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Risk of Infection in Patients with Atopic Dermatitis Treated with Dupilumab: A Meta-Analysis of Randomized Controlled Trials

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Abstract:

Background: Atopic dermatitis (AD) is characterized by skin barrier defects, Th2 activation, and increased risk for cutaneous and extracutaneous infections. In clinical trials, dupilumab appeared to decrease rates of skin infections in AD.

Objective: We aimed to determine the impact of dupilumab on rates of skin and other infections in patients with moderate-to-severe AD.

Methods: We conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) of dupilumab for AD. We searched the PubMed database for relevant studies. Risk ratios (RR) and 95% confidence intervals (CI) for skin infections, herpesvirus infections and overall infections and infestations were calculated for dupilumab compared with placebo using binary random-effects meta-analysis. For the analysis of eczema herpeticum, Peto odds ratios (OR) were calculated.

Results: Eight RCTs in 4 publications with 2,706 participants were included with follow-up time ranging from 4-52 weeks. Meta-analysis including all dosing schedules and follow-up times showed a RR of skin infection of 0.54 (95% CI: 0.42-0.70) and an OR of eczema herpeticum of 0.34 (95% CI: 0.14-0.84) for dupilumab compared with placebo. No significant association was found for dupilumab with overall herpesvirus infections (RR=1.16, 95% CI: 0.78-1.74) and overall infections (RR=0.98, 95% CI: 0.83-1.16).

Limitations: Our analysis is limited by short follow-up time in most trials and relatively low number of patients treated with dupilumab to date.

Conclusion: Dupilumab is associated with a decreased incidence of skin infections and eczema herpeticum in adults with moderate-to-severe AD. The mechanism underlying this association is uncertain, but is likely related to improvement in AD severity.

Clinical Implications:

Dupilumab, a monoclonal antibody targeting IL-4 and IL-13, appears to significantly decrease the risk of skin infections and eczema herpeticum in adults with moderate-to-severe atopic dermatitis.

Capsule Summary:

- Atopic dermatitis is often associated with increased risk for cutaneous and extracutaneous infections
- Our meta-analysis demonstrated that dupilumab was associated with a statistically significant decrease in cutaneous infection, but not overall infections.
- Clinicians using dupilumab should be aware there is substantially decreased risk of skin infections and eczema herpeticum

Introduction:

Atopic dermatitis (AD) is a chronic skin condition affecting approximately 7% of US adults.¹ The pathogenesis of AD involves skin barrier defects, including abnormal epidermal lipid and protein structure and function, and activation of the Th2 immune pathway.² Bacterial diversity is also thought to play a role, with abnormal colonization of gram positive bacteria including *Staphylococcus aureus* among patients with AD.³

Patients with AD have an increased risk of cutaneous bacterial infection.⁴ Reasons for these infections are likely multifactorial, including decreased expression of anti-microbial peptides, skin barrier disruption and an overabundance of *S. aureus*.⁵ AD patients are also at risk for eczema herpeticum, a severe form of herpes virus infection, because of skin barrier disruption and decreased cathelicidin and interferon-gamma production.⁶ AD patients are also at increased risk for extra-cutaneous infections, suggesting that systemic immune dysregulation plays a significant role in infection risk.^{4, 7}

Dupilumab is a fully-human monoclonal antibody that inhibits signaling of the Th2 cytokines IL-4 and IL-13 by targeting the IL-4R α subunit.⁸ A recent meta-analysis of randomized controlled trials (RCTs) concluded that dupilumab was effective and safe compared with placebo.⁹ In phase III trials, dupilumab appeared to be associated with fewer skin infections compared with placebo.¹⁰ To date, no studies have specifically examined the effects of dupilumab on infection risk among AD patients. Given the important role of infections in the morbidity of AD, we aimed to estimate the effect of dupilumab therapy on the risk of skin and other infections in AD patients using a systematic review and meta-analysis of RCTs.

Materials & Methods:

We followed the recommendations of the Preferred Items for the Reporting of Systematic Reviews and Meta-Analysis (PRISMA) statement as applicable and a PRISMA checklist is provided in the supplementary material.¹¹ Our study protocol was registered with PROSPERO (http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016048855). Ethics review is not required for this type of research at our institutions. We followed the PICOS format in devising our research questions:

Population: AD patients

Intervention: Dupilumab

Comparator: Placebo

Outcomes:

1. Skin infection;

2. Overall herpetic infections (of any organ system);

3. Eczema herpeticum; and

4. Overall infections or infestation of any organ system.

Setting: Randomized controlled trials

There was some heterogeneity among the RCTs in the terms used for overall skin infections. Terms from the RCTs included in our study as skin infections were “skin infections,”⁸ “skin structures and soft tissue infections,”¹² “adjudicated skin infection”¹⁰ and “non-herpetic skin infections.”¹³

We included randomized, placebo-controlled trials of the use of subcutaneous dupilumab in patients with AD. We excluded observational studies, reviews, and case reports and studies

examining the use of dupilumab for other conditions, such as asthma. We included only English-language studies.

Search Strategy and Screening:

We searched PubMed using “dupilumab” as our search term without any limitations on October 6, 2016. Searching beyond PubMed has been shown to have minimal effect on the results of systematic reviews and meta-analyses.¹⁴ Titles and abstracts were independently screened by both authors using abstrackr (Beta Version; Providence, RI)¹⁵ based on our pre-determined inclusion criteria. Full text review for inclusion in the study was conducted by both authors (PF & AMD). We planned to adjudicate any disagreement by consensus. The reference lists of included studies were manually searched for potentially relevant studies. During peer review, it was suggested that we update our search to include newly published literature; this was done on June 15, 2017.

Data Extraction:

One reviewer extracted data on study characteristics (study author, year, study design, study duration, number of participants randomized, number of participants analyzed in safety analysis and industry funding), participant characteristics (age in years, sex (% male), race (% Caucasian), average baseline Eczema Activity Severity Index (EASI) score, and study intervention (dose and route of dupilumab and whether concomitant topical steroids were allowed) and outcome data (overall skin infections, overall herpetic infections, eczema herpeticum, overall infections of any organ systems). When data for an outcome was not

available for a study, the study sponsors were contacted to obtain results; we were unable to obtain any unpublished data.

Statistical Analysis:

Our outcomes were compared between study subjects with AD receiving dupilumab and those receiving placebo. For skin, herpes and overall infections, we conducted binary random effects meta-analysis using the DerSimonian-Laird method and a correction factor of 0.5 to calculate risk ratios (RR) and 95% confidence intervals (CI). For the analysis of eczema herpeticum, we calculated odds ratios (OR) using the Peto method as this is a more appropriate method for rare outcomes. Alpha was set at 0.05 and all statistical tests were 2-sided. We calculated the I^2 statistic and chi-squared test for heterogeneity.

For each outcome, the primary analysis included all doses of dupilumab or placebo used as monotherapy or with concomitant topical corticosteroids over the full duration of each trial. We conducted secondary analyses that separately examined each of the 2 most common dupilumab dosing schedules (300 mg once weekly and 300 mg every other week). We conducted sensitivity analyses in which studies that allowed for concomitant use of topical corticosteroids were excluded. During peer review, it was suggested that we analyze results by treatment duration; sensitivity analyses were therefore conducted limiting inclusion to trials of 16 weeks' duration, which was the only duration used in more than 2 trials. All statistical analyses were conducted using OpenMeta[Analyst] software (<http://www.cebm.brown.edu/openmeta/>).

Risk of Bias:

We completed a detailed risk of bias assessment at the study level using the Cochrane Risk of Bias tool.¹⁶ To assess for publication bias, we searched the gray literature using clinicaltrials.gov and the WHO ICTRP databases.

Deviations from the Registered Protocol:

Eczema herpeticum was added as an outcome of interest after registration of the protocol. The secondary and sensitivity analyses were also added after protocol registration once we examined the included studies' designs in detail.

Results:

Our initial search yielded 62 articles (Figure 1). After full-text review, we included 7 RCTs from 3 publications.^{8, 10, 12} Our updated search retrieved an additional 28 new titles and abstracts, with 1 additional RCT meeting our inclusion criteria.¹³ In total, we included 8 RCTs with 2706 adult participants with moderate-to-severe AD randomized to dupilumab or placebo (Table 1). Two of the trials reported in *Beck et al.* were combined in the safety analysis of the published trial manuscript.⁸ The included trials ranged from Phase I to Phase III with durations ranging from 4 to 52 weeks.

In our analysis including all dosing schedules, dupilumab was associated with a decreased risk of skin infections (RR=0.54, 95% CI: 0.42-0.70; Figure 2). There was no significant association between dupilumab and herpes infections (RR=1.16 95% CI: 0.78-1.74; Figure 3). Dupilumab was associated with decreased odds of eczema herpeticum (OR=0.34, 95% CI: 0.14-0.84; Figure 4). There was no association between dupilumab and overall infection risk (RR=0.98, 95% CI: 0.83-1.16; Figure 5). There was no statistically significant heterogeneity in any of our primary analyses.

The effect estimates for skin infections, herpes infections and overall infections were similar for the 300 mg once weekly and 300 mg every other week dosing schedules. The negative association between dupilumab and eczema herpeticum was attenuated and was no longer significant when the analysis was limited to the 300 mg weekly dosing arms. For skin infections, herpes infections and overall infections, there were no material changes in the sensitivity analyses excluding trials with concomitant topical corticosteroid use or restricted to trials of 16 weeks' duration. Dupilumab was no longer associated with lower risk of eczema

herpeticum when excluding RCTs with concomitant topical corticosteroid use or restricted to only 16 weeks' duration, primarily due to exclusion of the 1-year RCT.¹³

All studies were considered to be generally at low risk of bias (Table 2). However, *Beck et al.* does not present data on overall herpes infections and overall infections and *Thaçi et al.* does not present data on overall infections.^{8, 12} Additionally, there are minor discrepancies in the number randomized and number included in the safety analysis for SOLO1 and SOLO2 and *Blauvelt et al.*, including sample sizes being larger in the safety analysis than the number randomized.^{10, 13} All included studies were industry-sponsored. Our search of trial registries returned 3 completed but unpublished studies and 2 ongoing studies. After our updated search, 1 of those studies (*Blauvelt et al.*) had been published.¹³

Discussion:

In this meta-analysis of published RCTs, treatment with dupilumab was associated with a 46% decrease in skin infections compared with placebo. This finding was robust to sensitivity analyses examining results by different doses, treatment duration and dupilumab monotherapy. Dupilumab was also associated with a decrease in eczema herpeticum, primarily driven by the results of an RCT with 1 year follow-up.¹³ Dupilumab was associated with a non-significant increase in herpes infections and we found no association with overall infection risk.

The reason for the decrease in skin infections and eczema herpeticum with dupilumab is unknown, but normalization of the skin barrier and microbiome and treatment of the aberrant immune response in AD are likely candidates. Other anti-inflammatory treatments, namely topical betamethasone and pimecrolimus, have been shown to improve epidermal barrier dysfunction in AD.¹⁷ Treatment with topical anti-inflammatory treatments has also been shown to improve microbial diversity.¹⁸ Excess IL-4 and IL-13 are associated with lower beta-defensins; as such, a dupilumab-induced decrease in IL-4 and IL-13 signaling may lead to an increase in beta-defensins and a corresponding decrease in infection risk.¹⁹

Placebo-controlled RCTs of other systemic and topical agents for AD have not consistently reported infection rates, making external comparisons difficult.²⁰⁻²⁴ Topical crisaborole, an inhibitor of phosphodiesterase-4, appeared to decrease skin infection rates in patients with mild-to-moderate AD in its Phase III RCTs.²⁵ In a recent RCT comparing topical emollients and cortisocosteroids vs. topical or oral antibiotics for mildly infected pediatric AD, anti-inflammatory treatment alone was sufficient to treat the infection.²⁶ These findings suggest that the lower rates of skin infection seen in our study are related to improvement in AD disease activity, rather than a specific effect of dupilumab. Examining patient-level data on AD severity

and skin infections in the dupilumab RCTs would help provide further insights into this relationship.

Eczema herpeticum is an uncommon but serious complication of AD caused by herpes simplex viruses that can lead to death and requires treatment with systemic antiviral medications.^{27, 28} Studies have shown that IL-4 and IL-13 decrease epidermal LL-37, an antimicrobial peptide active against herpes simplex viruses²⁹⁻³¹ and that IL-4 and IL-13 enhance HSV-1 replication.³² Thus, blocking IL-4 and IL-13 may have specific antiviral effects.

The effect of dupilumab on other herpes infections is less clear. Counting statistics and effect measures such as relative risk are insufficient to fully understand the impact on herpes virus infections. Episodes of orogenital herpes simplex may be recurrent and treatment is often aimed at abbreviating an episode; therefore, details such as frequency and duration of outbreaks would be beneficial. Future studies examining the impact of dupilumab on herpesviruses in more detail are warranted.

Given associations between AD and extracutaneous infections,^{4, 7} one could hypothesize that disease control with targeted therapy has the potential to decrease overall infection risk. Conversely, it is unknown what, if any, immunosuppressive effects targeting of IL-4 and IL-13 with dupilumab in humans may have. In our study, we found no association between dupilumab and overall infection risk in AD patients. In an RCT of dupilumab for asthma, bacterial infections were seen in 2% of subjects in the placebo arm and 0-1% of subjects in the dupilumab arms.³³

Our study has several strengths and limitations. Our analyses are comprehensive and include all published RCTs to date. We registered our protocol in advance, but one outcome (eczema herpeticum) was added after protocol registration. Our inclusion of 4 primary outcomes

may have led to issues with multiplicity and over-estimation of statistical significance; however, correcting for multiplicity is generally not encouraged for meta-analyses.¹⁶ We rely exclusively on data from RCTs which typically have high internal validity but low generalizability. Heterogeneous terms were used in the RCTs to describe overall skin infections and, for 2 outcomes (herpes infections and overall infections), data was not reported in all trials. Future RCTs of treatments for AD should report infectious adverse events in a more standardized fashion to enable comparisons. Most included studies are of short duration (≤ 16 weeks); longer studies with more patients will enable more precise estimates of the impact of dupilumab on various infections will be possible.

Conclusion:

Dupilumab was associated with decreased skin infections and eczema herpeticum in our meta-analysis of 8 placebo-controlled RCTs. We did not find an association between dupilumab and overall herpes virus infections or infections and infestations. The mechanism underlying dupilumab's effects on skin infections is uncertain, but is likely related to improvement in AD severity.

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Table Legends:**Table 1 - Description of included studies****Supplementary Table 1 – Risk of bias assessment for included studies****Figure Legends:****Figure 1 – PRISMA flow diagram****Figure 2 – Forest plot for the relative risk of skin infections for all doses of dupilumab compared with placebo****Figure 3 – Forest plot for the relative risk of herpes virus infections for all doses of dupilumab compared with placebo****Figure 4 - Forest plot for the odds ratio of eczema herpeticum for all doses of dupilumab compared with placebo****Figure 5 - Forest plot for the relative risk of overall infections and infestations for all doses of dupilumab compared with placebo**

Table 1. Description of included studies

Study ID	Study Design & Duration	TCS Use	Intervention Arms	Number randomized	Age, years (mean, SD)	Sex (n, % male)	N, % Caucasian	Mean Baseline EASI (SD)
Beck et al., 2014A/B	Phase 1 RCT (Combined US and Global study) with 4-week follow-up	Not individually reported	Placebo	16	37.4 (4.3)	11 (69%)	13 (81%)	22.8 (3.0)
			Dupilumab 75 mg (n=8), 150 mg (n=22), or 300 mg (n=21) once weekly	51	42.6 (1.9)	28 (55%)	39 (76%)	30.0 (2.0)
Beck et al., 2014C	Phase 2a RCT with 12-week follow-up	Not individually reported	Placebo	54	39.4 (1.7)	27 (50%)	54 (100%)	30.8 (1.9)
			Dupilumab 300mg once weekly	55	33.7 (1.4)	31 (56%)	55 (100%)	28.4 (1.8)
Beck et al., 2014D	Phase 2a RCT with 4-week follow-up	Yes	Placebo + TCS	10	37.8 (5.3)	5 (50%)	10 (100%)	24.1 (4.0)
			Dupilumab 300mg once weekly + TCS	21	36.0 (2.5)	8 (38%)	20 (95%)	23.1 (2.7)
ThaçI et al., 2015	Phase 2b RCT dose-finding study of Dupilumab with 16-week follow-up	Not individually reported (counted as non-responders with other therapies)	Placebo	61	37.2 (13.1)	40 (66%)	NR	32.9 (12.8)
			Dupilumab 300 mg every other week	64	39.4 (12.1)	41 (64%)	NR	33.8 (14.5)
			Dupilumab 300 mg once weekly	63	36.2 (10.7)	43 (68%)	NR	30.1 (11.2)

			Dupilumab 200 mg every other week	62	35.8 (14.9)	36 (59%)	NR	32.9 (15.5)
			Dupilumab 300 mg every 4 weeks	65	36.8 (10.8)	40 (62%)	NR	29.4 (11.5)
			Dupilumab 100 mg every 4 weeks	65	36.6 (11.6)	34 (52%)	NR	32.2 (13.5)
Simpson et al., 2016A (SOLO 1)	Phase 3 RCT with 16-week follow-up	Not individually reported	Placebo	224	Median (IQR): 39.0 (27.0–50.5)	118 (53%)	146 (65%)	Median (IQR): 31.8 (22.2–43.8)
			Dupilumab 300mg every other week	224	Median (IQR): 38.0 (27.5–48.0)	130 (58%)	155 (69%)	Median (IQR): 30.4 (21.5–40.8)
			Dupilumab 300mg once weekly	223	Median (IQR): 39.0 (27.0–51.0)	142 (64%)	149 (57%)	Median (IQR): 29.8 (22.0–41.2)
Simpson et al., 2016B (SOLO 2)	Phase 3 RCT with 16-week follow-up	Not individually reported	Placebo	236	Median (IQR): 35.0 (25.0–47.0)	132 (56%)	156 (66%)	Median (IQR): 30.5 (22.1–41.7)
			Dupilumab 300mg every other week	233	Median (IQR): 34.0 (25.0–46.0)	137 (59%)	165 (71%)	Median (IQR): 28.6 (21.0–40.1)

			Dupilumab 300mg once weekly	239	Median (IQR): 35.0 (25.0–46.0)	139 (58%)	168 (70%)	Median (IQR): 29.0 (21.2–41.8)
Blauvelt et al. 2017	Phase 3 RCT with 1 year follow-up	Yes	Placebo + TCS	315	Median (IQR): 34.0 (25.0–45.0)	193 (61%)	208 (66%)	Median (IQR): 29.6 (22.2–40.8)
			Dupilumab 300 mg every other week + TCS	106	Median (IQR): 40.5 (28.0–49.0)	62 (58%)	74 (70%)	Median (IQR): 30.9 (22.3–41.6)
			Dupilumab 300 mg every week + TCS	319	Median (IQR): 34.0 (26.0–45.0)	191 (60%)	208 (65%)	Median (IQR): 29.0 (21.6–40.7)

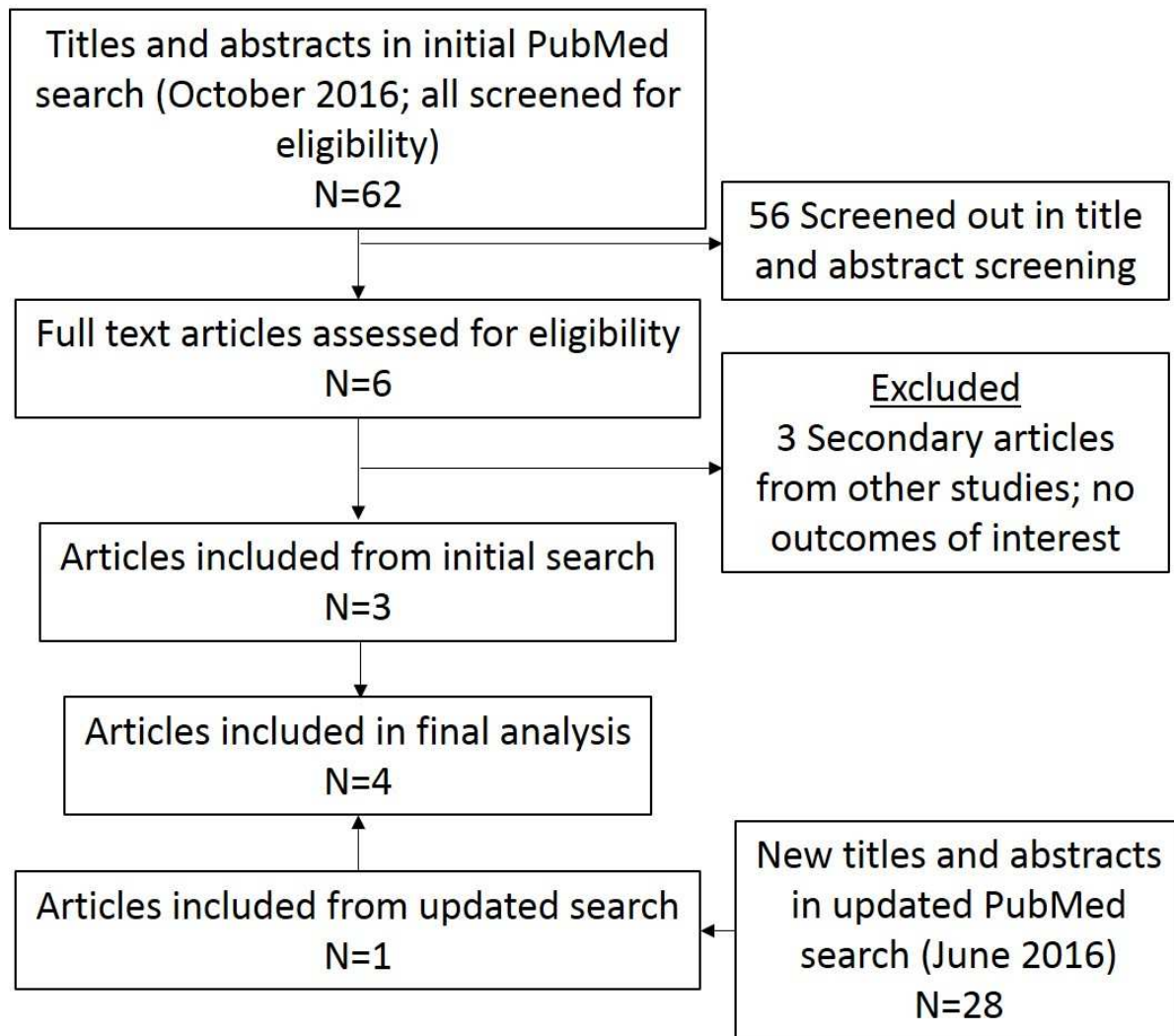
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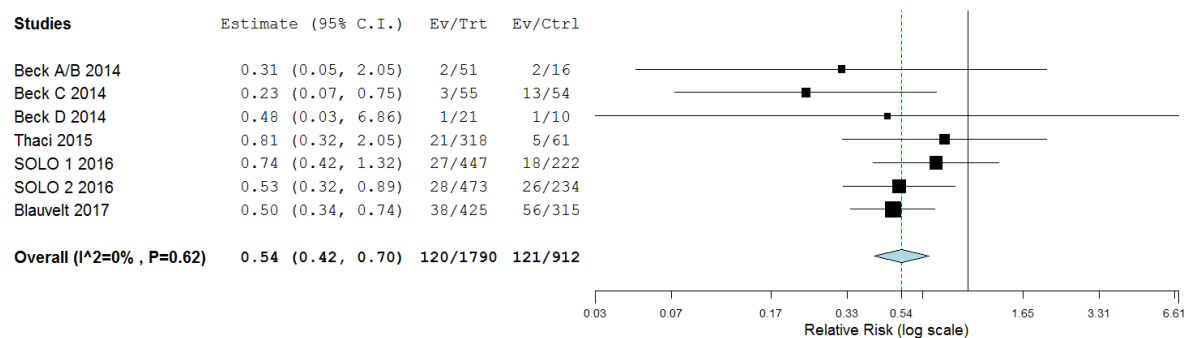
415 Table 1 continues on next page

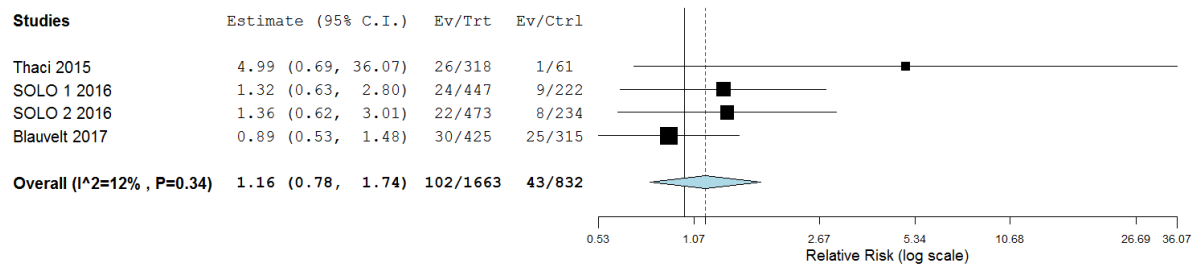
<i>Note these 2 columns are placeholders and can be deleted if the entire table can be fitted on 1 page in the journal</i>						
Study ID	Study Intervention	Number in Safety Analysis	Overall Skin Infections (n, %)	Overall Herpetic Infections (n, %)	Eczema Herpeticum (n, %)	Overall Infections of All Organ Systems (n, %)
Beck et al., 2014A/B	Placebo	16	2 (13%)	NR	0 (0%)	NR
	Dupilumab	51	2 (4%)	NR	0 (0%)	NR
Beck et al., 2014C	Placebo	54	13 (24%)	NR	2 (3.6%)	NR
	Dupilumab	55	3 (6%)	NR	0 (0%)	NR
Beck et al., 2014D	Placebo	10	1 (10%)	NR	0 (0%)	NR
	Dupilumab	21	1 (6%)	NR	0 (0%)	NR
Thaçi et al., 2015	Placebo	61	5 (8%)	1 (2%)	0 (0%)	NR
	Dupilumab 300 mg every other week	64	5 (8%)	5 (8%)	0 (0%)	NR
	Dupilumab 300 mg once weekly	63	3 (5%)	3 (5%)	1 (2%)	NR
	Dupilumab 200 mg every other week	61	5 (8%)	6 (10%)	1 (2%)	NR
	Dupilumab 300 mg every 4 weeks	65	3 (5%)	4 (6%)	0 (0%)	NR
	Dupilumab 100 mg every 4 weeks	65	5 (8%)	8 (12%)	0 (0%)	NR
Simpson et al., 2016A (SOLO 1)	Placebo	222	18 (8%)	9 (4%)	2 (1%)	63 (28%)
	Dupilumab 300mg every other week	229	13 (6%)	15 (7%)	1 (0.4%)	80 (35%)

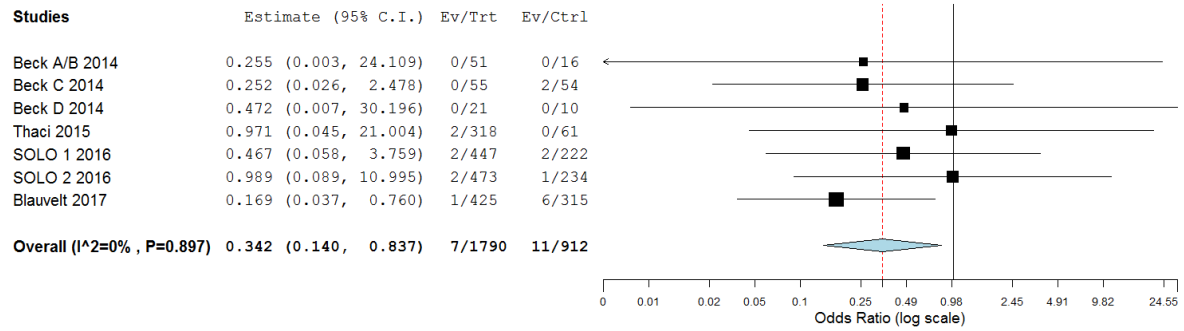
	Dupilumab 300 mg weekly	218	14 (6%)	9 (4%)	1 (0.5%)	74 (34%)
Simpson et al., 2016A (SOLO 2)	Placebo	234	26 (11%)	8 (3%)	1 (0.4%)	76 (32%)
	Dupilumab 300mg every other week	236	13 (6%)	10 (4%)	2 (0.8%)	65 (28%)
	Dupilumab 300 mg weekly	237	15 (6%)	12 (5%)	0 (0%)	68 (29%)
Blauvelt et al. 2017	Placebo	315	56 (18%)	25 (8%)	6 (2%)	182 (58%)
	Dupilumab 300mg every other week	110	12 (11%)	8 (7%)	1 (1%)	63 (57%)
	Dupilumab 300 mg weekly	315	26 (8%)	22 (7%)	0 (0%)	166 (53%)

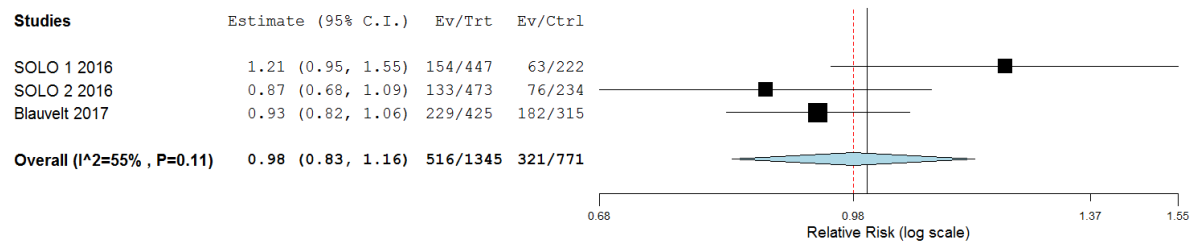
EASI: Eczema Area and Severity Index; NR: Not reported; RCT: Randomized controlled trial; TCS: Topical corticosteroids











Supplementary Table 1. Risk of bias assessment

Study ID	Adequate Generation of a Random Sequence	Adequate Allocation Concealment	Adequate Blinding of Participants	Adequate Blinding of Treaters	Adequate Blinding of Outcome Assessors	Complete Outcome Data	Complete Reporting	Other Bias
Beck et al., 2014A/B	Yes	Yes	Yes	Yes	Yes	Yes	No	None identified
Beck et al., 2014C	Yes	Yes	Yes	Yes	Yes	Yes	No	None identified
Beck et al., 2014D	Yes	Yes	Yes	Yes	Yes	Yes	No	None identified
Thaçi et al., 2015	Yes	Yes	Yes	Yes	Yes	Yes	No	None identified
Simpson et al., 2016A (SOLO 1)	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	None identified
Simpson et al., 2016A (SOLO 2)	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	None identified
Blauvelt et al., 2017	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	None identified