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Improvement in Health-Related Quality of Life with Rizatriptan 10mg Compared with Standard Migraine Therapy

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Abstract

Objective: To compare the effects of rizatriptan and patients' usual migraine medication(s) on health-related quality of life.

Design and Setting: The study was a non-blinded, parallel-group, extension trial in which patients who had completed a randomised, placebo-controlled trial of the treatment of migraine with rizatriptan at 23 study sites in the United States were randomly assigned in a 4 : 1 ratio either to rizatriptan or to standard care.

Patients: 265 migraineurs, 18 to 65 years of age.

Interventions: Patients received either rizatriptan 10mg or their usual migraine medication(s).

Main Outcome Measures and Results: The main outcome measures were: (a) migraine-specific quality of life during the 24-hour period of an attack, as determined by the 24-Hour Migraine-Specific Quality-of-Life Questionnaire (24-HrMQoLQ), for attacks in the first month; (b) general health-related quality of life as determined by the eight domain scores and the Mental and Physical Component Scales of the Short Form Health Survey (SF-36) after 2, 6 and 12 months. The 24-HrMQoLQ domains were scored from 3 to 21, and the SF-36 from 0 to 100, higher scores indicating better performance for both instruments. Patients receiving rizatriptan had significantly better scores in all five domains of the 24-HrMQoLQ compared with patients receiving standard care. Mean scores (standard error) for the rizatriptan and usual care groups were, respectively: Work Functioning, 13.9 (0.4), 12.5 (0.8), $p = 0.05$; Social Functioning, 13.6 (0.4), 11.8 (0.8), $p = 0.015$; Energy/Vitality, 13.7 (0.5), 11.6 (0.8), $p < 0.01$; Feelings/Concerns 13.3 (0.4), 10.6 (0.8), $p < 0.001$; and Migraine Symptoms 14.1 (0.4), 12.1 (0.7), $p < 0.01$. There was a trend for patients receiving rizatriptan to have higher scores on the Mental Component Scale of the SF-36: mean score (SE) 50.3 (0.6) for rizatriptan, 48.0 (1.1) for usual care, $p = 0.068$. There was no difference between the treatment groups in the Physical Component Scale: mean score (SE) 48.4 (0.6) for rizatriptan, 49.7 (1.1) for usual care, $p = 0.202$.

Conclusion: Quality of life in the 24-hour period following a migraine attack was better in patients treated with rizatriptan 10mg than in patients treated with their usual migraine medication.

Migraine is a chronic neurovascular disorder characterised by recurrent episodes of intense headache pain with associated symptoms of nausea and/or vomiting, photophobia, and phonophobia.[1] Migraine attacks have a negative effect on health-related quality of life (HR-QoL). During a migraine attack, headache pain and associated symptoms interfere with the ability of migraineurs to work, enjoy daily activities, and interact socially.[2] Several studies have demonstrated that the HR-QoL of migraineurs is significantly impaired even between migraine attacks.[3,4]

Migraine attacks have traditionally been treated with a variety of drugs, including analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, corticosteroids and ergot derivatives.[1] Triptans, which are serotonin receptor 5-$HT_{1B/1D}$ agonists, have recently become the gold standard of migraine treatment. Rizatriptan is a selective 5-$HT_{1B/1D}$ receptor agonist. In several multicentre, randomised, placebo-controlled trials, rizatriptan 10mg produced rapid pain relief and freedom from pain, and reduced the incidence of migraine-associated symptoms.[5-8] In randomised trials comparing rizatriptan with oral sumatriptan, rizatriptan provided faster pain relief and reduced nausea to a greater extent.[8-10] Patients completing three of these trials entered three long-term extension trials in which patients were randomly assigned to rizatriptan or standard care.[11] Standard care in the extension trials was most often sumatriptan, but also included NSAIDs, paracetamol (acetaminophen), barbiturates and opioids.

We report HR-QoL data from one of the extension trials of rizatriptan 10mg versus standard care.[7,11] We hypothesised that rizatriptan 10mg would improve HR-QoL to a greater extent than standard care during a migraine attack, and that rizatriptan might improve some aspects of HR-QoL between migraine attacks. Results using a migraine-specific instrument, the 24-Hour Migraine-Specific Quality-of-Life Questionnaire (24-HrMQoLQ),[12,13] indicate that rizatriptan improved HR-QoL over standard care during migraine attacks. There was no dramatic difference between rizatriptan and standard care in HR-QoL between migraine attacks, as measured with a generic HR-QoL instrument, the Short Form Health Survey (SF-36).

Patients and Methods

Patients

All patients completing a randomised, triple-blinded, placebo-controlled, crossover trial of the treatment of four consecutive headache attacks with rizatriptan (the 025 trial)[7] were invited to participate in the extension study. Of 313 patients invited, 265 (85%) elected to enter the study.

Study Design

This was a 12-month, parallel-group, non-blinded extension trial in which patients were randomly assigned in a 4 : 1 ratio either to rizatriptan 10mg or to their usual migraine therapy [medication(s) used routinely to relieve their migraine attacks, as prescribed by the investigators]. The efficacy and safety results of this US-based trial (the 025 extension) and two other extension trials have been described previously.[11]

Patients in the rizatriptan group were not to use sumatriptan, ergot derivatives or isometheptine for 24 hours before or after treating a migraine attack with the test drug; monoamine oxidase inhibitors and methysergide were prohibited for the duration of the study. Most patients (66%) in the usual care group used sumatriptan (oral or subcutaneous) for treatment of most (80%) attacks, either alone or in combination with other therapies. Other frequently used abortive therapies in the standard care group included (given as the percentage of patients treating at least one attack; percentage of attacks treated): NSAIDs (70%; 45%), barbiturates (40%; 66%), paracetamol (40%; 66%) and opioids (30%; 52%).

Migraine Diary

After initiating migraine therapy for each moderate or severe migraine attack during the 12-month duration of the extension study, patients completed a migraine attack diary card. The diary

card recorded the migraine headache severity (no headache, mild, moderate or severe), functional disability (normal, mildly impaired, severely impaired or unable to perform activities and requiring bed rest), and associated symptoms (nausea, vomiting, photophobia, phonophobia). Patients recorded this information at initiation of study therapy and 2 and 4 hours after drug administration. They recorded the need for additional migraine medications and adverse experiences as they occurred.

24-Hour Migraine-Specific Quality of Life Questionnaire

Patients completed the 24-HrMQoLQ over the first month of the extension. The 24-HrMQoLQ assesses the impact of migraine and migraine therapy on the quality-of-life decrement associated with an acute migraine attack in the 24-hour period following headache onset.[12,13] The 24-HrMQoLQ consists of 15 questions, with three questions each in five domains: Work Functioning, Social Functioning, Energy/Vitality, Symptoms and Feelings/Concerns. The domain scores range from a minimum of 3 (worst possible functioning/migraine symptoms all of the time) to a maximum of 21 (best possible functioning/no symptoms). Patients were instructed to complete the 24-HrMQoLQ 24 hours after initiating therapy for a migraine headache that they rated as moderate or severe, and to consider their entire migraine experience over the 24-hour period.

Short Form Health Survey

The SF-36 is a generic health survey questionnaire consisting of eight domains, each scored from 0 to 100, with 100 representing the best possible health-related quality of life. Mental Health and Physical Health Summary scores can be computed from the eight domains, based upon principal components analysis of data from a survey of the US population.[14] The SF-36 was completed during a clinic visit at baseline and at months 2, 6 and 12 (± 30 days from the scheduled visit).

Data Analysis

Between-group differences in domains of the 24-HrMQoLQ were analysed in a mixed model.[15] Subjects were treated as random effects, and age, gender, study site and baseline severity (i.e. severity at the beginning of a migraine attack) were treated as fixed effects. Wald F tests were used to test for differences between the rizatriptan and usual care groups while controlling for these baseline co-variates. Analysis of variance (ANOVA) was used to analyse between-group differences in SF-36 change-from-baseline scores adjusting for age, gender and study site. Individuals with baseline and at least one follow-up measurement were analysed, and the average of available follow-up scores was used. Statistical significance was defined as $p \leq 0.05$.

Results

Patient Population

Fifty subjects were randomised to receive their usual migraine therapy and 215 to receive rizatriptan. The demographics of these patients at baseline are shown in table I. Patients were predominantly female (83.4%) and their mean age was 41 years.

Table I. Patient demographics

Characteristic	Rizatriptan (n = 215)	Usual treatment (n = 50)
Age (y)		
Mean (SD)	41 (10.2)	42 (9.5)
Range	19-65	19-60
Gender [no. (%)]		
Female	177 (82.3)	44 (88)
Male	38 (17.7)	6 (12)
Race [no. (%)]		
White	207 (96.2)	45 (90)
Black	3 (1.5)	1 (2)
Other	5 (2.3)	4 (8)

SD = standard deviation.

Table II. Headache severity and functional disability by treatment group

Characteristic	Rizatriptan (n = 214)	Usual treatment (n = 48)
Severity		
No.	684	98
Moderate (%)	59.2	66.3
Severe (%)	40.8	33.7
Functional disability		
No.	678	97
Normal (%)	3.4	3.1
Mildly impaired (%)	52.4	53.6
Severely impaired (%)	29.9	25.8
Required bed rest (%)	14.5	17.5

Headache Severity and Functional Disability

The percentage of headaches by treatment group according to severity and functional disability is shown in table II. The rizatriptan 10mg group had more patients rating their baseline headache severity as severe (40.8%) compared with the standard care group (33.7%). Functional disability at baseline was roughly comparable between the two groups.

Migraine-Specific Quality of Life

Patients randomised to receive rizatriptan 10mg had statistically significantly better scores in all five domains of the 24-HrMQoLQ instrument (figure 1). The magnitude of the increases ranged from 11.2% in the Work Functioning domain to 25.5% in the Feelings/Concerns domain.

Short Form Health Survey

There were no statistically significant between-group differences in average follow-up scores, over the three timepoints in the extension, in any of the eight SF-36 domains except Mental Health, where the rizatriptan group scored higher than the control group ($p = 0.048$). Average mean follow-up scores rose by 0.8% to 7.2% points from the baseline values for seven, and declined by 1.1% point in one, of the eight SF-36 domain scores for patients randomised to rizatriptan. Average mean follow-up scores rose by 0.6 to 11.9% points for three, and declined by 2.6 to 10.3% points for five, of the SF-36 domains scores for patients

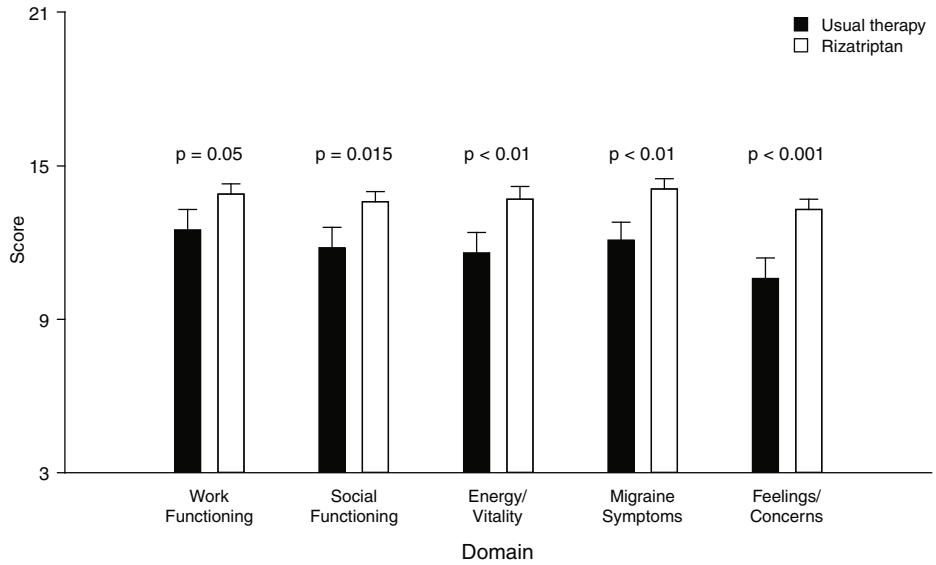

Fig. 1. Migraine-specific quality of life, showing mean (standard error) scores for the 24-Hour Migraine-Specific Quality-of-Life Questionnaire for 174 patients on rizatriptan and 35 on usual therapy. Domain scores range from 3 (worst possible functioning/migraine symptoms all of the time) to 21 (best possible functioning/no symptoms).

Table III. SF-36 domain and physical and mental component scores

SF-36 construct	Rizatriptan (n = 164)	Usual care (n = 42)	p-Value
Physical functioning			
Baseline [a]	89.6 (1.2)	90.1 (2.1)	
Follow-up [b]	90.4 (1.1)	90.9 (1.9)	0.772
Role physical			
Baseline	62.6 (3.3)	59.5 (6.7)	
Follow-up	69.8 (3.2)	71.4 (5.3)	0.762
Bodily pain			
Baseline	59.7 (1.6)	62.4 (3.7)	
Follow-up	62.3 (1.6)	63.0 (2.7)	0.792
Social functioning			
Baseline	75.2 (1.5)	78.3 (3.0)	
Follow-up	77.5 (1.7)	76.0 (2.8)	0.613
Mental health			
Baseline	74.2 (1.4)	77.7 (2.0)	
Follow-up	75.8 (1.2)	72.0 (1.9)	0.048
Role emotional			
Baseline	77.6 (2.8)	88.1 (3.6)	
Follow-up	84.7 (2.7)	77.8 (4.4)	0.139
Vitality			
Baseline	58.4 (1.6)	63.2 (2.2)	
Follow-up	61.0 (1.3)	61.4 (2.2)	0.844
General health			
Baseline	77.3 (1.5)	79.7 (2.9)	
Follow-up	76.2 (0.9)	76.0 (1.6)	0.887
Physical component scale			
Baseline	47.8 (0.6)	47.2 (1.3)	
Follow-up	48.4 (0.6)	49.7 (1.1)	0.202
Mental component scale			
Baseline	48.8 (0.8)	52.0 (1.1)	
Follow-up	50.3 (0.6)	48.0 (1.1)	0.068

a Mean (standard error).

b Least-squares mean (standard error) adjusted for age, gender and baseline value.

SF-36 = Short Form Health Survey.

randomised to standard care. The rizatriptan group showed a trend towards significantly higher scores on the Mental Component Scale (p = 0.068), but there was no statistically significant between-group difference in either the Mental Component Scale or the Physical Component Scale (table III).

Discussion

The migraine-specific quality-of-life instrument used in this study was used previously in several of the randomised, placebo-controlled trials designed to test the efficacy and safety of rizatriptan.[6,9,16] In a substudy of a triple-blinded, rizatriptan dose-ranging trial,[17] patients receiving rizatriptan 10mg showed a significantly better response than those receiving placebo in three of five domains of the 24-HrMQoLQ (Social Functioning, Migraine Symptoms and Feelings/Concerns).[16] (Note that patients randomised to placebo in that trial were allowed a blinded dose of rizatriptan 10mg at 2 hours, which may have tended to diminish the difference in HR-QoL between the placebo and rizatriptan arms.) In a multicentre, double-blinded trial of rizatriptan 10mg versus placebo (in which patients receiving placebo were not allowed a blinded dose of rizatriptan at 2 hours), rizatriptan improved patients' HR-QoL across all five domains of the 24-HrMQoLQ.[6] Randomised, controlled trials comparing rizatriptan with sumatriptan have shown that rizatriptan provides faster pain relief.[9,10] In one of these trials,[10] patients receiving rizatriptan 10mg had statistically significantly better 24-HrMQoLQ scores than patients receiving placebo in all five domains, whereas scores with sumatriptan 100mg were statistically significant from placebo in only three domains (Migraine Symptoms, Feelings/Concerns, and Energy/Vitality).[10] Assessment with the 24-HrMQoLQ in another trial[9] indicated that rizatriptan 10mg had effects on HR-QoL similar to those of sumatriptan 50mg, except in the Work Functioning domain where rizatriptan 10mg was superior to sumatriptan 50mg. In the present study, rizatriptan 10mg was compared with patients' usual medication(s) in a non-blinded, parallel group, randomised trial.[11] Patients randomised to rizatriptan had a better HR-QoL during the 24-hour period following initial drug administration for a migraine attack than patients on their usual medication, as evidenced by statistically significantly higher scores in all five domains of the 24-HrMQoLQ.

The 24-HrMQoLQ[12,13] is episode-specific, while other migraine-specific quality-of-life instruments[18-20] were designed to measure HR-QoL over a several-week period. The SF-36 is a generic instrument that can be used to assess HR-QoL over extended time periods punctuated by migraine attacks and which, in conjunction with the 24-HrMQoLQ, can provide a more complete picture of the migraineur's life experience. Compared with US norms, individuals with migraine have reduced scores in all eight SF-36 domains, but in particular in the Social Functioning, Physical Functioning, Role Physical and Bodily Pain domains, with the magnitude of the reductions being proportional to migraine severity.[2,4] In several studies in which the SF-36 was used to measure the effect of sumatriptan on HR-QoL, Social Functioning scores improved most consistently.[2] In an uncontrolled non-blinded study, treatment of migraine with sumatriptan for up to 24 months was associated with improvements over baseline in the Social Functioning, Bodily Pain and General Health Perceptions domains.[21] In the present randomised, parallel-group trial comparing rizatriptan 10mg with standard care, a statistically significant difference between treatment groups was seen only in the Mental Health domain; however, rizatriptan recipients showed a trend towards better scores in the Mental Health Component Scale of the SF-36.

The scores on the individual SF-36 domains in this study were within the range of values reported elsewhere for migraine.[2] Comparison with other studies is, however, complicated by the fact that baseline SF-36 values in this extension study reflected patients' status at the end of a randomised, blinded trial of rizatriptan for multiple migraine attacks.[7] In that trial, 80% had their last migraine attack treated with rizatriptan and 20% with placebo. Thus, most patients randomised to rizatriptan in the extension trial would not be expected to experience any change in their SF-36 scores, whereas scores might be expected to rise for a minority of these patients. Consistent with this, mean scores rose by 0.8% to 7.2% points from the baseline values for seven of the eight SF-36 domains for patients randomised to rizatriptan. Conversely, scores decreased from their baseline values for five of the domains in the standard care group. The Mental Component Scale increased from baseline by 1.5% points for the rizatriptan group, but decreased by 4% points in the standard care group. While not reaching statistical significance, the SF-36 results are consistent with better mental health with rizatriptan than with patients' usual medication.

The 24-HrMQoLQ measures HR-QoL across five dimensions. The 24-HrMQoLQ domain scores in this study were weakly negatively correlated with changes in migraine severity and functional disability as recorded by patients in their diaries at 2 and 4 hours post administration. Correlations between the 24-HrMQoLQ and the 0- to 2-hour changes in migraine severity and functional disability were statistically significant ($p < 0.01$) for all five domains, but were relatively modest, ranging from –0.34 to –0.19 (Spearman's correlation coefficient). Correlations for the 0- to 4-hour changes in diary measures were weaker (–0.10 to –0.22) and in most cases were not statistically significant. The 0- to 4-hour correlations might be confounded by patients either re-taking rizatriptan or using additional rescue medications 2 hours after initial drug administration. These correlations are similar in magnitude to the correlations between the five domains of the 24-HrMQoLQ, which range from 0.08 to 0.38, indicating minimal overlap of the domains.[12] Thus, the effects of rizatriptan measured by the 24-HrMQoLQ represent improvement in HR-QoL dimensions beyond simply pain and disability, which are the most obvious manifestations of a migraine attack.

The rapid action of rizatriptan compared with patients' usual therapy might explain the improved HR-QoL during the period following an attack. In the 025 extension trial, the odds ratios for pain relief and freedom from pain at 2 hours were 3.64 and 2.61, respectively, for rizatriptan compared with standard care.[11] The improved migraine-specific HR-QoL with rizatriptan might also be related to better tolerability. Patients' usual migraine

therapy comprised a number of different drugs (most often sumatriptan, NSAIDs or barbiturates) and several of these medications have well established adverse effects. Several items of the 24-HrMQoLQ might be sensitive to the adverse effects of barbiturates and other drugs, e.g. the ability to stay alert, operate machinery or sleep. The overall incidence of adverse experiences in the extension trials was similar in the rizatriptan 10mg (80%) and the usual care (78%) groups.[11] However, patient's fears or expectations of adverse drug effects might influence their HR-QoL to a greater extent than the adverse effects themselves. Such fears are tested in the Feelings/Concerns domain of the 24-HrMQoLQ, which queries whether respondents feel 'concern that your migraine medication will not relieve migraine symptoms'. Other relevant items in the Feelings/Concerns domain ask whether respondents 'feel physically uncomfortable' and whether they 'feel upset about having migraine headaches'.

This study has several limitations. First, selection bias might plausibly have contributed to the positive effects of rizatriptan on HR-QoL. Of the migraineurs from the blinded, randomised trial that preceded the extension study, 85% chose to enrol in the extension phase. Some patients might have chosen not to participate due to a lack of efficacy of rizatriptan. Patients categorised as responders in the previous blinded trial were more likely than non-responders to enter the non-blinded extension (68.5% versus 54.7%; 'response' defined as pain relief in the last attack experienced). Patients receiving rizatriptan were more assiduous in recording their headaches in their study diaries. A greater proportion of rizatriptan patients completed the 24-HrMQoLQ (80.9% versus 70.0%). The significance of this is that HR-QoL improvements might not be as good in an unselected population of migraineurs as in the population in the current study. Finally, since patients in the usual care group reported a slightly lower incidence of severe headaches, it is possible that they selectively under-reported severe headaches, which would tend to bias the 24-HrMQoLQ results against the rizatriptan group.

In the treatment of migraine, the clinical goals are to alleviate headache pain and associated symptoms rapidly and to restore normal functioning in the period following onset of a migraine attack. In this study, these goals were met more often for patients receiving rizatriptan than for patients receiving usual care. Patients receiving rizatriptan faired better in terms of their migraine symptoms, their energy and vitality, their functioning both socially and at work, and their concerns about migraine and their migraine treatment. Faster relief of headache pain and improved quality of life are likely to result in better patient satisfaction with the migraine therapy.

Conclusion

Treatment with rizatrpitan resulted in a better migraine-specific HR-QoL than did patients' usual medication, according to results from a validated instrument measuring short-term migraine-specific HR-QoL.

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