Quality of Life of Patients with Refractory Chronic Rhinosinusitis: Effects of Filgrastim Treatment

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ABSTRACT

In this double-blind placebo-controlled randomized clinical trial, we investigated the influence of filgrastim administration on the quality of life (QOL) of refractory chronic sinusitis patients who did not respond to regular treatments. QOL was considered to be an important outcome measurement because apart from classic sinusitis parameters, it measures the overall burden of the symptomatology of chronic sinusitis patients caused by general malaise, tiredness, and social impediments. The QOL of 56 patients was assessed five times during the 24-week trial with the EuroQol, the Short Form (SF)-36, and the McGill pain questionnaire (MPQ). The QOL scores were all well below population norm scores and scores in a group of patients with chronic sinusitis who had sinus surgery. QOL scores of the filgrastim group suggested a better QOL than the placebo group, although none of the differences were statistically significant. There were indications that it might be possible to determine a subpopulation in which the results are better. Although the QOL measurements were not able to show a significant treatment effect of filgrastim in this group of patients with refractory chronic sinusitis, these measurements are important in studying chronic sinusitis because they enable the comparison of the burden of illness of patients with chronic sinusitis with other patient groups. (American Journal of Rhinology 15, 231–237, 2001)

The interest in chronic rhinosinusitis in the past 10 years has been aimed primarily at medical treatment of sinusitis before functional endoscopic sinus surgery (FESS) and FESS and its outcomes.1–4 Although there is ample literature describing various aspects of FESS in relation to its success rates, very little has been reported about what possibilities exist if there is recurrent failure, i.e., patients in whom after a series of surgical procedures with maximum postoperative management, chronic sinusitis and/or chronic polyps do not seem to be responding to a functional approach.5–7 Patients with persistent rhinosinusitis despite optimal FESS have been proven to be very difficult to treat. Although the disease can be reduced (usually not totally) by maximal treatment with local and systemic therapy, the recurrence rates are high.

In the protection of the paranasal sinuses against bacterial and fungal rhinosinusitis, neutrophils seem to play a role.8 The proliferation and differentiation of neutrophils are promoted by the administration of recombinant human granulocyte colony-stimulating factor (rG-CSF).9,10 Clinical studies in subjects who are nonneutropenic indicate that rG-CSF may be beneficial as adjunctive therapy for treatment of serious bacterial and opportunistic fungal infections in patients who are nonneutropenic, including those with alterations in neutrophil function.11 A pilot study at the Erasmus University Medical Center Rotterdam indicated that patients without known predisposing or aggravating factors for per-
sistent chronic rhinosinusitis, low neutrophil counts, and unsuccessful response to conventional treatments might benefit from filgrastim treatment. In this double-blind placebo-controlled randomized clinical trial, the effects of filgrastim recombinant human granulocyte colony-stimulating factor (r-met-HuG-CSF) on the quality of life (QOL) of patients with chronic sinusitis were investigated.

QOL was seen as an important outcome measure because in most available treatments it is not possible to cure the patients totally and apart from classic symptoms of chronic sinusitis, many of these patients complain of more distant symptomatology such as general malaise, tiredness, and social retardation. So far, QOL measurements in patients with chronic sinusitis are limited and generally disease-specific questionnaires such as the Rhinosinusitis Disability Index,\textsuperscript{12} the Chronic Sinusitis Survey Score,\textsuperscript{13–15} and the SinoNasal Outcome Test-16 (SNOT-16)\textsuperscript{16} have been used. A disadvantage of these disease-specific questionnaires is that they do not allow for comparisons between different therapeutic interventions and different patient groups, which complicates the interpretation of the effect size. The Short Form (SF)-36 has been used before in patients with chronic sinusitis, but only to evaluate the effects of endoscopic sinus surgery.\textsuperscript{13,17,18} We assured QOL by using three general QOL questionnaires: the EuroQol, the SF-36, and the McGill pain questionnaire (MPQ).

MATERIALS AND METHODS

Patients and Treatment

This trial was conducted between June 1995 and November 1997 at the Eramus Medical Center Rotterdam, the University Medical Center Utrecht, and the University Hospital Nijmegen. Patients were included if no response was shown to all conventional treatments (such as antibiotics, nasal decongestants, FESS, frontal sinus surgery, and Caldwell-Luc procedures) and when no indication for surgical interventions of any kind to improve the chronic sinusitis was found.

After randomization (official study entry at T\textsubscript{0}), all patients were treated with a combination of 500–750 mg of ciprofloxacin twice daily and 450–600 mg of clindamycin three times a day for 14 days. Patients were randomized to 300 μg subcutaneously (s.c.) of filgrastim or placebo s.c. once a day for the first 14 days (until T\textsubscript{2}) and for another 10 weeks (until T\textsubscript{12}) with either 300 μg s.c. of filgrastim or placebo s.c. every other day. After this treatment period, patients were followed for another 12 weeks until T\textsubscript{24} (post-treatment observation period). Patients were asked to complete QOL questionnaires at trial inclusion (T\textsubscript{-4}), at randomization (T\textsubscript{0}), and at T\textsubscript{2}, T\textsubscript{4}, T\textsubscript{12}, and T\textsubscript{24} (Fig. 1).

This study was approved by the local medical ethics committees and informed consent was obtained from all patients.

QOL Measurements

The SF-36 scores are measured on nine subscales, which can be aggregated into two sum scores, physical health and mental health.\textsuperscript{19} These two sum scores were used as primary outcomes and the subscales were used as secondary outcomes.

The EuroQol questionnaire, consisting of two parts, originally was designed to estimate utilities for the calculation of quality-adjusted life years (QALYs).\textsuperscript{20} The first part is a generic five-dimensional questionnaire, the EQ-5D. This profile can be transformed to a value given by the general public: the EQ-5D index.\textsuperscript{21} This societal value of the health state represents the societal perspective, which is the preferred perspective in economic evaluation of health care.\textsuperscript{20,22,23} The second part of the EuroQol questionnaire is

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\text{QOL measurement} = \text{SF36} + \text{McGill Pain questionnaire} + \text{EuroQol}
\]

\[
\text{AB} = 2 \text{ weeks of treatment with Ciprofloxacin 500–750 mg twice a day and Clindamycin 450–600 mg three times a day.}
\]
a visual analog scale, the EQ\textsubscript{vas}. The EQ\textsubscript{vas} represents the patient’s judgment of his/her own health state. This patient perspective is useful in clinical decision making without cost considerations.

Because pain was considered to be a domain of special attention, the MPQ\textsuperscript{24,25} was added. In this investigation, the Dutch translation (the MPQ-DLV) was used.\textsuperscript{26–28} The pain-rating index total score (PRI-T) was chosen as the primary outcome score for this questionnaire.

**Questionnaire Timing**

The patients completed questionnaires at T\textsubscript{-4} (trial inclusion), at T\textsubscript{0} (randomization), at T\textsubscript{2} (dose of study medication was halved), at T\textsubscript{4}, at T\textsubscript{12} (end of study medication) and at T\textsubscript{24} (end of trial). The questionnaires were filled in at the day the clinician was visited or at home at the prescribed date. At all times, all questionnaires were administered, except the SF-36 at T\textsubscript{2}.

Three periods of interest were distinguished:
1. The period before randomization (T\textsubscript{-4} and T\textsubscript{0}).
2. The period in which the drug can have an effect on the outcome parameters T\textsubscript{2}, T\textsubscript{4}, and T\textsubscript{12};
3. The period after the end of the treatment (T\textsubscript{24}).

**Covariates**

During the data collection of this double-blind trial, clinicians suspected that some of the included patients could be labeled as less responsive to the drug than others. For instance, after several surgical interventions, the amount of scar tissue and the changes in anatomy might be so large that a restoration to a normal situation is impossible. In addition, some of these patients experience pain in any case, irrespective of therapy. Another aspect may be that the patients profit socially from the illness, \textit{e.g.}, in terms of attention and respect. In an effort to control for these effects, the clinicians categorized the patients into three groups: “probably not responsive,” “not clear,” and “probably responsive.” As part of the secondary analysis, this covariate was used in the analyses of the primary outcome measures.

**Missing Values**

Missing values were imputed by using the algorithms published in the manuals of the questionnaires\textsuperscript{29,30} and by using the Missing Value Module of SPSS for Windows, release 9.0.0.

**Statistical Analysis**

Data were analyzed using SPSS for Windows, release 9.0.0 (SPSS Inc., Chicago, IL). For comparison of patients characteristics, the chi-square test and the Mann-Whitney test were used. Differences between the treatment groups in the QOL questions were analyzed using repeated measures analysis (MANOVA). A statistical significance level of 5% was used.

**RESULTS**

Fifty-nine patients were randomized in the trial, of which one was removed from the analysis at T\textsubscript{0}, because this patient turned out to have cystic fibrosis. Characteristics of the remaining 58 patients are shown in Table I. Most patients had a long history of sinonasal complaints (mean, 11 years [SD, 10]) and had been operated on 4.5 (2.7) times. After having passed T\textsubscript{0}, two more patients were removed (one withdrew because of bone pain and another was mistakenly randomized before the bacterial infection was confirmed).

All of the remaining 56 patients returned at least two of the questionnaires T\textsubscript{2}, T\textsubscript{4}, and T\textsubscript{12}. Totally, 330 of the 336 distributed questionnaires were returned (98.2%). The number of delayed responses was small and occurred mostly at the end of the trial. Two patients had difficulty reading the questionnaires because of language problems. Of these patients, only the scores of the questionnaires that were simple to administer (EQ-5D and EQ\textsubscript{vas}) were included in the analysis.

**Primary End Points**

Primary end points of the QOL questionnaires of the patients at baseline are presented in Table II. From the reference values in this table and from Figs. 2 and 3, it can

<table>
<thead>
<tr>
<th>TABLE I</th>
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<table>
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<tr>
<th>Patient Characteristics</th>
<th>Filgrastim</th>
<th>Placebo</th>
<th>( p ) Value</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>27</td>
<td>31</td>
<td>0.694</td>
<td>58</td>
</tr>
<tr>
<td>Male</td>
<td>8</td>
<td>18</td>
<td>0.078</td>
<td>26</td>
</tr>
<tr>
<td>Female</td>
<td>19</td>
<td>13</td>
<td>0.377</td>
<td>32</td>
</tr>
<tr>
<td>Currently employed</td>
<td>14</td>
<td>16</td>
<td>0.809</td>
<td>30</td>
</tr>
<tr>
<td>Age</td>
<td>45 (10)</td>
<td>42 (11)</td>
<td>0.356</td>
<td>44 (10)</td>
</tr>
<tr>
<td>Work hours per week per working patient</td>
<td>33.0 (9.6)</td>
<td>35.7 (14.4)</td>
<td>0.552</td>
<td>34.4 (12.2)</td>
</tr>
</tbody>
</table>

\( \text{Mean (SD).} \)
### TABLE II

<table>
<thead>
<tr>
<th>Primary and Secondary End Points from T&lt;sub&gt;−4&lt;/sub&gt;–T&lt;sub&gt;24&lt;/sub&gt;</th>
<th>Reference</th>
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<tbody>
<tr>
<td></td>
<td>Filgrastim</td>
</tr>
<tr>
<td>Primary endpoints</td>
<td></td>
</tr>
<tr>
<td>SF-36 Physical composite score</td>
<td>34.68</td>
</tr>
<tr>
<td>SF-36 Mental composite score</td>
<td>45.52</td>
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<tr>
<td>EuroQol EQ&lt;sub&gt;eq&lt;/sub&gt;</td>
<td>58.00</td>
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<tr>
<td>EuroQol EQ-5D</td>
<td>0.59</td>
</tr>
<tr>
<td>Secondary end points</td>
<td></td>
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<tr>
<td>McGill Affective pain rating index</td>
<td>3.86</td>
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<tr>
<td>McGill Evaluative pain rating index</td>
<td>5.09</td>
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<tr>
<td>SF-36 Physical functioning</td>
<td>67.82</td>
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<tr>
<td>SF-36 Role-physical</td>
<td>24.07</td>
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<tr>
<td>SF-36 Bodily pain</td>
<td>43.11</td>
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<tr>
<td>SF-36 General health</td>
<td>40.04</td>
</tr>
<tr>
<td>SF-36 Vitality</td>
<td>42.59</td>
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<tr>
<td>SF-36 Social functioning</td>
<td>56.94</td>
</tr>
<tr>
<td>SF-36 Role-emotional</td>
<td>62.96</td>
</tr>
<tr>
<td>SF-36 Mental health</td>
<td>66.96</td>
</tr>
</tbody>
</table>

Reference values relate to (1) general population in the United States (Ware et al.,<sup>19</sup>), (2) general population in the United Kingdom (Kind et al.,<sup>11</sup>), and (3) general Dutch population (Aaronson et al.,<sup>32</sup>). No reference values for the general population are available for the MPQ.
be seen that all scores on the primary end points are well below the population averages, which indicates a serious impaired QOL in this patient group.

In almost all primary end points, the scores of the filgrastim group suggested a better QOL than the placebo group. However, none of these differences were statistically significant. Figure 2 presents the scores of this patient group on the EuroQol EQ-5D index compared with scores of the general population of the United Kingdom.11

**Secondary End Points**

Secondary end points of the QOL questionnaires of the patients at baseline are presented in Table II.

None of the analyses of the secondary variables showed significant differences between the placebo group and the filgrastim group. The power of the design at T2, T4, and T12 was improved when the covariant “responsiveness” was included (most p-values dropped). Nevertheless, none of the p-values dropped below 0.10.

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**Figure 2.** Mean scores of the study group on the EuroQol EQ-5D index compared with mean scores of the general population of the United Kingdom (Kind et al.31). SDs of the general population group and the placebo group are indicated.

**Figure 3.** Mean scores of the study group on the SF-36 physical composite score compared with mean scores of the general population in the United States and with mean scores of patients with other chronic morbidities: hypertension, diabetes, and angina (Ware et al.19). SDs of the general population group and the placebo group are indicated.
DISCUSSION

This study describes the use of QOL measures in the evaluation of a randomized clinical trial in which 58 patients with chronic sinusitis were treated with filgrastim or placebo.

We tested the effects on the MPQ, the EuroQol, and the SF-36. All scores were well below the population norm scores, indicating a lower QOL in this patient group. In addition, all scores were well below the scores in the only other group of patients with chronic sinusitis in which the SF-36 was used as outcome measurement (Table III). This is in accordance with the refractory nature of the disease in this group of patients. This comparison again emphasizes the importance of QOL measurements in patients with chronic sinusitis as indicated by Metson and Glicklich. It shows that within one disease entity, the severity and impact on QOL can vary essentially, which indicates the need for the use of these methods to describe patient populations. The application of the SF-36 and the EuroQol in these patients also enables a comparison with scores of the general population. Figures 2 and 3 clearly indicate that the difference of the QOL scores between these patients with refractory chronic sinusitis and the general population is noticeable. For the MPQ, no reference values for the general population are available. We compared the scores of the patients with chronic sinusitis to scores of a group of 92 Dutch patients who had physiotherapy, because this is a typical patient group known to be suffering from pain. However, the scores of our group of patients with chronic sinusitis were even worse than the scores of the physiotherapy patients.

All mentioned comparisons indicate that the burden of illness in patients with chronic sinusitis is high. This implies that large health improvements can be gained in these patients, while the costs of the regular antibiotic treatments are still at a low level. Therefore, additional investments in new therapeutic modalities for patients with chronic sinusitis have high chances of being cost-effective.

In this study, the scores of the filgrastim group suggested a better QOL than the placebo group, but none of the differences were significant. We further controlled for responsiveness, an ordinal variable that was based on the clinical impression. This covariate improved the power of the analysis, but it did not result in significant differences between the filgrastim group and the placebo group. The lack of significant results in this trial could be the result of an insensitivity of the QOL questionnaires for the effects of chronic sinusitis. However, this explanation seems implausible given that all questionnaires measured lower QOL values than the values of a “healthy” population and therefore appear to be sensitive for the impact of chronic sinusitis on QOL. Moreover, Gliklich and Metson were able to show significant effects of ethmoid sinus surgery on a number of subscales such as bodily pain, vitality, and social functioning.

Although the white blood cell counts were significantly elevated during the 12-week treatment period, disease-specific symptom scores did not reveal any statistically significant differences (data not shown).

Frequently, an unexpectedly high number of missing responses plague clinical trials using QOL questionnaires. This problem is often responsible for the lack of significant differences. In the current trial, the nonresponse was extremely low. Furthermore, the quality of the response was very good, only a minimal number of questionnaires were unusable. This high quality of the response supports the conclusions of the trial.

The anticipated number of patients in this trial was based on practical considerations. One could speculate that the number of included patients is just not high enough to show significant differences. Nevertheless, based on the observations in the current trial, the effect sizes of a larger trial in the same patient population can be expected only to be modest.

The aforementioned conclusions are of course only valid for the population of patients included in this trial. It could

| TABLE III | Mean Scores of the Study Group Compared with Mean Scores of 108 Patients with Chronic Sinusitis Who Were Responsive to Ethmoid Surgery

<table>
<thead>
<tr>
<th>SF-36 Subscales</th>
<th>Refractory Chronic Rhinosinusitis Before Start of Treatment (T−4)</th>
<th>Chronic Sinusitis Patients Undergoing Ethmoid Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Filgrastim</td>
<td>Placebo</td>
</tr>
<tr>
<td>Physical functioning</td>
<td>67.8</td>
<td>72.1</td>
</tr>
<tr>
<td>Role-physical</td>
<td>24.1</td>
<td>50.1</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>43.1</td>
<td>55.9</td>
</tr>
<tr>
<td>General health</td>
<td>40.0</td>
<td>45.6</td>
</tr>
<tr>
<td>Vitality</td>
<td>42.6</td>
<td>48.2</td>
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<tr>
<td>Social functioning</td>
<td>56.9</td>
<td>37.3</td>
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<tr>
<td>Role-emotional</td>
<td>63.0</td>
<td>71.6</td>
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<tr>
<td>Mental health</td>
<td>67.0</td>
<td>71.3</td>
</tr>
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</table>
well be that other patient groups or subpopulations might benefit more from filgrastim treatment. This investigation gives some indications that such patient groups indeed exist. It was found that the power of the investigation increased when the clinical interpretation of the patient’s response was included in the analysis. This means that the clinicians were able to determine a subpopulation in which filgrastim had better effects. It would be interesting to explore this observation more thoroughly because it might open the way to a more effective administration of filgrastim in patients with chronic sinusitis.

An important conclusion from this study is that QOL measurements are extremely important in studying chronic sinusitis. Not only does this study show that the QOL scores of this patient group were all well below population norm scores but it also shows well below scores from a group of patients with average chronic sinusitis responsive to ethmoid surgery.

ACKNOWLEDGMENTS

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REFERENCES