumab; tyrosine kinase 2 (TYK2) inhibitor: deucravacitinib (new)
Comparator	Comparisons with another included drug and/or placebo
Outcomes	▪ risk to develop depression ▪ risk of suicide ideation and completed suicide
Study Design	Inclusion: Primary: Systematic reviews

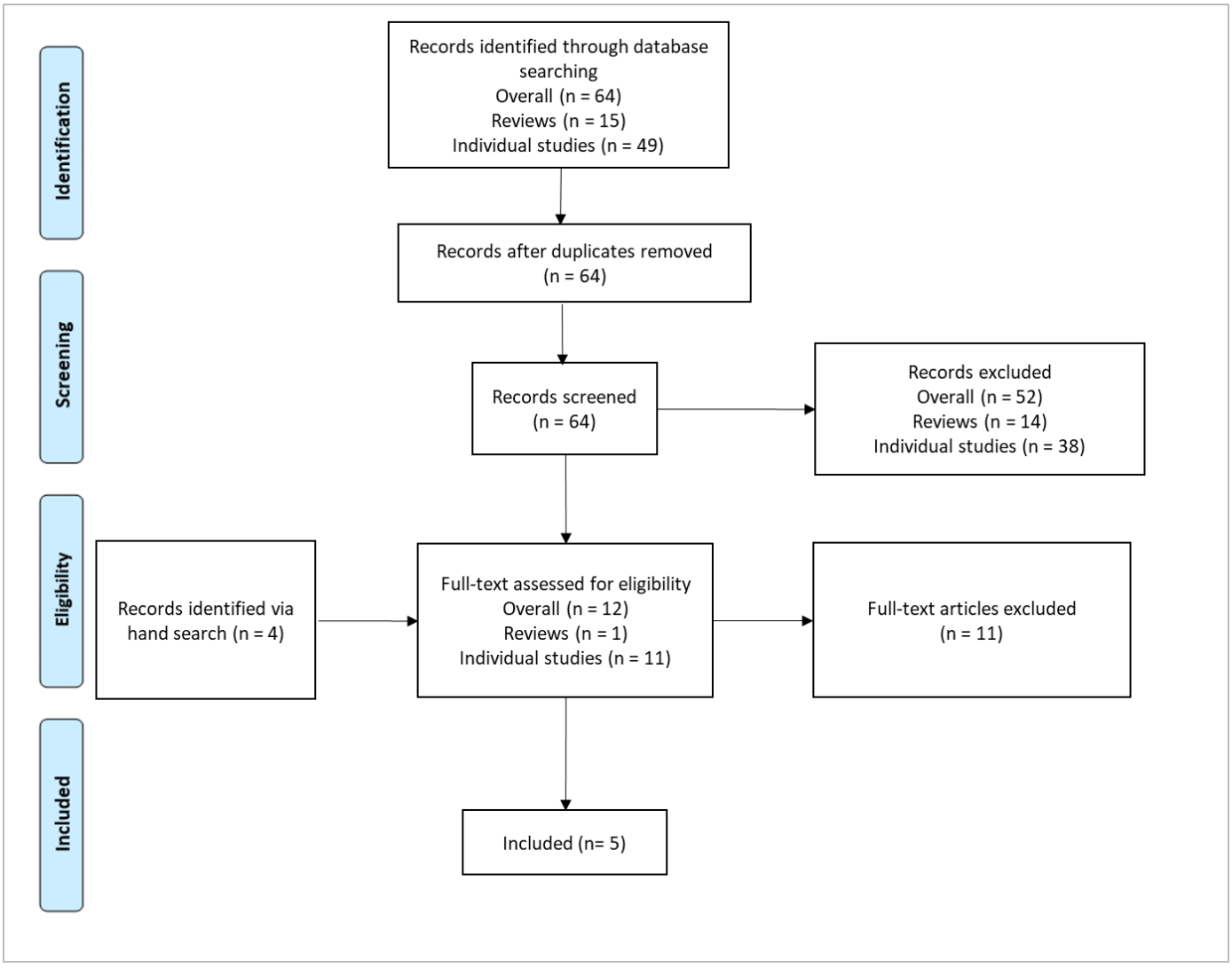
	Criteria
	Secondary: randomized controlled trials, clinical trials (with and without comparison group), cohort studies, case control studies and cross sectional studies, case series, case reports, retrospective studies Exclusion: non-systematic reviews, letter, comments

6.1.2 Information source and screening process

The search strategy was updated and the database MEDLINE via Ovid from 1946 was searched for the period October 2019 to 17 January 2023 (see Table 28). One methodologist conducted a topic specific but non-systematic screening. The authors of the chapter then screened included full texts based on the above listed eligibility criteria.

1.3. Results

Figure 6 Flow chart (depression)



1.4. Appendix: Search strategy

Filter for detecting systematic reviews: Wong SSL, Wilczynski NL, Haynes RB. Comparison of top-performing search strategies for detecting clinically sound treatment studies and systematic reviews in MEDLINE and EMBASE. J Med Libr Assoc 2006; 94(4): 451-455. https://pubmed.ncbi.nlm.nih.gov/17082841/ (Strategies minimizing difference between sensitivity and specificity)

Ressource: Ovid MEDLINE(R) ALL <1946 to January 17, 2023>

Table 28 search strategy (depression)

ID	Search term	Result
1	depression*.ti,ab.	403831
2	depress*.ti,ab.	541248
3	Depression/	146458
4	exp Depressive Disorder/	120214
5	**or/1-4**	**585928**
6	exp Methotrexate/	40879
7	methotrexate$.mp.	59566
8	amethopterin.mp.	401
9	mtx.ti,ab.	14592
10	exp Fumarates/	5316
11	(fumar$ and esters).mp.	468
12	dimethylfumarate.mp.	205
13	fae.ti,ab.	1021
14	dmf.ti,ab.	9700
15	fumarate$1.mp.	20781
16	Etretinate/	1352
17	Acitretin/	1286
18	((oral or orally or systemic) and retinoid$).ti,ab.	2931
19	Isotretinoin/	3942
20	isotretinoin.ti,ab.	3695
21	etretin$.mp.	1745
22	acitretin.mp.	2023
23	Retinoids/	6308
24	Ustekinumab.mp.	2952
25	secukinumab.mp.	1851
26	apremilast.mp.	1027
27	guselkumab.mp.	524
28	exp antibodies, monoclonal/	271864
29	monoclonal antibod$.mp.	204408
30	exp Interleukin-23/ or exp Interleukin-12/ or Interleukin-17/	30052
31	exp Interleukin-12 Subunit p40/ or p40 subunit.mp.	1901
32	exp Tumor Necrosis Factors/ or exp Tumor Necrosis Factor-alpha/ or exp Receptors, Tumor Necrosis Factor, Type II/ or exp Receptors, Tumor Necrosis Factor/ or exp Receptors, Tumor Necrosis Factor, Type I/ or exp TNF-Related Apoptosis-Inducing Ligand/	196082
33	(anti tumour necrosis factor or anti tumor necrosis factor).mp.	6177
34	(tumor necrosis factor-alpha or tumour necrosis factor-alpha).mp.	189039

ID	Search term	Result
35	anti tnf.mp.	12449
36	(tnf antibod$ or tnf alpha antibod$).mp.	2387
37	(tumour necrosis factor antibod$ or tumor necrosis factor antibod$).mp.	161
38	(antitumor necrosis factor or antitumour necrosis factor).mp.	918
39	exp Immunoglobulin Fab Fragments/	29391
40	(infliximab$ or monoclonal antibody cA2).mp.	17256
41	etanercept$.mp.	9583
42	adalimumab$.mp.	10560
43	Cyclosporine/	30456
44	(Ciclosporin or cyclosporine or cyclosporin).mp.	59498
45	brodalumab.mp.	498
46	ixekizumab.mp.	934
47	certolizumab.mp.	1554
48	Certolizumab Pegol/	726
49	tildrakizumab.mp.	243
50	bimekizumab.mp.	105
51	risankizumab.mp.	336
52	**or/6-51**	**777987**
53	exp Psoriasis/	46876
54	psoria*.ti,ab.	57249
55	palmoplantar$ pustulosis.ti,ab.	664
56	pustulosis palmaris et plantaris.ti,ab.	173
57	(pustulosis and palms and soles).ti,ab.	107
58	**or/53-57**	**63986**
59	deucravacitinib.mp.	45
60	TYK2 Kinase/	609
61	(TYK2 or tyrosine kinase 2).ti,ab.	2131
62	**or/59-61**	**2252**
63	5 and 52 and 58	206
64	5 and 58 and 62	0
65	("201910*" or "201911*" or "201912*" or "2020*" or "2021*" or "2022*" or "2023*").dt.	5035956
66	63 and 65	64
67	meta analysis.mp,pt. or review.pt. or search:.tw.	3569837
68	**66 and 67**	**15**
69	**66 not 68**	**49**

7 Krebserkrankungen

7.1 Methods

7.1.1 Inclusion criteria

Table 29 Screening criteria (cancer)

	Criteria
Patients	adult patients with a clinical diagnosis of psoriasis and ▪ No malignancy in history ▪ pre-cancer (such as cervical dysplasia, colonic polyps or Barrett’s esophagus),

	Criteria
	▪ low risk cancer (NMSC, cancer with a long period of non-recurrence, usually defined as more than 5 years), ▪ high-risk cancer (active cancer, recent aggressive cancer), ▪ or history of malignancy
Intervention	acitretin, apremilast, ciclosporin, fumarates, methotrexate anti TNF alpha: adalimumab, etanercept, certolizumab pegol, infliximab; anti-IL12/23: ustekinumab; anti-IL17: bimekizumab, brodalumab, ixekizumab, secukinumab; anti-IL23: guselkumab, risankizumab, tildrakizumab; tyrosine kinase 2 (TYK2) inhibitor: deucravacitinib (new)
Comparator	Comparisons with another included drug and/or placebo
Outcomes	Incidence of cancer Risk of cancer recurrence Other safety concerns
Study Design	Inclusion: Systematic reviews, guidelines Exclusion: randomized controlled trials, clinical trials (with and without comparison group), cohort studies, case control studies and cross sectional studies, case series, case reports, retrospective studies with less than 100 patients, non-systematic reviews, letter, comments

7.1.2 Information source and screening process

The search strategy was updated and the database MEDLINE via Ovid (from 1946) was searched for the period September 2019 to 11 January 2023 (see Table 30). One methodologist conducted a topic specific but non-systematic screening. Afterwards, the authors of the chapter screened full texts based on the above listed eligibility criteria.

7.1.3 Documented search for guidelines on psoriasis and cancer

We did not identify guidelines with our search in PubMed. Guidelines, which were cited in the previous version of the EuroGuiDerm Psoriasis, have not been updated yet. Therefore, we conducted a documented search in guideline databases and interdisciplinary guideline providers.

7.1.3.1 Update search for guidelines already cited in previous version (February 2022)

Search date: 16 January 2023

Amatore F, Villani AP, Tauber M, et al. French guidelines on the use of systemic treatments for moderate-to-severe psoriasis in adults. J Eur Acad Dermatol Venereol 2019;33(3):464-83. doi: 10.1111/jdv.15340 [published Online First: 02/22]

- Search in https://www.sfdermato.org/page-24-recommandations: no update identified

Holroyd CR, Seth R, Bukhari M, et al. The British Society for Rheumatology biologic DMARD safety guidelines in inflammatory arthritis. Rheumatology 2018;58(2):e3-e42. doi: 10.1093/rheumatology/key208

- Search in https://www.rheumatology.org.uk/practice-quality/guidelines: no update identified

Lewinsohn DM, Leonard MK, LoBue PA et al. Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children. Clin Infect Dis 2017; 64: 111-5

- Search in https://www.cdc.gov/tb/publications/guidelines/testing.htm: no update identified

7.1.3.2 Documented guideline search

7.1.3.2.1 Search terms

Psoriasis, inflammatory bowel disease, rheumatoid arthritis, ankylosing spondylitis, psoriasis arthritis

Explanation: A search for other disease than psoriasis was conducted to identify information on a possible association between drugs, prescribed for different conditions, and the risk of malignancy.

7.1.3.2.2 Search date

18 January 2023

7.1.3.2.3 Limits

Published after 2019

7.1.3.2.4 List of guideline databases and interdisciplinary guideline providers

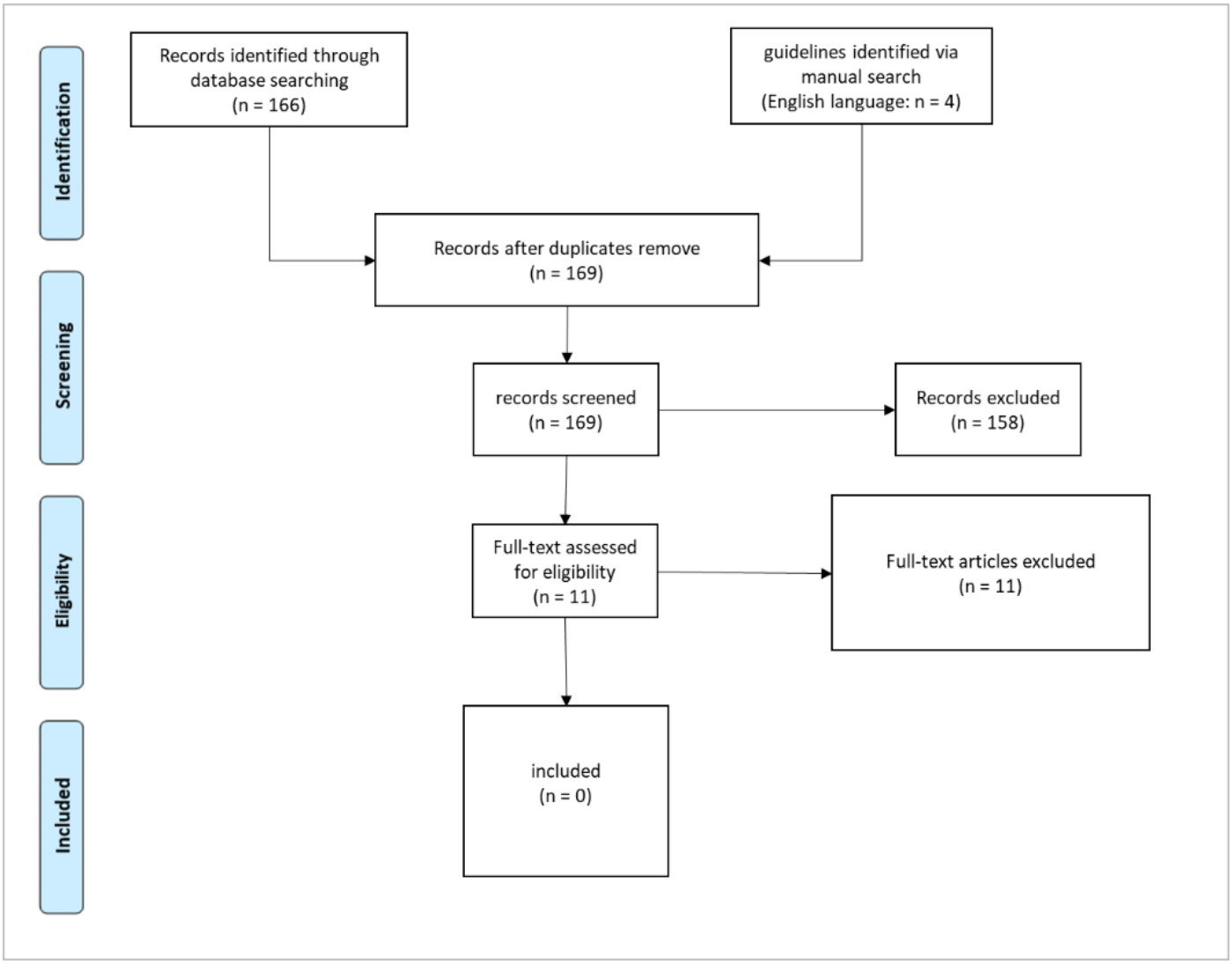
- Guidelines Central, US
    - Hits per search term: 17/ 17/ 10/ 6 /7; 3 included:
    - Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with awareness and attention to comorbidities (https://www.jaad.org/article/S0190-9622(18)33002-0/fulltext), p. 1098
    - Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics (https://www.jaad.org/article/S0190-9622(18)33001-9/fulltext), e.g. pp. 1043, 1048, 1053, 1054
    - Joint American Academy of Dermatology - National Psoriasis Foundation guidelines of care for the management of psoriasis with systemic nonbiologic therapies (https://pubmed.ncbi.nlm.nih.gov/32119894/), e.g. pp 1463, 1472
- Tripdatabase (UK)
    - Only search terms psoriasis (n=99, 0 included) and psoriasis arthritis (n=57, 1 included):
    - Brazilian Society of Rheumatology 2020 guidelines for psoriatic arthritis (https://advancesinrheumatology.biomedcentral.com/articles/10.1186/s42358-021-00219-y), p. 20, ref. [196]
- Canadian Medical Association (CPG Infobase), CA
    - 0 hits for all search terms
- ECRI-Guidelines Trust, US
    - 3 hits, 0 included
- Guidelines International Network (GIN), AUS
    - 27 hits, 0 included
- National Institute for Health and Clinical Excellence (NICE), GB
    - Hits per search term: 8/ 20/ 14/ 3/ 9; 0 included
- Scottish Intercollegiate Guidelines Network (SIGN)

- List of guidelines checked, 0 included

- In German language only: Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF), DE
  - Total number of hits not presented; list of hits checked; 3 included
  - S3-Leitlinie Colitis ulcerosa (https://register.awmf.org/de/leitlinien/detail/021-009); p. 32/85; ref. [358]
  - S3-Leitlinie Diagnostik und Therapie des Morbus Crohn (https://register.awmf.org/de/leitlinien/detail/021-004) P. 38/87; ref. [490]; p. 56/87 ref. [750-753]
  - S3-Leitlinie Management der frühen rheumatoiden Arthritis (https://register.awmf.org/de/leitlinien/detail/060-002) P. 40/123 ref. [209, 221, 222, 225-228, 229-231]

1.5. Results

Figure 7 Flow chart (cancer)



1.6. Appendix: Search strategy

Filter for detecting systematic reviews: Wong SSL, Wilczynski NL, Haynes RB. Comparison of top-performing search strategies for detecting clinically sound treatment studies and systematic reviews in MEDLINE and EMBASE. J Med Libr Assoc 2006; 94(4): 451-455. https://pubmed.ncbi.nlm.nih.gov/17082841/ (High specificity strategy)

Filter for detecting guidelines: Lunny C, Salzwedel D M, Liu T, Ramasubbu C, Gerrish S, Puil L, Mintzes B, Wright J M. Validation of five search filters for retrieval of clinical practice guidelines produced low precision. J Clin Epidemiol 2019. 117:109-116. https://pubmed.ncbi.nlm.nih.gov/31610216/ (CADTH narrow – see Publication appendix 1)

Ressource: Ovid MEDLINE(R) ALL <1946 to January 11, 2023>

Table 30 Search strategy (cancer)

ID	Search term	Result
1	exp Neoplasms/	3779499
2	neoplasm.ti,ab.	64174
3	malignan*.ti,ab.	663610
4	malignom*.ti,ab.	796
5	cancer*.ti,ab.	2137123
6	lymphom*.ti,ab.	200257
7	carcinom*.ti,ab.	743752
8	tumor*.ti,ab.	1685080
9	tumour*.ti,ab.	298690
10	**or/1-9**	**4930505**
11	exp Psoriasis/	46840
12	Psoria*.ti,ab.	57169
13	palmoplantar$ pustulosis.ti,ab.	664
14	pustulosis palmaris et plantaris.ti,ab.	173
15	(pustulosis and palms and soles).ti,ab.	107
16	**or/11-15**	**63906**
17	10 and 16	10014
18	("201909*" or "201910*" or "201911*" or "201912*" or "2020*" or "2021*" or "2022*" or "2023*").dt.	5093719
19	17 and 18	1802
20	cochrane database of systematic reviews.jn. or search.tw. or meta analysis.pt. or MEDLINE.tw. or systematic review.tw.	657794
21	(guideline or practice guideline or consensus development conference or consensus development conference, NIH).pt. or (guideline* or standards or consensus* or recommendat*).ti. or (practice parameter* or position statement* or policy statement* or CPG or CPGs or best practice*).ti. or (care adj2 (path or paths or pathway or pathways or map or maps or plan or plans or standard)).ti. or ((critical or clinical or practice) adj2 (path or paths or pathway or pathways or protocol*)).ti. or (algorithm* and (pharmacotherap* or chemotherap* or chemotreatment* or therap* or treatment* or intervention*)).ti. or (algorithm* and (screening or examination or test or tested or testing or assessment* or diagnosis or diagnoses or diagnosed or diagnosing)).ti.	239503
22	**20 or 21**	**883463**
23	**19 and 22**	**166**

8 Schwangerschaft

8.1 Methods

8.1.1 Research question

How should psoriasis patients with a wish for pregnancy in the near future or who are pregnant be managed?

8.1.2 Screening criteria

Table 31 Screening criteria (pregnancy)

	Inclusion criteria	Exclusion criteria
Patients	1. Adult patients with psoriasis or psoriasis arthritis with wish for child (maternal, paternal) or who are pregnant 2. Adult patients, regardless of the type of autoimmune disease, who are receiving the treatments listed below with wish for child (maternal, paternal) or who are pregnant	
Intervention	**Maternal population - conventional systemic treatment:** ciclosporin, fumarates **paternal population - conventional systemic treatment:** ciclosporin, fumarates, acitretin, MTX **both populations - biologicals:** anti TNF alpha: adalimumab, etanercept, certolizumab pegol, infliximab anti-IL12/23: ustekinumab anti-IL17: bimekizumab, brodalumab, ixekizumab, secukinumab anti-IL23: guselkumab, risankizumab, tildrakizumab **Both populations - small molecules:** PDE4i: Apremilast tyrosine kinase 2 (TYK2) inhibitor: deucravacitinib (new, no filter for publication date applied))	**maternal population:** MTX and retinoids (rationale: No need to investigate further as contraindications are clear)
Comparator (if possible)	another included drug and/or placebo	
Outcomes	Maternal and fetal health outcomes Male and female fertility	
Study Design	Systematic reviews on human studies	Systematic reviews on animal studies non-systematic reviews primary studies in-vitro studies expert opinions without primary data

8.1.3 Information source and screening process

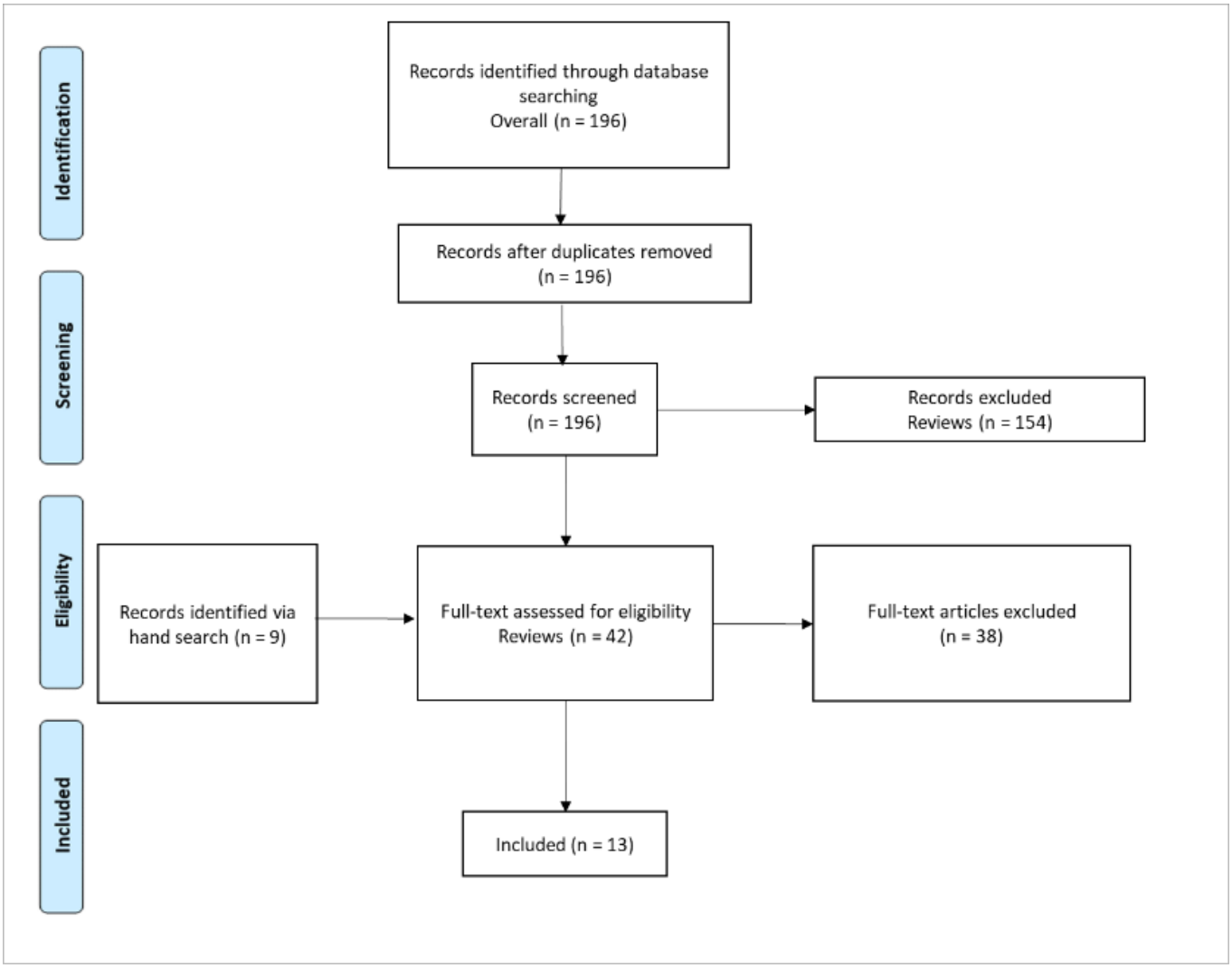
We conducted a search to identify new systematic reviews that have become available since the last guideline [83] was published. We searched MEDLINE via Ovid.

The search strategy included text words and MeSH terms for: pregnancy, fertility, maternal and paternal care, psoriasis, systemic treatments and use of biologics. We restricted the search to the article types ‘systematic review’ and ‘meta-analysis’ and to publication dates from September 2019 onwards, as shown below (see Table 34).

One methodologist conducted a topic-specific but non-systematic screening. The chapter authors then screened the included full texts based on the eligibility criteria, listed above.

1.7. Results

Figure 8 Flow chart (pregnancy)



8.1.4 Full text screening and quality appraisal

8.1.4.1 Explanations

One methodologist assessed the methodological quality of the systematic reviews (SRs) using the AMSTAR-2 tool [84]. It can be rated as high, moderate, low and critically low.

The tool [84] contains 16 items, 7 of which are predefined as critical. If 1 of these critical items is not fulfilled, the quality of the SR can only be rated as low. If ≥ 2 critical items are not fulfilled, the SR is rated as critically low.

Table 32 AMSTAR-2 results

Quality	High	Moderate	Low	Critically low	Retracted/ off topic/ additional value unclear
Number (n/N)	1/42	0	5/42	33/42	3/42

3 of the low rated SRs were conducted for paternal population, one in mothers with PsA and one in mothers with atopic diseases, treated with Omalizumab and Rituximab.

In case the information from low quality SRs is not sufficient to process the chapter and a critically low SR has to be included, we have attempted to distinguish by the number of critical items not met and to identify critically low SRs whose methodological quality appears to be just acceptable:

Table 33 Quality categories

Category	Explanation	Frequency
1	low quality or better	6
2	Critically low quality with 2 critical items not fulfilled	4

Category	Explanation	Frequency
3	Critically low quality with > 2 critical items not fulfilled	23
4	Critically low quality and Item 4 (comprehensive search) not fulfilled	6

1.8. Appendix: Search strategy

Filter for identification of systematic reviews and meta-analysis: *adapted* according to Wong et al., 2006 (high specificity) (https://pubmed.ncbi.nlm.nih.gov/17082841/)

Ovid MEDLINE(R) ALL <1946 to May 04, 2023>

Table 34 Search strategy (pregnancy)

No.	Search term	Results	Comment
1	exp Methotrexate/	41173	Relevant for paternal population
2	methotrexate$.mp.	60167	
3	amethopterin.mp.	401	
4	mtx.ti,ab.	14821	
5	exp Fumarates/	5371	Relevant for maternal and paternal population
6	(fumar$ and esters).mp.	477	
7	dimethylfumarate.mp.	209	
8	fae.ti,ab.	1035	
9	dmf.ti,ab.	9886	
10	fumarate$1.mp.	21083	
11	Acitretin/	1301	Relevant for paternal population
12	((oral or orally or systemic) and retinoid$).ti,ab.	2962	
13	acitretin.mp.	2052	
14	Retinoids/	6346	
15	Ustekinumab.mp.	3091	Relevant for maternal and paternal population
16	secukinumab.mp.	1918	
17	apremilast.mp.	1057	
18	guselkumab.mp.	567	
19	exp antibodies, monoclonal/	274579	
20	monoclonal antibod$.mp.	206097	
21	exp Interleukin-23/ or exp Interleukin-12/ or Interleukin-17/	30452	
22	exp Interleukin-12 Subunit p40/ or p40 subunit.mp.	1906	
23	exp Tumor Necrosis Factors/ or exp Tumor Necrosis Factor-alpha/ or exp Receptors, Tumor Necrosis Factor, Type II/ or exp Receptors, Tumor Necrosis Factor/ or exp Receptors, Tumor Necrosis Factor, Type I/ or exp TNF-Related Apoptosis-Inducing Ligand/	197732	
24	(anti tumour necrosis factor or anti tumor necrosis factor).mp.	6277	
25	(tumor necrosis factor-alpha or tumour necrosis factor-alpha).mp.	191232	
26	anti tnf.mp.	12600	
27	(tnf antibod$ or tnf alpha antibod$).mp.	2392	
28	(tumour necrosis factor antibod$ or tumor necrosis factor antibod$).mp.	161	
29	(antitumor necrosis factor or antitumour necrosis factor).mp.	934	
30	exp Immunoglobulin Fab Fragments/	29525	
31	(infliximab$ or monoclonal antibody cA2).mp.	17477	
32	etanercept$.mp.	9656	
33	adalimumab$.mp.	10788	
34	Cyclosporine/	30551	
35	(Ciclosporin* or cyclosporin*).mp.	61903	
36	brodalumab.mp.	521	
37	ixekizumab.mp.	981	
38	certolizumab.mp.	1565	
39	Certolizumab Pegol/	728	
40	tildrakizumab.mp.	253	
41	bimekizumab.mp.	116	
42	risankizumab.mp.	370	
43	**or/5-10,15-42**	**723456**	
44	deucravacitinib.mp.	60	Relevant for maternal and paternal population
45	TYK2 Kinase/	626	
46	(TYK2 or tyrosine kinase 2).ti,ab.	2182	
47	**or/44-46**	**2308**	
48	psoria$.ti,ab.	58266	
49	exp Psoriasis/	47550	
50	palmoplantar$ pustulosis.ti,ab.	683	
51	pustulosis palmaris et plantaris.ti,ab.	173	
52	(pustulosis and palms and soles).ti,ab.	113	

No.	Search term	Results	Comment
53	**or/48-52**	**65051**	
54	(pregnan* or gravid* or gestation* or maternal* or mother* or pre-concept* or preconcept* or periconcept* or peri-concept* or antepart* or ante-part* or prepart* or pre-part* or antenatal* or ante-natal* or prenatal* or pre-natal* or inutero or in-utero or intrauterin* or intra-uterin* or f?etal* or f?eto* or f?etus* or embryo* or fertil* or infertil*).ti,ab,kf.	1717938	
55	Pregnant Women/	14127	
56	exp Pregnancy/	1000354	
57	exp Pregnancy Trimesters/	44646	
58	exp Pregnancy Complications/	472218	
59	Maternal Exposure/	11053	
60	Maternal Health/	2271	
61	Preconception Injuries/	54	
62	exp Prenatal Injuries/	34340	
63	Embryo, Mammalian/	51569	
64	exp "Embryonic and Fetal Development"/	309780	
65	exp Fetus/	166832	
66	Infertility, Female/	30893	
67	exp Fertility/	45938	
68	exp Fertilization/	25118	
69	**or/54-68**	**2239569**	
70	Paternal Exposure/	1194	
71	exp Infertility, Male/	31020	
72	exp Spermatozoa/	73332	
73	exp Semen Analysis/	29099	
74	exp Spermatogenesis/	22072	
75	exp Fathers/	10876	
76	exp Fertility/	45938	
77	exp Fertilization/	25118	
78	(sperm* or semen* or father* or paternal* or paternit* or fertil* or infertil*).ti,ab,kf.	441343	
79	or/70-78	473675	
80	cochrane database of systematic reviews.jn. or search:.tw. or meta analysis.mp,pt. or MEDLINE.tw. or systematic review.tw.	823840	Adapted filter for systematic reviews and meta-analyses
81	("201909*" or "201910*" or "201911*" or "201912*" or "2020*" or "2021*" or "2022*" or "2023*").dt.	5585359	Time filter
82	exp animals/ not humans.sh.	5118239	Filter to exclude animal studies
83	43 or 53	773337	
84	69 and 83	40637	
85	81 and 84	4508	
86	47 and 69	114	
87	85 or 86	4620	**Maternal population**
88	or/1-42,53	829616	
89	79 and 88	6616	
90	81 and 89	869	
91	47 and 79	19	
92	90 or 91	888	**Paternal population**
93	87 or 92	5003	Both populations
94	93 not 82	3742	Both populations without animal studies
95	**94 and 80**	**196**	**Final result: Aggregated evidence on both populations**

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