

What's new in psoriasis treatment?

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Title

What's new in psoriasis treatment? An analysis of systematic reviews published in 2015.

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Abstract

This review provides a summary of key findings from 27 systematic reviews of 51 articles first published or indexed during 2015, focusing on the treatment of psoriasis as well as precision medicine in psoriasis. Evidence supports weight loss interventions by dieting and exercise for the improvement in disease severity in overweight and obese patients with psoriasis. No significant increased risk of serious infections were reported for the biologic therapies adalimumab, etanercept and ustekinumab when compared with appropriate comparators. Evidence could not provide reliable estimates of rare adverse events, underscoring the need for large prospective registries. Polymorphisms in the tumour necrosis factor (TNF) alpha gene may confer improved responses to TNF inhibitor (TNFI) therapy, but studies to date lack power to detect true association. From limited available evidence, multidisciplinary management is both more effective and more satisfactory for patients with psoriasis and psoriatic arthritis than conventional consultations. This summary of reviews provides a succinct guide for clinicians and patients wishing to remain up-to-date with high quality evidence for the treatment of psoriasis.

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Background

The aim of this evidence update is to highlight the clinical findings from systematic reviews (SRs) published during 2015 on the treatment of psoriasis as well as precision medicine in psoriasis. Prior evidence updates on psoriasis demonstrate the details of the search methods used [<http://www.nottingham.ac.uk/research/groups/cebd/resources/annual-evidence-updates.aspx>].

Biologic therapies

Safety of biologic therapies

In a SR of 19 Randomised controlled trials (RCTs) of the safety of adalimumab, etanercept and ustekinumab for moderate-to-severe psoriasis, Sorenson et al. did not show an increase in adverse events (AEs) such as serious infection when compared with appropriate comparators ¹. However, the RCT evidence was too imprecise to provide reliable estimates of rare adverse events, underscoring the need for large prospective registries such as the British Association of Dermatologists Biologics Intervention Register (BADBIR) ². In a SR of 13 RCTs of the safety of adalimumab, etanercept and ustekinumab, Messori et al. ³ ranked biologics by risk of any serious AE and any infections. None of the indirect comparisons between active agents reached statistical significance, but for the end-point of any serious AE, ustekinumab ranked first (i.e. safest). For the end-point of infectious AE, low-dose etanercept ranked better than other therapies.

Efficacy of biologic agents

Secukinumab is a human monoclonal antibody targeting interleukin (IL)-17A. A SR of eight RCTs, Xiong et al. reported secukinumab to be highly effective compared with placebo at 12

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weeks of therapy (Psoriasis Area and Severity Index reduction of 75% [PASI 75]; 150mg dose schedule odds ratio 49.25, statistically significant compared to placebo) ⁴. The results of the meta analysis (MA) reported no statistically significant increase in the incidence of SAEs with secukinumab therapy compared to placebo at 12 weeks of therapy, a finding to be anticipated given clinical trial powering for efficacy and 12 week primary end point.

Efficacy and safety of biosimilars

A SR by Nast et al. ⁵ identified no trial data on biosimilar use in patients with psoriasis but emphasised that RCTs of biosimilars of adalimumab, etanercept and infliximab were ongoing.

Biologics in the paediatric population

A Cochrane systematic review of the efficacy and safety of the TNFI agents for paediatric psoriasis ⁶ found only one 12-week randomised, double-blind, placebo-controlled RCT of etanercept use in patients (age 4-17, median 13) with severe psoriasis suitable for inclusion ⁷. At week 12, PASI 75 was reached by 57% of participants taking etanercept versus 11% receiving placebo achieved PASI 75 (RR 4.95, CI 2.83-8.65) with an increase in non-serious AEs. This single trial meant that the authors could not make recommendations on the use of TNFI in the paediatric population but drew attention to five further relevant trials in progress.

Biologic agent drug pipeline

A SR of the evidence for brodalumab, a monoclonal antibody directed against the IL-17 receptor highlighted promising efficacy of its use in moderate to severe psoriasis in Phase III

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of clinical trials⁸, however its clinical trial programme was subsequently stopped for evaluation of an increase in suicidality amongst study participants.

Oral systemic therapies

Methotrexate

Conway et al. performed a SR to evaluate the relative risk of pulmonary disease in patients treated with methotrexate (MTX)⁹. Evaluation of seven studies (in patients with psoriasis, psoriatic arthritis (PsA) and inflammatory bowel disease) reported no increased risk of adverse respiratory events (RR 1.03, 95% CI 0.90-1.17), respiratory infections (RR 1.20, 95% CI 0.88-1.19) or non-infectious respiratory events (1.02, 95% CI 0.58-1.96) when treated with oral MTX (up to 52 weeks). Furthermore, Conway et al. performed a SR to evaluate the relative risk and severity of liver disease among patients treated with MTX (for psoriasis, PsA, rheumatoid arthritis and inflammatory bowel disease). In evidence from 32 studies (only two of which evaluated cohorts of patients with psoriasis) the authors reported that MTX use was associated with increased risk of elevated liver transaminase, but not with increased risk of liver failure, cirrhosis or death¹⁰.

Fumaric acid esters

Oral fumaric acid esters are commonly used in the treatment of moderate to severe psoriasis. A SR of fumaric acid ester use in psoriasis identified six RCTs meeting inclusion criteria¹¹. The MA, which only included two studies, reported the number of participants attaining PASI 50 was greater with fumaric acid ester treatment than with placebo (RR 4.55 95% CI 2.8-7.4, $p < 0.001$). The authors acknowledged the low quality of the evidence from

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the included studies and highlighted inadequate reporting of AE, which should be based on the Consolidated Standards of Reporting Trials ¹².

Maintenance of response to systemic and biologic treatments

In a SR of 25 studies of psoriasis therapies, Nast et al. reported pooled risk ratios for achieving PASI 75 with systemic and biologic therapies for psoriasis which comprised; infliximab (13.07, 95% CI 8.06-19.87), secukinumab (11.97, 95% CI 8.83-16.23), ustekinumab (11.39, 95% CI 8.94-14.51), adalimumab (8.92, 95% CI 6.33-12.57), etanercept (8.39, 95% CI 6.74-10.45) and apremilast (5.83, 95% CI 2.58-13.17) at 24 weeks of treatment ¹³. Whilst highlighting the crucial point that effective long-term and safe strategies are required for the effective management of this chronic disease, the conclusions are limited since the definition of long-term therapy was only 24 weeks.

A further SR aimed to evaluate long-term treatment success through the assessment of rates of maintaining treatment response after successful induction therapy with either systemic or biologic therapy for patients with psoriasis ¹⁴. High quality data on ustekinumab therapy were omitted since patients in Phase III studies were re-randomised following induction at nine months rather than the authors' chosen cut off of six months. In a SR of 19 studies, conclusions including the suggestion that ciclosporin both at 5mg kg⁻¹ twice weekly or 3 mg kg⁻¹ daily is effective in maintenance were of limited clinical value.

Topical therapies

In a SR of 60 studies, Jacobi et al. highlighted the lack of well-designed studies to evaluate the use of topical treatments as adjuvant therapy in chronic plaque psoriasis ¹⁵. The authors reported that regular use of emollients may reduce scaling and improve itch in patients with

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chronic plaque psoriasis, but concluded that there was no evidence to support their role in clearance of disease. Regarding keratolytic agents, salicylic acid was the best studied compound, and results supported its use as monotherapy in scalp disease (as per NICE guidance¹⁶).

Screening, monitoring, adherence, multidisciplinary management and comorbidities

Screening and monitoring

Ahn et al., highlighted the lack of high quality evidence to support the use of screening and monitoring tests currently in practice for those prescribing systemic and biologic therapies for patients with psoriasis and PsA ¹⁷. The authors reported increasing evidence to support hepatitis B virus (HBV) testing given the possibility of refinement of management options based on specific HBV serology.

Adherence

It is well recognized that non-adherence to medication is common in the management of chronic plaque psoriasis ¹⁸ and successful interventions to improve adherence would therefore be of benefit to this patient population. Depont et al. ¹⁹ conducted a SR of interventions to improve adherence in patients with any immune-mediated inflammatory disease (IMID) but of the 15 eligible studies, only one pilot study of patients with psoriasis ²⁰ was included, thus the authors were unable to make conclusions regarding the effectiveness of interventions in this cohort. Vangeli et al. ²¹ considered the factors affecting non-adherence in the treatment of IMID in an SR that analysed 73 studies, including 11 studies of patients with psoriasis. The authors reported the strongest evidence for non-adherence across diseases related to psychosocial factors, yet these were least likely to be evaluated in

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psoriasis studies. The authors concluded that addressing treatment concerns, increasing understanding of treatment necessity and enhancing the relationship with the healthcare provider might facilitate adherence across diseases.

Cardiovascular risk in patients with psoriasis

Roubille et al. assessed the association between the use of TNFI, MTX, non-steroidal anti-inflammatory drugs and corticosteroids and cardiovascular events (CVE) ²². A total of six studies of patients with psoriasis and/or PsA met inclusion criteria, but results did not distinguish between those with either skin or joint disease alone, and the term “systemic therapy” included studies on biologic therapy with TNFI as well as systemic agents e.g. MTX. The authors reported that systemic therapy versus no therapy or topical therapy was associated with a significantly decreased risk of all CVEs in psoriasis and/or PsA (RR 0.75; 95% CI 0.63 to 0.91; p=0.003).

Another SR considered whether use of oral MTX, in the treatment of either psoriasis or rheumatoid arthritis, conferred protection against CVEs ²³. The authors extrapolated their findings to conclude that MTX use was associated with lower rates of cardiovascular disease in patients with ‘chronic inflammation’, but no comment could be made regarding patients with psoriasis since the meta-analysis included only one historic study of patients with chronic plaque disease ²⁴.

Patient reported outcomes

Kitchen et al. ²⁵ considered the use of patient reported outcome measures (PROMs) in relation to guidelines and clinical practice, providing a comprehensive and comprehensible review of the 16 psoriasis-specific English language PROMs in use. The authors concluded

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that no single PROM has adequate evidence of validity, reliability and sensitivity to change or fully captures the emotional well-being and coping strategies of patients and suggested a new assessment for psoriasis in clinical practice may be warranted.

Multidisciplinary management

Cobo-Ibanez et al. ²⁶ aimed to analyse the efficacy and satisfaction of multidisciplinary dermatology-rheumatology management for patients with psoriasis and PsA. Their SR identified two case series with a retrospective analysis and one descriptive study, and concluded that from limited available evidence, multidisciplinary management is both more effective and more satisfactory for patients with psoriasis and PsA than conventional consultations.

Other treatments/interventions

Weight loss interventions

A MA aimed to evaluate the association between weight loss interventions by dieting and exercise and improvement in disease severity in overweight and obese patients with psoriasis ²⁷. A total of seven RCTs involving 878 participants, 443 who were overweight or obese (body mass index [BMI] $\geq 25\text{kg m}^{-2}$), were reviewed and five were included in a MA. The authors reported a pooled odds ratio of achieving PASI 75 in participants receiving weight loss intervention versus control in four of the studies as 2.92 (95% CI 1.39-6.13, $p = 0.005$), with a pooled mean difference across three studies in reduction of PASI score in participants receiving weight loss intervention versus control by -2.49 (95% CI -3.90- -1.08, $p = 0.004$).

Educational interventions for improving quality of life

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A SR by Pickett et al.²⁸ considered the cost-effectiveness of educational interventions for improving health-related quality of life in patients with chronic inflammatory skin disease. Studies evaluated interventions that varied in terms of delivery modes (including group, face-to-face, online and text messaging), topics covered, provider and duration and intensity of education and the poor quality of the low number of included studies prevented conclusions on support for clinical effectiveness or cost-effectiveness of these interventions.

Alternative therapies for psoriasis

Aloe vera is a species of succulent plant with a history of use as a topical application for skin disease. An SR of aloe vera for psoriasis that was limited to English language studies found four RCTs of low to moderate quality and was not able to come to any firm conclusions on efficacy despite the lack of significant AEs²⁹.

A SR to evaluate the efficacy and safety of acupuncture therapies for psoriasis identified six studies on a diverse range of interventions such as acupuncture, bloodletting and moxibustion (a form of heat therapy using a preparation of Artemisia leaves)³⁰. Conflicting evidence from the highly heterogeneous studies and a global failure to report on health-related quality of life meant there was insufficient evidence to support for the use of acupuncture therapies in the treatment of psoriasis.

The efficacy of Chinese herbal medicine, when used in conjunction with narrowband ultraviolet B phototherapy (NB-UVB), in the treatment of psoriasis was assessed in an SR by Yang et al³¹. A total of 18 RCTs were included and involved 1416 participants with psoriasis. Herbs with a high content of psoralens were not used in included studies, and no two studies used the same herbal formula. The mean percentage of participants who achieved

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the outcome of PASI 60 at treatment completion was 83% in the combination group and 59% in the NB-UVB group (RR 1.35, 95% CI 1.26-45 p < 0.01) but quality of evidence was low according to Grading of Recommendations, Assessment, Development and Evaluations (GRADE) with common problems including a very short follow up of study participants.

Precision medicine

Precision medicine refers to the tailored selection of treatment for an individual, based on factors such as their genetic makeup. Huang et al.³² provided a systematic review of the literature concerning the role of small non-coding RNAs (miRNAs) that impact cellular function and whose role has been demonstrated to be important in skin homeostasis and inflammation³³. They considered that given the expanding field of personalised medicine, miRNAs might present the opportunity for the development of biomarkers of disease severity and treatment response.

Song et al.³⁴ considered the role of TNF-alpha polymorphisms in the response to TNFI therapy across IMIDs. The systematic review identified ten papers, of which only one³⁵ analysed a cohort of patients with psoriasis, thus their conclusion that White patients carrying specific TNF-alpha polymorphisms demonstrate improved responses to TNFI therapy has limited generalisability. Chen et al.³⁶ also included studies by Vasilopoulos et al.³⁵, along with Gonzalez-Lara et al.³⁷ in their systematic review and meta-analysis of TNF receptor superfamily member 1B polymorphisms in the prediction of TNFI therapy. They concluded that the presence of polymorphisms that were evaluated did not allow prediction of response. Both of these studies identified commonalities across IMIDs but their conclusions were hampered by their inclusion of heterogeneous studies in terms of patient

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phenotyping and treatment types (multiple biologic therapies) and thus their conclusions were of limited value.

Conclusion

There has been a great increase in the number of SR's in the field of psoriasis since our last evidence based update in 2010, with a large increase in those related to biologic therapies, which have transformed our management of patients with moderate to severe disease.

Focus on long-term management of patients with psoriasis with biologic therapy and their use in cohorts including the paediatric population demonstrates progress in their use. There is a trend towards synthesis of evidence for patients with psoriasis and those across IMID.

As well as relative merits, we must ensure information is not extrapolated to our population of patients without care. Whilst systemic and biologic therapies form important treatments for patients with psoriasis, evidence supporting weight loss interventions demonstrates our need to consider our patients holistically and adjust lifestyle factors where possible.

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Learning points

1. Over the last five years, clinicians have seen incredible change in the field of psoriasis, with increasing numbers of licensed approved biologic agents, an exciting drug pipeline and a rising interest in stratified medicine.
2. Research supports weight loss interventions in patients who are overweight or obese are associated with a reduction in disease severity.
3. Licensed approved biologic therapies for moderate to severe chronic plaque psoriasis comprise monoclonal antibodies, which target TNF, IL12/23 and IL17A.
4. Biologic therapies in development for the treatment of moderate to severe chronic plaque disease include monoclonal antibodies that target IL17R and IL23.
5. Apremilast is an oral phosphodiesterase 4 inhibitor that was approved for use in moderate to severe psoriasis by NICE in November 2016.
6. Oral methotrexate therapy in psoriasis reports no increased risk of lung disease (for treatment up to 52 weeks) and with regard to liver disease, an increased incidence of elevated transaminases but not of cirrhosis, liver failure or death.

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CPD questions

Learning objective

To demonstrate knowledge of the findings of recent systematic reviews in psoriasis.

Question 1

In the use of biologic therapies for psoriasis; the risk of malignancies was not reported to be significantly increased amongst psoriasis patients receiving treatment compared to the general US population, except for:

- a) Malignant melanoma*
- b) Non-melanoma skin cancer*
- c) Lymphoma*
- d) Breast cancer*
- e) Lung cancer*

Answer to question

- a) Incorrect; the risk of malignant melanoma was not reported to be significantly increased amongst psoriasis patients receiving treatment compared to the general US population*
- b) Correct; the risk of non-melanoma skin cancer was reported to be significantly increased amongst psoriasis patients receiving treatment compared to the general US population*
- c) Incorrect; the risk of lymphoma was not reported to be significantly increased amongst psoriasis patients receiving treatment compared to the general US population*
- d) Incorrect; the risk of breast cancer was not reported to be significantly increased amongst psoriasis patients receiving treatment compared to the general US population*
- e) Incorrect; the risk of lung cancer was not reported to be significantly increased amongst psoriasis patients receiving treatment compared to the general US population*

Question 2

Secukinumab is a human monoclonal antibody that targets:

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- a) IL17A
- b) IL17R
- c) IL17F
- d) IL25
- e) IL23

Answer to question 2

- a) Correct; Secukinumab is a human monoclonal antibody that targets IL17A.
- b) Incorrect; IL17R(A) is targeted by brodalumab
- c) Incorrect; IL17F forms a heterodimer to the molecule IL17A
- d) Incorrect; IL25 is also known as IL17E and is not targeted by secukinumab
- e) Incorrect, IL23 is the target of pipeline agents, including guselkumab

Question 3

In the use of oral methotrexate therapy for the treatment of chronic plaque psoriasis, a 2015 systematic review reported MTX use was associated with which of the following;

- a) Elevated transaminases
- b) Viral hepatitis
- c) Liver failure
- d) Cirrhosis
- e) Death

Answer to question 3

- a) Correct; MTX use was associated with increased risk of elevated transaminases (at ≤ 3 upper limit of normal and > 3 upper limit of normal reference range)
- b) Incorrect; An SR to evaluate the relative risk and severity of liver disease among patients treated with MTX did not report on an association with viral hepatitis
- c) Incorrect; MTX use was not associated with increased risk of liver failure
- d) Incorrect; MTX use was not associated with increased risk of cirrhosis

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- e) *Incorrect; MTX use was not associated with increased risk of death*

Question 4

Which of the following statements is true;

- a) *Polymorphisms in the TNF-alpha gene have been validated to predict response to TNFI therapy in psoriasis*
- b) *Polymorphisms in the TNF alpha gene have been validated to predict response to TNFI therapy across IMIDs*
- c) *Conclusions in existing work result from homogenous studies in terms of patient phenotyping, treatment types (multiple biologic therapies)*
- d) *Precision medicine refers to the tailored selection of treatment for an individual, based on factors such as their genetic makeup*
- e) *Small non-coding RNAs (miRNAs) are validated markers of treatment response in psoriasis*

Answer to question 4

- a) *Incorrect; Polymorphisms in the TNF alpha gene are under investigation as predictors of response to TNFI therapy in psoriasis: their role has not yet been validated*
- b) *Incorrect; Polymorphisms in the TNF alpha gene are under investigation as predictors of response to TNFI therapy across IMID: their role has not yet been validated*
- c) *Incorrect; Conclusions are limited due to heterogeneity of existing studies*
- d) *Correct; Precision medicine refers to the tailored selection of treatment for an individual, based on factors such as their genetic makeup*
- f) *Incorrect; Small non-coding RNAs (miRNAs) are under investigation as predictors of response to therapy in psoriasis*

Question 5

A recent systematic review supports the use of which topical keratolytic agent as monotherapy in scalp psoriasis;

- a) *Urea*
- b) *Glycolic acid*
- c) *Lactic acid*
- d) *Poly-hydroxy Acids*

What's new in psoriasis treatment?

e) *Salicylic acid*

Answer to question 5

- a) *Incorrect; Urea containing products were not supported as monotherapy in scalp disease*
- b) *Incorrect; Alpha-hydroxy acid (including glycolic acid) containing products were not supported as monotherapy in scalp disease*
- c) *Incorrect; Alpha-hydroxy acid (including lactic acid) containing products were not supported as monotherapy in scalp disease*
- d) *Incorrect; Poly-hydroxy acid containing products were not supported as monotherapy in scalp disease*
- e) *Correct; Salicylic acid was the best studied compound and results supported its use as monotherapy in scalp disease (as per NICE guidance; Psoriasis: Assessment and Management)*

Instructions for answering questions

This learning event is freely available online at <http://www.wileylearning.com/ced>.

Users are encouraged to

- Read the article in print or online, paying particular attention to learning points and any author conflict of interest disclosures
- Reflect on the article
- Register or login online at <http://www.wileyhealthlearning.com/ced> and answer the CPD questions
- Complete the required evaluation component of the activity

Once the test is passed, you will receive a certificate and the learning activity can be added to your CPD diary as a self-certified entry.