Review Article

The effect of statins on severity of psoriasis: A systematic review

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Abstract

Background: Psoriasis is becoming increasingly recognized as a chronic systemic inflammatory disease. Statins are generally well-tolerated drugs with pleiotropic effects including decreasing inflammation and may have the potential to reduce psoriasis severity.

Aims: To examine whether oral statins reduce the severity of psoriatic skin disease.

Methods: We searched MEDLINE, EMBASE and adapted for Google Scholar, Cochrane Central Register for Controlled Trials and Clinical trials.gov to January 6, 2016. We primarily examined randomized controlled trials that assessed the change in PASI score over a follow-up period of at least 8 weeks, for participants with an established diagnosis of psoriasis taking an oral statin versus placebo or other active treatment. Beyond this, we also examined other interventional studies that investigated the effect of statins on psoriasis severity using other designs. We extracted efficacy and adverse event data. The two study authors examined issues of study quality and study inclusion independently.

Results: Three studies were identified which measured the change in psoriasis severity using PASI, comparing statin with placebo or standard therapy alone in a prospective, randomized study design; these showed conflicting results. However, among the excluded studies, majority of which used a single arm, non-placebo controlled study design, most showed an improvement in PASI scores after statin use.

Limitations: Included studies were of limited sample size and quality. They were not amenable to pooled analysis.

Conclusions: This review highlights the paucity of high quality, randomized, double-blinded, placebo-controlled trials investigating the effects of statins on psoriasis severity using clinically objective measures. There is insufficient evidence that the use of oral statins as an adjunctive therapy can reduce the severity of psoriasis.

Key words: Psoriasis, psoriasis area and severity index score, PASI, statins

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Introduction

Psoriasis is a chronic inflammatory disease of the skin, scalp, nails and sometimes joints that affects 1–2% of the general population.[1,2] It is associated with a significant physical and psychological morbidity and is becoming increasingly recognized as a systemic inflammatory disease.[3]

The mainstay of psoriasis treatment involves topical agents (e.g., vitamin D analogs and corticosteroids) for milder disease and systemic therapy (e.g., oral immunosuppressants, phototherapy, or biological agents) for more severe disease.[4] The latter are effective, but their long-term use is often limited by potential toxicity.

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In clinical terms, improvement in psoriasis management leads to a reduction in cutaneous lesions which can be objectively measured using the PASI score. This is a numerical score of the extent and activity of a patient's psoriasis (ranging from 0 [no disease] to 72 [most severe disease]) and is calculated by a reproducible formula based on the surface area and cutaneous features of the disease.[5]

Statins are a class of reversible competitive inhibitors of 3-hydroxyl-3-methylyglutaryl-coenzyme A reductase known for their cholesterol lowering effects.[6] 3-hydroxyl-3-methylyglutaryl-coenzyme A reductase is the

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rate-limiting step in cholesterol biosynthesis. Its inhibition thereby increases the synthesis of low-density lipoprotein receptors leading to an increased clearance of plasma low-density lipoprotein cholesterol. Statins are generally well-tolerated drugs used for prevention of atherosclerosis and cardiovascular events.

Statins have also been found to exert pleiotropic effects and decrease inflammation, atherogenesis and cardiovascular morbidity.[7] This is associated with a reduction in the release of C-reactive peptide, chemokines, cytokines and adhesion molecules, as well as modulation of T-cell activity.[8] Based on their immunomodulatory properties, statins may have the potential to attenuate the inflammatory component of psoriatic disease.

Methods

Objective

The objective of this work is to explore whether oral statins improved the severity of psoriatic skin disease.

P-participants aged over 18 and over with psoriasis, I-statin therapy, C-placebo or other active treatment, O-change in Psoriasis Area and Severity Index score.

Protocol and registration

Methods of the analysis and inclusion criteria were specified in advance as detailed below and registered on PROSPERO (http://www.crd.york.ac.uk/PROSPERO/).

Eligibility studies

- Types of participants: Trials including participants over age 18 with an established diagnosis of psoriasis were considered
- Types of intervention: Trials involving the initiation of an oral statin in any dose to statin-naive participants compared with placebo or other active treatment were considered
- Types of outcome: Studies had to include change in Psoriasis Area and Severity Index score over a follow-up period of at least 8 weeks as either a primary or secondary outcome.

Information sources

Studies were identified by searching electronic databases and scanning reference lists of articles. No limits were applied for language and foreign papers were translated using the Google Translate function. A translator confirmed the accuracy of translation and also assisted with any areas that required clarification. This search was applied to MEDLINE (1946 - January 6, 2016), EMBASE (1947 - January 6, 2016) and adapted for Google Scholar (January 6, 2016). Adapted searches [Appendix 1] for the Cochrane Central Register for Controlled Trials and Clinical trials.gov databases were also performed to January 6, 2016. We searched reference lists of retrieved articles and relevant reviews to identify potential additional eligible studies.

Search

We used the following search terms to search all trials registers and databases [Appendix 2]: statin, statins, simvastatin, atorvastatin, pravastatin, rosuvastatin, fluvastatin, psoriasis, randomized controlled trial, randomized controlled trials, controlled clinical trial, random allocation, double-blind method, single-blind method, clinical trials, clinical trial, placebos, placebo, random, research design, comparative study, evaluation studies, follow-up studies and prospective studies.

Study selection

We determined eligibility by reading the title and abstract of each study identified in the search. We eliminated studies that clearly did not satisfy the inclusion criteria and obtained full copies of the remaining studies. The two authors read these studies independently and reached agreement by discussion in any cases of discrepancy. The studies were not anonymized in any way before assessment. A summary of the study selection process is shown in Figure 1.

Data extraction and management

The two review authors extracted and agreed on data, using a standard form, before any analysis was undertaken. Data extracted included information about the study design, characteristics and number of participants, drug and dose regimen, permitted concomitant therapies, follow-up period, change in skin disease outcomes, adverse effects and withdrawals.

Assessment of risk of bias in included studies

During data extraction, we assessed the risk of bias in each trial included in the review using the Cochrane Collaboration's risk of bias tool.[9] This requires reviewers to evaluate the risk of five types of bias and to judge each of these as either "low," "high," or "unclear" (usually when there is insufficient information).[10]

Data synthesis

We described the characteristics and results of trials in table format [Table 1] and also considered whether statistical synthesis of the findings by meta-analysis was appropriate.

Measures of treatment effect

We planned to use continuous data to calculate the mean difference between change in PASI scores in the statin and placebo groups with 95% confidence intervals using a fixed-effect model, unless

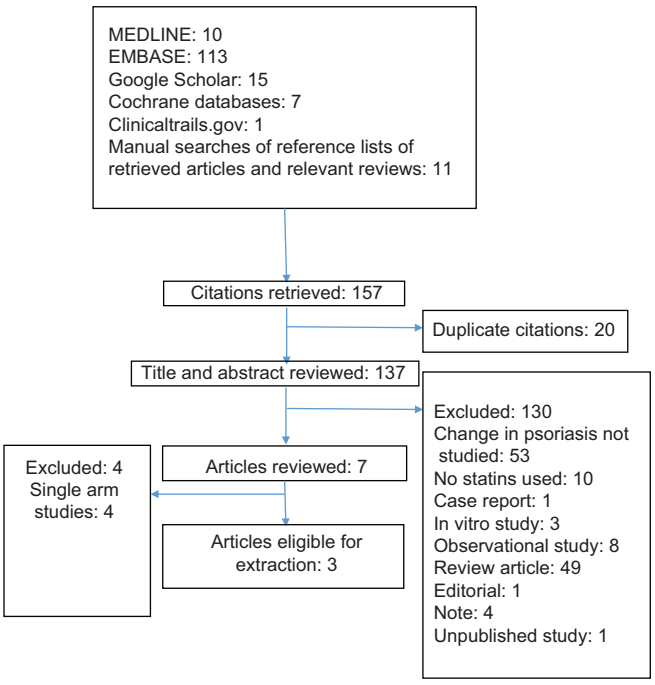

Figure 1: A flowchart summarizing the study selection process

Table 1: Included and excluded study characteristics and main results

Trial		Participants		Interventions	Results			
Group	**Study type**	**Inclusion criteria**	**Sample characteristics**		**Mean change in PASI score (±SD)**	**Statistical significance**	**Clinical significance**	**Withdrawals/adverse events**
Faghihi (2011)	Randomized, double-blinded, placebo-controlled trial	Diagnosis of acute or chronic plaque psoriasis made by a dermatologist with BSA >10%, 1 month washout from systemic therapy, 2 weeks washout from topical therapy	*n*=42, age 16-60 Age (±SD): Statin group - 43.85±14.32 Placebo group - 36.55±12.11 Baseline PASI score (±SD): Statin group - 7.42 (±1.90) Placebo group - 6.92 (±1.76)	Oral atorvastatin 40 mg/day (*n*=20), placebo (*n*=20). Permitted topical steroids, emollients, keratolytics. 12 weeks follow-up period	Statin group - 4.48±2.14 Placebo group - 4.33±1.93	*F* paired-*t*-test; *P*=0.72	Mean difference in change in PASI score (±SD)=0.15±0.21	One participant developed somnolence in treatment group. One participant withdrew consent from placebo group
Naseri (2010)	Randomized, double-blinded, placebo-controlled trial	Established diagnosis of psoriasis, 1 month washout from topical or systemic therapy	*n*=30, age 16-70 Age (±SD): Statin group - 38.5 Placebo group - 45.4 (SD not available) Baseline PASI score: Statin group - 9.51 Placebo group - 5.64 (SD not available)	Oral simvastatin 40 mg/day (*n*=15), placebo (*n*=15). Permitted topical steroids. 8 weeks follow-up period	Statin group - 5.68 Placebo group - 1.66 (SDs not available)	Mann–Whitney U-test; *P*=0.001	Mean difference in change in PASI score=4.02 (SD not available and insufficient data to impute)	No withdrawals or adverse events noted
Vasiuk (2010)	Randomized, open-label, nonplacebo controlled trial	Men with an established diagnosis of psoriasis and arterial hypertension	*n*=63, age >18 Age (±SD): 55.0±11.6 (no age breakdown available for each treatment group) Baseline PASI score: Statin group - 22.2 Comparator group - 22.6 (SD not available)	Oral atorvastatin 20 mg/day plus "standard therapy" (*n*=48) versus "standard therapy" alone (*n*=15), 3 months and 6 months follow-up period	3 month follow-up: Statin group - 12 Comparator group - 5.5 (SDs not available)	Paired *t*-test; *P*≤0.05	Mean difference in change in PASI score=6.5 After 3 month Mean difference in change in PASI score=13.0 after 6 months (SD not available and insufficient data to impute)	No withdrawals or adverse events noted
Shirinsky (2007)	Nonrandomised, noncontrolled, open label, single arm pilot study	Diagnosed with plaque psoriasis with more than 10% BSA and PASI >12	*n*=7, age >18 Age (±SD): 54±19.1 Baseline PASI score (±SD): 24.1±3.8	40 mg/day oral simvastatin Follow-up: 4 weeks and 8 weeks Permitted therapies - emollients and low potency corticosteroids (Classes V-VII)	8 weeks follow-up: Statin group: 11.4±6.8	Wilcoxon signed-rank test *P*=0.03	No comparator group	One patient terminated study prematurely (at 4 weeks) due to severe headache Adverse effects: One patient suffered from hypertension. One patient had mild elevation of transaminase levels

Contd...

Table 1: Contd...

Trial		Participants		Interventions	Results			
Group	Study type	Inclusion criteria	Sample characteristics		Mean change in PASI score (±SD)	Statistical significance	Clinical significance	Withdrawals/adverse events
Aslam (2013)	Nonrandomised, noncontrolled, open-label, single arm study	Diagnosed with psoriasis with a PASI >12	*n*=60, age 18-70 Age (±SD): 35.47±12.39 Baseline PASI score (±SD): 29.11±12.47	40 mg/day oral simvastatin for 8 weeks Follow-up period: 12 weeks	Statin group: 7.12 (SDs not available)	No analysis performed	No comparator group	No withdrawals or adverse effects noted
Colesman (2010)	Nonrandomised, noncontrolled, open-label, single arm study	Diagnosed with moderate to severe plaque psoriasis and hypercholesterolemia 4 weeks washout period of systemic psoriatic therapy before trial	*n*=5, age >18 Baseline PASI score (±SD): 12.6±5.16	40 mg/day oral simvastatin Follow-up period: 12 weeks Permitted therapies - topical calcipotriol+topical corticosteroids continued	Statin group: 1.85 (SDs not available)	No analysis performed	No comparator group	No withdrawals or adverse effects noted but incomplete data for one patient at 12 weeks
Aronson (1992)	Nonrandomised, noncontrolled, open-label, single arm study	Diagnosed with psoriasis and hypercholesterolemia (fasting cholesterol >5.20 mmol/L) 2 weeks washout period from all psoriatic therapy	*n*=10, age >18	80 mg/day oral lovastatin Follow-up period - 8 weeks Permitted therapies - emollients and antipruritic therapy	Psoriasis severity not measure using PASI	No analysis performed	No comparator group	No withdrawals or adverse effects noted

PASI: Psoriasis area severity index, SD: Standard deviation, BSA: Body surface area

significant statistical heterogeneity was found (see below). Comparing the mean PASI scores as a way of measuring treatment effect is the most common comparative tool used in psoriasis trials which use this indicator.[11,12]

Assessment of heterogeneity

We intended to deal with statistical heterogeneity with the use of the I^2 statistic provided; there were a sufficient number of eligible studies to make the interpretation of the I^2 statistic reliable.[13]

Results

Results of the search

The searches yielded seven relevant studies [Figure 1].

Included studies

Three studies fulfilled the inclusion criteria [Table 1]. Faghihi *et al*. and Naseri *et al*. both studied the effect of statin use on psoriasis severity using a prospective, single center, randomized, double-blinded, placebo-controlled study design and measured psoriasis severity using PASI.[14,15] Vasiuk *et al*. used a prospective, single-center, randomized, open-label, nonplacebo controlled trial with parallel groups to study the effect of oral atorvastatin on psoriasis severity as measured by change in PASI score.[16]

Excluded studies

Shirinsky and Shirinsky, Aslam *et al*., Colsman and Sticherling, Aronson and Friedman all used a non-randomized, single-arm, open-label, study design, and were thus excluded because there was no comparator group [Table 1].[17-20] All of these studies yielded an improvement in psoriasis severity but did not provide raw data and only performed statistical analysis to show what the authors deemed a statistically significant improvement.

Risk of bias in included studies

Selection bias

Faghihi *et al*. adequately described their method of randomization (permuted block randomization table) but did not describe whether they performed allocation concealment. Naseri *et al*. and Vasiuk *et al*. did not comment on randomization method or whether allocation concealment was performed.

Blinding

Naseri *et al*. did state that the assessors of outcome were blinded to treatment identifications before the initiation of the treatment and at the end of the treatment period. Faghihi *et al*. did not describe any method of outcome assessment blinding, whereas Vasiuk *et al*. undertook an open-label study.

Incomplete outcome data

Faghihi *et al*. had a low withdrawal rate (2/40 participants) but did not use intention to treat analysis. This is unlikely to contribute to significant attrition bias since one participant withdrew from each treatment group and the overall withdrawal rate was low. Naseri *et al*. and Vasiuk *et al*. had no withdrawals.

Other potential sources of bias

Treatment group size was an issue.[21] The sample size was 30 for the Naseri *et al*. study, 40 for the Faghihi *et al*. study and 62 for the Vasiuk *et al*. study. Studies with small group sizes tend to overestimate efficacy; thus, this is a potential additional source of bias.[22] Figures 2 and 3 summarise the risk of bias in included studies.

Effects of interventions

The included studies were not amenable to pooled meta-analysis because Naseri *et al*. and Vasiuk *et al*. did not assess for variation in the change in PASI score measurements.[10]

Faghihi *et al*. (2011) found that the mean change in PASI scores (± standard deviation) for the atorvastatin group was 4.48 ± 2.14 compared with the placebo group 4.33 ± 1.93, creating a mean difference in change in PASI score of 0.15 ± 0.21 between the two groups, which the authors stated was not statistically significant using a paired-sample *t*-test ($P = 0.72$).

Naseri *et al*. (2010) found that the mean change in PASI score was 5.68 in the simvastatin group and 1.66 in the placebo group creating a mean difference in change in PASI score of 4.02 between the two groups. The authors deemed this a statistically significant larger reduction in mean PASI score in the simvastatin group using a Mann–Whitney U-test statistical significance test ($P = 0.001$).

Vasiuk *et al*. (2010) found that the mean change in PASI score was 12 in the atorvastatin group and 5.5 in the placebo group after 3 months follow-up, thus creating a mean difference in change in PASI score of 6.5 between the two groups. In addition, participants were followed up at the 6-month time period yielding an even greater improvement of 13 in PASI scores.

Withdrawals and adverse effects

There were two withdrawals from the Faghihi *et al*. study. One participant developed somnolence in the atorvastatin group and had to discontinue the trial while another from the placebo group withdrew consent. There were no additional adverse effects noted in either

Figure 2: Risk of bias summary: Review authors' judgments about each risk of bias item for each included study

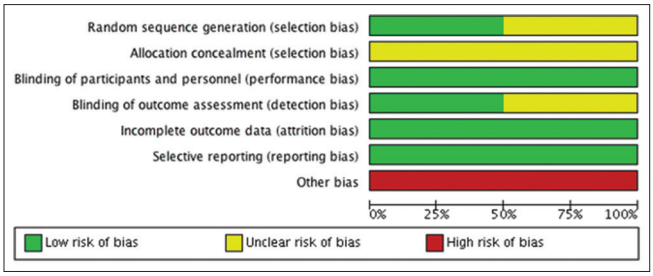

Figure 3: Risk of bias' graph: Review authors' judgments about each risk of bias item presented as percentages across all included studies

treatment group. There were no withdrawals or adverse effects noted in the Naseri *et al*. and Vasiuk *et al*. studies.

Discussion

Summary of main results

This systematic review found some relevant studies; we included three and excluded another five. Naseri *et al*. found a significant reduction in psoriasis severity in the statin group compared with placebo. Vasiuk *et al*. also found a statistically significant improvement when comparing statin with standard therapy alone. Faghihi *et al*. found no significant difference between the groups.

The difference in results between the studies is likely to be related to differences in methodological approach. Firstly, the Faghihi *et al*. study required established psoriasis diagnosis by a dermatologist but did not give a description of the types of psoriasis included or excluded. In contrast, neither Naseri *et al*. nor Vasiuk *et al*. explicitly state how the diagnosis of psoriasis was verified. Furthermore, Naseri *et al*. excluded erythrodermic and pustular psoriasis. Secondly, the baseline psoriasis severity varied for the included participants between the populations studied, as well as between the respective treatment arms within each study. Participants had different timescales of washout periods from topical therapies and the studies varied in permitted therapies that were allowed during the study period. These factors could contribute to differences in disease severity at the onset of the treatment period, which are likely to have a significant impact on the reliability with which one can interpret results for treatment effect in the respective studies.

It is likely that there is a significant demographic difference between the study populations. Naseri *et al*. (2010) and Faghihi *et al*. (2011) both studied men and women at different centers in Iran. However, Vasiuk *et al*. (2010) used a very homogenous study sample (men with arterial hypertension). Some studies suggest baseline psoriasis severity tends to be worse in men as compared to women, influencing the comparability of the results. It is also feasible that there is a gender difference in response to statin therapy.[23] It is not known whether other co-morbidities, especially cardiovascular risk factors, influence statin response.

The included studies used different statins - Faghihi *et al*. and Vasiuk *et al*. used atorvastatin, whereas Naseri *et al*. used simvastatin. Little is known about dose equivalence in terms of the anti-inflammatory action of statins and it is possible that certain statins may be more effective than others at improving psoriasis severity.[24] Faghihi *et al*. reassessed participants' PASI score after a period of 12 weeks, Naseri *et al*. reassessed the score after 8 weeks, whereas Vasiuk *et al*. reassessed response after 3 months and 6 months. This may account for some of the differences in the outcome, since the time scale of potential anti-inflammatory benefit is not known. Vasiuk *et al*. found a significantly greater reduction in psoriasis severity in the statin group which appeared to continue up to a 6-month period. This may suggest that the anti-inflammatory action of statins may endure beyond 3 months and thus has implications for interpreting the negative findings of the Faghihi *et al*. study which had a follow-up period of only 12 weeks.

Furthermore, the included studies differed in their statistical approach using different methods to assess statistical significance. None of the included studies stated whether measurements followed an approximate normal distribution. In addition, Faghihi *et al*. controlled for baseline characteristics unlike the other two included studies.

In terms of adverse effects, the statins were generally well tolerated with only one patient dropping out from the statin arm of the Faghihi *et al*. study (due to somnolence which is not a known side effect of atorvastatin).[25] There were no withdrawals from the other two included studies. These results are in accordance with the good tolerability of statins when used for their lipid-lowering effect.[26]

Quality of the evidence

The "risk of bias" assessment showed that all the included studies were at high risk due to small sample size and unclear risk of selection bias via potential lack of allocation concealment. Faghihi *et al*. did not describe a method of outcome assessment blinding and thus the risk of detection bias was unclear, whereas the other two studies did not specify a method of random sequence generation.[21] The possibility of publication bias from unpublished negative results cannot be excluded. This may have potentially large effects on any overall assessment given the paucity of any positive results.

Excluded studies

All of the excluded studies found an improvement in psoriasis severity in their respective statin groups and the statins were well tolerated which is in line with the findings of the included studies.

Shirinsky *et al*. used an open-label, single arm study design with seven participants, putting it at high risk of selection, performance and detection bias. Furthermore, the lack of a comparator made it difficult to ascertain whether the improvement in psoriasis severity was related to commencing the statin, or as a response to the permitted therapies used in the treatment period.[17] Colesman *et al*., Aronsen *et al*. and Shirinsky *et al*. used very small study samples; their results need to be interpreted with caution since they are likely to be vulnerable to the random play of chance.[17,19-20]

Conclusions

Limitations

Included studies were of limited sample size and quality. They were not amenable to pooled analysis.

Implications for practice

There is insufficient evidence that the use of oral statins as an adjunctive therapy, even though well tolerated, can reduce the severity of psoriasis. There is only one placebo-controlled, randomized control trial to date that has shown that they may be beneficial in reducing the severity of psoriasis.

Implications for research

This review highlights the paucity of high quality, randomized, double-blinded placebo-controlled trials investigating the effects of statins on psoriasis severity using clinically objective measures. Since these are well-tolerated drugs with promising non-randomised single arm trial results, it seems possible that larger evidence-based trials can be conducted. Future studies need to ensure that enrolled participants have a standardized diagnosis of psoriasis, preferably by a dermatologist, and need to be larger in size to ensure adequate statistical power. It would also be advisable for future studies to control for baseline characteristics since there is some evidence that gender differences may affect baseline psoriasis severity and thus, potentially affect disease response. Furthermore, it is feasible that a statin-induced disease response may extend beyond a 1–2 month time period and longer follow-up periods may detect delayed response.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Appendix 1: Google Scholar (all in title), Cochrane database (title, abstract, keywords) and Clinical trials.gov (all field) database search

1. Psoriasis
2. Statin
3. Statins
4. Atorvastatin
5. Simvastatin
6. Rosuvastatin
7. Pravastatin
8. Fluvastatin
9. 2 or 3 or 4 or 5 or 6 or 7 or 8
10. 1 and 9.

Appendix 2: MEDLINE (all fields) and EMBASE via OVID (keyword) database search

1. Psoriasis
2. Statin
3. Statins
4. Atorvastatin
5. Simvastatin
6. Rosuvastatin
7. Pravastatin
8. Fluvastatin
9. 2 or 3 or 4 or 5 or 6 or 7 or 8
10. 1 and 9
11. Randomized controlled trial
12. Randomized controlled trials
13. Controlled clinical trial
14. Random allocation
15. Double-blind method
16. Single blind method
17. Clinical trials
18. Clinical trial
19. Placebos
20. Placebo
21. Random
22. Research design
23. Comparative study
24. Evaluation studies
25. Follow-up studies
26. Prospective studies
27. 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
28. 10 and 27.

Data extraction sheet

Methods

1. Type of study
   a. Randomization
   b. Blinding
   c. Method of control.
2. Setting
   a. Number of centers
   b. Location of center (s) involved.

Participants

a. Number of patients
b. Baseline characteristics of participants
c. Diagnosis of psoriasis (type/practitioner diagnosing)
d. Washout period
e. Inclusion and exclusion criteria.

Interventions

a. Route
b. Type of statin
c. Dose
d. Follow-up period
e. Permitted concomitant therapies.

Outcomes

a. Primary outcomes
b. Secondary outcomes
c. Withdrawals
d. Adverse effects.

Risk of bias

a. Random sequence generation (selection bias)
b. Allocation concealment (selection bias)
c. Blinding of participants and personnel (performance bias)
d. Incomplete outcome data (attrition bias)
e. Selective reporting (reporting bias)
f. Size.