

tion of both CP and cisplatin. Hypersensitivity to mannitol was reported as a cause of apparent hypersensitivity to cisplatin.⁶ In case 2 the result of a skin test with mannitol was negative, whereas the result of a skin test with the commercial formulation containing CP and mannitol was positive, suggesting that CP was solely responsible for the hypersensitivity reaction.

In addition to the clinical tolerance induced by the desensitization protocol, skin responses to intradermal CP diminished. As shown in Table I, the ratio between wheal sizes of CP and histamine decreased more than 3.5 times after the desensitization. The observation of wheal-and-flare responses becoming negative has already been described in penicillin desensitization.⁷ This phenomenon supports an antigen-specific desensitization. The rate at which the drug concentration increases in the extracellular fluid seems to be the most important factor in a successful outcome of desensitization. As suggested by our two patients, this rate can differ in each individual case.

We conclude that the 4-hour desensitization protocol may not be suitable for all patients allergic to CP, whereas a modified prolonged protocol seems to be more tolerable. Until further data

have been accumulated, the short protocol may be attempted initially but should be replaced by the prolonged protocol if adverse effects appear. The prolonged protocol seems to be both safe and efficacious with regard to antitumor activity.

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Interpretation of rhinoconjunctivitis quality of life questionnaire data

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Many clinicians and investigators are now using the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) as part of their clinical evaluations, and they need to be able to place a meaningful clinical interpretation on the data that is generated. In clinical trials, investigators need to know

Abbreviations used

HRQL: Health-Related Quality of Life
MID: Minimal important difference
RQLQ: Rhinoconjunctivitis Quality of Life Questionnaire

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whether a statistically significant difference observed between two treatment groups also represents a clinically important difference. Clinicians, using a Health-Related Quality of Life (HRQL) questionnaire in routine clinical practice, need to know whether an intervention that changes an individual patient's HRQL score is really justified.

When we first developed the RQLQ in 1989,¹ we

TABLE I. Mean change in rhinoconjunctivitis quality of life scores for each category of global rating

	Global rating of change						
	+7 and +6	+5 and +4	+3 and +2	+1, 0 and -1	-3 and -2	-5 and -4	-7 and -6
Number	12	9	12	61	16	10	1
Change in RQLQ score (mean $\pm$ SD)	1.18 $\pm$ 1.03	0.68 $\pm$ 1.13	0.60 $\pm$ 0.97	0.06 $\pm$ 0.69	0.55 $\pm$ 0.98	1.09 $\pm$ 1.15	1.28

provided evidence of the conventional measurement properties of reliability, responsiveness, and construct validity; but we did not determine the minimal important difference (MID). The MID has been defined as "the smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient's management."² The aim of this study was to determine the MID for the RQLQ. The method for ascertaining the MID for a disease-specific quality of life instrument involves calculating change in HRQL scores between consecutive assessments and anchoring these to independent estimates of changes in experience that patients themselves consider important.²

METHODS

Patients

Sixty-one adults (17 to 66 years) with moderate to severe ragweed pollen-induced rhinoconjunctivitis participated in the study. All were participants in a clinical trial, and the method of recruitment and the subjects' demographic characteristics have been reported in detail elsewhere.³ All patients signed an informed consent form, which had been approved by the McMaster University Medical Centre Ethics Committee.

Study design

The main study was a randomized trial designed to determine whether better management of seasonal allergic rhinoconjunctivitis could be achieved by starting treatment with a nasal steroid spray, with additional nonsedating antihistamine for uncontrolled symptoms, or whether better HRQL could be achieved by starting treatment with the antihistamine, backed up by the nasal steroid. Patients were enrolled before the ragweed pollen season and completed the RQLQ at baseline, at the height of the ragweed pollen season, and at the end of it. The instrument has 28 items in seven domains (sleep, non-rhinoconjunctivitis symptoms, practical problems, nasal symptoms, eye symptoms, activity limitations, and emotional function). Patients are asked to recall impairments experienced during the previous week and to respond to each item on a 7-point scale (0 = no impairment, 6 = maximum impairment). At each follow-up visit, patients also completed a global rating of change questionnaire. This instrument asks patients

whether they have experienced any change in their rhinoconjunctivitis quality of life since their previous clinic visit. They respond on a 15-point scale from -7 (a very great deal worse) to 0 (no change) to +7 (a very great deal better). Previous studies have shown that global rating scores of -1, 0, and +1 are trivial; but changes of +2 or greater and -2 or less are important to patients and can be considered clinically important. Changes of +3, +2, -2, and -3 can be considered minimally important changes (i.e., the MID), changes of +5, +4, -4, and -5 can be considered moderate; and changes of +7, +6, -6, and -7 can be considered large.²

Analysis

Each patient contributed two sets of data (visit 1-2 and visit 2-3). We calculated the changes in RQLQ score between consecutive visits for each patient and related these to the individual patient's global rating of change score.

RESULTS

All 61 patients completed the first two visits, and 60 completed all three visits and provided complete data sets. Mean changes in score of the RQLQ between consecutive clinical visits for each ranking of global rating of change (no change, minimal, moderate, and large) are shown in Table I. The results for improvement and deterioration were symmetrical, and so we have combined the results to give a more precise estimate of the mean value for each category. For patients who remained stable or had trivial changes (global rating = +1, 0, or -1), there was very little change in RQLQ score (0.06 $\pm$ 0.69). For those who experienced an MID (global rating +3, +2, -2, or -3), the mean change in score was 0.57 $\pm$ 0.96; for those with a moderate change, the mean change in score was 0.89 $\pm$ 1.13; and for those in the large change category, the mean change in score was 1.19 $\pm$ 1.03.

DISCUSSION

The results provide evidence that mean changes in score from the RQLQ of greater than approximately 0.5 can be considered of clinical importance and would justify a change in the patient's treatment in the absence of troublesome side effects or excessive cost.

These results are very similar to the MID (approximately 0.5) determined for other disease-specific quality of life questionnaires that use 7-point response options (e.g., asthma, pediatric asthma, chronic respiratory disease, heart failure). Although we only tested the RQLQ in this study, the results are probably applicable to the Rhinitis Quality of Life Questionnaire,⁴ which is almost identical to the original instrument except that all references to eye symptoms have been removed. In addition, they should be applicable to the Adolescent Rhinoconjunctivitis Quality of Life Questionnaire,⁵ which is also very similar to the adult version, except that there is no sleep domain and there are additional questions concerning ability to concentrate.

Desensitization for fluconazole hypersensitivity

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The use of fluconazole continues to increase with present indications including fungal infections of the nails, skin, oral and vaginal mucosa, systemic candidiasis, and cryptococcal meningitis. Fluconazole is well tolerated with few adverse effects. The main toxicities include hepatitis, leukopenia, thrombocytopenia, gastrointestinal distress, headache, anaphylaxis, and rash.¹⁻⁴ Rashes have included: Stevens-Johnson syndrome, diffuse erythema, angioedema, maculopapular and fixed drug eruptions. Herein we present a case of hypersensitivity to fluconazole that first manifested as a rash. Because of the need to reinstitute fluconazole, we elected to test dose and desensitize the patient. This is apparently the first description of such a procedure with fluconazole.

CASE REPORT

T.P., a 36-year-old man, was referred because of a rash caused by fluconazole. His medical history was positive for HIV. His last T-4 lymphocyte count was

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below 50. His course was complicated with cryptococcal meningitis, *Pneumocystis pneumonia*, sinusitis, and drug allergies. Cryptococcal meningitis was initially treated with amphotericin B. After 3 weeks of therapy, the patient was switched to oral fluconazole therapy, 400 mg a day. On day 4 of therapy a pruritic rash in both axilla and hypereosinophilia developed. After 1 month, the dose was decreased to 200 mg a day, but his symptoms progressed and included hives, dyspnea, and tachycardia. During this time interval he was noted to have one oral ulceration. Within a few days after discontinuing fluconazole, his symptoms resolved.

He was switched to itraconazole as secondary prophylaxis. After 6 months, cryptococcal meningitis developed. Amphotericin was restarted with good response. After completion of 3 weeks of intravenous amphotericin, the patient was referred for evaluation to determine whether fluconazole could be restarted. Because of the lack of an acceptable protocol for skin testing, we elected to test dose the patient. We chose a prolonged test dosing protocol, starting at less than one one thousandth of the dose and gradually increasing the dose by doubling it each day. This procedure was complicated by a transient macular, papular, pruritic rash on the upper trunk and under the axilla area from days 4 to 6, which resolved despite increasing the dose. Signs of anaphylaxis did not develop, and mucus membranes remained normal. Within 15 days the patient was receiving full prophylactic doses of 400 mg of fluconazole orally each day. He has been receiving therapy for over

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