Quality of life and costs of Filgrastim® (G-CSF) treatment in patients with persistent chronic rhinosinusitis

drs. M. van Agthoven[1]
dr. J.J.V. Busschbach[1]
dr. W.J. Fokkens[2]
dr. J.P. van de Merwe[3]
dr. C.A. Uyl-de Groot[1]

1) Institute for Medical Technology Assessment, Erasmus University Rotterdam.
2) Department of Otorhinolaryngology, Erasmus University Rotterdam.
3) Departments of Immunology and Internal Medicine, Erasmus University Rotterdam.

Correspondence:
institute for Medical Technology Assessment
Erasmus University Rotterdam
P.O. Box 1738
3000 DR Rotterdam, The Netherlands
Tel: +31 10 408 85 33
Fax: +31 10 408 90 94
E-mail: vanagthoven@bmg.eur.nl

institute for Medical Technology Assessment 2000
Report number 00.53

Preface

In this study, the costs and quality of life effects of Filgrastim® treatment (r-met-HuG-CSF) in patients with persistent chronic rhinosinusitis were assessed. This economic evaluation was performed alongside a double blind randomized placebo controlled clinical trial in three Dutch university centres. The results of the cost analysis and the quality of life study are described separately in this report. This was done to emphasize the merits of both studies most clearly.

Beyond the clinical outcome parameters, quality of life was seen as an important outcome measure on it's own because the clinical symptoms of the disease were never expected to disappear entirely after the administration of Filgrastim®. It nevertheless seemed plausible that the symptoms should be reduced significantly, which presumably would be translated in the quality of life as reported by the patients themselves.

The cost analysis not only contains a comparison of the costs in the placebo group with the costs in the Filgrastim® group. Additionaly, as the trial costs were expected to be driven particularly by protocollary diagnostic tests and outpatient visits, a comparison of the costs in the trial interval with the costs of a regular treatment was made.

This manuscript is meant as a detailed research report. Journal articles resulting from this research will follow.

Rotterdam, August 2000

Michel van Agthoven
Jan J.V. Busschbach
Carin A. Uyl-de Groot

Summary

This is the first report of the double blind randomized clinical trial, in which we investigated the influence of Filgrastim® on the quality of life and treatment costs of chronic sinusitis patients who did not respond to regular treatments.

The quality of life of 56 patients was assessed 5 times during the 24-week trial with the EuroQol, the SF-36 and the McGill Pain questionnaire. We further controlled for "responsiveness", based on clinical impression.

Direct medical and indirect non-medical costs per patient during the trial were analyzed, based on data from clinical record forms and the hospital information system. We further compared the direct medical costs to the costs of regular treatment.

The quality of life scores were all below population norm scores. Quality of life scores of the Filgrastim® group suggested a better quality of life than the placebo group, although none of the differences were statistically significant. There were indications that controlling for responsiveness increased the power of the design.

The difference in costs between the trial groups were driven by the Filgrastim® costs (Euro 4899). When Filgrastim® costs were neglected, no difference in costs remained. Except for Filgrastim®, total direct costs summed up to Euro 2712 and the indirect costs to Euro 582. Total direct costs of a 24-week regular treatment were three times lower than the costs of the trial treatment.

While significantly increasing treatment costs, Filgrastim® administration does not lead to a better quality of life of chronic sinusitis patients, although there were some indications that it might be possible to determine a subpopulation in which the results are better.

Contents

QUALITY OF LIFE EFFECTS OF FILGRASTIM® (G-CSF) TREATMENT IN PATIENTS WITH PERSISTENT CHRONIC RHINOSINUSITIS

Introduction

The interest in chronic rhinosinusitis in the past decade has been aimed primarily at medical treatment of sinusitis before functional endoscopic sinus surgery (FESS) and FESS and its outcomes. FESS aims at restoring the normal anatomical structures enabling the diseased mucosa to repair. Little has been reported about possibilities in the case of recurrent or persistent chronic rhinosinusitis in patients who do not respond to the conventional treatments. In the protection of the paranasal sinusses against bacterial and fungal rhinosinusitis, neutrophils seem to play an important role (Dale & Hammond, 1988). The proliferation and differentiation of neutrophils is promoted by the administration of human hematopoetic granulocyte colony stimulating factors (G-CSF). In cancer patients, filgrastim (r-met-HuG-CSF) is currently administered to reduce neutropenia induced by cytostatic therapy. A pilot study at the Erasmus University Medical Centre Rotterdam showed that patients without known predisposing or aggravating factors for persistent chronic rhinosinusitis, low neutrophil counts and unsuccesful response to conventional treatments might benefit from filgrastim treatment. In this double blind randomized clinical trial, the effects of filgrastim (r-met-HuG-CSF) on the quality of life of patients with chronic sinusitis were investigated.

Quality of life was seen as an important outcome measure, since the bacterial infections were not expected to disappear completely, but it nevertheless seemed plausible that the effects of the infections would be reduced. The outcome measurement should therefore be the quality of life as measured by a subjective response of the patients themselves. This measurement has rarely been performed in chronic sinusitis, and it is a distinct approach compared to usual clinical measurements. So far, quality of life measurements in chronic sinusitis patients relied on the Rhinosinusitis Disability Index (Maune et al., 1999) and the Chronic Sinusitis Survey Score (Glicklich & Hilinski, 1995; Gliklich & Metson, 1995; Alsarraf et al., 1999). A disadvantage of these disease specific questionnaires is that they do not allow for comparisons between different interventions and patient groups, which complicates the interpretation of the effect size. Given the high costs of filgrastim, an estimation of the effect size was seen as highly relevant in this investigation. We therefore focused on generic quality of life questionnaires, which can be compared to other health care programs. We therefore measured quality of life by using the EuroQol, the SF-36 and the McGill Pain Questionnaire. Only the SF-36 has

been used before in chronic sinusitis patients, but only to evaluate the effects of endoscopic sinus surgery (Glicklich & Hilinski, 1995; Metson & Gliklich, 1998). A problem associated with the use of a battery of generic questionnaires is the high number of outcomes that have to be evaluated. This is especially true when multidimensional questionnaires are used, like in this investigation. In that case a serious risk of chance cumulation exists. For this reason, primary, secondary and explorative outcomes measures were defined at forehand.

Materials and methods

Patients and treatment

This study was performed as a double blind two-arm placebo controlled randomized trial. Patients were registered at T_{-4} for a pre-treatment observation of 4 weeks before being randomized. Between June 1995 and November 1997, 59 patients were randomized in the trial at the Eramus Medical Centre Rotterdam (35), the University Medcal Centre Utrecht (19) and the University Hospital Nijmegen (5). Only patients with symptoms lasting for more than 6 months were included in order to cover the group of severe chronic bacterial sinusitis patients. The included patients had been given all conventional treatments, such as antibiotics, nasal decongestants, functional endoscopic sinus surgery, frontal sinus surgery and Caldwell-Luc procedures, yet they still suffered from their disease as the treatments were unsuccessful. Patients were included when no indication for surgical interventions of any kind to improve the chronic sinusitis was found.

After randomization (official study entry at T_0), all patients were treated with a combination of Ciprofloxacin 750mg once a day and Clindamycin 600 mg 3 times a day for 14 days. Patients were randomized to Filgrastim 300 µg subcutaneously (s.c.) or placebo s.c. once a day for the first 14 days (until T_2) and for another 10 weeks (until T_{12}) with either Filgrastim 300 µg s.c. or placebo s.c. every two days. After this treatment period, patients were followed for another 12 weeks until T_{24} (post treatment observation period).

Patients were asked to complete quality of life questionnaires at trial inclusion (T_{-4}), at randomization (T_0) and at T_2, T_4, T_{12} and T_{24}. They were included in the quality of life analyses if they returned at least one of the questionnaires of the period in which the drug could be active (T_2, T_4 and T_{12}).

Quality of life measurements

As quality of life measurements have not been performed often in chronic sinusitis patients, a short description of each of the measurement instruments that we used is reported. These multidimensional questionnaires yield a high number of outcomes. In

order to control for the risk of chance cumulation, we categorized the outcomes into "primary outcomes" and "secondary outcomes". The primary outcomes were those outcomes which can be argued to have a contentual relationship with the problems experienced by chronic rhinosinusitis patients.

Three quality of life measurement instruments were used in the current study: the SF-36 and the EuroQol, which are both generic questionnaires. A more domain specific questionnaire used was the McGill Pain Questionnaire, as pain was considered to be an important outcome.

SF-36 scores are measured on 9 subscales, which can be aggregated into 2 sum scores, physical health and mental health (Ware et al., 1994). These two sum scores were used as primary outcomes. Secondary outcomes were the 9 subscales, of which 5 seemed closely related to chronic sinusitis: physical functioning, social functioning, physical role functioning, vitality and pain. A pilot study preceding the current study showed that chronic sinusitis patients scored well below the norm scores of the Dutch Population on these 5 subscales. Of the remaining 4 subscales measured, the subscales “emotional role functioning” and "mental health" do not have a contentual relation with chronic sinusitis and were therefore used as secondary outcomes. The content of the subscale "general health" was also measured by the EuroQol Visual Analogue Scale (EQ_{VAS}) and was therefore not used as a primary outcome measure. The subscale "health transition" was only part of the explorative analysis, because at forehand it was not clear at which moment a notable change in health state would occur.

The EuroQol questionnaire, existing of two parts, is originally designed to estimate utilities for the calculation of Quality Adjusted Life Years (Drummond et al., 1997). The first part is a generic 5 dimensional questionnaire, the EQ-5D. This profile can be transformed to a value given by the general public: the $EQ\text{-}5D_{index}$ (Dolan, 1997). This societal value of the health state represents the societal perspective, which is the preferred perspective in economic evaluation of health care (Hadorn, 1991; Drummond et al., 1997; Gold et al., 1996). The second part of the EuroQol questionnaire is a visual analogue scale, the EQ_{vas}. The EQ_{vas} represents the patient's judgement of his own health state. This patient perspective is useful in clinical decision making without cost considerations. In this study, both the societal and the patient perspective of the EuroQol were used as primary outcome measures.

Since pain was considered to be a domain of special attention, the McGill Pain Questionnaire (Melzack, 1975, 1987) was added. In this investigation, the Dutch

translation (the MPQ-DLV) was used (Kloot et al., 1995; Verkes et al., 1989; Kloot & Vertommen, 1989). The Pain Rating Index Total Score (PRI-T) was chosen as the primary outcome score for this questionnaire. The PRI-T-score is the sum of the rank values of the words "sensorial", "affective" and "evaluative" chosen by the patients. The rating indexes of the subscales were defined as secondary outcomes.

Questionnaire timing

The patients completed questionnaires at T_{-4} (trial inclusion), at T_0 (randomization), at T_2 (dose of study medication was halved), at T_4, at T_{12} (end of study medication) and at T_{24} (end of trial). The questionnaires were filled in at the day the clinician was visited or at home at the prescribed date, if the patient could not visit the clinician at this date. At all times, all questionnaires were administered, except the SF-36 at T_2.

Three periods of interest were distinguished:

1. The period before randomization (T_{-4} and T_0).
2. The period in which the drug can have an effect on the outcome parameters: T_2, T_4 and T_{12}. At T_2, the doses of the medication were halved by giving the treatment every other day.
3. The period after the end of the treatment is represented by T_{24}.

Covariates

During the data collection of this double blind trial, clinicians suspected that some of the included patients could be labelled 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. Also, some of these patients experience pain in any case, irrespective of therapy. Another aspect may be that the patients profit socially from the illness, for instance 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

Repeated measures are vulnerable for missing values or inadequate timing of the administration of the questionnaires. If a measurement is missing or its timing is wrong, the patient has to be removed from the analysis. Therefore, in the case of repeated measurements, missing values are often interpolated (Beacon & Thompson, 1996; Zwinderman, 1992). All interpolation algorithms make use of the assumption that the missings occur independently of the dependent variable: "missing at random" (Maas & Snijders, submitted). This means that missing values do not depend on the level of the quality of life. It is therefore essential to investigate if it is reasonable to assume that the missing occurred "at random". All missing values were discussed in a meeting with the participating clinicians. During this meeting it was determined if a missing value could be classified as "missing at random". If the missing value is "at random" or the number of missings is small (Gillings & Koch (1991) suggest a maximum of 10%), interpolation methods can be used. In this investigation four types of interpolation methods were used.

1. Sometime it was possible to give an exact alternative, for instance for the variable gender, age, etc.
2. The second method was the use of published algorithms when some items of a scale are missing. Such an algorithm was used for the SF-36 (Ware et al., 1993). When a patient marked two discreet alternatives instead of one (this can be the case in the EuroQol and the SF-36), the worse alternative was chosen. In the case of a continuous response variable, the mean of the two values was used.
3. Sometimes the patient completed the questionnaire some days later. If the delayed response still made sense in relation to the event to which it relates, the delayed response was used as a proxy. For instance, a delay of 10 days at T_{24} interferes only little with the purpose of that particular measure, but a delay of 10 days at T_2 interferes with measurement at T_4.
4. In all other cases, the value was imputed using the expectation-maximization method using the known variables of the specific measure as predictors (by using the "Missing Value Analysis" in SPSS for Windows, release 9.0.0).

In all cases a statistical significance level of 5% was chosen.

Results

59 patients were randomized in the trial, of which one was removed from the analysis at T0, since this patient turned out to have cystic fibrosis. Characteristics of the remaining 58 patients are shown in Table 1. After having passed T_0, two more patients were removed (one quitted because of bone pain and the other was mistakenly randomized before the bacterial infection was confirmed).

Table 1. Patient characeteristics at baseline (T_0). Mean (standard deviation).

Patient characteristics	*filgrastim*	*placebo*	*P-value*	*total*
Number	27	31	0.694	58
Male	8	18	0.078	26
Female	19	13	0.377	32
Currently employed	14	16	0.809	30
Age	45 (10)	42 (11)	0.356	44 (10)
Work hours per week per working patient	33.0 (9.6)	35.7 (14.4)	0.552	34.4 (12.2)

Primary endpoints of the quality of life questionnaires of these patients at baseline are presented in Table 2. From the reference values in this table and from the Figures 1 and 2, it can be seen that all scores on the primary end points are below the population averages, which indicates an impaired quality of life in this patient group.

Table 2. Primary and secondary endpoints from T-4 to T24. Reference values relate to (1) physiotherapy patients before start of treatment, Kloot et al., 1995; (2) General U.S. population, Ware et al., 1994; (3) General U.K. population, Kind et al., 1999; (4) General Dutch population, Aaronson et al., 1998.

		T-4			T0			T2			T4			T12			T24			Ref.
		Filgr.	*Plac.*	*Total*	*Filgr.*	*Plac.*	*Total*	*Filgr.*	*Plac.*	*Total*	*Filgr.*	*Plac.*	*Total*	*Filgr.*	*Plac.*	*Total*	*Filgr.*	*Plac.*	*Total*	
Primary endpoints:																				
McGill	pain rating index total score	14.12	15.57	14.87	13.38	18.08	15.69	12.44	13.15	12.81	12.04	14.8	13.45	11.77	13.86	12.96	12.71	13.54	13.18	11.55 [(1)]
SF-36	physical composite score	34.68	33.73	34.21	35.15	32.76	33.94	-	-	-	35.62	35.57	35.62	39.47	35.15	37.21	37.43	36.74	37.09	55.26 [(2)]
SF-36	mental composite score	45.52	46.73	46.15	46.25	47.53	46.91	-	-	-	47.68	46.14	46.85	47.74	45.29	46.41	44.89	44.89	44.88	53.43 [(2)]
EuroQol	EQ $_{VAS}$	58.00	52.00	55.00	58.00	47.00	52.00	57.00	56.00	57.00	58.00	55.00	56.00	59.00	51.00	55.00	59.00	52.00	55.00	82.48 [(3)]
EuroQol	EQ $_{5D\text{-}index}$	0.59	0.6	0.59	0.58	0.54	0.56	0.67	0.58	0.62	0.62	0.54	0.58	0.66	0.56	0.61	0.62	0.59	0.6	0.86 [(3)]
Secondary endpoints:																				
McGill	sensorial pain rating index	6.35	6.81	6.58	6.12	8.71	7.39	6.09	6.48	6.3	6.14	6.92	6.54	5.89	6.77	6.41	6.05	5.96	6,00	6.15 [(1)]
McGill	affective pain rating index	3.86	4.63	4.26	4.26	4,00	4.11	4.44	2.92	3.57	3.61	3.39	3.49	3.64	3.91	3.81	4.54	3.64	3.97	1.96 [(1)]
McGill	evaluative pain rating index	5.09	5.64	5.38	4.75	5.96	5.35	4.41	5.13	4.78	4.24	5.25	4.78	4.86	5.19	5.04	4.35	5.52	5,00	3.45 [(1)]
SF-36	physical functioning	67.82	63.1	65.3	64.14	59.91	61.91	-	-	-	67.96	70.05	69.06	72.15	68.97	70.45	70.23	67.69	68.87	83.0 [(4)]
SF-36	role-physical	24.07	36.29	30.6	31.76	32.48	32.13	-	-	-	34.32	36.58	35.51	50.77	31.12	40.25	35.48	39.11	37.42	76.4 [(4)]
SF-36	bodily pain	43.11	42.23	42.98	45.89	46.1	46.53	-	-	-	49.03	45.97	47.58	55.85	44.8	50.31	47.29	47.82	47.77	74.9 [(4)]
SF-36	general health	40.04	35.6	37.66	42.38	33.37	37.57	-	-	-	40.04	35.6	37.66	45.52	34.64	39.7	45.49	37.43	41.18	70.7 [(4)]
SF-36	vitality	42.59	46.4	44.63	42.64	40.27	41.39	-	-	-	44.3	42,00	43.07	48.18	42.7	45.25	45.32	47.47	46.47	68.6 [(4)]
SF-36	social functioning	56.94	53.63	55.17	61.03	59.68	60.31	-	-	-	64.33	23.18	62.26	37.31	23.77	64.12	56.74	59.13	58.02	84.0 [(4)]
SF-36	role-emotional	62.96	70.97	67.24	65.56	69.33	67.58	-	-	-	71.97	71.35	71.64	71.57	61.78	66.29	67.65	59.02	63.04	82.3 [(4)]
SF-36	mental health	66.96	67,00	66.98	66.67	69.47	68.18	-	-	-	68.86	66.63	67.67	71.32	66.13	68.56	64.5	66.11	65.36	76.8 [(4)]

All of the remaining 56 patients returned at least two of the questionnaires T_2, T_4 and T_{12}. Totally, 330 of the 336 distributed questionnaires were returned (98,2%). The number of delayed responses was small and occured mostly at the end of the trial. Two patients had difficulties reading the questionnaires, due to language problems. Of these patients, only the scores of the simple to administer EQ-5D and EQ_{vas} were included in the analysis.

End points

In almost all primary end points, the scores of the filgrastim group suggested a better quality of life than the placebo group. However, none of these differences were significant. Figure 1 presents the development of the $EQ\text{-}5D_{index}$.

None of the analyses of the secondary variables showed significant differences between the placebo group and the filgrastim group. Including the covariant "responsiveness" improved the power of the design at T_2, T_4 and T_{12}: most p-values dropped. Nevertheless, none of them dropped below 0,10.

All primary and secondary endpoints of each questionnaire are shown in Table 2.

Figure 1. Scores of the study group on the EuroQol EQ-5D index compared to scores of the general U.K. population (Kind et al., 1999).

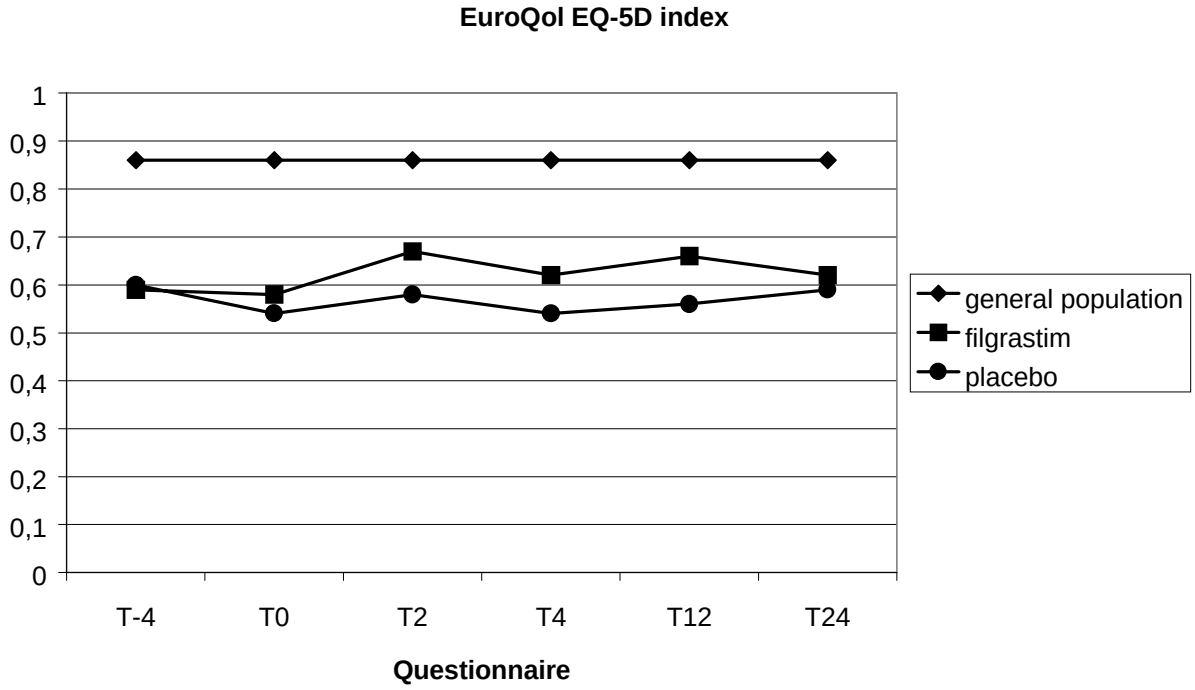
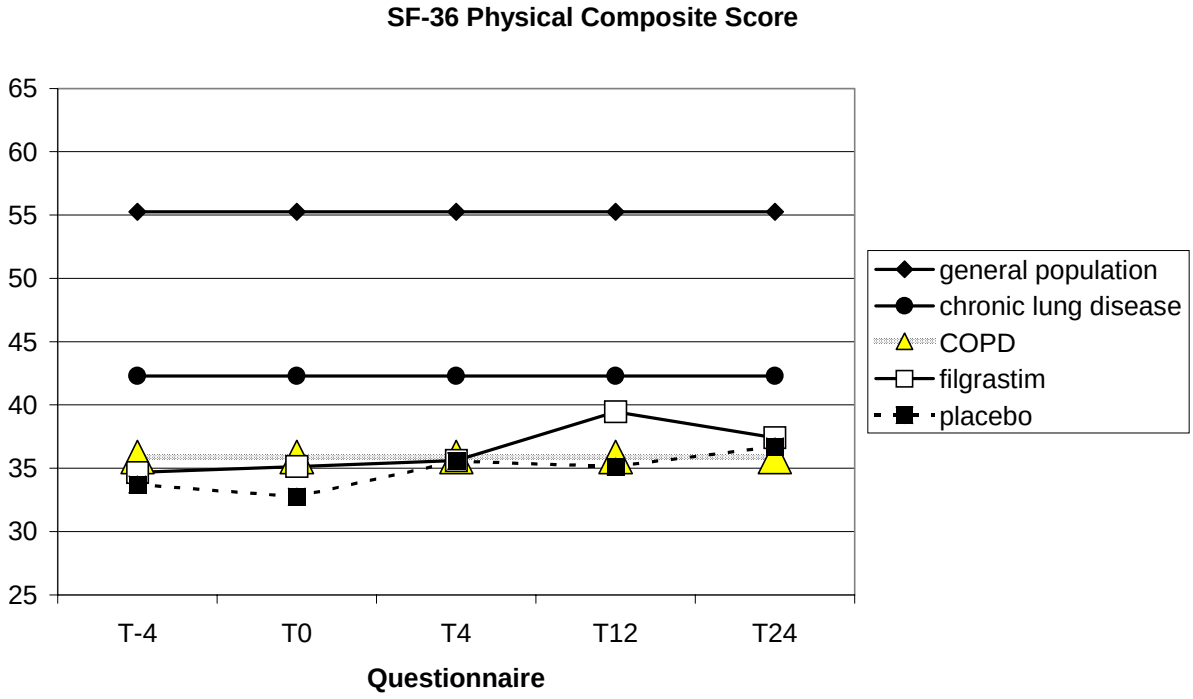


Figure 2. Mean scores of the study group on the SF-36 Physical Composite Score compared to scores of the general U.S. population, of patients with chronic lung disease and of patients with chronic obstructive pulmonary disease (COPD) (Ware et al., 1994).



Discussion

In this randomized clinical trial 58 patients with chronic sinusitis were treated with filgrastim or placebo. We tested the effects on several quality of life measures, including the McGill Pain Questionnaire, The EuroQol and the SF-36. All scores were well below the population norm scores, indicating a lower quality of life in this patient group. The scores of the filgrastim group suggested a better quality of life than the placebo group, but none of these differences were significant. We further controlled for "responsiveness", an ordinal variable which 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 quality of life questionnaires for the effects of chronic sinusitis. However, this explanation seems implausible given that all questionnaires measured lower quality of life values than the values of a "healthy" population and therefore appear to be sensitive for the impact of chronic sinusitis on quality of life.

The results of this quality of life investigation were in line with the examination of the clinical end points of the trial. These clinical end points were defined as complete clinical response, partial clinical response, no clinical response, clinical deterioration and indeterminate. The differences in scores between the placebo group and the filgrastim group at this 5 point scale where not statistically significant.

Frequently, an unexpected high number of missing responses plague clinical trials. This difficulty is often held responsible for the lack of significant differences. In the current trial, the non-response 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, instead of a power analysis of the quality of life measures. One could speculate that the number of included patients is just not high enough to demonstrate significant differences. Nevertheless, on the basis of the observations in the current trial, the effect sizes can only expected to be modest. So before discussing the opportunities associated with more observations, the moderate effect of filgrastim in this patient population should be considered.

We were the first to use both the generic SF-36, the EuroQol and the McGill Pain questionnares in chronic sinusitis patients undergoing a drug regimen. Although the SF-36 has been used in chronic sinusitis patients undergoing endoscopic sinus surgery, most quality of life research in chronic sinusitis patients is based on disease specific questionnaires. Particularly our application of the SF-36 and the EuroQol in these patients enables a comparison with scores of the general population. Figure 1 and 2 clearly indicate that the difference of the quality of life scores between chronic sinusitis patients and the general population is noticeable. This implies that large health improvements can be gained in these patients. As the costs of the regular antibiotic treatment are still at a relative low level, additional investments in this patient group have high chances of being cost-effective.

The conclusions above are of course only valid for the population of patients included in this trial. It could well be that other patients groups or subpopulations might benefit more from the treatment of filgrastim. 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, as it might open the way to a more effective administration of filgrastim in patients with chronic sinusitis.

References

Aaronson NK, Muller M, Cohen PDA, Essink-Bot ML, Fekkes M, Sanderman R, Sprangers MAG, te Velde A, Verrips E (1998) Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. J Clin Epidemiol 51 (11): 1055-1068.

Alsarraf R, Kriet JD, Weymuller EA JR (1999) Quality-of-life outcomes after osteoplastic frontal sinus obliteration. Otolaryngol Head Neck Surg 121 (4): 435-40.

Dale DC, Hammond WP 4th (1988) Cyclic neutropenia: a clinical review. Blood Rev 2 (3): 178-185.

Dolan P (1997) Modeling valuations for the EuroQol health states. Med Care 35:1095-1108.

Drummond MF, O'Brien BJ, Stoddart GL, Torrance GW (1997) Methods for the Economical Evaluation of Health Care Programmes. Oxford University Press.

Gillings D, Koch G (1991) The application of the principle of intention-to-treat to the analysis of clinical trails. Drug Information Journal 25: 411-24.

Gliklich RE, Metson R (1995) Techniques for outcomes research in chronic sinusitis. Laryngoscope 105 (4 Pt 1): 387-90.

Gliklich RE, Hilinski JM (1995) Longitudinal sensitivity of generic and specific health measures in chronic sinusitis. Qual Life Res 4: 27-32.

Gold MR, Siegel JE, Russell LB, Weinstein MC (1996) Cost-effectiveness in health and medicine. Oxford University Press.

Hadorn DC (1991) The role of public values in setting health care priorities. Soc Sci Med 32: 773-781

Kind P, Hardman G, Macran S (1999) UK Population Norms for EQ-5D. University of York: Centre for Health Economics. Discussion Paper 172.

Kloot WA, Oostendorp RAB, Meij J vd, Heuvel J vd (1995) The Dutch version of the McGill pain questionnaire: a reliable pain questionnaire [in Dutch]. Ned Tijdschr Geneesk 139: 669-673.

Kloot A vd, Vertommen H (1989). The MQQ-DLV: A standard Dutch version of the McGill Pain Questionnaire. Backgrounds and manual [in Dutch]. Swets & Zeitlinger, Lisse.

Maas CJM, Snijders TAB (2000) The multilevel approach to repeated measures for complete and incomplete data. Submitted.

Maune S, Rudert H, Heissenberg MC, Schmidt C, Eggers S, Landmann K, Kuchler T (1999) Concepts for measuring quality of life in patients with chronic sinusitis. Laryngorhinootologie 78 (9): 475-80.

Melzack R (1975) The McGill Pain Questionnaire: major properties and scoring methods. Pain 1: 277-99.

Melzack R (1987) The short-form McGill Pain Questionnaire. Pain 30: 191-97.

Metson R, Gliklich RE (1998) Clinical outcome of endoscopic surgery for frontal sinusitis. Arch Otolaryngol Head Neck Surg 124 (10): 1090-1096.

Verkes RJ, Vanderiet K, Vertommen H, Kloot WA vd, Meij L vd (1989) The MPQ-DLV. Swets en Zeitlinger, Lisse.

Ware JE, Kosinski M, Keller SD (1994) SF-36 Physical and Mental Health Summary Scales: A User's Manual. The Health Institute, New England Medical Center, Boston, Massachusetts.

Ware JE, Snow KK, Kosinski M, Gandek B (1993) SF-36 Health Survey. Manual and Interpretation Guide. The Health Institute, New England Medical Center, Boston, Massachusetts.

COSTS OF FILGRASTIM® (G-CSF) TREATMENT IN PATIENTS WITH PERSISTENT CHRONIC RHINOSINUSITIS

Introduction

Chronic sinusitis can be disabling and it can cause long-term reduction of quality of life. Patients need to be treated with repeated anti-infective therapy and many chronic sinusitis patients undergo a number of surgical procedures. Functional endoscopic sinus surgery has been reported to offer substantial relief of chronic sinusitis in 80% of the patients (Beam et al., 1992; Chow et al., 1992). This leaves a substantial number of patients who do not respond to therapy with documented efficacy. Research results suggest that some chronic sinusitis patients who do not respond to regular treatment might benefit from filgrastim (vd Merwe & Hooijkaas, 1994). The additional costs of filgrastim might be compensated by savings, if regular treatment is reduced. Furthermore, if the productivity of the patient is increased by the filgrastim administration, additional savings may occur. To test this hypothesis, we performed a randomized clinical trial in which the costs of filgrastim (r-met-HuG-CSF) treatment in patients with chronic sinusitis are analyzed for a 24-week interval.

The costs during the trial were expected to be driven by a large amount of protocollary prescribed diagnostic tests and protocollary scheduled outpatient visits. Due to the trial protocol, only little variance in costs probably occurs, since most procedures are prescribed protocollary and therefore show more or less the same average numbers. In order to estimate the difference with the costs of "real practice", we also performed a cost analysis of the 24-week period before trial inclusion. This second analysis gives information about "regular costs" of chronic sinusitis patients undergoing antibiotic treatments, without costs that are driven by the trial protocol.

Materials and methods

Patients and treatment

This study was performed as a double blind two-arm placebo controlled randomized trial. Patients were registered at T_{-4} for a pre-treatment observation of 4 weeks before being randomized. Between June 1995 and November 1997, 59 patients were randomized in the trial at the Eramus Medical Centre Rotterdam (35), the University Medical Centre Utrecht (19) and the University Hospital Nijmegen (5). Only patients with symptoms lasting for more than 6 months were included in order to cover the group of severe chronic bacterial sinusitis patients. The included patients had been given all conventional treatments, such as antibiotics, nasal decongestants, functional endoscopic sinus surgery, frontal sinus surgery and Caldwell-Luc procedures, yet they still suffered from their disease as the treatments were unsuccessful. Patients were included when no indication for surgical interventions of any kind to improve the chronic sinusitis was found.
After randomization (official study entry at T_0), all patients were treated with a combination of Ciprofloxacin 750mg once a day and Clindamycin 600 mg 3 times a day for 14 days. Patients were randomized to Filgrastim 300 µg subcutaneously (s.c.) or placebo s.c. once a day for the first 14 days (until T_2) and for another 10 weeks (until T_{12}) with either Filgrastim 300 µg s.c. or placebo s.c. on alternate days. After this treatment period, patients were followed for another 12 weeks until T_{24} (post treatment observation period).

Costs during the trial

In this cost analysis, the societal perspective was taken (Drummond et al., 1997). This means that direct medical costs (costs of health care consumption) as well as indirect costs (costs of lost production due to a disease) were calculated.

Direct medical costs consisted of the costs of all medical procedures performed in the hospital and the costs of prescribed medication. Data concerning performed procedures, prescribed medication, outpatient visits, hospital days, performed laboratory services and

diagnostic procedures were recorded on the case registry forms (CRFs) and in the hospital information system

Cost prices were based on 1996 data from the University Hospital Rotterdam and the University Hospital Utrecht. To determine full costs, the method of absorption costing was followed, which implies that not only costs of direct measurable units were determined, but "non-measurable" costs (e.g. overhead) are accounted for as well (Horngren, 1991). Using this method of absorption costing, the costs of an otorhinolaryngology hospitalization day were Euro 221 (of which 43% personnel costs, 10% material costs and 47% overhead costs). The price of a visit to the otorhinolaryngology outpatient clinic was Euro 86 (54% personnel costs, 5% material costs and 41% overhead costs), whereas the price of performing a CT-scan of the sinus was Euro 169 (32% personnel costs, 21% material costs and 47% overhead costs). Costs of laboratory services and diagnostic procedures are based on Dutch tariffs, since they match well with the concerning full costs. Costs of medication were determined with prices mentioned in the "Pharmaceutical Compass 1996" (vd Kuy, 1996).

Indirect costs of chronic sinusitis were estimated according to the friction cost method by Koopmanschap and Rutten (1996). Compared to traditional methods of calculating costs of productivity losses, this methods assumes that the initial production level will be gradually restored when the patient is absent (Drummond et al., 1997). Within this method, a value of a lost production day is specified to age and gender of the patient.
Information on the time absent from work was collected by the Health and Labour questionnaire on T_{-4}, T_0, T_2, T_4, T_{12} and T_{24} (Van Roijen et al., 1996). One of the items in this questionnaire aimed to measure the number of days the patient was impeded to do paid work due to chronic sinusitis during the last 14 days. For each time interval, the total number of days absent from work was determined on the basis of this question.

Costs before the trial

To estimate costs of "real practice" we analyzed the costs of a 24-week period before the trial in which a regular treatment was administered (T_{-28}-T_{-4}). We choosed to end the "before trial" period at T_{-4}, since the period T_{-4}-T_0 was used to determine the eligibility of patients with the trial criteria, for which additional diagnostic tests were performed.

We used the data of the patients treated in the University Hospital Rotterdam (n=35) to determine "real practice costs" since these data were easily accessible. Data were selected by using the hospital information system. Data concerning the medication described from T_{-28}-T_{-4} were collected by the pharmacists of the patients, after 33 patients gave informed consent to collect these data. Twenty-six pharmacists provided the requested data. Indirect costs were not determined for this interval, since the required information could not be measured retrospectively.

Statistical analysis

Costs per patients were entered into the statistical software package SPSS for Windows (release 9.0.0) and analyzed by Mann-Whitney testing. A significance level of 5% was used.

Results

Of the 59 randomized patients, 3 were excluded from the analysis. One of them turned out to have cystic fibrosis, one stopped because of pain in the bones and one was mistakenly randomized before the bacterial infection was confirmed. The remaining 56 patients were randomized to the filgrastim group (25, of which 8 males and 17 females) and the placebo group (31, of which 18 males and 13 females). The mean age in the filgrastim group was 45 years, whereas it was 42 years in the placebo group ($p > 0.05$).

Direct medical costs during the trial

In Table 1, the total direct costs of the treatment period (T_0-T_{24}) were presented. The only significant result was the difference in total treatment costs including filgrastim ($P=0.00$). In the filgrastim group, the costs of the study medication determined 64% of the total treatment costs. Without the costs of the study medication, costs between the study groups did not differ (see Figure 1).

Table 1. Total average direct costs per patient from T_0 to T_{24} in Euros on the 1996 price level [median, 95% confidence interval].

Cost item	*filgrastim (n=25)*		*placebo (n=31)*		*total (n=56)*	
Hospital days	136	0; -144-417	0	0; 0-0	62	0; -62-187
Outpatient visits	746	686; 677-814	739	686; 709-769	742	686; 708-776
Diagnostic tests	1567	1672; 1468-1666	1561	1638; 1487-1635	1564	1655; 1506-1623
Medication	336	265; 216-456	351	382; 270-432	344	297; 276-412
Total direct costs	**2785**	**2650; 2321-3250**	**2651**	**2665; 2560-2742**	**2712**	**2652; 2502-2923**
Filgrastim	4899	5228; 4522-5277	0	0; 0-0	2235	0; 1561-2909
Total direct costs including filgrastim	**7685**	**7868; 7064-8306**	**2651**	**2665; 2560-2742**	**4947**	**2944; 4221-5673**

Except for the costs of filgrastim, the main treatment costs consisted of the costs of diagnostic tests (accounting for approximately 41% of the total costs when the costs of filgrastim are excluded). This cost item contained laboratory services, biopsies and sinus scopes.

During the trial, patients were rarely admitted to the hospital: patients in the filgrastim group were averagely 0.61 days hospitalized and patients in the placebo group had 0.00 hospital days (averagely 0.28 in the entire group). The patients had on average 8,65 outpatient visits in the filgrastim group and 8.57 visits in the placebo group (averagely 8.61 in the entire group). Seven of these visits were planned protocollary at forehand, the remaining visits are supplemental visits.

Indirect costs during the trial

For each patient in the study group, the value of a lost production day was determined according to age and gender. Subsequently, these amounts were multiplied by the number of days on which the patients were absent from work due to chronic sinusitis. Account was given for the fact that not every study subject performed paid labour. The average number of absence days and the average costs of lost production are reported in Table 2.

Table 2. Average number of days absent from work and costs of lost production in Euros on the 1996 price level due to chronic sinusitis.

Time interval	*filgrastim (n=25)*		*placebo (n=31)*		*total (n=56)*	
	number of absence days	*costs of lost production*	*number of absence days*	*costs of lost production*	*number of absence days*	*costs of lost production*
T_0-T_2	0.46	16.10	1.54	108.00	1.06	66.97
T_2-T_4	1.00	26.60	1.50	105.39	1.28	70.22
T_4-T_{12}	0.00	0.00	5.29	360.27	2.93	199.44
T_{12}-T_{24}	2.08	130.55	5.14	337.25	3.77	244.97
Total: T_0-T_{24}	**3.54**	**173.25**	**13.47**	**910.91**	**9.04**	**581.60**

Although the result presented in Table 2 may suggest a difference between the filgrastim and the placebo group, the difference is not significant due to a relative small numbers of patients performing paid labour in both group (in both groups 50%). Besides, the total indirect costs are distorted by the greater proportion of females in the filgrastim group (68% as compared to 42% in the placebo group) for whom the fixed values of lost production days are lower than for males in the friction cost method. There was no significant age difference between the two groups which might distort the calculation of indirect costs.

Direct medical costs before the trial

Table 3 compares the trial costs to the costs of a 24-week interval preceding the trial inclusion. These costs can be considered as the regular antibiotics treatment. Again, the total costs are mainly determined by the costs of diagnostic procedures (31%). Costs during the trial (excluding filgrastim) are approximately 3 times higher than the costs before the trial. The only exception are costs of hospitalization, which were higher before the study inclusion (p=0.00). Patients were hospitalized for averagely 1.22 days in the 24-week interval preceding the trial inclusion (95% CI: 0.48-1.97). Costs of outpatient visits, diagnostic tests, medication and total costs were significantly higher during the trial period (p = 0.00). Patients had on average 1.63 otorhinolaryngology outpatient visits in the period before the trial inclusion (95% CI: 1.44-1.83).

Table 3. Average costs per patient during the trial (T_0-T_{24}) compared to regular treatment costs in a 24-week interval (T_{-28}-T_{-4}) in Euros on the 1996 price level [median, 95% confidence interval].

Cost item	*Costs during trial (T_0-T_{24}; n=56) costs of filgrastim are excluded*		*Costs before trial (T_{-28}-T_{-4}; n=35) "regular antibiotics treatment"*	
Hospital days	62	0; -62-187	270	0; 106-435
Outpatient visits	742	686; 708-776	141	158; 124-157
Diagnostic tests	1564	1655; 1506-1623	268	257; 241-296
Medication	344	297; 276-412	180	181; 155-205
Total direct costs	**2712**	**2652; 2502-2923**	**859**	**626; 666-1054**

Discussion

In this cost analysis concerning the treatment of patients with chronic bacterial sinusitis with filgrastim, there were no significant differences in costs between the filgrastim group and the placebo group when the costs of filgrastim (Euro 4899) are left out of consideration. On average, the total 24-week direct health care costs (hospitalization, outpatient visits, diagnostic tests and medication, excluding filgrastim) were Euro 2712.

It could be claimed that the power of the analysis is restricted by the strict trial protocol: only little variance in costs was possible as nearly all diagnostic tests and outpatient visits were scheduled in advance. The costs of protocollary diagnostic tests were the most important cost item, except from the filgrastim costs. Additional hospital days and outpatient visits and additional diagnostic tests only occured rarely. For these reasons, savings from filgrastim treatment can hardly be expected within the trial setting.

A drawback of cost studies that are conducted alongside a clinical trial like the current analysis is the restricted focus of the research question. Only patients with symptoms lasting for more than 6 months were included to ensure that only patients with severe chronic bacterial sinusitis entered the trial. Besides, the included patients had already been given all conventional treatments. Filgrastim probably may have different effects in patients who have not been given other treatments before, as they may be expected to be more sensitive for the treatment.

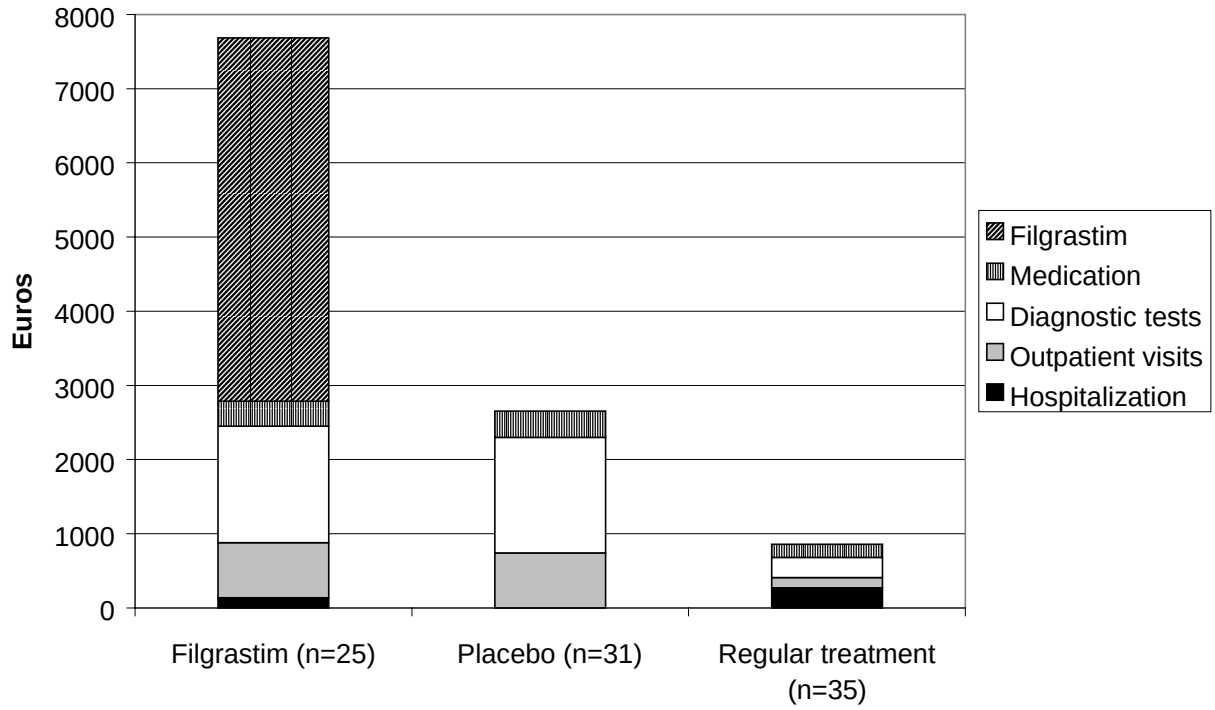
However, this study comprises the first analysis of *full* micro-economic costs in chronic sinusitis patients based on real cost prices. Gliklich and Metson (1998) have calculated micro-economic costs, but they mainly make a comparison of sinusitis medication costs before and after surgery. Their calculations of hospital expenditures are not comparable to our calculations, since they only used reimbursement tariffs for estimation of the costs, instead of full prices based on real hospital costs. Ray et al. (1999) only make an estimation of the total yearly macro-economic burden of sinusitis, but did not calculate micro-economic costs of specific treatments.

We additionally analyzed such full micro-economic costs during a regular antibiotics treatment of chronic sinusitis patients, since it was expected that the health care consumption of the patients might decrease during the trial when a protocollary outpatient visit was planned in the short run. It was hypothesized that patients who would normally visit the outpatient clinic immediately with specific troubles now waited

for the next protocollary visit. However in the end, just because of these protocollary scheduled visits, the total number of outpatient visits during the trial (8.61) turned out to be much higher than the average number of visits during a regular 24-week interval (1.63). Therefore, the total health care costs during the trial (Euro 2,712) were approximately three times higher than the costs during a regular antibiotics regimen (Euro 859; p=0.000).

Our findings indicate that the administration of filgrastim does not result in a decrease of all other health care costs, neither could a difference in indirect costs be found. Figure 1 clearly shows that the additional filgrastim costs can never be compensated by savings on other cost items. Given the relative high costs of the filgrastim administration as compared to a regular antibiotics treatment, the cost-effectiveness of the filgrastim treatment would only be favourable if the additional costs were justified by a major clinical improvement of chronic sinusitis patients or a major advance in the experienced quality of life.

Figure 1. Total 24-week direct costs during the trial (filgrastim and placebo, T_0-T_{24}) and during a regular treatment (T_{-28}-T_{-4}).



Acknowledgements

This investigation was supported by an unrestricted grant from AMGEN Inc. We would like to thank M. van Bolhuis and K. Ingels for their contributions in the data collection and K. Vanschoubroek and M.L. Sprenger (AMGEN) for the continuous interest and cooperation during this investigation.

References

Beam TR Jr, Gilbert DN, Kunin CM (1992) General guidelines for the clinical evaluation of anti-infective drug products. Infectious Diseases Society of America and the Food and Drug Administration. Clin Infect Dis 15 Suppl 1: S5-S32.

Chow AW, Hall CB, Klein JO, Kammer RB, Meyer RD, Remington JS (1992) Evaluation of new anti-infective drugs for the treatment of respiratory tract infections. Infectious Diseases Society of America and the Food and Drug Administration. Clin Infect Dis 15 Suppl 1: S62-S88.

Drummond MF, O'Brien BJ, Stoddart GL, Torrance GW (1997) Methods for the Economical Evaluation of Health Care Programmes. Oxford University Press.

Kuy A vd (Ed.) (1996). Pharmacotherapeutical Compass 1996. Dutch Health Care Board, Amstelveen, The Netherlands.

Gliklich RE, Metson R (1998) Economic implications of chronic sinusitis. Otolaryngol Head Neck Surg 118: 344-349.

Horngren CT (Ed.) (1991) Cost accounting: a managerial emphasis. Prentice Hall International, London.

Koopmanschap MA, Rutten FFH (1996) A practical guide for calculating indirect costs of disease. Pharmacoeconomics 10 (5): 460-466.

Merwe JP vd, Hooijkaas H (1994) Sjögren's syndrome in patients with chronic bacterial respiratory infections and a diminished chemotactic responsiveness of monocytes and/or granulocytes: treatment with G-CSF. In: Homma M, Sugai S, Tojo T, Niyasaka N, Akizuki M (Eds.) Proceedings of the Fourth International Symposium, Tokyo, Japan, August 11-13, 1993, Sjögren's Syndrome - State of the Art, Kugler Publications, Amsterdam / New York, pp. 373-376.

Ray NF, Baraniuk JN, Thamer M, Rinehart CS, Gergen PJ, Kaliner M, Josephs S, Pung YH (1999) Healthcare expenditures for sinusitis in 1996: Contributions of asthma, rhinitis and other airway disorders. J Allergy Clin Immunol 103: 408-414.

Van Roijen L, Essink-Bot ML, Koopmanschap MA, Bonsel G, Rutten FFH (1996) Labour and health status in economic evaluations of health care. Int J Techn Assessment in Health Care 12; 3: 405-415.