Bijlage 7: Studiekarakteristieken en risico op bias

Studiekarakteristieken MPE

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size
Chattopadhyay, 2012	Type of study: cross-sectional Setting: Outdoor department of Oral and Maxillofacial Surgery and Pharmacology in a Dental teaching institute and department of General Medicine in a Govt. medical College Country: India Source of funding: not reported	Inclusion criteria: All patients suspected of having drug reactions Exclusion criteria: Not reported N total at baseline: 4000 patients of which 275 developed a cutaneous drug reaction, of which 152 (55%) MPE Important prognostic factors: Causative agents: Antimicrobials (47.5%), NSAIDs (45%), antidepressants	Intervention was reported for all patients with adverse cutaneous reactions - 35% “required” antihistaminic and topical corticosteroid - 25% “required” a combination of antihistaminics, topical and systemic corticosteroïds Reasons for “requiring” a certain treatment were not reported	- 40% “required” only antihistaminic	Length of follow-up: 3 years Loss-to-follow-up: Not reported Incomplete outcome data: Not reported	Treatment effects, as well as effect on quality of life, mortality and pruritus were not reported

		(5%), antiepileptic drugs (5%)				
Hashimoto, 2021	Type of study: Retrospective Setting: University Hospital Country: Japan Source of funding: This research received no external funding	Inclusion criteria: Patients using immune checkpoint inhibitors who underwent skin biopsy and received a diagnosis of cutaneous immune related adverse event (irAE) Exclusion criteria: (1) those with inflammatory eruption attributed to another drug type other than ICIs (e.g., NSAIDs and antibiotics) (2) those with an irAE of vitiligo alone or pruritus without inflammatory eruption N total at baseline:	- 7 patients (all in class 1 and 2) received systemic steroids (<0,4 mg/kg prednisolone) - 9 patients (all in class 3 and 4) received systemic steroids (0,4 – 1,0 mg/kg prednisolone) and/or topical steroids - 7 patients (all in class 3 and 4) received systemic steroids (>1,0 mg/kg prednisolone) or methylprednisolone 1000 mg/day pulse and/or topical steroids	- 28 patients (all in class 1 and 2) received topical steroids or systemic antihistaminics	Length of follow-up: Loss-to-follow-up: Not reported Incomplete outcome data: Not reported	7 of 51 cases (13.7%) resulted in temporary interruption and 7 (13.7%) resulted in permanent discontinuation due to cutaneous irAEs 50/51 cutaneous irAEs improved with appropriate dermatologic therapy, interruption of immunotherapy, or both. The study did not report how ‘improvement’ was defined/measured

		51 with cutaneous rAE of which 38 (74,5%) MPE				
Phillips, 2019	Type of study: Retrospective Setting: Country: USA, Italy Source of funding: National Cancer Institute Cancer Center Support Grants, Beca Exelencia Fundacion Piel Sana	Inclusion criteria: Patients with a variety of solid tumors treated with anti–CTLA-4 (ipilimumab, tremelimumab), anti–PD-1 (nivolumab, pembrolizumab), or anti–PD-L1 (atezolizumab, avelumab, durvalumab) therapy who were diagnosed with an ircAE, received dermatologic management, and had follow-up records for assessment of treatment outcome	- 133 (47%) patients received systemic therapies, of which 51 patients received systemic steroids	- 213 patients (75%) received topical steroids of which 94 (44%) only topical steroids	Length of follow-up: Until resolution of symptoms or end of treatment (max 2277 days) Loss-to-follow-up: Outcomes were available for 331 of 427 cutaneous reactions Incomplete outcome data: Not reported	Outcome measures and effect size Outcome (n = 331) Significant improvement 151 (46%) Moderate improvement 103 (31%) No improvement 77 (23%) The largest improvement was observed in MPR (mean grade reduction, 21.40; standard deviation, 0.96) Patients who were treated with systemic therapies had higher-grade ircAEs compared with patients who were treated with topical therapies (mean grade, 2.23 v 1.53; P , .001)

		Exclusion criteria: Not reported N total at baseline: 285 patients with 427 cutaneous eruptions of which 120 (28%) MPE				
Wang, 2020	Type of study: Retrospective study Setting: Country: Source of funding:	Inclusion criteria: Patients who participated in an alpelisib trial and developed a dermatologic Adverse Event (dAE) Exclusion criteria: Not reported N total at baseline: 102 patients. 41 patients (40.2%) had a rash. Of those patients where morphology was	Grade 1 or 2 rash (n=22): 10 (45,5%) received oral antihistaminics with topical steroïds, 4 received only oral antihistaminics Grade 3 rash (n=19): 12 (63%) received topical and systemic steroïds and oral antihistaminics. 3 (16%) received oral antihistaminics met topicale steroïds en 3 (16%) received only systemic corticosteroïds.	4 patients in the Grade 1 or 2 rash group received no dermatologic treatment.	Length of follow-up: Loss-to-follow-up: Intervention: N (%) Reasons (describe) Control: N (%) Reasons (describe) Incomplete outcome data: Intervention: N (%) Reasons (describe) Control: N (%) Reasons (describe)	Outcome measures and effect size (include 95%CI and p-value if available):

		reported, 26 (89,7%) had MPE				

RoB MPE

Beoordeling risk of bias middels Newcastle-Ottawa scale (NOS).

		Selection				Comparability	Outcomes			
Study	Study design	Representativeness of the intervention cohort	Selection of the non intervention cohort	Ascertainment of intervention	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow up long enough for outcomes to occur	Adequacy of follow up of cohorts	Explanations
Chattopadhyay 2012	Crossectional	-	-	★	★	-	★	-	-	- Only 50.5% of patients with a cutaneus reaction had MPE, there was no subgroup presentation of results - Reasons for starting or abstaining from intervention were not given - Follow-up not mentioned
Hashimoto 2021	Retrospective	-	-	★	★	-	-	-	-	- Only 74,5% of patients with a cutaneous reaction had MPE. There was no subgroup presentation of results - Reasons for (not) treating were not clearly reported however patients with higher grade reactions received more treatment - Authors did not describe how 'improvement' was determined - Follow-up was not reported
Philips 2019	Retrospective	-	-	★	★	-	★	★	-	- Only 28% of patients with a cutaneous reaction had MPE. There was no subgroup presentation of results - Reasons for (not) treating were not clearly reported however patients with higher grade reactions received more treatment - Patients were followed until resolution of symptoms

Wang 2020	Retrospective	-	-	★	★	-	★	-	-	- Only 89,7% of patients with a cutaneous reaction had MPE. No subgroup data was presented - Patients received treatment depending on severity of symptoms

Studiekarakteristieken DRESS

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Nam 2015	Type of study: Retrospective analysis of prospectively collected data Country: Korea Source of funding: Not reported Inclusion criteria: Patients with DRESS: acute skin rash; fever of more than 38 ◦C in a patient after taking a specific drug; at least one of the following internal organ abnormalities: lymphadenopathy at a minimum of two sites, hepatitis, nephritis, and/or pneumonitis, haematological abnormalities with eosinophilia, the presence of atypical lymphocytes, thrombocytopenia and/or leucopoenia Exclusion criteria: Cases of typical manifestations of	N total at baseline: 45 Intervention: Control: Important prognostic factors: Mean Age (SD) 57,6 yrs (15,7) 42,2% male Mean RegiSCAR score: 4,4 (SD 1,4)	Systemic corticosteroids (n=10) Dosage and frequency not reported	Topical steroids and antihistamines (n=35)	Length of follow-up: Until resolution of symptoms or death/referral to other hospital <u>Loss-to-follow-up</u>: Not applicable	Outcome measures and effect size (include 95%CI and p-value if available): Mean time of admission Systemic corticosteroids: 46,0 days (SD 30,1) Topical steroids and antihistamines: 18,4 days (SD 11,7) P<0.05 Prognosis - 43 patients (95,6%) recovered completely - 1 patient in SCS group died due to sepsis - 1 patient (treatment group not reported) was referred to other hospital due to progressive hepatic failure Recurrence rate: 11% (n=5, treatment groups not reported)	There is probably confounding by indication

	Stevens---Johnson syndrome and toxic epidermal necrolysis						
Nguyen 2020	Type of study: retrospective case-control Country: USA Source of funding: Not reported Inclusion criteria: DRESS diagnosed by dermatology consultation and regiSCAR score >5, who received IV or oral cyclosporine and controls were age&sex matched Exclusion criteria: Not reported	N total at baseline: 26 Important prognostic factors: Age (SD) I: 43 (13,1) C:44,5 (16,6) Sex: I: 20 % M C: 33,3% M Time from disease onset to treatment Days (SD): I: 6,5 (3,0) C: 6 (5,8)	Cyclosporine (n=5) treated with intravenous or oral cyclosporine (3-5 mg/kg divided twice daily for 7 days, tapered to 1.5-2.5 mg/kg divided twice daily for 7 days) Reasons for receiving cyclosporine: - history of steroid induced psychosis (n=2) - history of diabetes (n=1) - After starting with SCS and obtaining mucosal lesions (n=1) - not reported (n=1)	Systemic corticosteroids (n=21) Treated with IV methylprednisolone 1-2 mg/kg daily with variable prednisone taper dose	Length of follow-up: Until resolution of symptoms <u>Loss-to-follow-up</u>: Not applicable	Time from treatment initiation to halted progression (days) Mean (SD) I: 2,0 (1,2) C: 2,8 (2,3) Time from treatment initiation to improvement of erythema (days) Mean (SD) I: 3,5 (2,4) C: 5,5 (3,7) Time to resolution of erytroderma (days) Mean (SD) I: 15,7 (3,1) C: 21,7 (8,1) Length of hospital stay (days) Mean (SD) I: 8,1 (5) C: 16,2 (9,7) Length of treatment (days) Means (SD) I: 12,5 (4,0) 48,5 (53,0) No statistical analysis was performed.	

RoB DRESS

Beoordeling risk of bias door middel van AMSTAR

Study First year, author	Appropriate and clearly focused question? Yes/no	Comprehensive and systematic literature search? Yes/partial yes/ no	Description of included and excluded studies? Yes/partial yes/ no	Description of relevant characteristics of included studies? Yes/partial yes/no	Assessment of scientific quality of included studies? Yes/partial yes/no	Enough similarities between studies to make combining them reasonable? Yes/partial yes/ no	Potential risk of publication bias taken into account? Yes/partial yes/ no	Potential conflicts of interest reported? Yes/partial yes/ no
Afiouni, 2021	Yes	Yes	Partial Yes Reasons for exclusion are briefly mentioned but studies are not referenced	No No data of individual studies was shown and no description of possible heterogeneity was provided	No Not reported	Partial yes Although no individual data is reported, in- and exclusion criteria should garantuee some similarities. However outcomes are provided for the total group while treatment and severity of disease may influence results. There was no confounder analysis	No Not reported	No
Kim, 2020	Partial yes Research question is not very clear, PICO can be deducted from search strategy and in/exclusion criteria	Yes	No Reasons for exclusion and references are not included	No No data of individual studies was shown and no description of possible heterogeneity was provided	No Not reported	Partial yes Although no individual data is reported, in- and exclusion criteria should garantuee some similarities. However outcomes are provided for the total group while treatment and severity of disease may influence results. There was no confounder analysis	No Not reported	Yes

Beoordeling risk of bias middels Newcastle-Ottawa scale (NOS).

		Selection				**Comparability**	**Outcomes**			
Study	Study design	Representativeness of the intervention cohort	Selection of the non intervention cohort	Ascertainment of intervention	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow up long enough for outcomes to occur	Adequacy of follow up of cohorts	Explanations
Nam 2015	Retrospective analysis of prospectively collected data	★	-	★	★	-	★	★	★	- Although reasons for non-intervention were not stated, there is a very high risk of confounding by indication. - patients were followed until resolution of symptoms and description of those lost was provided
Nguyen 2020	Retrospective case-control	★	★	★	★	-	-	★	★	- Selection of controls was age- and sex-matched - Although patients and controls were age and sex matched, it is unclear if the severity of disease was similar in both groups. Baseline comparison was not performed. - It is unclear how some outcomes, e.g. improvement of erythema, were assessed

Studiekarakteristieken AGEP

Study reference	Study characteristics	Patient characteristics	Intervention (I)	Comparison / control (C)	Follow-up	Outcome measures and effect size	Comments
Alniemi 2017	Type of study: Retrospectieve review van 28 patiënten met AGEP uit 1 kliniek. Country: USA Source of funding: None.	Inclusion criteria: -Patienten met AGEP -Euroscore 5-12 middels biopsie van iedereen te bekijken en zo een score te geven afhankelijk van de infiltratie van neutrofielen en eosinofielen. Exclusion criteria: -Euroscore <5 -onbekende oorzaak AGEP. N total at baseline: N=28 N=26 na exclusie. Intervention: N= 3 Control: N= 18 Overige hebben een combinatie behandeling gehad van lokaal en systemisch. Important prognostic factors[2]: Mean age : 56 (20-88 jaar)	Systemische corticosteroiden N=2 alleen prednisone N= 1 prednison en antihistaminica	Topicale corticosteroiden. N= 12 alleen topicaal N= 6 topicaal en antihistaminica.	Length of follow-up: Tot aan symptoom vrije periode en bij 1 persoon tot na de tweede AGEP reactie. Meeste waren <15 dagen klachten vrij. Gemiddeld 7.6 dagen. Loss-to-follow-up: Niet beschreven. Incomplete outcome data: N=2 (niet duidelijk wat de oorzaak van AGEP was)	All study patients achieved the full resolution of their AGEP eruption post-treatment. There was no difference in clinical outcome based on which treatments the patients received. Zeer kleine interventie groep die systemische medicatie heeft gehad. Onderzoek is niet opgezet voor vergelijkend onderzoek tussen systemische en lokaal, maar er blijken meerdere combinatie behandelingen gedaan te zijn met tevens antihistaminica toegevoegd bij enkele groepen.	

Thienvibul 2015	Retrospectieve studie N= 19 Thailand Inclusion criteria: -Iedereen met diagnose AGEP in dossier. -EuroSCAR score>5 Exclusion criteria: -Geen duidelijke diagnose. -Bekend met psoriasis in VG.	Important prognostic factors: Age 19-84, mean 52 jaar Sex V: 52.6% M: 47.4% Gemiddelde duur tot klachten na inname culprit drug: 1 uur tot 25 dagen AGEP symptomen - 17 patiënten hadden gegeneraliseerde letsels - 2 gelokaliseerde letsels. Ziekenhuisopname 16 patiënten werden opgenomen in het ZH en 3 buiten het ziekenhuis behandeld.	1. Topicale corticosteroïden. N= 11 2. Orale corticosteroïden. N= 6 (allen met uitgebreide huidletsels en/of systemische betrokkenheid.	Supportive care N=2	Niet beschreven.	Time to resolution of erytroderma (days) Median: 3 dagen (2-12 dagen) Geen verschil tussen de groepen (p=0.171) (ANOVA) I: 1. Topicale corticosteroïden. 2 dagen 2. Orale corticosteroïden. 3 dagen C: Supportive care 2,5 dagen	There were no differences between various treatment regimens regarding the median duration of medication cessation to resolution of pustules which were 2 days for topical corticosteroid, 3 days for oral prednisolone, and 2.5 days for supportive care (P = 0.171).

RoB AGEP

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Alniemi 2017	Retrospectief	★	-	★	★	-	★	★	-	- Alleen patiënten met een EuroSCARscore van 5-12 werden meegenomen. - Rede voor interventie werd niet genoemd. - patiënten werden gevolgd tot de klachten verdwenen waren.
Thienvibul 2015	Retrospectief	★	-	★	★	-	★	★	-	- Patienten met een EuroSCAR score > 5 werden meegenomen. - Geen beschrijving van de groepen en therapie keuze. Niet duidelijk of de ernst van de klachten invloed heeft gehad. - Alle patiënten werden gevolgd tot genezing van klachten.