First-line treatment of seasonal (ragweed) rhinoconjunctivitis

A randomized management trial comparing a nasal steroid spray and a nonsedating antihistamine

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Abstract

Objective: To determine whether better health-related quality of life (HRQL) is achieved by initiating treatment of seasonal (ragweed) rhinoconjunctivitis (hay fever) with a nasal steroid (fluticasone) backed up by a nonsedating antihistamine (terfenadine) or whether it is better to start with the antihistamine and add the nasal steroid when necessary.

Design: Randomized, nonblind, parallel-group management study during the 6 weeks of the ragweed pollen season in 1995.

Patients: Sixty-one adults with ragweed pollen hay fever recruited from patients who had participated in previous clinical studies and from those who responded to notices in the local media.

Setting: Southern Ontario.

Interventions: Nasal steroid group: 200 μg of fluticasone nasal spray when needed (up to 400 μg/d) starting about 1 week before the ragweed pollen season and continued throughout, with 1 to 2 tablets of terfenadine daily (maximum 120 mg/d) if needed. Antihistamine group: 1 60-mg tablet of terfenadine when needed (maximum 120 mg/d) starting about 1 week before the ragweed pollen season and continued throughout, with 200–400 μg/d of fluticasone nasal spray (maximum 400 μg/d) if needed.

Outcome measures: HRQL before, at the height of and toward the end of the ragweed pollen season; HRQL was measured using the Rhinoconjunctivitis Quality of Life Questionnaire.

Results: Overall, HRQL tended to be better in the group of patients whose first-line treatment was with fluticasone ($p = 0.052$), but the difference between the 2 groups was small and not clinically important. Just over half (52% [16/31]) of the patients in the fluticasone group did not need additional help with terfenadine, whereas only 13% (4/30) of those in the terfenadine group did not need additional help with fluticasone ($p = 0.002$).

Conclusions: There is little difference in the therapeutic benefit between the 2 approaches for the treatment of ragweed pollen hay fever. Therefore, the approach to treatment should be based on patient preference, convenience and cost. Regardless of the treatment, at least 50% of patients will need to take both types of medication in combination to control symptoms adequately.

Résumé

Objectif : Déterminer si l'on améliore la qualite de vie liée à la santé par un traitement initial de la rhinoconjonctivite (fièvre des foins) saisonnière (herbe à poux) aux stéroïdes par voie nasale (fluticasone) appuyé par un antihistaminique non sédatif (terfénadine), ou s'il est préférable de commencer par l'antihistaminique et d'ajouter les stéroïdes par voie nasale au besoin.

Conception : Étude randomisée, non à l'insu, de traitement en groupe parallèle au cours des 6 semaines de la saison du pollen de l'herbe à poux en 1995.

Evidence

Études

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This article has been peer reviewed.

Can Med Assoc J 1997;156:1123-31

Patients : Soixante et un adultes souffrant de fièvre des foins causée par le pollen de l'herbe à poux et recrutés parmi les patients qui avaient participé à des études cliniques antérieurs et parmi les personnes qui avaient répondu à des avis dans les médias locaux.

Contexte : Sud de l'Ontario.

Interventions : Sujets traités aux stéroïdes par voie nasale : 200 µg de fluticasone en vaporisateur nasal au besoin (jusqu'à 400 µg/j) à compter d'environ 1 semaine avant la saison du pollen de l'herbe à poux et pendant toute la saison, et 1 ou 2 comprimés de terfénadine par jour (maximum : 120 mg/j) au besoin. Groupe traité aux antihistaminiques : un comprimé de 60 mg de terfénadine au besoin (maximum : 120 mg/j) à compter d'environ 1 semaine avant la saison du pollen de l'herbe à poux et pendant toute la saison, et de 200 à 400 µg/j de fluticasone en vaporisateur nasal au besoin (maximum : 400 µg/j).

Mesures des résultats : Résultats relatifs à la qualité de vie liée à la santé avant la saison du pollen de l'herbe à poux, en plein coeur de la saison et vers la fin de celle-ci. Les résultats ont été mesurés au moyen du questionnaire sur la qualité de vie liée à la rhinoconjonctivite.

Résultats : Dans l'ensemble, les patients traités d'abord à la fluticasone avaient tendance à avoir une meilleure qualité de vie (p = 0,052), mais l'écart entre les 2 groupes était faible et sans importance sur le plan clinique. Un peu plus de la moitié (52 % [16/31]) des patients traités à la fluticasone n'ont pas eu besoin de terfénadine supplémentaire, tandis que 13 % (4/30) seulement de ceux qui ont été traités à terfénadine n'ont pas eu besoin de fluticasone supplémentaire (p = 0,002).

Conclusions : Il y a peu de différence sur le plan des avantages thérapeutiques entre les 2 méthodes de traitement de la fièvre des foins causée par le pollen de l'herbe à poux. Il faudrait donc choisir le mode de traitement en fonction de la préférence du patient, de la commodité et du coût. Peu importe le traitement, au moins 50 % des patients devront prendre les 2 médicaments combinés pour bien contrôler les symptômes.

At least 25% of adults report experiencing seasonal allergic rhinoconjunctivitis (hay fever),[1] and despite efficacious over-the-counter drugs about 20% of the population seek help from their primary care physician.[2] Hay fever not only produces troublesome symptoms, it also impairs normal daily activities and productivity.[3–5]

A large number of clinical trials have demonstrated the individual efficacy and safety of fast-acting, nonsedating antihistamines and inhaled nasal steroids for the treatment of hay fever. A much smaller number of randomized trials have compared antihistamines with nasal steroids.[6–11] Although in most of the comparison studies the results tended to favour the latter, the artificial environment of the trials (regular and sustained daily use plus double-dummy techniques to achieve blinding) bears little resemblance to how patients use these medications in real life.

It is impossible to determine from all of these studies whether it is better to start treatment with an antihistamine and add a nasal steroid for uncontrolled symptoms or whether the nasal steroid should be used first, with the antihistamine used as back-up.[5] We therefore performed a management (effectiveness) study to determine whether adults with ragweed pollen hay fever would achieve better health-related quality of life (HRQL) by starting treatment with fluticasone propionate nasal spray and adding terfenadine tablets when needed, or whether they would benefit more by starting treatment with terfenadine tablets and adding fluticasone nasal spray when needed.

Methods

Patient population

We recruited 61 adults (aged 17–66 years) from southern Ontario who had either participated in previous clinical studies or had responded to notices in the local media. The entry criteria were as follows: a diagnosis of seasonal allergic rhinoconjunctivitis; troublesome nasal symptoms requiring medication during the ragweed pollen season the previous year; positive skin-prick test result to ragweed pollen extract (wheal greater than 3 mm with 25 000 Noon units); no perennial rhinoconjunctivitis (allergic or nonallergic) requiring treatment; no chronic nasal obstruction, polyposis or sinusitis; no history of allergen injection therapy during the previous 12 months; and no history of a serious illness that might impair quality of life. Pregnant and nursing mothers were excluded, as were patients with other illnesses requiring treatment with antihistamines or

oral steroid therapy and those who could not communicate in English. All patients agreed to remain in the ragweed pollen area (southern Ontario) for the duration of the study. Participants signed an informed consent form that had been approved by the Ethics Committee of the McMaster University Health Sciences Centre.

Study design

We used a randomized, nonblind study design to compare the 2 treatment regimens over a 6-week period that encompassed the ragweed-pollen season in 1995. Before the start of the season each patient underwent duplicate skin-prick tests with 10-fold serial dilutions of ragweed pollen extract (2.5 to 25 000 Noon units) and single dilutions of extracts of mixed grass pollen (prevalent in the month before the ragweed season) and of the fungal spores *Alternaria* and *Cladesporium* (present during the first half of the ragweed season in southern Ontario). Sensitivity to the extract in each skin-prick test was estimated from the mean of 2 wheal diameters, measured at right angles to each other. The estimated sensitivity to the ragweed pollen extract was determined from the mean wheal diameter of the 5 duplicate skin pricks.

Participants were matched into pairs using the following criteria in the following order: 1) severity of ragweed pollen hay fever during the previous year; 2) skin sensitivity to the ragweed pollen extract; 3) skin sensitivity to the fungal spore extracts; 4) skin sensitivity to the mixed grass pollen extract; and 5) sex. With the use of a random numbers table, 1 patient in each pair was randomly allocated to start treatment with the nasal steroid spray and the other to start with the antihistamine.

Interventions

We provided patients with enough medications for the whole ragweed pollen season and gave them both oral and written instructions on their optimal use. We told all patients that fluticasone nasal spray is a topical steroid that is slower acting than terfenadine but that nasal steroid sprays, if applied as soon as symptoms develop, can be used quite effectively as needed.[12–14] We also told them that terfenadine is a fast-acting, nonsedating antihistamine. Compliance with the recommended dosing was left entirely to the individual patient's discretion. We asked patients to use only the medications we provided for their hay fever, not to give it to their friends and relatives and to contact us if they experienced any troublesome symptoms or adverse effects.

Patients were told which treatment group they were in and provided with the medications only after all baseline values of the outcome measures had been recorded.

Nasal steroid group

Patients were told that the optimal approach to treatment was to start using 2 puffs (each puff 50 μg) of fluticasone nasal spray in each nostril each morning (200 μg/d) on Aug. 8, about 1 week before the start of the ragweed pollen season, and to continue with this dosage throughout the season. They were told that using the nasal spray only when needed might result in less effective control of their symptoms. We recommended they increase the dose to 2 puffs in each nostril twice daily (maximum 400 μg/d) if their nasal symptoms became troublesome. If the symptoms continued to be troublesome we advised patients to *add* terfenadine (60 mg) when needed, up to 120 mg/d, and to cut back on the terfenadine once the symptoms were controlled.

Antihistamine group

Patients in this group were told that the optimal approach to treatment was to start using terfenadine on Aug. 8 and to take a 60-mg tablet every morning and evening (total 120 mg/d) throughout the ragweed pollen season. They were told that using less terfenadine might result in less effective control of their symptoms. We advised patients to *add* fluticasone nasal spray when needed (1–2 puffs in each nostril, up to a maximum of 400 μg/d) if symptoms became troublesome once they were already taking the 120 mg of terfenadine daily and to cut back on the fluticasone once the symptoms were controlled.

Eye symptoms

We provided all patients with naphazoline eye drops and recommended that they use 1 drop in each eye when needed, up to 4 times per day. Patients who reported troublesome eye symptoms in previous years were also provided with sodium cromoglycate eye drops and advised to supplement the naphazoline eye drops with 1 drop of cromoglycate in each eye 4 times per day until the symptoms were controlled.

Asthma

Patients with asthma were instructed to continue taking their regular asthma medication throughout the study. If an inhaled β-agonist was required every day, we recommended 200 μg of beclomethasone dipropionate twice daily. If patients had already been prescribed an inhaled steroid and were needing their β-agonist daily, we recommended increasing the steroid dose to that recommended for an exacerbation by the physician treating their asthma.

Outcome measures

Health-related quality of life

Patients were seen 1 week before ragweed pollen was expected in the air (the first week of August), at the height of the ragweed pollen season (the first week of September) and toward the end of the season (the third week of September). At each visit they were asked to complete the Rhinoconjunctivitis Quality of Life Questionnaire.[3] This 28-item disease-specific instrument is designed to measure the 7 domains of functional impairment that are most important to patients with seasonal allergic rhinoconjunctivitis: sleep impairment, non-nasal symptoms (e.g., headache and fatigue), practical problems, nasal symptoms, eye symptoms, activity limitations and emotional function. Patients are asked to consider their experiences during the previous 7 days and to score their degree of impairment on a 7-point scale (0 = not bothered, 6 = extremely bothered). The questionnaire has excellent reliability, responsiveness and construct validity and has been used successfully in a number of clinical trials over the last 6 years.[3,11–14]

Medication use

Patients were asked to return all used and unused fluticasone bottles and terfenadine packages at the final visit. We recorded the weight loss from each bottle of fluticasone and the number of terfenadine tablets used. To estimate the number of puffs of fluticasone used by each patient, we first estimated the mean weight loss per puff by weighing a bottle before and after 10 consecutive discharges into the air until the bottle was empty.

In addition to estimating the actual amount of medication used by each patient, we calculated the number of bottles of fluticasone and packages of terfenadine each patient would have needed to provide the actual amount of medication used.

Statistical analysis

We examined differences between the treatment groups using a repeated measures analysis of variance, considering p values less than 0.05 (two-sided) as significant. Covariate analysis was used to adjust for differences between the 2 groups at baseline. All of the randomized subjects were included in the analysis (intention-to-treat analysis). The number of puffs of fluticasone used by each patient was based on a mean weight per puff of 0.0867 g, and the number of bottles of fluticasone that each patient needed was based on each bottle containing 170 puffs. Terfenadine (Seldane) can be purchased over the counter in Canada in packages of 12, 24 and 36 tablets. After surveying about 10 pharmacies in the Hamilton area, we determined that the 36-tablet package had the highest sales during the ragweed pollen season. Therefore, we used this size to estimate the number of packages required by each patient.

With sufficient statistical power, even the most trivial differences between the treatment groups can reach statistical significance. To interpret HRQL data that reaches statistical significance, it is important to know what magnitude of change or difference can be considered clinically important. The minimal important difference (MID) is defined as "the smallest difference in score in the domain of interest which patients perceive as beneficial and would mandate, in the absence of troublesome side effects or excessive cost, a change in the patient's management."[15] Using a standardized "anchor-based" method[16] we have determined that the MID for the Rhinoconjunctivitis Quality of Life Questionnaire is about 0.5.[17] The sample size for our study was determined on the basis of the MID, the pooled variance[3,12–14] and error rates of $\alpha = 0.05$ (two-sided) and $\beta = 0.1$.

Results

The profile of the study is summarized in Fig. 1. The demographic characteristics and allergy history of the 61 patients are shown in Table 1. Complete data sets were provided by 60 of the patients; the remaining patient, in the nasal steroid group, experienced nausea using the fluticasone and asked to be changed to beclomethasone. In keeping with the management study philosophy, this was permitted, but the patient failed to keep the final appointment.

Although the patients were carefully matched, those in the fluticasone group appeared to have slightly better HRQL than those in the terfenadine group before the ragweed pollen season (Fig. 2). Even though this difference was small (0.24 for overall quality of life, where MID = 0.5) and not statistically significant ($p > 0.05$) and was probably due to residual symptoms induced by grass pollen and fungal spores, we investigated the treatment effect after doing a covariate adjustment for baseline differences.

For overall rhinoconjunctivitis-specific quality of life and for each of the 7 domains covered by the questionnaire, both groups of patients experienced a deterioration in HRQL between the beginning and the height of the ragweed season which resolved toward the end of the season (Fig. 2, Table 2) ($p < 0.001$). However, the deterioration in HRQL was small, and only in the eye-symptom domain could it be considered clinically important.

At the height of the ragweed pollen season the patients whose first-line treatment was with fluticasone tended to

have better HRQL than those whose first-line treatment was with terfenadine (Table 2). For overall HRQL, this difference was on the borderline of statistical significance ($p = 0.052$); however, the mean difference in scores, after we adjusted for differences at baseline, was only 0.11 (MID = 0.5) and therefore of little clinical importance. Similar trends were seen for all domains except the eye-symptom domain, for which there was no evidence of any difference between the 2 groups. For the nasal-symptom domain the difference between the 2 groups was statistically significant ($p = 0.005$), but the difference in scores was only 0.21 and still of little clinical importance.

Table 3 shows the amount of medication used by the 2 groups. Of the 31 patients in the fluticasone group 16 (52%) never needed to use any terfenadine, whereas only 4 (13%) of the 30 patients in the terfenadine group never used fluticasone ($p = 0.002$). Although we instructed patients not to use more than 2 terfenadine tablets per day, the mean use in the terfenadine group was 2.07 tablets per day, which suggested that a number of patients ignored this instruction.

Discussion

The patients whose first-line treatment of seasonal allergic rhinoconjunctivitis was with fluticasone nasal spray

Table 1: Characteristics of patients with seasonal (ragweed) rhinoconjunctivitis entered into study comparing fluticasone nasal spray with terfenadine tablets as first-line treatment

Characteristic	Treatment group; no. of patients*	
	Fluticasone *n = 31*	Terfenadine *n = 30*
Sex (male/female)	15/16	16/14
Mean age (and SD†), yr	41.0 (11.4)	45.7 (10.5)
Mean diameter (and SD) of wheals after duplicate skin-prick test with 5 concentrations of ragweed pollen extract	3.77 (1.23)	3.77 (1.26)
Severity of hay fever symptoms the previous year		
Mild	14	11
Moderate	12	12
Severe	5	7
Medications taken for hay fever the previous year	16	10
Antihistamine alone	6	11
Nasal steroid alone	9	9
Antihistamine + nasal steroid	13	15
Skin sensitivity to fungal spores	25	23
Skin sensitivity to grass pollen		
No previous experience in clinical studies	8	7
Nasal steroid used within 6 weeks before randomization	0	2

*Unless otherwise stated.
†SD = standard deviation.

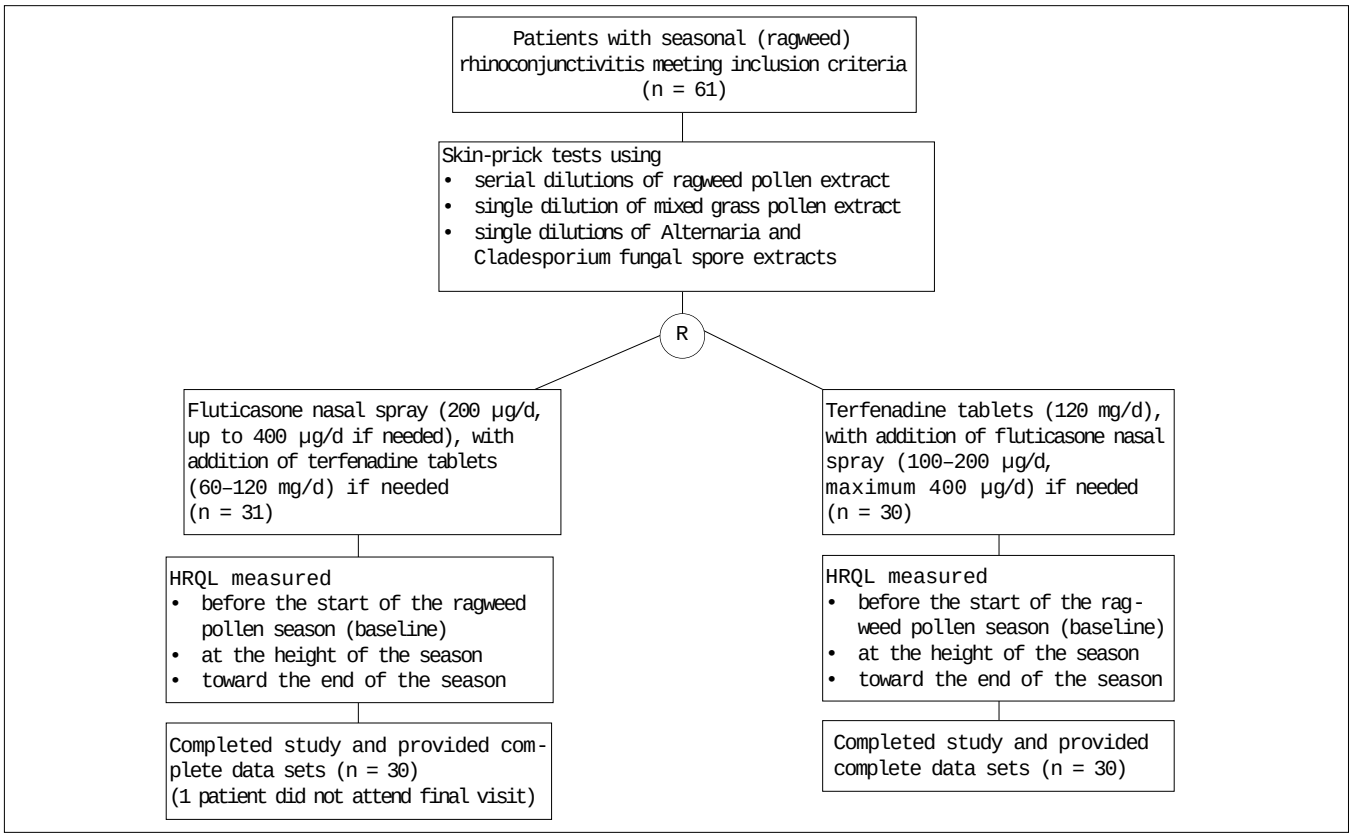

Fig. 1: Trial profile. See Methods for inclusion criteria. R = randomization, HRQL = health-related quality of life.

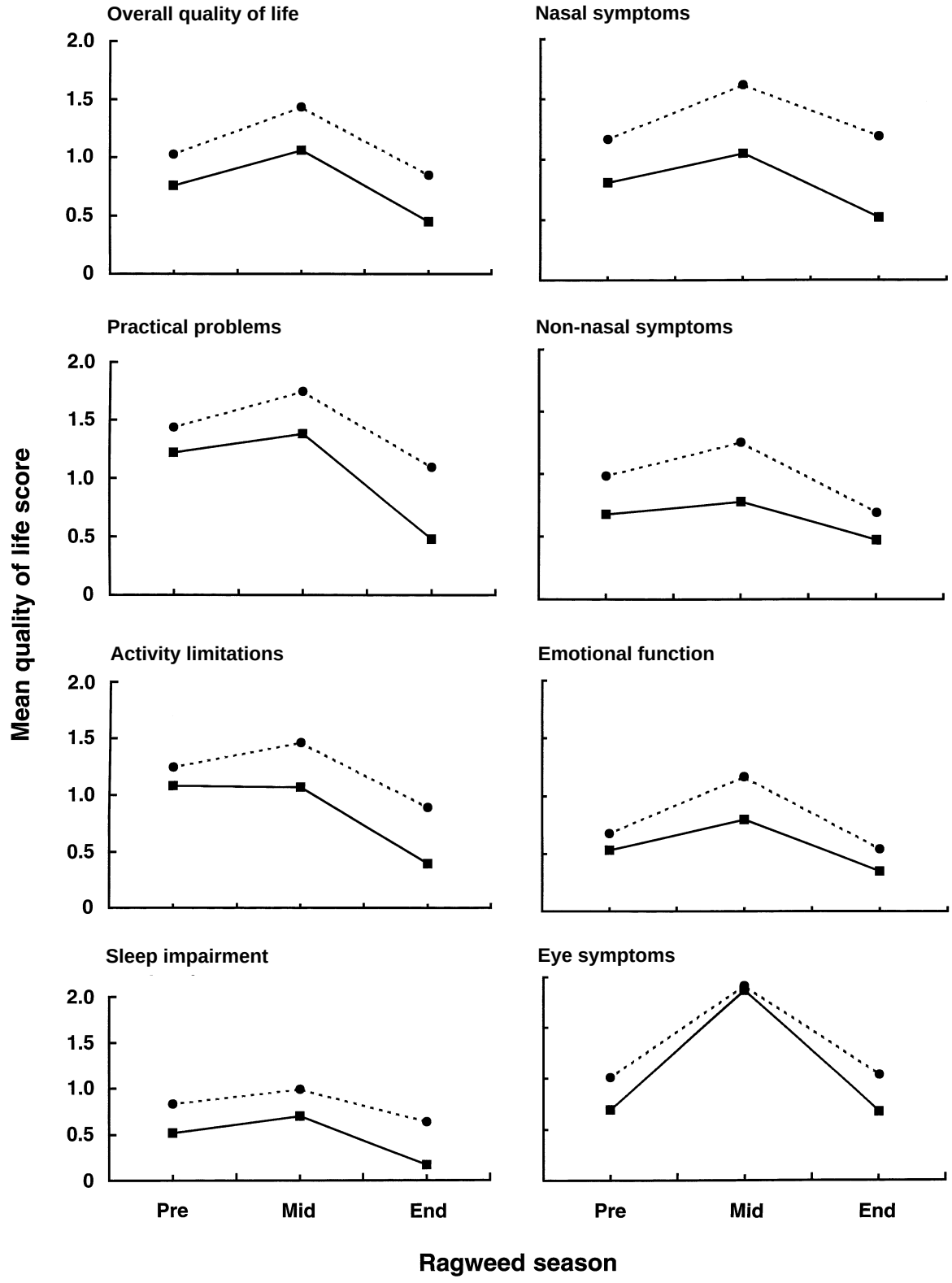

Fig. 2: Mean scores for HRQL for patients with seasonal (ragweed) rhinoconjunctivitis measured before, at the height of and toward the end of the ragweed pollen season. Solid lines represent patients whose first-line treatment was fluticasone nasal spray, with terfenadine tablets as back-up; broken lines represent patients whose first-line treatment was terfenadine tablets, with fluticasone nasal spray as back-up. Scores range from 0 (not bothered) to 6 (extremely bothered).

tended to experience better HQRL during the ragweed pollen season than those who started with terfenadine. However, the differences in mean scores between the 2 groups at the height of the season were small and of little clinical importance. Because there was little difference in the therapeutic benefit, even for eye symptoms, between the 2 regimens, other factors such as patient preference (patient perception of efficacy, patient preference for topical or systemic preparations, and side effects), convenience and cost should be considered when making treatment recommendations. With regard to convenience and cost, it is noteworthy that 52% of the patients who started with fluticasone never needed additional terfenadine, whereas only 13% of those who started with terfenadine managed without additional fluticasone.

Even at the height of the ragweed pollen season patients experienced minimal impairment of HRQL (Fig. 2). We recognize that there was no placebo control group. Nevertheless, all of the patients had moderate to severe sensitivity to ragweed pollen and a history of troublesome symptoms the previous year. Therefore, these results strongly suggest that both treatment regimens were effective. The regimens had 3 important features that we believe contributed to the success. First, the back-up medication was *added* when the first medication, on its own, was insufficient to control symptoms. Patients frequently change medication at the height of the season, complaining that "nothing works" and not realizing that 2 different types of treatment in combination may be necessary. Second, the patients were advised to start taking their medications either just before pollen was expected in the air or immediately after they experienced their first symptoms. It is much easier to keep symptoms under control from the beginning than to try and bring severe symptoms under control. Third, the patients were given written instructions on the use of the medications.

In designing clinical trials, there is a continuum from the explanatory or efficacy study (under optimum and highly controlled conditions does the intervention have a biological effect?) to the management or effectiveness study (what is the effect on clinically important outcomes in real life?). There are a large number of explanatory studies of inhaled nasal steroids and nonsedating antihistamines, none of which has taken into account how patients use these medications outside the artificial environment of the explanatory clinical trial. We wanted our study to be as close to real life as possible and to provide practical information for clinicians. Therefore, we chose a design as close to the management end of the continuum as possible. That was why we omitted a placebo group, which would have required a double-dummy design, introduced artificiality into the study, interfered with patient

Table 3: Medication use during study period

	Treatment group	
Medication use	Fluticasone	Terfenadine
No. of patients using		
Fluticasone alone	16	0
Terfenadine alone	0	4
Both	15	26
Fluticasone		
Mean no. of puffs daily per patient (and SD)	5.27 (1.62)	2.61 (1.97)
No. of patients using		
0 bottles	0	4
1 bottle	7	17
2 bottles	24	9
Total no. of bottles used	55	35
Terfenadine		
Mean no. of tablets daily per patient (and SD)	0.13 (0.28)	2.07 (0.43)
No. of patients using		
0 packages	16	0
1 package*	13	0
2 packages	2	6
3 packages	0	24
Total no. of packages used	17	84

*One package = 36 tablets.

Table 2: Differences in mean scores for health-related quality of life (HRQL)* between the treatment groups (after adjustment for differences at baseline)

	Difference in mean scores†		*p* value§	
Sleep impairment	−0.03	0.15	0.054	0.0037
Non-nasal symptoms	0.17	0.09	0.274	0.0052
Practical problems	0.15	0.39	0.015	0.0001
Nasal symptoms	0.21	0.31	0.005	0.0035
Eye symptoms	−0.27	0.04	0.614	0.0001
Activity limitations	0.20	0.33	0.037	0.0002
Emotional function	0.23	0.05	0.165	0.0003

*HRQL determined using Rhinoconjunctivitis Quality of Life Questionnaire[3] scores (0 = not bothered, 6 = extremely bothered).
†Minimal important difference = 0.5.
‡Positive differences indicate better HRQL for patients in the fluticasone group.
§Repeated measures analysis with covariate adjustment for differences in baseline score.

dosing choices and probably altered the results. Our study design allowed many opportunities for patients to make their own decisions. For instance, patients were free to read and respond to the package inserts for both fluticasone and terfenadine. If they asked for additional information on allergen avoidance, it was provided. We advised patients on the best way to use the medications; they were free to follow or ignore this advise.

There is no doubt that some patients like to keep their symptoms as well controlled as possible and take their medication regularly and prophylactically throughout the entire pollen season. Others prefer to tolerate some mild impairments in order to keep medication use to a minimum. It was this observation, made a number of years ago, that led us to compare the regular use of beclomethasone dipropionate nasal spray with its use as needed for seasonal allergic rhinoconjunctivitis.[12,13] Although explanatory studies suggested that prophylactic, regular use of nasal steroids should provide optimum symptom control, such a regimen is unacceptable to patients who like to keep medication use to a minimum and who know that the condition will resolve spontaneously at the end of the pollen season. Our randomized trials showed that there was minimal impairment of HRQL at the height of the pollen season in the both the regular and the as-needed treatment groups.[12,13] When we examined patient satisfaction, most of the patients in the group instructed to use the medication as needed were very satisfied with the level of symptom control.[13] It was on the basis of those findings, the results from another management study of nasal steroid use for seasonal allergic rhinoconjunctivitis[14] and the recognition that some patients want to minimize their medication use that we decided, in the present study, to tell patients how to use nasal steroids effectively on an as-needed basis.

Although we tried to replicate real life as much as possible, there were 3 problems that we could not overcome and that may have affected the results. First, our patients were volunteers. Although they represented both sexes and a wide range of age, academic achievement and socioeconomic backgrounds, they were all interested in the management of their condition. Second, our patients were provided with hay fever medication before the ragweed pollen season. In real life some patients become severely symptomatic and limited before they buy medications or seek help. Third, none of our patients paid for their medications.

We did not compare costs in the 2 treatment groups because they differ greatly across national health care systems. Instead, we calculated the number of bottles of fluticasone and packages of terfenadine patients needed so that direct costs in any given country can be determined. In some countries both nasal steroid sprays and nonsedating antihistamines are available over the counter, and the costs are borne entirely by the patient. In other countries, both are available only by prescription, and the cost of the drugs, the dispensing fees and the physician visits (possibly 2 or more) are carried by the health care provider. Elsewhere it is a mixture, often with the costs of the drugs being borne by different payers. In addition, we did not attempt to calculate indirect costs. However, because there was little evidence of any difference in HRQL between the 2 treatment groups, indirect costs (e.g., loss of earnings) would have probably been similar.

Our primary aim was to compare drug types, but for study purposes we had to select a representative of each class. We selected fluticasone and terfenadine because they are used extensively for hay fever and we believe both are acceptable representatives of nasal steroids and nonsedating antihistamines. However, caution should be exercised when extrapolating these results to other nasal steroid sprays and nonsedating antihistamines.

With regard to convenience and cost, our results favour starting treatment with fluticasone because over half the patients in the fluticasone group did not need to add the back-up medication. However, a limitation of any clinical trial is that it only provides mean data about a group of patients. Some patients respond better to and prefer using a topical nasal steroid spray, whereas others prefer a systemic nonsedating antihistamine. Only by trying each approach in an individual patient is it possible to determine which will be more beneficial. Whatever the final choice, at least 50% of patients are likely to require 2 different types of medication in combination to achieve optimal HRQL.

This study was supported by a grant from Glaxo Wellcome Inc.

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