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# Cost analysis of regular and filgrastim treatment in patients with refractory chronic rhinosinusitis*

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SUMMARY

*In this double blind randomized placebo controlled clinical trial of filgrastim in chronic sinusitus, we analyzed costs of a 24-week interval in which filgrastim was administered. Since we hypothesized that the scheduled preventive visits within the trial might cause savings as compared to the regular situation in which these patients have a strong tendency to visit the outpatient clinic immediately in case of complications, direct medical costs within the trial were also compared to costs of regular treatment.*

*The difference in costs between both trial groups was driven by the filgrastim costs (Euro 5108). If filgrastim costs were left out of consideration, no significant difference in direct medical costs remained between the filgrastim and placebo groups (Euro 2904 and Euro 2765, respectively). Indirect medical costs also showed no significant differences. Within a regular situation, costs of a 24-week interval were Euro 896. As filgrastim treatment had already been shown not to improve the quality of life, its cost-effectiveness in these patients can only be favourable in case of major clinical improvements. Furthermore, scheduled preventive visits in chronic sinusitis patients appear not to cause savings as compared to the situation in which patients are only seen in case of recurrences.*

*Key words: sinusitis, costs and cost analysis, filgrastim*

## INTRODUCTION

Chronic sinusitis is a common disorder, which affects for example 30 million people in the United States (Schappert, 1992). Functional endoscopic sinus surgery (FESS) has been reported to offer substantial relief of chronic sinusitis in 80% of the patients (Beam et al., 1992; Chow et al., 1992). However, patients with persistent rhinosinusitis infections 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 (King et al., 1994).

In the protection of the paranasal sinuses against bacterial and fungal rhinosinusitis, neutrophils seem to play a role (Dale and Hammond, 1988). The proliferation and differentiation of neutrophils was found to be enhanced by the administration of human recombinant granulocyte colony stimulating factor (rG-CSF) (Dale et al., 1995; Hartung et al., 1998). Clinical studies in non-neutropenic subjects have indicated that rG-CSF (filgrastim) may be beneficial as adjunctive therapy for treatment of serious bacterial and opportunistic fungal infections in non-neutropenic patients, including those with alterations in neutrophil function (Root et al., 1999). However, it was recently found that filgrastim treatment does not lead to an improvement in the quality of life of patients with chronic rhinosinusitis (van Agthoven et al., 2001). Although all quality of life scores of patients treated with filgrastim suggested such an improvement, neither of the differences was significant, which may be due to the limited sample sizes. Despite these results, it may be that the additional costs of filgrastim are compensated by savings, if regular treatment is reduced as a consequence of filgrastim treatment. To test this hypothesis, we performed a randomized clinical trial in which the costs of filgrastim treatment in patients with chronic sinusitis were analyzed in 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. However, it was expected that patients who would normally visit the outpatient clinic immediately when encountering specific problems would now wait for the next protocollary visit prescribed by the trial protocol. It was therefore hypothesized that scheduled outpatient visits with short in-between intervals would lead to less addi-

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tional visits. This would cause a reduction in costs compared to the regular situation, particulary because complications were expected to be noticed earlier within a short-interval outpatient visit regimen, which would prevent patients from being hospitalised. In order to estimate the difference with the costs of "regular practice", we also performed a cost analysis of the 24-week period before trial inclusion. This second analysis provides information about "regular costs" of chronic sinusitis patients, 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, patients were randomized in the trial at the Eramus Medical Centre Rotterdam, the University Medical Centre Utrecht and the University Hospital Nijmegen. Only patients with symptoms lasting for more than 6 months were included in order to cover the group of severe chronic bacterial sinusitis patients. 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 500-750mg twice a day and Clindamycin 450-600 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).

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

### *Costs during the trial*

The cost analysis was based on the total medical consumption (performed procedures, prescribed medication, outpatient visits, hospital days, performed laboratory services and other diagnostic procedures) of the patients during the trial, which was recorded on Case Registry Forms (CRFs) and in the hospital information systems.

This cost analysis was performed using the societal perspective (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 hospital days, outpatient visits, and medical procedures performed in the hospital and the costs of prescribed medication. We determined average unit costs for these items, reflecting real resource use, including a raise for overhead costs (Oostenbrink et al., 2000). To determine the unit costs, we followed the micro-costing method, which is based on a detailed inventory and measurement of all resources consumed (Gold et al., 1996). The valuation of the resource use and overhead costs was based on financial data from the University Hospital Rotterdam and the University Hospital Utrecht (1998 level, 1 Euro = 2.20371 Dutch Guilders). The contents of the overhead costs (which primarily determine costs of hospital days) were thoroughly checked to prevent double-counting costs that were already recorded. Following this method, the costs of an otorhinolaryngology hospitalization day were Euro 230 (of which 43% personnel costs, 10% material costs and 47% overhead costs). The price of a visit to the otorhinolaryngology outpatient clinic was Euro 90 (54% personnel costs, 5% material costs and 41% overhead costs), whereas the price of performing a CT-scan of the sinus was Euro 176 (32% personnel costs, 21% material costs and 47% overhead costs). Costs of laboratory services and diagnostic procedures were based on Dutch tariffs, since they match well with the concerning full costs. Costs of medication were based on Dutch wholesale prices (van der Kuy, 1998).

Indirect costs were estimated according to the friction cost method (Koopmanschap and Rutten, 1996). In contrast 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. Within this method, the 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 perform 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 of regular treatment*

To estimate costs of "regular practice" we analyzed the costs of a 24-week period before the trial in which a regular treatment was administered ($T_{-28}$-$T_{-4}$). This treatment consisted of medical treatment like antibiotics, (local) corticosteroids, nasal douches, and other non-surgical interventions. We chose to end the "regular practice" 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 retrospectively used the data of the patients treated in the University Hospital Rotterdam (n=35) to determine regular practice costs as 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 from 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*

Medical consumption and costs per patients were entered into the statistical software package SPSS for Windows release 9.0.0 and analyzed by Mann-Whitney U-testing because of the non-parametric distribution of the analyzed variables. A two-sided significance level of 5% was used. All results are presented as mean values.

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 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. The mean age in the filgrastim group was 45 years vs. 42 years in the placebo group ($p>0.05$).

*Direct medical costs during the trial*

In Table 1, the total direct costs during the trial period ($T_0$-$T_{24}$) are presented. The only significant result was the difference in total treatment costs including filgrastim (filgrastim group Euro 8012 vs. placebo group Euro 2765; $p=0.00$). In the filgrastim group, the costs of the study medication determined 64% of the total treatment costs. When the costs of filgrastim were left out of consideration, costs between the study groups showed no differences (filgrastim group Euro 2904 vs. placebo group Euro 2765; see Figure 1).

Except for the costs of filgrastim, the main costs consisted of diagnostic tests (accounting for approximately 41% of the total costs when the costs of filgrastim are left out of consideration). 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 hospitalized for 0.61 days and patients in the placebo group had 0.00 hospital days (0.28 in the entire group on average). The patients had 8.65 (filgrastim) and 8.57 (placebo) visits to the otorhinolaryngology outpatient clinic (averagely 8.61 in the entire group). Seven of these visits were planned protocollary at forehand, the remaining visits were 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. The average number of absence days and the average costs of lost production are reported in Table 2.

Although the result (filgrastim group Euro 181 vs. placebo group Euro 948) may suggest a difference between the filgrastim and the placebo group, the difference was not significant due to relative small numbers of patients performing paid labour in both groups (50% in both groups). Besides, the total indirect costs were 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 using the friction cost method. There was no significant age difference between the two groups, which might further distort the calculation of indirect costs.

*Direct medical costs of regular treatment*

Table 3 compares the trial costs to the costs of the 24-week interval preceding the trial inclusion. These costs can be considered as the costs of a regular treatment. Again, the total costs were mainly determined by the costs of diagnostic procedures (31%). Costs during the trial (Euro 2829, excluding filgrastim) were approximately 3 times higher than the costs during a regular treatment (Euro 896). The only exception are costs of hospitalization, which were higher during the regular

Table 1. Average total direct costs from $T_0$ to $T_{24}$ in Euros on the 1998 price level [median, 95% confidence interval].

| *Cost item* | *filgrastim (n=25)* | | *placebo (n=31)* | | *total (n=56)* | |
|---|---|---|---|---|---|---|
| Hospital days | 142 | 0; -150-435 | 0 | 0; 0-0 | 65 | 0; -65-195 |
| Outpatient visits | 778 | 715; 706-849 | 771 | 715; 739-802 | 774 | 715; 738-809 |
| Diagnostic tests | 1634 | 1743; 1531-1737 | 1628 | 1708; 1551-1705 | 1631 | 1726; 1570-1692 |
| Medication | 350 | 276; 225-475 | 366 | 398; 282-450 | 359 | 310; 288-430 |
| **Total direct costs** | **2904** | **2763; 2420-3389** | **2765** | **2779; 2669-2859** | **2829** | **2765; 2609-3048** |
| Filgrastim | 5108 | 5451; 4715-5503 | 0 | 0; 0-0 | 2331 | 0; 1628-3033 |
| **Total direct costs including filgrastim** | **8012** | **8204; 7366-8661** | **2765** | **2779; 2669-2859** | **5160** | **3070; 4401-5915** |

Table 2. Average number of days absent from work and costs of lost production in Euros on the 1998 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 | 17 | 1.54 | 113 | 1.06 | 70 |
| $T_2$-$T_4$ | 1.00 | 27 | 1.50 | 109 | 1.28 | 73 |
| $T_4$-$T_{12}$ | 0.00 | 0 | 5.29 | 375 | 2.93 | 208 |
| $T_{12}$-$T_{24}$ | 2.08 | 137 | 5.14 | 351 | 3.77 | 255 |
| **Total: $T_0$-$T_{24}$** | **3.54** | **181** | **13.47** | **948** | **9.04** | **606** |

Table 3. Average costs 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 1998 price level [median, 95% confidence interval].

| *Cost item* | *Costs during trial ($T_0$-$T_{24}$; n=56) costs of filgrastim are excluded* | *Costs during regular treatment ($T_{-28}$-$T_{-4}$; n=35)* |
|---|---|---|
| Hospital days | 65 0; -65-195 | 282 0; 111-454 |
| Outpatient visits | 774 715; 738-809 | 147 165; 129-164 |
| Diagnostic tests | 1631 1726; 1570-1692 | 279 268; 251-309 |
| Medication | 359 310; 288-430 | 188 189; 162-214 |
| **Total direct costs** | **2829 2765; 2609-3048** | **896 653; 694-1099** |

treatment period (p=0.00). Patients were hospitalized for 1.22 days on average during 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 1.63 otorhinolaryngology outpatient visits on average during the regular treatment period (95% CI: 1.44-1.83).

## DISCUSSION

In this cost analysis on 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 itself (Euro 5108) were left out of consideration. Mean direct medical costs in the filgrastim group and placebo group without filgrastim were Euro 2904 and Euro 2765, respectively (Figure 1). Indirect medical costs also showed no significant differences between both groups.

It could be claimed that the power of the analysis was 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 rarely occured. For these reasons, savings from filgrastim treatment can hardly be expected within the trial setting.

In this study a group of patients with very serious refractory chronic sinusitis was investigated to enhance the chances of reaching a cost-effective treatment plan. A drawback of cost studies conducted alongside clinical trials is the narrow focus of the research question. However, this study comprised the first analysis of full micro-economic costs in chronic sinusitis patients based on average unit costs. Gliklich and Metson (1998) have calculated micro-economic costs, but they mainly made a comparison of sinusitis medication costs before and after surgery. Their calculations of hospital expenditures are not comparable to our calculations, as they only used reimbursement tariffs for estimation of the costs, instead of average unit costs based on real hospital costs. Ray et al. (1999) have calculated an estimation of the total yearly macro-economic burden of sinusitis, but they did not calculate micro-economic costs of specific treatments.

We additionally analyzed such micro-economic costs during a regular treatment, because it was expected that the health care consumption of the patients might have been decreased during the trial. It was hypothesized that the scheduled outpatient visits with short in-between intervals prescribed by the trial proto-

col would lead to less additional visits. This may have lead to a reduction in costs as compared to the regular situation, particulary because complications were expected to be noticed earlier within a short-interval outpatient visit regimen, which would prevent patients from being hospitalised. However, the number of *additional* visits did not differ between the regular situation (1.63) and the trial regimen (1.61) with its 7 scheduled short-interval outpatient visits. The scheduled visits may only have lead to a lower hospitalisation rate: the number of hospital days was significantly lower (0.28) during the trial as compared to the regular 24-week interval (1.22). Nevertheless, the savings from this lower hospitalisation were overshadowed by the costs of the scheduled visits. Therefore, the mean total health care costs during the trial (Euro 2829) were approximately three times higher than the mean costs during a regular antibiotics regimen (Euro 896; p=0.000). Scheduled preventive visits in chronic sinusitis patients do not cause savings as compared to the situation in which the patient is only seen in case of complications.

Our attempt to calculate the costs of a regular treatment in patients with a chronic condition turned out to be one of the first times such costs were ever calculated in this patient group. Grossman et al. (1998) have made a proper comparison of the costs of ciprofloxacin versus standard antibiotic care in patients with an initial acute exacerbation of chronic bronchitis (AECB) or recurrent AECBs. Unfortunately, their assessed time interval and the contents of their cost categories are different from ours, which impede a justified comparison. In a 1-year period, the total costs of their patients receiving standard antibiotic care were CDN$ 2617 (including CDN$ 628 indirect costs of disease), which correspond to approximately Euro 2000 per year (or Euro 1500 if the indirect costs are left out of consideration). Grandjean et al. (2000) have compared costs of N-acetylcysteine to treatment with antibiotics, corticosteroids, and broncholidators in case of AECBs in patients with chronic bronchitis, but they seem not to have followed standard costing methodologies and the contents of their cost items are not clear, which make a comparison not legitimate.

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 in this patient group. We have reported earlier that filgrastim treatment was not found to result in an improvement of quality of life of these patients (van Agthoven et al., 2001). From these results, filgrastim administration in patients with refractory chronic rhinosinusitis does not appear to be a cost-effective treament strategy. The cost-effectiveness of filgrastim treatment can only be favourable if the additional costs are justified by a major clinical improvement of chronic sinusitis patients.

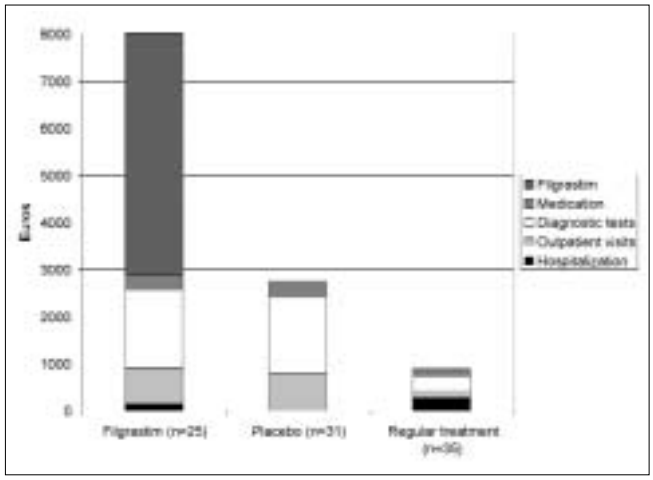


Figure 1. Total 24-week direct costs during the trial (filgratim and placebo, T0-T24) and during a regular treatment (T-28-T-4).

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REFERENCES

1. Beam TR Jr, Gilbert DN, Kunin CM (1992) General guidelines for the clinical evaluation of anti-infective drug pro-ducts. Infectious Diseases Society of America and the Food and Drug Administration. Clin Infect Dis 15 Suppl 1: S5-S32.
2. 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 Admi-nistration. Clin Infect Dis 15 Suppl 1: S62-S88.
3. Dale DC, Hammond WP 4th (1988) Cyclic neutropenia: a clinical review. Blood Rev 2: 178-185.
4. Dale DC, Liles WC, Summer WR, Nelson S (1995) Review: granulocyte colony-stimulating factor. Role and relationships in infectious diseases. J Infect Dis 172: 1061-1075.
5. Drummond MF, O'Brien BJ, Stoddart GL, Torrance GW (1997) Methods for the Economical Evaluation of Health Care Programmes. Oxford University Press, New York.
6. Gliklich RE, Metson R (1998) Economic implications of chronic sinusitis. Otolaryngol Head Neck Surg 118: 344-349.
7. Gold MR, Siegel JE, Russell LB, Weinstein MC (1996) Cost-effectiveness in Health and Medicine. Oxford Univer-sity Press, New York.
8. Grandjean EM, Berthet Ph, Ruffmann R, Leuhenberger Ph (2000) Cost-effectiveness analysis of oral N-acetylcysteine as a preventive treatment in chronic bronchitis. Pharmacol Res 42: 39-50.
9. Grossman R, Mukherjee J, Vaughan D, Eastwood C, Cook R, LaForge J, Lampron N (1998) A 1-year community-based health economic study of ciprofloxacin vs usual antibiotic treatment in acute exacerbations of chronic bronchitis. Chest 113: 131-141.
10. Hartung T, von Aulock S, Wendel A (1998) Role of granulocyte colony-stimulating factor in infection and inflammation. Med Microbiol Immunol (Berl) 187: 61-69.
11. King JM, Caldarelli DD, Pigato JB (1994) A review of revision functional endoscopic sinus surgery. Laryngoscope. 104: 404-408.
12. Koopmanschap MA, Rutten FFH (1996) A practical guide for calculating indirect costs of disease. Pharmacoecono-mics 10: 460-466.
13. Kuy A vd (Ed.) (1998) Pharmacotherapeutical Compass 1998. Dutch Health Care Board, Amstelveen, The Netherlands.

14. Oostenbrink JB, Koopmanschap MA, Rutten FFH (2000) Manual for costing research [in Dutch]. Health Care Board, Amstelveen, The Netherlands.
15. 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.
16. Root RK, Dale DC (1999) Granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor: comparisons and potential for use in the treatment of infections in non-neutropenic patients. J Infect Dis 179: S342-S352.
17. Schappert SM (1992) National Ambulatory Medical Care Survey: 1991 Summary. National Center for Health Statis-tics, Maryland.
18. van Agthoven M, Fokkens WJ, van de Merwe JP, van Bolhuis EM, Uyl-de Groot CA, Busschbach JJV (2001) Quality of life of patients with refractory chronic rhinosinusitis, effects of filgrastim treatment. Am J Rhinol 15: 231-238.
19. 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: 405-415.

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