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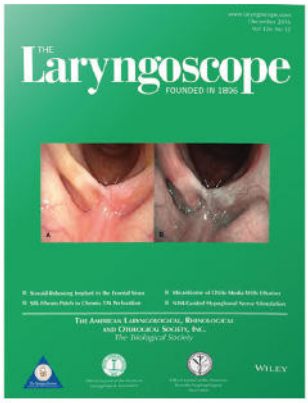

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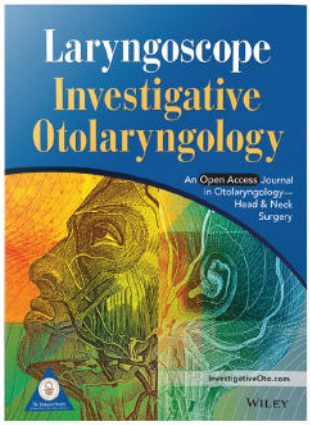

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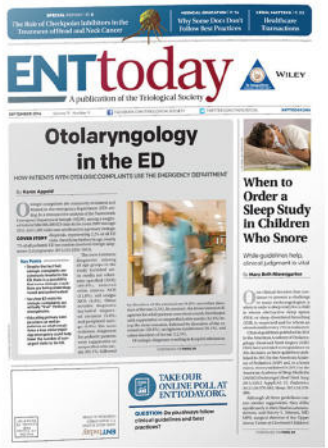

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REVIEW

Laryngoscope Investigative Otolaryngology

Intramuscular corticosteroid injections in seasonal allergic rhinitis: A systematic review

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Abstract

Objective: Seasonal allergic rhinitis (SAR) is an exaggerated immunological reaction to allergens (pollen) in the air. In a small subgroup of patients, SAR can be difficult to control with first-line therapy. Intramuscular corticosteroid injections (IMCIs) are an additional treatment in this subgroup of SAR patients. The aim of this systematic review is to investigate the efficacy and safety of IMCIs in SAR.

Methods: Titles and abstracts were independently screened, followed by full-text screening based on predefined criteria. Included articles were critically appraised using the Cochrane Risk of Bias 2 (RoB 2) tool. The primary outcome is reported as the final conclusion about efficacy that was stated in the included studies. The secondary outcome is the safety of IMCIs with regard to long lasting side-effects.

Results: The search yielded 2139 records, of which 10 were relevant and valid for our clinical question. Critical appraisal showed high risk of bias, which was due to unclear description of methods. Four out of four placebo-controlled, randomized controlled trials reported a significant and relevant difference in efficacy in favor of IMCIs compared with placebo. The occurrence of side-effects was not different between IMCIs and placebo or oral corticosteroids (OCs).

Conclusion: The outcome of this systematic review on trials concerning intramuscular steroid injections, despite being based on individual studies claiming favorable outcome with their use, is "inconclusive." This is because of the epidemiological high risk of bias in these studies that were mostly executed more than 30 years ago. The "inconclusive" rating allows for a description as an "optional therapy" for severe cases in guideline formation.

KEYWORDS

hay fever, intramuscular corticosteroids, seasonal allergic rhinitis, treatment

1 | INTRODUCTION

Seasonal allergic rhinitis (SAR), also known as hay fever, is an exaggerated immunological reaction to allergens (grass, weed, and/or tree pollen) in the air. SAR is a common disease with a prevalence of 230-300 cases per 1000 patients in the Netherlands.[1] SAR is characterized by clinical symptoms such as a running nose, sneezing, and itching eyes; its intensity can range from mildly irritating to incapacitating.[2] The vast majority of patients experience sufficient relief of complaints with first-line therapy, which includes nasal corticosteroids, oral and intranasal antihistamines, and topical ophthalmic products.[2,3] However, in a small subgroup of patients, severe symptoms can adversely affect quality of life and disrupt normal activities, despite the use of first-line therapy.[2,3] The current international and Dutch guidelines advise immunotherapy to reduce the underlying immune response permanently in severe cases.[1,4] But, this therapy is not always an instant adequate option for every patient, because the patients often visit the outside department in the pollen season, a moment at which immunotherapy should not be started.[5] Immunotherapy is time-consuming; it takes several years of intensive therapy before the desired effect is accomplished. Therefore, there is a need for temporary therapies that may bridge patients suffering till immunotherapy is fully effective. Ostergaard et al[3] performed a systematic review on the safety and efficacy of intramuscular corticosteroids injections (IMCIs), demonstrating that IMCIs could be a safe and effective treatment option. The advantage of an IMCI is that it provides rapid relief of symptoms. However, this treatment is advised against in current guidelines and reviews.[6,7] The negative advise mainly stems from concerns about its safety; especially the usual corticosteroid-related side-effects[8] such as adrenal suppression, have hampered IMCI use for SAR in nowadays otolaryngology practice.[2,6,9] However, a recent position paper by the EAACI has left oral corticosteroids (OCs) as an optional treatment for SAR patients with very severe and therapy-resistant symptoms.[10] Considering that OCs are recommended as an optional treatment modality in very severe and therapy-resistant SAR, and IMCIs are recommended against for the same patient population, a new systematic review was performed. In this systematic review, an update of the review by Ostergaard et al[3] was performed on the efficacy and safety of IMCIs in SAR patients.

2 | METHODS

2.1 | Data sources and searches

PubMed, Embase, and the Cochrane Database of Systematic Reviews were systematically searched up to December 2020 for published studies, using the keywords "seasonal allergic rhinitis" and "corticosteroid" with MeSH terms and synonyms (queries in Appendix S1). This electronic search strategy was augmented by a manual examination of references cited in articles, recent reviews, editorials, and meta-analyses. No restrictions were imposed on the language, study period, or sample size.

2.2 | Study selection and outcome definition

After removal of duplicates, two authors (AB and EB) independently performed title and abstract screening. They resolved any differences in a consensus meeting (with IS). Full article screening was done likewise. Included studies were used for this study after full text screening which included manual search of articles through references. The following inclusion and exclusion criteria were used according to the PICOS-principle:

Population: Patients with SAR (as mentioned in the individual article, at least based on clinical grounds with symptoms [ie, paroxysms of sneezing, rhinorrhea, nasal obstruction, nasal itching, postnasal drip, cough, irritability, and fatigue] or/and clinical history).

Intervention: Intramuscular corticosteroids.

Comparator: Oral corticosteroids, different sorts of intramuscular corticosteroids, placebo or other therapies.

Outcome: The primary outcome was the efficacy outcomes as published by the individual studies. The secondary outcome was side-effects, and in particular adrenal suppression.

Study design: Randomized-controlled trials (RCTs) were included in this review. Case reports, observational studies or (narrative) reviews were excluded.

Further exclusion criteria were animal studies and studies without full-text availability. Two authors (AB and FS) independently assessed the applicability and validity of the included RCTs. The Cochrane Risk of Bias tool (Rob2) was used for the critical assessment. Details about the Rob2 can be found on the Cochrane website.[11] Differences about the quality of the articles were resolved in a consensus meeting with IS.

2.3 | Data extraction and quality assessment

From the included studies the following data were extracted: first author's name, year of publication, number of patients, study arms, generic formula of the corticosteroid, used dosage, length of follow-up, and patient characteristics (mean age and gender). To show the differences between the IMCIs and the comparator, the primary outcome of efficacy mentioned by the individual studies was reported in Table 1. Additionally, the significance of the difference between treatment groups in individual studies was assessed. If a study showed statistical significance, it classified was as *superiority IMCI*. If the outcomes were similar or worse, it was classified as *equal* or *inferiority IMCI*, respectively. Studies that compared IMCIs to OCs or placebo were used for efficacy analysis. This study was reported according to the PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Healthcare Interventions: Explanation and Elaboration.[12]

3 | RESULTS

3.1 | Search and critical appraisal

The search (Figure 1) identified 2139 potentially relevant articles. After screening, 10 articles[13–23] that fulfilled the inclusion criteria

TABLE 1 Characteristics of included studies (n = 10)

Year	Author	Methods	Participants	Interventions	Outcomes
1960	Brown (n = 95)	RCT-placebo controlled 1 center	Adults poorly responding to hyposensitization or no previous treatment Setting: hospital Study location: United States	6-methylprednisone IM 80 mg weekly Placebo	Symptom-free at final follow-up Side-effects
1968	Chervinsky (n = 97)	RCT 1 center	Adults poorly responding to hyposensitization or no previous treatment Setting: hospital Study location: United States	Methylprednisone IM 80 mg Betamethasone phosphate/acetate IM 6/6 mg Dexamethasone acetate/phosphate disodium 16/4 mg Dexamethasone acetate IM 16 mg	Patients' satisfaction (none, poor, fair, good, and excellent) Side-effects
1969	Hermance (n = 70)	RCT 1 center	Patients with perennial allergic rhinitis. Setting: hospital Study location: United States	Dexamethasone actetate 16 mg or 8 mg Cortisone acetate 10 mg	Maximum relief of symptoms (none, slight, moderate, marked, or complete)
1972	Axelsson (n = 38)	RCT-placebo controlled 1 center	Adults with severe non-infectious rhinitis (allergic and vasomotor rhinitis) Setting: hospital Study location: Sweden	Triamcinolone acetonide IM 40 mg once Placebo	Subjective improvement of symptoms. Side-effects
1979	Kronholm (n = 42)	RCT 1 center	Patients with fairly stable seasonal allergic rhinitis. Setting: hospital Study location: Denmark	Betamethasone dipropionate/phosphate IM 10/4 mg Methylprednisone acetate 80 mg	Symptoms (nasal congestion, rhinorrhea, sneezing, itch (nose and eyes), lacrymation and conjunctivitis) were scored (0 to 3) Various time points were used (1, 2,3, 4 and 5 weeks).
1980	Ohlander (n = 59)	RCT 1 center	Patients with severe seasonal allergic rhinoconjunctivitis. Setting: hospital Study location: Sweden	Betamethasone dipropionate IM 5 mg Betamethasone disodium phosphate/acetate IM 3/3 mg4 Methylprednisone acetate 40 mg	Onset and duration of symptom-free state. Plasma cortisol
1987	Borum (n = 24)	RCT-placebo controlled 1 center	Adults with rhino-conjunctivitis in June-July over the last 2 years which required symptoms. Positive skin prick test to timothy grass. Setting: hospital Study location: Denmark	Methylprednisolone IM 80 mg once Placebo Permitted to use eyedrops or anti-histamine tablets.	Reduction of symptoms (rhinorrhea, sneezing, and eye itching). Side-effects
1987	Laursen (n = 36)	RCT 1 center	Pollen-allergic patients with seasonal rhinoconjuctivitis Setting: hospital Study location: Denmark	Oral prednisolone 7.5 mg daily for 3 weeks Betamethasone dipropionate IM 2 mL Betamethasone disodium phosphate IM 2 mL.	Reduction of symptoms (nasal blockage, nasal running, sneezing, nasal itching, and eye symptoms). Eosinophils ACTH measurements Side-effects
1988	Laursen (n = 30)	RCT-placebo controlled 1 center	Birch pollen allergic outpatients with seasonal rhinoconjunctivitis Setting: hospital Study location: Denmark	Betamethasone dipropionate IM 5 mg Betamethasone disodium Phosphate IM 2 mg Beclomethasone dipropionate nasal (100 μg) Placebo	Symptom score (nasal blockage, nasal running, sneezing, nasal itching, and eye symptoms) Side-effects
1988	Pichler (n = 30)	RCT 1 center	Patients with allergy to pollen Setting: hospital Study location: Sweden	Methylprednisone IM 80 mg Nasal aerosol budesonide 400 μg	Symptom score (absent, slight, moderate, good, and very good) White-blood cell count, plasma cortisol, and ACTH Side-effects

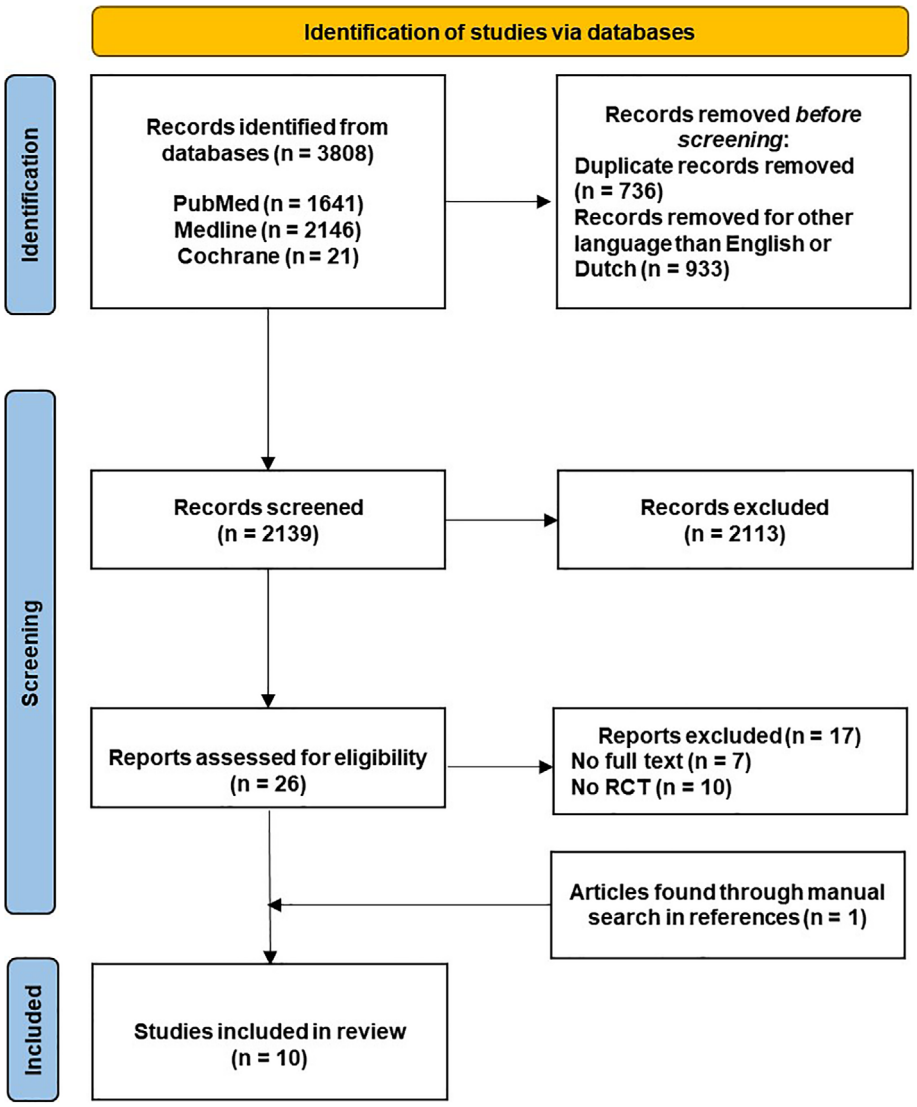

FIGURE 1 Flowchart of included studies

were included for quality assessment. The baseline characteristics of these studies are presented in Table 1. The applicability and quality of the included studies is represented in Figure 2. All included studies were applicable on the domain, determinant and outcome of the research question. A high risk of bias was often noted due to limited description of the used research method. None of the studies published a prior study protocol to verify potential selective reporting or mentioned potential conflict of interest.

3.2 | Outcomes

3.2.1 | Study characteristics

The summary of study characteristics can be found in Table 1. All studies were RCTs that investigated IMCIs for SAR. Tables 2 and 3 describe the main findings of the included articles. In total, there were 387 patients treated with IMCIs, 77 patients treated with placebo and 44 patients treated with steroids via other routes of administration (19 patients with OCs and 25 patients with nasal steroids). Six studies[13,15–17,20,22] showed superiority of IMCI compared with placebo or other therapies. The remaining four studies[14,18,19,21] showed equal efficacy outcomes in comparison with the control groups.

3.2.2 | Placebo controlled trials

Four placebo controlled randomized trials were performed that assessed the efficacy of IMCIs.[13,16,20,22] Brown et al[13] performed a placebo-controlled randomized trial for methylprednisolone IMCIs for SAR. Patients received an injection weekly of either placebo or treatment, depending to what group the patient was randomized. After the first injection, 26 (9%) and 10 (4%) patients had complete relief of symptoms in the treatment (n = 294) and placebo (n = 231) groups. After the second injection, 35 (12%) and 11 (5%) had complete relief of symptoms, and after the third injection 60 (20%) and 17 (7%) patients had complete

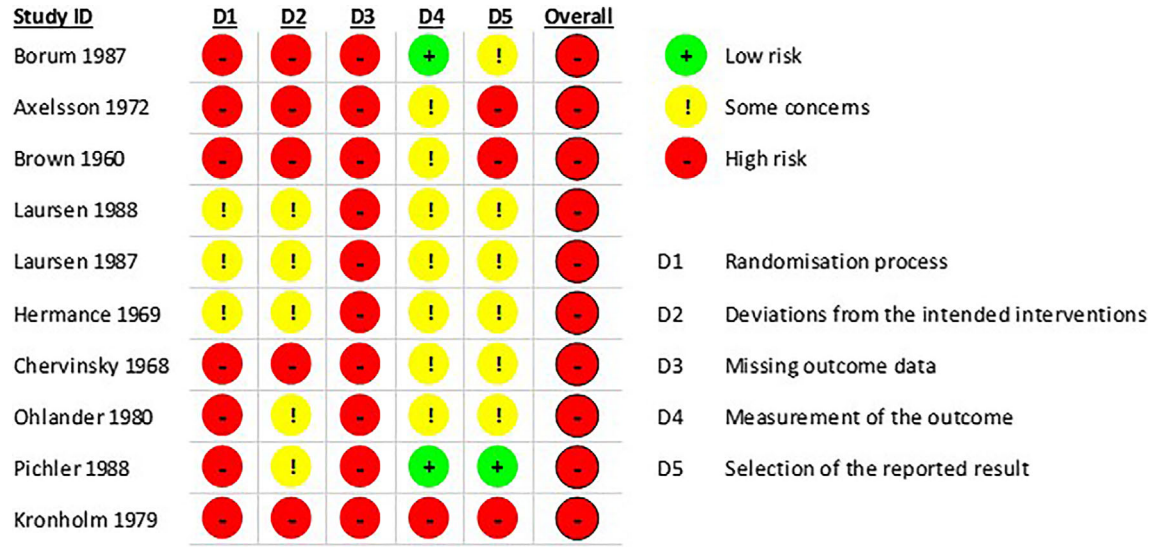

FIGURE 2 Summary of risk of bias assessment

relief. After the third injection, 5 (2%) and 46 (20%) patients were still suffering from moderate or severe complaints. Axelsson et al[16] compared triamcinolone acetonide IM to placebo for SAR in a randomized trial. Ten days after the injection, 16 (94%) and 2 (10%) patients restored or improved after treatment (n = 17) and placebo (n = 21). The unimproved patients were given a triamcinolone acetonide IM injection. The remaining patient in the treatment group did not improve, whereas 16 (84%) out of 19 unimproved placebo patients restored or showed improvement after IMCI. Furthermore, Borum et al[20] performed a double-blind, placebo-controlled randomized trial comparing intramuscular methylprednisolone versus placebo. They performed two trials, one at the start of the pollen season ("early medication") and another trial at the peak of the pollen season ("late medication").

In the early medication trial, reduction of nose blockage symptoms (mean score, no numbers given in trial) was in favor of the IMCI group (except in week 4, no significant difference). In the late trial, a significant difference between the two groups in favor of the IMCI group was reached in week 3-4 after treatment. Regarding rhinorrhea, a significant difference in symptom scores between the two groups was only found in week 3 (early trial), and in the late trial the difference in symptom scores was found in week 3-4. Significant improvements in favor for relief of eye itching were found in week 2-3 (early trial) and week 4-5 (late trial). No significant difference was found for the frequency of sneezing between the groups neither in the early, nor the late medication trial. The symptom score for sneezing was the lowest for the steroid group in week 3-4 in the late trial. Laursen et al[22] compared betamethasone dipropionate IMCIs to beclomethasone nasal spray and placebo. In the first 2 weeks, the so called "run-in period," the total daily symptom score for the IMCI (week 1 and 2:3.2 [0.7] and 2.6 [0.9]), nasal beclomethasone (2.6 [0.8] and 3.1 [0.4]) and placebo (1.7 [0.3] and 2.0 [0.8]) were determined. After 6 weeks of follow-up the total daily symptom score for the IMCIs (0.9 ± 0.3) were significantly better compared with nasal beclomethasone (total daily symptom score: 3.0 ± 0.8, $P < .01$) and placebo (total daily symptom score: 4.7 ± 0.7, $P < .01$). In the other weeks no statistics were performed, the outcomes can be found in Table 2.

3.3 | Different IMCI formulas

Four studies compared different IMCI formulas.[14,15,17,18] Kronholm et al[17] compared betamethasone dipropionate + betamethasone phosphate IM to methylprednisolone acetate IM. They showed significant differences in average symptom scores for nose symptoms (sneezing, congestion, and rhinorrhea) after 1 (1.5 vs 3.2; $P < .005$), 2 (2.1 vs 4.6; $P < .005$), 3 (2.4 vs 4.6; $P < .025$), and 4 (2.3 vs 5.5; $P < .025$) weeks in favor of betamethasone compared with methylprednisolone. However, after 5 weeks of treatment, there was no significant difference (3.5 vs 6.2; $P > .05$). No significant differences were found for eye symptoms in all the 5 weeks. Chervinsky et al[14] compared four different intramuscular steroid preparations: dexamethasone phosphate; dexamethasone acetate; betamethasone phosphate/acetate; and methylprednisolone acetate. They found no difference between the four different steroid preparations in terms of efficacy and side-effects (patient reported appraisal means: 4.0 vs 3.8 vs 3.6 vs 4.0, $P > .05$). Ohlander et al[18] compared three different IMCIs (betamethasone dipropionate, betamethasone disodium phosphate and betamethasone acetate, and methylprednisolone acetate) for patients with SAR. All three preparations improved nasal symptoms. There were no individual differences in onset or duration of action. Exact numbers of patients who improved symptoms were not given. Furthermore, Hermance et al[15] performed a study that compared three different IMCI formulations (dexamethasone acetate 16 or 8 mg or cortisone acetate 10 mg). Complete relief of symptoms was found in four (17%), three (13%) and four patients (17%) who

TABLE 2 Placebo-controlled studies involving intramuscular corticosteroids for severe allergic rhinitis

Year	Author	Mean age + range (years)	Females (n/N)	Steroid	Dose (mg)	Frequency IMCI	Side-effects (n, %)	Comparative	Dose (mg)	Side-effects (n, %)	Length of follow-up	Efficacy	Notes
1960	Brown	31.6	MP: 30/50 Placebo: 20/45	MP (n = 50)	80	Single	35 (70%)	Placebo (n = 45)	–	36 (80%)	30 days	Superiority ICMI	Symptoms first injection (day 1-7): $P < .001$ MP • None: 26% • Slight: 28% • Moderate: 34% • Severe 12% Placebo • None: 10% • Slight: 25% • Moderate: 42% • Severe: 23% Second injection (day 8-14): $P < .001$ MP • None: 35% • Slight: 47% • Moderate: 16% • Severe 2% Placebo • None: 11% • Slight: 37% • Moderate: 33% • Severe: 19% Third injection (day 15-21): $P < .001$ MP • None: 60% • Slight: 35% • Moderate: 5% • Severe: 0% Placebo • None: 17% • Slight: 36% • Moderate: 36% • Severe: 10%
1972	Axelsson	28 (18-51)	22/38	TC (n = 17)	40 (n = 21)	Single	–	Placebo	–	–	20 days	Superiority ICMI	Restored or improved IMCI: 16 (94%) Placebo: 16 (76%) [after IMCI as rescue medication]

TABLE 2 (Continued)

Year	Author	Mean age + range (years)	Females (n/N)	Steroid	Dose (mg)	Frequency IMCI	Side-effects (n, %)	Comparative	Dose (mg)	Side-effects (n, %)	Length of follow-up	Efficacy	Notes
1987	Borum	24 (18-36)	8/24	MP (n = 12) (early: start of pollen season)	80	Single	–	Placebo (early) MP (n = 12) (late: pollen peak)	–	–	5 weeks	Superiority ICMI	Early medication *Nasal blockage*: $P < .05$ (week 4 no significant difference). *Sneezing*: $P > .05$ *Eye itching*: $P < 0.05$ (week 2-3) *Rhinorrhea*: $P < .05$ (week 3) Late medication *Nasal blockage*: $P < .05$ (week 3-4) *Sneezing*: $P < .05$ (score value, not frequency) *Eye itching*: $P < .05$ (week 4-5) *Rhinorrhea*: $P < .05$ (week 3-4)
1988	Laursen	32 (17-52)	13/30	BM P (n = 10)	7	Single	2 (13%)	Placebo (n = 11) BM (n = 9)	– (nasal)	0 (0%)	6 weeks (4 weeks after treatment)	Superiority ICMI	IMCI was superior to both topically applied steroid and placebo after 6 weeks of treatment ($P < .01$) *Total daily symptom score* IMCI Week 1 3.2 (0.7) Week 2 2.6 (0.9) Week 3 2.9 (0.6) Week 4 2.4 (0.8) Week 5 1.4 (0.6) Week 6 0.9 (0.3) BM Week 1 2.6 (0.8) Week 2 3.1 (0.4) Week 3 5.1 (0.5) Week 4 9.1 (1.3) Week 5 5.0 (0.9) Week 6 3.0 (0.8) [$P < .01$] Placebo Week 1 1.7 (0.3) Week 2 2.0 (0.8) Week 3 4.8 (0.7) Week 4 8.0 (0.7) Week 5 6.3 (0.6) Week 6 4.7 (0.7) [$P < .01$]

Note: The outcome was the amount of patients with complete remission or improvement of symptoms as described the individual studies.
Abbreviations: A, acetate; BM, betamethasone; CA, cortisone acetate; DM, dexamethasone; MP, methylprednisone; P, dipropriate; TC, triamcinolone.

TABLE 3 Comparative studies involving intramuscular corticosteroids for severe allergic rhinitis

Year	Author	Mean age + range (years)	Females (n/N)	Steroid	Dose (mg)	Frequency of IMCI	Side-effects (n, %)	Comparative	Dose (mg)	Side-effects (n, %)	Length of follow-up	Efficacy	Notes
1968	Chervinsky	N.R.	N.R.	MP (n = 24) i.m.	80	Single	0 (0%)	BM A + P (n = 20) i.m. DM A + P (n = 23) i.m. DM A (n = 17) i.m.	6-6 16-4 16	0 (0%) 3 (13%) 3 (18%)	14 days	Equal	Scoring system effect therapy (1: none, 2: poor, 3: fair, 4: good, 5: excellent) Mean score MP: 4.0 BM A + P: 3.6 DM A + P: 3.8 DM A: 4.0
1969	Hermance	14-62	32/70	DM (n = 23) i.m.	16	Single	2 (9%)	DM (n = 24) i.m. CA (n = 23) i.m.	8 10	4 (17%) 4 (17%)	4 weeks	Superiority ICMI	DM 16 mg Complete relief: 4 (17%) Marked relief: 12 (52%) Moderate relief: 2 (9%) Slight relief: 2 (9%) None relief: 3 (13%) Mean score: 3.5* DM 8 mg Complete relief: 3 (13%) Marked relief: 13 (54%) Moderate relief: 3 (13%) Slight relief: 3 (13%) None Relief: 2 (8%) Mean score: 3.5* CA 10 mg Complete relief: 4 (17%) Marked relief: 1 (4%) Moderate relief: 0 (0%) Slight relief: 4 (17%) None Relief: 14 (58%) Mean score: 2.0 * $P < .05$
1979	Kronholm	26 (9-47)	N.R.	BM D + P (n = 21) i.m.	BM D (10 mg) BM P (4 mg)	Single	0	MP (n = 21) i.m.	80 mg	0	6 weeks	BM > MP	Difference in response between BM and MP (significance level) Nose Initial 90-95% **1 week 99.5%** **2 weeks 99.5%** **3 weeks 97.5%-99%** **4 week 97.5%-99%** 5 weeks 90%-95% Eye Initial 70%-80% 1 week 92.5%-95%

TABLE 3 (Continued)

Year	Author	Mean age + range (years)	Females (n/N)	Steroid	Dose (mg)	Frequency of IMCI	Side-effects (n, %)	Comparative	Dose (mg)	Side-effects (n, %)	Length of follow-up	Efficacy	Notes
													2 weeks 70%-80% 3 weeks 90%-95% 4 week 70%-80% 5 weeks 60%-70% Total Initial 80%-90% **1 week 99%-99.5%** **2 weeks 97.5%** **3 weeks 97.5%** **4 week 95%-97.5%** 5 weeks 90%-95% **Bold** is statistically significant.
1980	Ohlander	30	21/59	BM D (n = 20) i.m.	5	Single	–	BM P + A (n = 20) i.m. MP A (n = 19) i.m.	3 40	–	4 weeks	Equal	Onset and duration of action were similar for the three preparations as was efficacy. There were no statistically significant differences among them.
1987	Laursen	N.R.	22/36	BM D + P (n = 17) i.m.	5-2	Weekly treatment (3 weeks)	4 (23%)	Prednisone (n = 19) oral	7.5 (oral)	2 (11%)	3 weeks	Equal	Adrenal gland function decreased after treatment with prednisolone ($P < .001$) contrary to treatment with Diprospan.
1988	Pichler	25 (16-45)	15/30	MPA (n = 14) i.m.	80	Single	5 (36%)	Budesonide (n = 16) (nasal aerosol)	400 μg	4 (25%)	21 days	Equal	Control of symptoms Very good • BM: 7 (47%) • MPA: 3 (21%)Good • BM: 4 (27%) • MPA: 7 (50%)Moderate • BM: 2 (13%) • MPA: 3 (21%)Slight • BM: 2 (13%) • MPA: 1 (7%)Absent • BM: 0 (0%) • MPA: 0 (0%)

Note: The outcome was the amount of patients with complete remission or improvement of symptoms as described the individual studies.
Abbreviations: A, acetate; BM, betamethasone; CA, cortisone acetate; D, dipropriate; DM, dexamethasone; MP, methylprednisone; P, phosphate; TC, triamcinolone.

received dexamethasone actetate 16 mg (n = 23) or 8 mg (n = 24) or cortisone acetate 10 mg (n = 23). Marked relief of symptoms was found in 12 (52%), 13 (54%), and 1 (4%) patients receiving the same treatments. No relief of symptoms was noted in 3 (13%), 2 (9%), and 14 (58%) patients. The entire list of outcomes can be found in Table 3.

3.4 | IMCIs versus oral corticosteroids

One study was performed that compared OCs with IMCIs. A comparison of oral prednisone to intramuscular betamethasone performed by Laursen et al[19] concluded that both treatments were equally effective in reducing symptoms (no difference in mean score for nasal blockage, nasal running, sneezing, itching, or eye symptoms) after 3 weeks of follow-up.

3.5 | IMCIs versus nasal corticosteroids

Two studies were performed that compared nasal corticosteroids to intramuscular corticosteroids.

Laursen et al[22] was already discussed here above. Pichler et al[21] compared budesonide (BUD) nasal spray with intramuscular methylprednision (MPA). It was found that the patients' reported effects for control of symptoms was: absent (BUD 0 patients, MPA 0 patients), slight (BUD 2, MPA 1 patient), moderate (BUD 2, MPA 3 patients), good (BUD 4, MPA 7 patients), and very good (BUD 7, MPA 3 patients). The duration of follow-up was 21 days. No statistical tests were reported for these comparisons. An important criticism might be that the initial severity score differed too much between the study arms.

3.6 | Safety

With regard to side-effects, no difference was seen between treatments and placebo in the number of side-effects in the included studies. In total 48 side-effects were described in eight studies[13–15,17–19,21,22]; altogether 0%-70% of all patients suffered from side-effects in these studies. The mentioned effects were: pain at injection site, fatigue, nervousness, and local subcutaneous atrophy. No severe and lasting side-effects were described in all 10 reviewed studies. The highest number of patients with side-effects (n = 35, 70%) were described by Brown et al.[13] These side-effects were mild in all but one patient for whom glycosuria was found. In their placebo group 36 patients (80%) were suffering from "side-effects." Laursen et al[22] reported that two patients in the betamethasone group suffered from itching rash in the first 3-4 days after treatment. Hermance et al[15] reported side-effects rates of 9%, 17%, and 17% in the dexamethasone 16 mg, dexamethasone 8 mg, and cortisone groups. The duration of follow-up was 4 weeks. Chervinsky et al[14] described that minor systemic side-effects occurred in three patients (flushing, headache, and vertigo) in the dexamethasone phosphate group, and also in three patients (acne, insomnia, and headache) in the dexamethasone phosphate/acetate group. Pichler et al reported that four (25%) and five (35%) patients in the budesonide and methylprednisolone groups were suffering from side-effects.

Four studies published results about the effects of IMCIs on adrenal function. Laursen et al[19] found in both the oral and intramuscular corticosteroids groups that the HPA axis was suppressed, however in both groups the cortisol levels normalized within 3 weeks. The basal plasma cortisol level was less suppressed after intramuscular betamethasone injection compared with oral prednisone.

Ohlander et al[18] reported that in all the three formulations the endogenous cortisol levels decreased significantly. The plasma cortisol levels did not normalize following the betamethasone dipropionate or methylprednisolone acetate injections after 2 weeks. Furthermore, Kronholm et al[17] did not show any effect of either betamethasone or methylprednisolone on adrenal function. Pichler et al[21] found that MPA significantly reduced plasma cortisol levels with −16.5% 1 week after treatment ($P < .05$), whereas BUD did not show a significant raise of cortisol level (+7.4%, $P > .05$). However, there was still a normal response to ACTH-stimulation in both groups.

4 | DISCUSSION

This systematic review on the efficacy and safety of IMCIs showed that IMCIs are associated with a statistical significant and, by patients determined, clinical relevant relief of symptoms when compared with placebo. Moreover, as secondary outcome IMCIs did not cause more lasting side-effects than OCs or placebo in these studies.[13,16,20,22] The different generic formulas of the corticosteroids (betamethasone, dexamethasone, and methylprednisolone) used in the studies seemed equally good in relieving symptoms.[15,18,19] The only study in which a significant difference was shown between two different generic formula's is Kronholm et al,[17] which was in favor of betamethasone compared with methylprednisolone in the first 4 weeks for nasal symptoms. It is important to note that this study had an unclear description of methods and potentially a high risk of attrition bias (Figure 2). Furthermore, no significant difference was found for nose and symptoms between the two groups after 5 weeks of follow-up. The studies that were included in this systematic review were all of high risk of bias. The included studies dated back more than 30 years ago, and were not according the current standards for randomized controlled trials. The outcome of this systematic review is considered inconclusive, therefore the option of prescribing or not prescribing IMCIs for very severe or therapy-resistant SAR should still be open in guidelines.

4.1 | Single intramuscular injections of corticosteroids

Regarding the efficacy of single IMCIs, four studies[13,15,16,21] in this review have published results of patients who had substantial remission of symptoms after single IMCIs. The results of these studies do suggest that there is a beneficial effect of a single IMCI in SAR.

However, it must be noted that no study investigated the effect of a single IMCI as rescue therapy in SAR patients who were therapy-resistant, and that the duration of follow-up was quite short in some studies.[13,16] Next, we reassessed the observational studies that were mentioned by Ostergaard et al[3] In eight out of these nine observational studies, good to excellent (70%-90% of patients had [almost] complete remission of symptoms) results were found in terms of efficacy. Only the study of Ganderton et al[24] describing only eight patients had disappointing results. Additionally, we found one observational study by Bodger et al,[25] they described the use of intramuscular methylprednisolone in a cohort of 45 university students who suffered from SAR during a severe grass pollen season. They showed that 75% obtained partial or complete relief of symptoms, and that further treatment with antihistamines was not necessary.

Guidelines often recommend immunotherapy for the severe cases in a way as if immunotherapy is mutually exclusive with IMCIs. Aasbjerg et al[26] assessed the use of IMCIs before and after the introduction of immunotherapy. In the IMCIs group the annual corticosteroid injection rate was 1.6, whereas in the immunotherapy group the annual rate was 1.0. It was found that 84% of patients did not need to use IMCIs after immunotherapy. Still, in a subgroup of patients IMCIs were used despite being on immunotherapy.

This suggests that there is a continuing need for additional symptom-relief with IMCIs in the period that immunotherapy has not yet achieved its full effect. A single IMCI might temporary relieve symptoms in very severely affected SAR patients, to bridge the allergy season till the immunotherapy has fully achieved its effects.

4.2 | Safety concerns

The first concerns about the safety of IMCIs were proposed by Ganderton et al[24] who treated eight patients with two intramuscular injections of 80 mg of methylprednisolone. The second injection was given 2 weeks after the first injection. Their patients received a relative high cumulative dose of 160 mg of methylprednisolone, whereas for this review we are especially interested in effects of a single dosage, preferably of 40 mg intramuscular triamcinolone acetonide as we prescribe in our practice.[27] Furthermore, in their study, three patients developed asthma during the clinical course of treatment, one patient had a severe exacerbation of a peptic ulcer, one developed an anterior uveitis, and another patient reported recurrence of infantile eczema. It was also found that the adrenocortical function recovered to normal in all cases after the first injection, but did not show complete normality recovery in one patient after the second injection.

However, in the placebo controlled trials, IMCIs did not show to have more side-effects compared with placebo.[13,16,20,22] HPA-axis suppression is a risk of concern in both IMCI and OC therapies.

Two of the included studies indeed reported suppression of plasma cortisol; however, it normalized within 3 weeks.[18,20] This rapid normalization pattern is supported by data from other studies that assessed IMCIs for SAR.[17,22,23,25]

4.3 | Comparison with literature

The literature concerning safety and efficacy of IMCIs in other diseases was also assessed. Recently, one large systematic review, consisting of 62 studies, was published on the effectiveness and safety of intramuscular corticosteroids in dermatological disease. It was concluded that IMCIs can be viewed as effective and safer compared with OCs.[28]

Kirkland et al[29] published a Cochrane review on IMCIs vs OCs in patients with acute asthma. In total nine studies involving 804 participants were included. IMCIs were not inferior to OCs in terms of efficacy, whereas fewer side-effects were noted with IMCIs. In 2018, Dorleijn et al[30] published a blinded randomized controlled trial on ICMI vs placebo in 107 patients with hip osteoarthritis. They showed that there was significant reduction of hip pain during walking for the entire 12-week follow-up. Avascular hip necrosis, the feared side effect from the Nasser[31] case report, was not reported. In mid-2020, an article was published comparing the pharmacokinetics of intramuscular and oral betamethasone and dexamethasone.[32] The results of this article suggest that the pharmacokinetics and pharmacodynamics (effects on glucose and plasma cortisol) are similar for both the oral and intramuscular preparations for dexamethasone and betamethasone. These results combined with the fact that there is no clinical difference in HPA axis suppression make it feasible that there is no difference between oral and intramuscular corticosteroid delivery methods in terms of HPA axis suppression. Based on the literature mentioned above, there is no reason for the major concerns regarding long-lasting suppression of plasma cortisol after a single IMCI as compared with OCs as described by the current guidelines. Hence, similar clinical and pharmacokinetic outcomes seem to exist for OCs and IMCIs, therefore an IMCI should also be considered as optional treatment modality for very severe and therapy-resistant SAR patients.[6,7,10]

4.4 | Strengths and limitations

When looking at strengths and weaknesses of this systematic review, it can be concluded that all 10 included studies are relevant to answer the research question (see Figure 2). Despite this, comparison of the studies was difficult due to heterogeneity of primary outcome measures and selected patients. Furthermore, it should be mentioned that the outcome measures in most studies were unclear and invalidated. Therefore, we chose to report as primary outcome the final conclusion that was stated in the included studies. Also, none of the studies performed a long-term follow-up period; the longest observed effect was 5 weeks after treatment. Therefore, there is no data on the effectiveness of IMCIs during the entire allergy season, which might be longer than 5 weeks. However, the peak of complaints fluctuates during the allergy season, hence only for a short period of time there might be a need for additional therapy in SAR patients treated with "first line" treatments. Moreover, none of the studies published a protocol or reported on conflicts of interest. Another limitation is that the

included studies are dated; the most recent publication year is 1989. Many of these studies had two major drawbacks with regard to clinical applicability. The first limitation is that they included patients with all grades of severity; whereas the indication for IMCIs would nowadays be only for very severe or therapy-resistant SAR. In line with that is the second drawback, that studies compared IMCIs with other therapies, whereas IMCIs should be used as an optional, rescue therapy in addition to first-line treatments. Consequently, the ideal trial would compare the added value of a single rescue IMCI vs rescue OC, and assess the side-effects of both these treatment options.

4.5 | Benefit-harm analysis

Severe SAR is a serious condition, which can have disastrous outcomes if not treated adequately.[33–36] In the Netherlands, a single injection of intramuscular triamcinolone-acetonide costs approximately €4,50 ($5).[37] Like with any other therapy, the frequency and severity of side-effects should be discussed with patients. Mygind et al[38] calculated the risk of side-effects as only one out of 11 785 injections. Based on all the data published so far, a single intramuscular injection of corticosteroids for severe SAR seems to be a cogent, cost-effective, and safe enough treatment option for patients who do not respond to conventional therapies. It is also applicable for those who will start or recently started immunotherapy, but did not yet have adequate benefit from it.

5 | CONCLUSION

The outcome of this systematic review on trials concerning IMCIs, despite being based on individual studies claiming favorable outcome with their use, is inconclusive. This as result of the epidemiological high risk of bias in the included studies that were mostly executed more than 30 years ago. Given the fact that the available "best evidence" presented herein is inconclusive, the option of prescribing or not prescribing IMCIs should still be open in guidelines. Pro's and con's should be weighed in individual patients and be the subject of shared decision making. We recommend to conduct high quality RCTs comparing OCs with a single intramuscular triamcinolone injection as additional therapy for severe cases of SAR, to establish the efficacy and safety of these prescriptions to come to a more solid therapeutic advice in the future.

CONFLICT OF INTEREST

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter of materials discussed in the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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