

Review article

Systemic corticosteroid treatment for seasonal allergic rhinitis: a common but poorly documented therapy

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Accepted for publication 17 September 1999

An International Consensus Report recommends that first-line therapy in the management of seasonal allergic rhinitis (SAR) be antihistamines in mild cases with intermittent symptoms, and intranasal corticosteroids (INCS) in severe cases with daily symptoms (1). If a patient, in spite of first-line therapy, suffers a symptom breakthrough at the peak of the pollen season, it is common practice to give a short course of systemic corticosteroids (SCS). However, no study has addressed the important question of whether SCS treatment adds to the efficacy of the first-line therapy. Generally, the effect of SCS for SAR has been poorly studied, and we have been able to find only five placebo-controlled trials (2–6).

SCS can be given orally or as an intramuscular injection of the slow-release formulation of a micro-crystalline suspension. This therapy was primarily developed and used for intra-articular injection for the treatment of arthritis (7). Only a single study has compared the two types of SCS administration with regard to the therapeutic index; i.e., the ratio between antirhinitis effect and effect on the HPA axis (8). Sales figures indicate that general practitioners often use an IMCS injection for SAR (9).

In this paper, we present a review of the few published placebo-controlled trials of SCS for SAR and of open, randomized drug-comparative studies. We

aim to stimulate colleagues to perform placebo-controlled studies in this quite neglected field of rhinitis therapy.

Studies of systemic activity

Ganderton & James (10) gave two injections of methylprednisolone acetate 80 mg, with a 14-day interval, to eight patients with SAR. Plasma cortisol levels were depressed maximally 72 h after an injection, and then they gradually returned to normal within 3 weeks.

McMillin (11) gave a single injection of triamcinolone acetonide 80 mg to 18 patients with severe SAR and measured morning plasma cortisol for 21 days. The values were decreased for varying times but had returned to initial levels within 3 weeks.

Ohlander et al. (12) gave, in a random order, a single injection of three IMCS preparations (betamethasone dipropionate 5 mg, betamethasone phosphate 3 mg plus betamethasone acetate 3 mg, or methylprednisolone acetate 40 mg) to 60 patients with severe SAR. Betamethasone dipropionate and methylprednisolone acetate reduced endogenous cortisol production for at least 14 days, while betamethasone phosphate/acetate did not suppress plasma cortisol beyond 12 days. Blood glucose was increased for 1–2 days after the injection.

Hedner & Persson (13) gave a single injection of methylprednisolone acetate 80 mg to 14 patients with SAR. The HPA function (basal plasma cortisol and plasma cortisol response to hypoglycemia) was moderately, but significantly, reduced for 2 weeks but returned to normal within 4 weeks.

Wolthers & Pedersen (14) gave either a single injection of methylprednisolone acetate 60 mg ($n=12$) or daily intranasal budesonide (200 mg b.i.d.) ($n=12$) for 6 weeks to schoolchildren with SAR. Both treatments caused a significant reduction of short-term lower-leg growth, measured by knemometry, and, surprisingly, INCS showed a tendency to a more marked reduction (0.54 mm/week) than IMCS (0.28 mm/week). In contrast, in a study of adults, Pichler et al. (15) found a significant reduction of plasma cortisol 3 weeks after a single injection of methylprednisolone acetate 80 mg, but not during treatment with intranasal budesonide (200 mg b.i.d.) for 3 weeks.

Thus, studies have shown reduced plasma cortisol levels after an IMCS injection. The effect is maximal after 3 days and disappears within 3 weeks (2–4 weeks) (10–13). These published data do not support the fear of a long-lasting suppression of HPA function from a single IMCS injection.

Studies of antirhinitis effect

The first placebo-controlled study of SCS for SAR was published in 1960 by Brown et al. (2). They gave a total of 240 mg methylprednisolone acetate, given as three injections with weekly intervals. Not surprisingly, it was the authors' overall impression that the injections resulted in "a marked relief of symptoms". Details of the results are not presented in this report and, to our knowledge, such a high-dose regimen is not used or recommended in other publications.

Axelsson & Lindholm (3) gave a single injection of triamcinolone acetonide or placebo to 38 patients with severe SAR. Symptoms were improved in 16/17 in the IMCS group and in 2/21 in the placebo group.

Borum et al. (4) performed two separate trials in 24 patients with SAR. The patients received one injection of methylprednisolone acetate 80 mg in the first study at the beginning of the pollen season (early treatment), and in the second study at the peak of the season (late treatment). The effect on nasal blockage was marked and apparent within 1–2 days. After early treatment, the effect lasted for the entire pollen season; i.e., at least for 5 weeks. Late treatment resulted in a rapid and marked fall in blockage scores. A few days after the injection, nasal blockage almost disappeared and did not recur during the remaining 4.5 weeks of the pollen season. The results for sneezing and rhinorrhea were not impressive and reached a statistically significant

level only in single weeks. However, the use of rescue medication (antihistamine tablets) was significantly higher in the placebo group than in the IMCS group.

Laursen et al. (5) gave one injection of betamethasone dipropionate 5 mg plus betamethasone phosphate 2 mg immediately before the birch-pollen season. Actively treated patients had significantly fewer symptoms, nasal blockage in particular, than the placebo-treated patients. The effect lasted for the entire observation period of 4 weeks.

Brooks et al. (6) performed the only published study on OCS. They treated a total of only 31 patients with SAR for 5 days with either placebo or methylprednisolone tablets in a daily dose of 6, 12, or 24 mg, divided into three daily doses. A statistically significant effect was obtained with 6 mg for nasal blockage, and with 24 mg for all symptoms, except itching.

While there is good evidence that SCS are highly effective in nasal blockage, the effect on sneezing and rhinorrhea seems to be less pronounced (4, 6). OCS are often used as second-line therapy in different doses, but the documentation of efficacy and choice of dosage has been evaluated only in a single placebo-controlled study of OCS used as first-line therapy (6). Apparently, methylprednisolone 6 mg daily (corresponding to 7.5 mg of prednisolone) has only a marginal effect. A dosage of 24 mg (corresponding to 30 mg of prednisolone) seems to be necessary to obtain a significant effect on all nasal symptoms. Obviously, more dose-response studies are needed to define a suitable dosage of OCS.

Comparison between OCS and IMCS

Only one double-blind study has compared these two types of SCS administration. Laursen et al. (8) gave 36 birch-pollen-allergic patients either an injection of betamethasone dipropionate 5 mg plus betamethasone phosphate 2 mg, or oral prednisolone 7.5 mg daily for 3 weeks. There was no difference between the two treatment groups with regard to effect on any nose or eye symptoms. Plasma cortisol level, measured after 3 weeks, was significantly reduced in the prednisolone group, but not in the IMCS group.

Making a choice between OCSs and IMCSs cannot be based on the results from a single published report (8). Supporters of OCS (mainly specialists) correctly argue that medication with tablets can follow the varying pollen count better than an injection. Those who use IMCS (mainly general practitioners) argue that this treatment places medication in the hands of the physician, a fact which may be of special value in a busy general practice.

Theoretically, there is no reason to believe that the therapeutic index, with regard to antirhinitis effect and systemic activity, differs between the two types of CS administration. An asthma study has indicated that a

single administration of oral prednisolone shows an effect on lung function lasting for only 12 h (16). Therefore, it is possible that twice daily oral medication gives a better 24-h protection in both asthma and rhinitis, but it may also have more effect on the HPA axis. Therefore, the choice of treatment for SAR could just as well be between prednisolone once or twice daily as between oral prednisolone once daily and IMCS.

At present, the fact that a number of controlled trials have fairly well established the dosage favors an IMCS preparation, although no dose-response study has been published. The choice of OCS dosage seems to reflect personal experience and subjective opinion, and the question of dosage has not been sufficiently clarified by the only published dose-response study, which was performed with a low number of patients (6). In addition, the clinical efficacy of a low dose of OCS has not been definitely proven. For example, it is noteworthy that one injection of methylprednisolone (80 mg) corresponds to only 20 prednisolone tablets of 5 mg.

Open comparisons between the antirhinitis effect of different IMCS preparations

Chervinsky (17) compared the efficacy (onset, degree, and duration of action) of four IMCS preparations, with special reference to the use of quickly absorbed preparations (phosphate salt) and slowly absorbed preparations (acetate ester). A total of 100 patients with severe SAR were allocated at random to receive either one injection of 1) methylprednisolone acetate 80 mg, 2) betamethasone acetate 6 mg plus betamethasone phosphate 6 mg, 3) dexamethasone acetate 16 mg plus dexamethasone phosphate 4 mg, or 4) dexamethasone acetate 16 mg. The median onset of action, reported by the patients, 3–5 h, was the same for all four groups. The degree of efficacy was similar in all groups. The median duration of action was insignificantly shorter for betamethasone acetate/phosphate than for the other preparations. The author concluded that there is no indication for adding a rapidly absorbed CS to the IMCS preparation.

Kronholm (18) gave 42 patients with SAR one injection of either 1) betamethasone dipropionate 5 mg (a slow-release preparation) plus betamethasone phosphate 2 mg (a quickly absorbed preparation) or 2) methylprednisolone acetate 80 mg (a slow-release preparation). Both preparations had a marked effect on nasal symptoms after 1 week, and the effect lasted for at least 5 weeks. The author concluded that betamethasone dipropionate/phosphate is more effective than methylprednisolone acetate, but no *P* values were presented.

Ohlander et al. (12) gave, in random order, to 60 patients with severe SAR, a single injection of three

IMCS preparations: 1) betamethasone dipropionate 5 mg, 2) betamethasone acetate 3 mg plus betamethasone phosphate 3 mg, or 3) methylprednisolone acetate 40 mg. All three preparations improved nasal symptoms, and there were no differences with respect to onset, degree, or duration of action.

These open comparisons between different IMCS preparations have not shown any definite advantage of one preparation over the others (12, 17, 18). As a pure slow-release formulation has shown a relatively quick onset of action within a few days, it is theoretically difficult to find a rationale for adding a quickly absorbed compound.

Comparison between SCS and INCS

In the study of Laursen et al. (5), a third arm with intranasal beclomethasone dipropionate (200 µg b.i.d.) was added. Remarkably, the INCS was not better than placebo, and, consequently, it was significantly worse than IMCS treatment. This unexpected result may be explained by the low number of patients in each group ($n=9-11$), or by the device used (an aerosol with a very short nozzle).

Pichler et al. (15) compared the effect of IMCS with INCS in a double-dummy study. They gave either an injection of methylprednisolone acetate 80 mg or intranasal budesonide for 3 weeks (200 µg b.i.d.) to 30 grass-pollen-allergic patients. There was no difference between the two therapies in nasal blockage, but there was a trend in favor of the topical treatment for sneezing and rhinorrhea (only significant when related to certain pollen counts).

These two comparative studies between IMCS and INCS have given equivocal results (5, 15). This type of comparison may not be very relevant, as a local treatment is recommended as first-line therapy for rhinitis (1). It is amazing that no study has addressed the important question of whether SCS can add to the effect of an inadequate topical therapy. Perhaps a doubling of the INCS dosage is just as effective. Controlled studies are highly warranted.

Comparison between IMCS and immunotherapy

Ganderton et al. (19) randomized 300 patients with SAR to either immunotherapy with an alum-precipitated pyridine extract (given preseasonally or coseasonally) or a single injection of methylprednisolone acetate 80 mg. A significant improvement of nasal symptoms was obtained in the coseasonal immunotherapy group (improvement in 78%) and in the IMCS group (improvement in 70%), but not in the coseasonal immunotherapy group.

Recorded sale of OCS preparations

To our knowledge, there has been no study on the frequency of use of OCS for SAR.

A single study from Denmark has estimated the sales figures of IMCS injections based on the increase in sales figures during the months April through June, a period which coincides with the production of birch and grass pollen (9). If we assume that the sales surplus of IMCS injections in the study population of about 1.5 million persons is representative of the entire Danish population of 5 million inhabitants, this gives an estimated number of 33 000 IMCS injections for SAR in Denmark per pollen season. In other words, every year, 0.66% of the Danish population receive an IMCS injection for the treatment of SAR.

It is surprising that the Danish sales figures from 1984 and 1985 showed that IMCS are prescribed more than twice as often as INCS for SAR (9), although opinion leaders for years have advocated INCS as first-line therapy. It is a likely explanation of this Danish peculiarity that four out of the six published placebo-controlled studies of IMCS therapy for SAR have been performed in Denmark.

Reported side-effects

Laursen (9) requested all reports of side-effects of IMCS with the content of methylprednisolone, betamethasone, and triamcinolone made to the Danish Register for Side-Effects of Drugs (Lægemiddelstyrelsens Bivirkningsregister) within the 10-year period 1985–94. A total of 26 side-effects (22 women and four men) were reported in all Denmark. With an estimated annual sale of 33 000 IMCS treatments, this gives the risk of side-effects as one out of 11 785 injections. Side-effects were reported to be reversible in 18 cases, and the outcome was not stated in three cases. Eight patients reported sustained side-effects (two cases of subcutaneous atrophy, five "local reactions", and one change in skin pigmentation on the injection site). The mean age for these eight patients was 24 years and all were women.

There have been earlier reports describing subcutaneous atrophy at the injection site (20–22). However,

the study of Laursen (9) is the first to correlate reported side-effects to sales figures. A report of local side-effects in only one out of more than 11 000 injections indicates that the therapeutic index, with regard to local side-effects, is high and is acceptable even for the treatment of a benign disease such as SAR. However, it must be realized that there is a general, and probably considerable, underreporting of side-effects to the health authorities. Nevertheless, this method may be considered a useful way to get an impression of the frequency of side-effects. The fact that women were overrepresented in reporting this side-effect may reflect a higher level of cosmetic concerns in women than in men. Furthermore, women could be more prone to erroneous subcutaneous injections due to their thicker subcutaneous layer.

Concluding remarks

When first-line therapy of SAR is insufficient, a short course of SCS, given orally or as an intramuscular injection, is often used. However, the documentation of this second-line therapy is amazingly poor. While more than 100 placebo-controlled studies on INCS have been published (23), we have only been able to find five placebo-controlled studies of SCS. This lack of controlled studies has left us with very uncertain guidelines on how to use SCS for SAR. There is a definite need for more placebo-controlled studies, particularly dose-response studies of oral treatment, and studies showing whether second-line therapy with SCS has an additive effect to first-line treatment with INCS. In theory, oral treatment is preferable to an injection, as the dosage can vary with the degree of pollen exposure. However, at present, it is uncertain whether patients can cope with this flexible self-management therapy, and the dose-range of OCS to be chosen is not well established. When OCS are given as single therapy, a low dose, corresponding to prednisolone 7.5 mg a day, seems marginally effective, while a high dose, about 30 mg a day, seems to be effective for all symptoms. Whether the dose-effect relationship is the same when OCS are added to a basic INCS treatment is unknown.

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