Review article

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CPD

Effects of systemic therapies on pruritus in adults with atopic dermatitis: a systematic review and meta-analysis

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Summary

Pruritus is a hallmark of atopic dermatitis (AD), which affects disease severity and patient quality of life. In AD uncontrolled with first-line topical therapies or in moderate to severe AD, systemic therapies are used; however, there is a paucity of head-to-head trials comparing the effectiveness of these therapies. The aim of this study was to compare the effectiveness of systemic therapies in relieving pruritus in moderate to severe AD in adults, using a meta-analysis. The PubMed, EMBASE, Medline and CINAHL databases were searched from inception up to 31 May 2020 for randomized, placebo-controlled trials investigating the effectiveness of systemic therapies on pruritus with moderate to severe AD in patients aged ≥ 16 years. In total, 26 studies (n = 5190 participants) were identified. Compared with placebo, there was a large and statistically significant ($P < 0.001$ for all) reduction in pruritus [standard mean difference (SMD); 95% CI] with dupilumab every 2 weeks (−0.88; −1.13 to −0.63), dupilumab every 2 weeks plus topical corticosteroids (−0.77; −0.91 to −0.62), dupilumab once weekly (−0.99; −1.29 to −0.68), dupilumab once weekly plus topical corticosteroids (−0.70; −0.81 to −0.59). There was also a large and statistically significant reduction with ciclosporin (−1.30; −2.34 to −0.26; $P = 0.01$) and a large, although not statistically significant reduction with azathioprine (−0.85; −2.07 to 0.35). There was a small reduction with both mepolizumab (−0.27; −0.89 to 0.35) and interferon-γ (−0.31; −0.75 to 0.12). Of the investigational drugs, nemolizumab 2.0 mg/kg was the most effective (−8.13; −9.31 to −6.94). The majority of systemic therapies were superior to placebo in reducing pruritus. In particular, the dupilumab studies consistently showed large improvements in pruritus, while nemolizumab showed the strongest antipruritic effects. However, future head-to-head trials are required for conclusive evidence.

Introduction

Atopic dermatitis (AD), also known as atopic eczema, is a chronic pruritic inflammatory skin disease, affecting 3%–5% of the adult population and up to 20% of children worldwide.[1] AD is ranked as the most burdensome skin condition worldwide and has a significant impact on quality of life (QoL). Much of this impact is attributed to pruritus, an unpleasant sensation that elicits an urge to scratch, which is the hallmark of AD.[1]

Until recently, systemic therapies were limited to immunosuppressive agents such as ciclosporin, and off-license use of methotrexate and azathioprine. However, advancements in the treatment of AD led to

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dupilumab being approved by the National Institute for Health and Care Excellence in August 2018 as the first biologic agent licensed for moderate to severe AD in adults.[2] Furthermore, Janus kinase (JAK) inhibitors are emerging as the next generation of agents to be licensed for AD.[3–5] Although these therapies have been shown to be effective in managing AD, their effectiveness against other systemic therapies is not known, owing to the paucity of head-to-head trials. Furthermore, as studies of AD drugs generally do not use the same outcome measures or composite scales to measure their effectiveness, conducting a direct comparison of all drugs is difficult. These heterogeneities are increasingly recognized, with initiatives by the international Harmonising Outcome Measures for Eczema founded in 2010 to standardize outcome measurement in AD clinical trials by developing a core outcome set.[6] However, many studies on commonly used systemic therapies for AD were conducted prior to this date. The assessment of pruritus is one of the only common comparators, and it has also been suggested to have a stronger correlation with patient-reported AD severity than outcome measures such as the Patient-Oriented Eczema Measure.[7]

Systematic review of the effectiveness of systemic therapies compared against placebo and solely focusing on pruritus in AD allows comparison of the majority of the systemic therapies against a single common comparator, which was not done in previous meta-analyses.[8,9] Placebo treatments have been shown to reduce itch by up to 24% in AD and thus a placebo control acts as an important comparator.[10] As dupilumab is currently only approved for moderate to severe AD, and most trials on investigational drugs conducted in this disease group and in adults, comparison of systemic therapies limited to this population would be beneficial in determining their effectiveness on relieving pruritus and would provide clinicians with evidence-based medicine in managing pruritus in moderate to severe AD in adults. We therefore conducted a meta-analysis to compare the effectiveness of systemic therapies in relieving pruritus in moderate to severe AD in adults (defined as $\geq$ 16 years of age in this study).

Methods

The Preferred Reporting Items for Systematic Reviews and Meta Analyses statement was followed and the checklist completed[11] (Table S1). The review was registered on PROSPERO, the international prospective register of systematic reviews (ID no. CRD42019156224).

Eligibility criteria

Inclusion criteria included: (i) randomized controlled trial (RCT) or crossover study, phase 2 or 3 clinical trial; (ii) systemic therapies including but not limited to ciclosporin, methotrexate, azathioprine, corticosteroids, interferon-γ, dupilumab and investigational therapies; (iii) comparison of treatment with placebo; (iv) measured change in pruritus from baseline to endpoint; (v) patients with AD aged $\geq$ 16 years; and (vi) moderate to severe AD, or AD inadequately controlled with topical therapies.

Exclusion criteria included: (i) pruritus assessed only as part of a composite score of AD symptoms and not independently; (ii) no systemic therapy, including phototherapy, used; (iii) systemic therapies administered with concomitant therapies and without a comparable placebo; and (iv) studies of localized AD and other types of dermatitis.

Information sources

We searched PubMed, EMBASE, Medline and CINAHL databases from inception up to 31 May 2020, using Medical Subject Headings and free-text terms of the following concepts: (i) 'atopic dermatitis' OR 'atopic eczema' OR 'eczema' OR 'dermatitis'; AND (ii) 'pruritus' OR 'itch'; AND (iii) systemic therapies including dupilumab, ciclosporin and azathioprine; AND (iiv) 'randomized controlled trials' OR 'clinical trials' OR 'cross-over trials'. (See Data S1 for the full search term and search strategy.)

Study selection

Titles and abstracts were screened for initial eligibility, then full-text publications were retrieved and assessed independently using the complete eligibility criteria in a standardized manner by two reviewers (XLT, YJT) (see Fig. 1 for flowchart and Data S2 for full details on data collection process). In total, 43 articles were deemed relevant and full-text publications for these were retrieved and assessed using the complete eligibility criteria.

Quality assessment

The methodological quality of the studies was assessed using the Cochrane Risk of Bias Tool (Fig. S1) and quality of evidence for each outcome was assessed by the Grading of Recommendations Assessment, Development and Evaluation criteria by two reviewers independently (XLT, YJT) (Table S2).

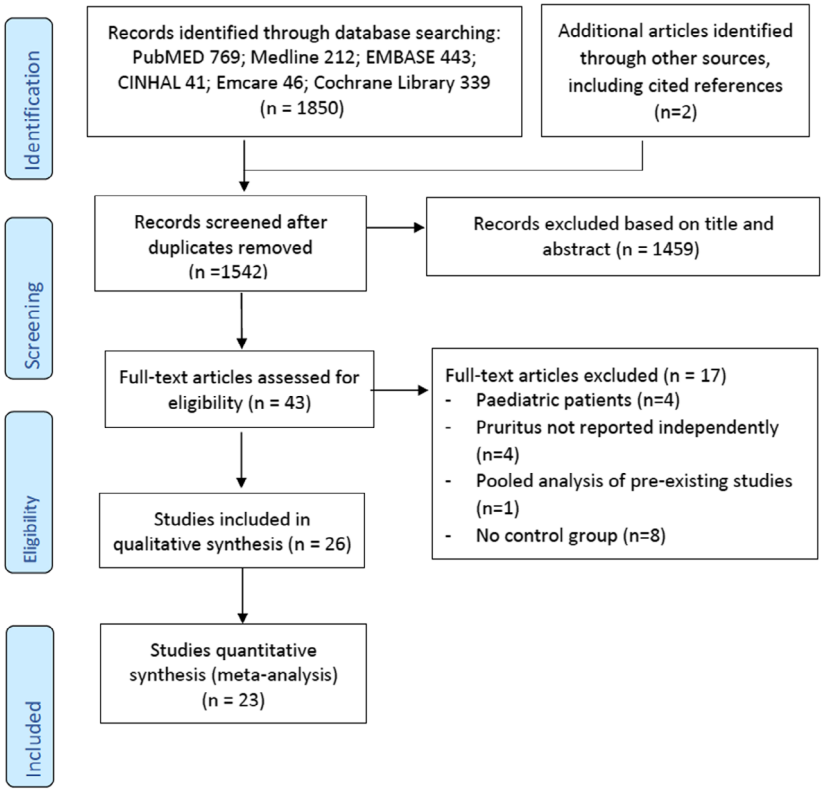

Figure 1 Flow diagram of study selection.

Statistical analysis

A meta-analysis was conducted in Review Manager (V5.3; https://training.cochrane.org) using the inverse-variance statistical method. A random-effect approach was used. The mean change in pruritus score in treatment and placebo groups were used to determine the standard mean difference (SMD) and 95% CI. The level of statistical heterogeneity for pooled data was established using χ^2 and I^2 statistics. Statistical significance was defined as $P < 0.05$.

Results

Study selection

In total, 26 studies[2–5,12–32] were selected for the review (Table 1). The included studies involved 5190 participants (n = 3435 randomized to the intervention treatment, n = 1755 to placebo), with an age range of 16–68 years. The intervention duration had a range of 2–52 weeks. The primary outcome measure was the change in pruritus score following treatment. Pruritus was assessed by visual analogue scale (VAS) with a range of 0–10 or 0–100 mm, or a numerical rating scale (NRS); for all scales, 0 indicates 'no itch' and 10 or 100 indicates 'the worst itch imaginable'.

Individual treatments

Summary of the forest plots of the systemic therapies are presented in Fig. 2 (see Figs S2–S15 for individual forest plots and Data S3 for summary of the qualitatively analysed studies).

Compared with placebo, there was a large reduction in pruritus (SMD; 95% CI) with dupilumab every 2 weeks (−0.88; −1.13 to −0.63; $P < 0.001$), dupilumab every 2 weeks plus topical corticosteroids (TCS) (−0.77; −0.91 to −0.62; $P < 0.001$), dupilumab once weekly (−0.99; −1.29 to −0.68; $P < 0.001$), and dupilumab once weekly plus TCS (−0.70; −0.81 to −0.59; $P < 0.001$). Comparing the two dosing regimens included (dupliumab 300 mg once weekly; dupilumab every 2 weeks plus TCS), there were no significant differences in the reduction of pruritus between them.

There was also a large reduction with ciclosporin (−1.30; −2.34 to −0.26; $P = 0.01$) and azathioprine (−0.85; −2.07 to 0.35; $P = 0.17$) though this needs

Table 1 Summary of the included studies.

Study	Duration, weeks	Outcome measures	Dosage and intervention[a]	Sample size (drug/placebo)
Dupilumab				
Beck *et al*., 2014[12]	12	P-NRS (%)	SC dupilumab 300 mg once weekly; placebo	55/54
Thaci *et al*., 2016[13]	16	P-NRS (/10)	SC dupilumab 300 mg once weekly; SC dupilumab 300 mg every 2 weeks; placebo	127/61
Simpson *et al*, 2016[14] SOLO 1	16	P-NRS (/10)	SC dupilumab 300 mg once weekly; SC dupilumab 300 mg every 2 weeks; placebo	447/224
Simpson *et al*., 2016[14] SOLO 2	16	P-NRS (/10)	SC dupilumab 300 mg once weekly; SC dupilumab 300 mg every 2 weeks; placebo	472/236
Blauvelt *et al*., 2017[15]	52	P-NRS (/10)	SC dupilumab 300 mg once weekly plus TCS; SC dupilumab 300 mg every 2 weeks plus TCS; placebo plus TCS	425/315
Simpson *et al*., 2018[2]	16	P-NRS (/10)	SC dupilumab 300 mg once weekly; SC dupilumab 300 mg every 2 weeks; placebo	127/61
de Bruin-Weller *et al*., 2018[16]	16	P-NRS (/10)	SC dupilumab 300 mg once weekly plus TCS; SC dupilumab 300 mg every 2 weeks plus TCS; placebo plus TCS	217/108
Systemic immunosuppressants				
Sowden *et al*., 1991[18]	16 (8 + 8)	P-VAS (/10)	Ciclosporin 5 mg/kg/day in phase 1 (Week 1–8): placebo in phase 2 (Week 9–16)	17/16
Munro *et al*., 1994[17]	16 (8 + 8)	P-VAS (/10)	Ciclosporin 5 mg/kg/day in phase 1 (Week 1–8); placebo in phase 2 (Week 9–16)	9/10
Hanifin *et al*., 1993[24]	12	Pruritus (%)	Interferon-γ 50 μg/m^2; placebo	40/43
Van Joost *et al*., 1994[19]	6	P-VAS (/10)	Ciclosporin 5 mg/kg/day; placebo	23/23
Jang *et al*., 2000[25]	12	Pruritus (%)	Interferon-γ 1.5 × 10^6 IU/m^2; interferon-γ 0.5 × 10^6 IU/m^2; placebo	21/20/10
Berth-Jones *et al*., 2002[20]	12	P-VAS (/100)	Azathioprine 2.5 mg/kg/day; placebo	19/18
Meggitt *et al*., 2006[21]	12	P-VAS (/10)	Azathioprine 1.0–2.5 mg/kg/day; placebo	41/20
Oldhoff *et al*., 2005[23]	2	P-VAS (/10)	Mepolizumab 750 mg once weekly; placebo	20/23
Friedmann *et al*., 2007[22]	8	P-VAS (/10)	Montelukast 10 mg; placebo	30/30
Antihistamine				
Hannuksela *et al.*,1993[26]	4	P-VAS (/100)	Cetirizine 40 mg; cetirizine 20 mg; cetirizine 10 mg; placebo	47/45/42/42
Investigational therapies				
Ruzicka and Mihara, 2017[27]	12	P-VAS (/100)	Nemolizumab 0.1 mg/kg; nemolizumab 0.5 mg/kg; nemolizumab 2.0 mg/kg; placebo	53/54/52/53
Simpson *et al*., 2018[2]	12	P-VAS/100	Lebrikizumab 125 mg single dose plus TCS; lebrikizumab 250 mg single dose plus TCS; lebrikizumab 125 mg every 4 weeks plus TCS; placebo plus TCS	52/53/51/53
Werfel *et al*., 2019[28]	8	P-NRS (/10)	Adriforant (ZPL-3893787) plus TCS; placebo plus TCS	65/33
Wollenberg *et al*., 2018[29]	12	P-NRS (/100)	Tralokinumab 45 mg plus TCS; tralokinumab 150 mg plus TCS; tralokinumab 300 mg plus TCS; placebo plus TCS	50/51/52/51
Simpson *et al*., 2019[31]	12	P-NRS (/10)	Tezepelumab plus TCS; placebo plus TCS	55/56
Gooderham *et al*., 2019[3]	12	P-NRS (/10)	Abrocitinib 10 mg; abrocitinib 30 mg; abrocitinib 100 mg; abrocitinib 200 mg; placebo	46/45/54/48/52
Guttman-Yassky *et al*., 2019[4]	16	P-NRS (/10)	Baricitinib 2 mg plus TCS; baricitinib 4 mg plus TCS; placebo plus TCS	37/38/49
Guttman-Yassky *et al*., 2019[30]	10	P-NRS (/10)	GBR830 10 mg/kg; placebo	40/16
Guttman-Yassky *et al*., 2020[5]	16	P-NRS (/10)	Upadacitinib 7.5 mg; upadacitinib 15 mg; upadacitinib 30 mg; placebo	42/42/42/41
Silverberg *et al*., 2020[32]	24	P-NRS (/10)	Nemolizumab 10 mg plus TCS; nemolizumab 30 mg plus TCS; nemolizumab 90 mg plus TCS; placebo plus TCS	55/57/57/57

P-NRS, pruritus numerical rating scale; P-VAS, pruritus visual analogue scale; SC, subcutaneous; TCS, topical corticosteroids; /10, 0–10 scale; /100, 0–100 scale. [a]For dupilumab, only studies with doses of 300 mg once weekly or every 2 weeks were included in the review.

to be interpreted with caution due to the small number of studies. Of the investigational therapies, nemolizumab was the most effective, particularly the dose of 2.0 mg/kg, which showed a large reduction in pruritus favouring nemolizumab (−8.13; −9.31 to −6.94, $P < 0.001$).

Discussion

This systematic review evaluated the effectiveness on the intensity of pruritus of systemic therapies available for adults with moderate to severe AD. No standardized outcome measures of AD symptoms were used across the studies, and there was a lack of consistency in the methods of quantifying the therapeutic effects of the treatments. By focusing on pruritus scores, this meta-analysis was able to include the majority of the licensed and investigational systemic therapies available, and to provide a quantitative estimation of the therapeutic effect size of the systemic therapies on pruritus.

Dupilumab was the most effective licensed systemic therapy analysed in the review. Investigational

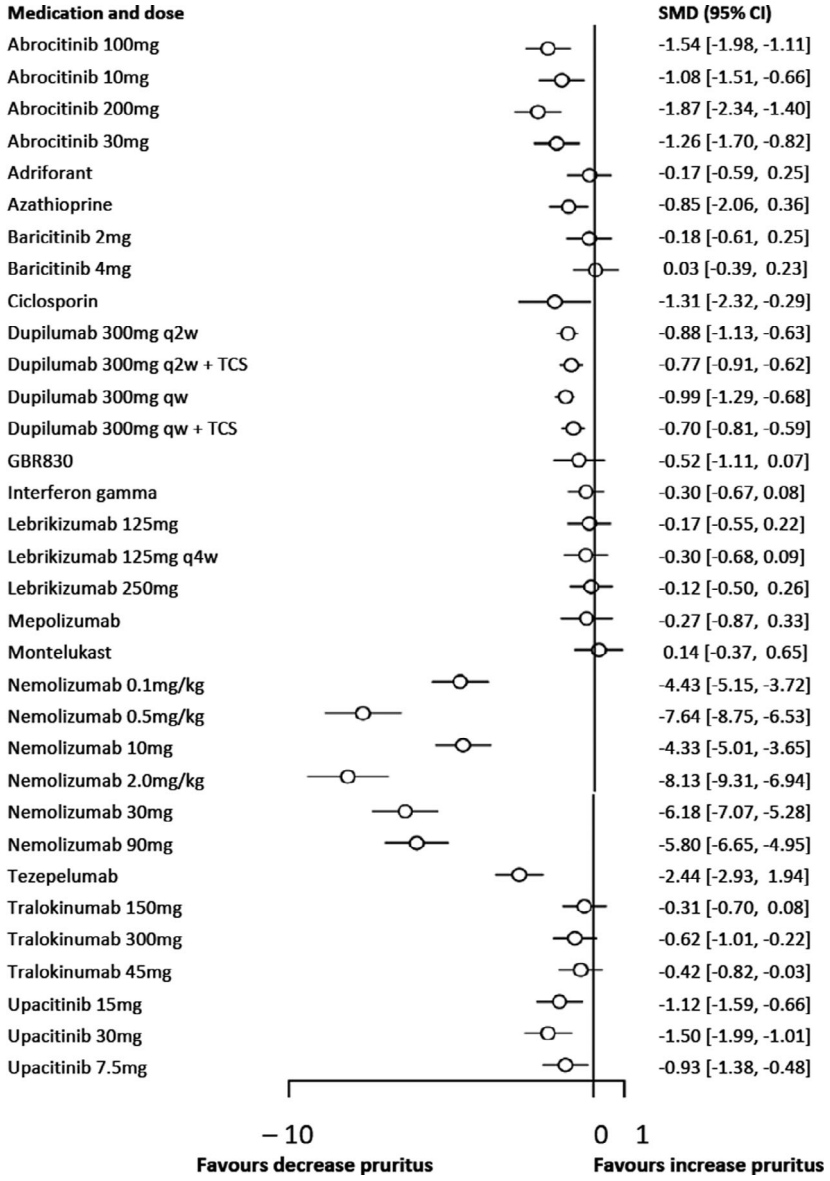

Figure 2 Summary of forest plots of systemic therapies compared against placebo. qw, once weekly; q2w, every 2 weeks; q4w, every 4 weeks; SMD, standard mean difference; TCS, topical corticosteroids.

therapies, such as nemolizumab, tezelumab and abrocitinib, generally outperformed licensed therapies in reducing pruritus. TCS was allowed in some studies in both treatment and placebo groups, and the placebo groups were reported to be more reliant on TCS.[2,4,28,32] These findings are promising as eczema treatment continues to advance, with JAK inhibitors expected to gain approval by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA).[3–5] Most outcomes of the investigational therapies included in the meta-analysis were informed by a single RCT, usually with a small number of patients, and hence the results need to be interpreted with caution. Nevertheless, the strong antipruritic effects of the reported drugs are encouraging, and they bring hope to patients for better symptomatic control in the near future.

The current analysis is limited to direct comparison against placebo. In addition, not all studies of systemic therapies in AD were included, as those that did not measure the changes in pruritus score from baseline to the end of the study were excluded. Studies without a placebo group were also excluded, in order to provide a common comparator between the studies. The included systemic therapies were fairly heterogeneous, with varying mechanisms of action, duration and sample sizes for each trial. We were not able to determine a conclusive hierarchy between these therapies, and the results were not always statistically significant. There was a lack of consistency across the studies in the inclusion criteria of moderate to severe AD as no established definition existed previously. Possible confounding variables, such as the participants' baseline AD treatment, intolerance to certain systemic therapies and presence of environmental triggers, should be addressed and monitored in future research.

Conclusion

This systemic review shows that most systemic therapies are effective at reducing pruritus, with dupilumab being the most effective licensed therapy. The strong antipruritic effects of investigational drugs, in particular nemolizumab, are promising. Overall, these findings encourage a placebo-controlled head-to-head RCT of systemic therapies available for moderate to severe AD in both adults and children, in order to establish conclusive evidence on the effectiveness of systemic therapies on relieving pruritus in AD, and ultimately to address the disease severity and the significant impact on patient QoL.

Acknowledgement

We thank A. Tocock, Medical Librarian at Barts Health NHS Trust, for assistance in conducting the search for this review.

Learning points

- AD is a chronic pruritic inflammatory skin disease affecting both children and adults.
- Pruritus contributes significantly to eczema disease progression and severity, and has a significant impact on QoL.
- Outcome measures quantifying the therapeutic effects of systemic therapies on eczema in clinical studies are not standardized.
- Dupilumab is the first biologic agent to be approved for clinical use for moderate to severe AD in adults.
- JAK inhibitors are expected to gain approval by the EMA and FDA for the treatment of moderate to severe AD in adults.
- Head-to-head trials on the available systemic therapies are needed to establish conclusive evidence on their effectiveness of relieving pruritus in AD.

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CPD questions

Learning objective

To appreciate the impact of atopic dermatitis (AD) on patients, methods of eczema assessment and eczema treatments.

Question 1

What is the mechanism of action of dupilumab in treating atopic dermatitis (AD)?

(a) Inhibits FLT3 tyrosine kinase inhibitors.
(b) Inhibits interleukin (IL)-4 and IL-13 cell signalling.
(c) Inhibits IL-6 cell signalling.
(d) Inhibits crosslinking of IgG Fc receptors to IgG on eosinophils.
(e) Inhibits STAT5-mediated activation of the JAK/STAT signalling pathway.

Question 2

Which of the following is a known complication of poorly controlled atopic dermatitis (AD)?

(a) Depression.
(b) Sleep deprivation.
(c) Low self-esteem.
(d) Missing school or work.
(e) All of the above.

Question 3

Which of the following is not used to assess the severity of atopic dermatitis (AD)?

(a) Patient Oriented Eczema Measure (POEM).
(b) Dermatology Life Quality Index (DLQI).
(c) The modified Rodnan skin score.
(d) Pruritus numerical rating scale (NRS).
(e) Physician Global Assessment (PGA).

Question 4

What is the indication for using cetirizine in atopic dermatitis (AD) according to National Institute for Health and Care Excellence (NICE) Clinical Knowledge Summaries?

(a) In moderate to severe eczema when severe itch or urticaria is uncontrolled.
(b) In any severity of eczema when severe itch or urticaria is affecting sleep.
(c) In severe eczema causing psychological distress.
(d) As an adjunct when severe itch or urticaria does not resolve after 2 weeks of topical treatment in any severity of eczema.
(e) Used as prophylaxis for patients in remission from eczema flare.

Question 5

According to the British National Formulary (BNF), what needs to be assessed prior to initiating patients on ciclosporin for atopic dermatitis?

(a) Serum lipid, liver function, renal function and serum magnesium.
(b) Renal function.
(c) Dermatological and physical examination.
(d) Dermatological and physical examination, renal function and serum lipid.
(e) Skin swab of affected area to exclude infection prior to initiation.

Instructions for answering questions

This learning activity is freely available online at http://www.wileyhealthlearning.com/ced

Users are encouraged to

- Read the article in print or online, paying particular attention to the 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 RCP CPD diary as a self-certified entry.

This activity will be available for CPD credit for 2 years following its publication date. At that time, it will be reviewed and potentially updated and extended for an additional period.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. Appendix 1: search terms and strategy.
Data S2. Appendix 1: data collation and processing.
Data S3. Appendix 1: qualitative analysis.
Figure S1. Risk of bias summary.
Figure S2. Forest plot of dupilumab 300 mg weekly
Figure S3. Forest plot of dupilumab 300 mg every 2 weeks.
Figure S4. Forest plot of ciclosporin.
Figure S5. Forest plot of systemic immunosuppressants.
Figure S6. Forest plot of azathioprine.
Figure S7. Forest plot of abrocitinib.
Figure S8. Forest plot of baricitinib.
Figure S9. Forest plot of GBR830.
Figure S10. Forest plot of upadacitinib.
Figure S11. Forest plot of nemolizumab.
Figure S12. Forest plot of lebrikizumab.
Figure S13. Forest plot of tezepelumab.
Figure S14. Forest plot of tralokinumab.
Figure S15. Forest plot of adriforant.
Table S1. Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) checklist.
Table S2. Grading of Recommendations Assessment, Development and Evaluation assessment.

