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Clinical report

Granulocyte colony stimulating factors: How different are they? How to make a decision?

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Two granulocyte colony stimulating factors (G-CSFs) are available for clinical use in Europe: filgrastim (Neupogen®) and lenograstim (Granocyte®). The purpose of this literature review is to study how they differ, the clinical implications of these differences (especially in terms of efficacy) and the economic impact of these differences. From a chemical point of view the two molecules are not identical. Their amino acid sequence is different and one is glycosylated, whereas the other is not. The important question to ask is what these structural differences mean for the patient. It appears that glycosylation has important consequences in terms of efficacy. Several recent comparative studies, both *in vitro* and *in vivo*, in animals and in humans, reinforce this idea which was often shared intuitively by physicians. In economical terms, in hospitals where the exact dosages are used (150 μg/m^2 or 19.2 million units (MU)/m^2 for Granocyte, and 5 μg/kg or 0.5 MU/kg for Neupogen), the choice of G-CSF must be made according to the daily cost of treatment which, for an average patient, means comparing the price of 325 μg of Neupogen and of 255 μg of Granocyte. This is in fact equal to comparing the price per MU of each product. In hospitals where one vial per patient per day is used whatever be their weight or body surface area, the price per MU and the price per vial should be considered together, puting into perspective the potential therapeutic benefit for patients, one vial of Granocyte 34 containing more MU than one vial of Neupogen 30. [© 2001 Lippincott Williams & Wilkins.]

Key words: Cost per biological unit, daily cost of treatment, efficacy, glycosylation, granulocyte colony stimulating factor.

Introduction

Although the concepts of dose-effect and dose-intensity have largely contributed to progress in cancer therapy, chemotherapy has long been limited by its hematological toxicity.[1,2] The use of hematopoietic growth factors, and in particular granulocyte colony stimulating factors (G-CSFs), has allowed an increase in the dose of cytotoxic drugs resulting in a better efficacy of chemotherapy which is no longer limited by hematologic toxicity.

Two G-CSFs are available for clinical use in Europe: filgrastim (Neupogen®) and lenograstim (Granocyte®). The purpose of this literature review is to study how they differ, the clinical implications of these differences (especially in terms of efficacy) and what is the economic impact of their differences.

Indications and dosage

Both drugs have the same indications in the areas of hematology and oncology (Table 1): reduction in the duration of neutropenia induced by cytotoxic drugs, reduction in the duration of neutropenia following auto- or allobone marrow transplantations and mobilization of hematopoietic stem cells in circulating blood with or without chemotherapy. It should be noted, however, that only Granocyte is indicated in hematopoetic stem cell mobilization in healthy donors.

In terms of dosage, the recommended daily dose in the reduction of chemotherapy-induced neutropenia (which accounts for the majority of prescriptions) is 150 μg/m^2 for Granocyte and 5 μg/kg for Neupogen. However, in practice, one vial a day is usually used irrespective of the weight and height of patients.[3]

There is a difference in the way the dosage of the two drugs is expressed. The dosage of Granocyte is expressed in μg/m^2, as is the normal practice in hematology and oncology, whilst the dosage of Neupogen is expressed in μg/kg. In practice, the tendency is rather to consider active units, as is the case with the majority of proteins used in medicine (insulins, interferons, etc.), which reflects biological reality more closely and allows a better comparison of products which do not have the same molecular

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Table 1. Indications[5]

Neupogen (filgrastim)	Granocyte (lenograstim)
Reduction in duration of chemotherapy-induced neutropenia Dosage: 5 μg/kg/day	Reduction in duration of chemotherapy-induced neutropenia Dosage: 150 μg/m^2/day
Reduction in duration of neutropenia following auto- or allobone marrow transplantation Dosage: 10 μg/kg/day until nadir has passed then 5 μg/kg/day	Reduction in duration of neutropenia following auto- or allobone marrow transplantation Dosage: 150 μg/m^2/day
Mobilization of hematopoetic stem cells in circulating blood Dosage: 5 μg/kg/day if associated with chemotherapy; 10 μg/kg if used alone	Mobilization of hematopoetic stem cells in circulating blood Dosage: 150 μg/m^2/day if associated with chemotherapy; 10 μg/kg if used alone
Prevention of neutropenia in patients suffering from congenital neutropenia or cyclic or idiopathic neutropenia Dosage: 12 μg/kg/day (congenital neutropenia) and 5 μg/kg/day (cyclic or idiopathic neutropenia) then in each case adjustment of dosage	

weight. Moreover, in 1994 the Committee of Biological Standardization at the World Health Organization recommended that biotechnology products should be compared on the basis of their biological activity and not on the basis of their weight.[4] It is for this reason that the two companies have associated the number of active units in millions to their brand names (Granocyte 13, Granocyte 34, Neupogen 30 and Neupogen 48) (Table 2).[3]

Table 2. Presentations

	Granocyte 13	Granocyte 34	Neupogen 30	Neupogen 48
MU/vial	13	34	30	48
μg/vial	105	263	300	480

Chemistry

From a chemical point of view the two molecules are not identical. Their amino acid sequence is different and one is glycosylated, whereas the other is not. This is due to their method of manufacture. Even though the two proteins are coded by identical human genes, they are not produced in the same way. Neupogen (non-glycosylated methionyl G-CSF) is produced in culture by bacteria, whilst Granocyte (glycosylated G-CSF) is produced in culture by mammalian cells. As the protein production system of bacteria is less developed than that of mammals, Neupogen does not have a structure that is exactly identical to the natural molecule. Neupogen has an additional amino acid and is not glycosylated (addition of a saccharide residue following the assembly of amino acids), whilst Granocyte is glycosylated—making it a true glycoprotein, identical to the endogenous human molecule (Table 3).[5]

The important question to ask is what these structural differences mean for the patient. It appears that glycosylation, which at the outset might seem an abstract concept, has important consequences in terms of efficacy. Several recent comparative studies, both *in vitro* and *in vivo*, in animals and in humans, reinforce this idea which was often shared intuitively by physicians. What is interesting is that these comparative studies, particularly clinical studies on humans, evaluate on criteria which are objectively quantifiable.

Activity *in vitro*

Physical chemistry

Firstly, it appears that the glycosylated nature of Granocyte imparts particular physico-chemical properties. Several studies[6–8] provided evidence that glycosylation confers molecular stability to lenograstim which allows protection from variations in pH, temperature and proteolysis. A possible mechanism[9] is that the sugar moiety may confer rigidity to the molecule, making it less susceptible to proteolysis. This hypothesis is supported by nuclear magnetic resonance analysis.[10] This property has an important practical implication for patients and pharmacists. Granocyte is relatively heat resistant and can be stored at room temperature, whereas Neupogen must be stored at 4°C, otherwise its activity will diminish. As a result, the

Table 3. Source and structure characteristics of various recombinant G-CSF preparations used in comparative *in vitro* and *in vivo* studies[5]

Lenograstim (Granocyte)	Deglycosylated lenograstim	Filgrastim (Neupogen)
Authentic glycosylated recombinant human granulocyte colony-stimulating factor (rHuG-CSF)	Deglycosylated rHuG-CSF	Non-glycosylated rG-CSF
Expressed in Chinese hamster ovary (CHO) cells	Expressed in CHO cells	Expressed in *Escherichia coli*
Has the authentic primary amino acid sequence of human G-CSF (174 amino acids)	Has the authentic primary amino acid sequence of human G-CSF (174 amino acids)	Polypeptide sequence is not authentic to that of human G-CSF because of N-terminal methionine extension (175 amino acids)
Proportion of isoform structures (monosialo- and disialoforms) corresponds to that in G-CSF obtained from human cell lines	Deglycosylation results in shift in isoelectric point (due to removal of sialic acid residues)	Isoelectric point similar to that of deglycosylated rHu-G-CSF
Greater resistance to inactivation (at neutral pH) by temperature or physiochemical changes than deglycosylated rHuG-CSF	Shift in isoelectric point results in loss of stability and resistance to thermal/physiochemical inactivation	Thermal/physicochemical stability profile corresponds to that of deglycosylated rHuG-CSF

storage of Neupogen is more constraining and costly, as much for the pharmacist as for the wholesaler. The consequence for the patients is that Neupogen must be delivered, transported to home and stored at home refrigerated, which is not the case with Granocyte.

Binding affinity and biological activity

The rigidity confered by glycosylation is probably a determinant factor in the affinity to cellular G-CSF receptors.[11] G-CSF activity occurs via the binding of G-CSF to a specific transmembrane receptor present on granulocyte progenitors and neutrophils. Scatchard analysis indicates that the G-CSF receptor binding affinity of Granocyte is approximately 3-fold higher than that of Neupogen.[12] This probably accounts for the higher activity of glycosylated G-CSF observed *in vitro* and *in vivo*, in animals and humans.[13] Indeed, the prescribing information of the two products indicates that 1 μg of Neupogen contains 100 000 biological units whereas 1 μg of Granocyte contains 127 750 units. It should be noted that this 27% difference observed *in vitro* is consistently observed in clinical trials.[14,15]

Proliferation activity

The formation of neutrophil colonies in cultures of normal human bone marrow samples has been compared with Granocyte, with artificially deglycosylated G-CSF and with Neupogen.[16] It was demonstrated that Granocyte stimulates neutrophil colonies at doses 16-fold lower than Neupogen or deglycosylated G-CSF, and that with Granocyte, peak stimulation is reached at concentrations half of those required with Neupogen or deglycosylated G-CSF. In addition, at equivalent doses, Neupogen or deglycosylated G-CSF induce formation of fewer colonies of smaller size. Other studies have looked at the effect of the two G-CSFs on the activity of polynuclear neutrophils.[17,18] The first[17] showed that the morphology of polynuclear neutrophils exposed to Neupogen *in vitro* was altered, whereas the polynuclear neutrophils exposed to Granocyte remained normal, which implied that, at least with regard to neutrophil chemotaxis, Granocyte acts in a more physiological way than Neupogen. The second study[18] showed that glycosylation improves the priming effect exerted by G-CSF on human neutrophil superoxide production, potentially contributing to a better clinical activity for Granocyte.

Activity in animals

In rats, comparative studies that have been published[19] also show a significant advantage in favor of Granocyte since, under the same conditions, the effect of 30 μg/kg of Granocyte is identical to that of 100 μg/kg of Neupogen. However, from a biological point of view, many things differ between rats and humans

(nature of receptors, affinity for receptors, etc.), thus it is more pertinent to look at differences observed in humans.

Activity in humans

Granocyte and Neupogen have been compared by different authors. The technique used is the simplest one, which is to measure the ability to increase the number of hematopoetic stem cells in an organism (measured in particular in circulating blood). These stem cells will be the origin of mature blood cells. Increasing the number of hematopoetic stem cells is in fact what is expected from a G-CSF whether it be in hematology (mobilization of stem cells, reduction in the duration of chemotherapy-induced neutropenia) or in oncology (reduction in the duration of chemotherapy-induced neutropenia). The stem cell count ($CD34^+$ cells) is an objective and more especially quantitative measure on the effect of G-CSF on bone marrow. The count is made by flow cytometry in accordance with validated and standardized methods.[20]

From a methodological point of view, two techniques have been used:[21]

- Identify the dosage which would give exactly the same number of circulating $CD34^+$ cells.
- Administer the same dosage of the two products to two groups of patients and measure the number of circulating $CD34^+$ cells.

In the first case a study was carried out on 127 patients with lymphoma or myeloma (pathologies where it is particularly difficult to mobilize $CD34^+$ cells). To obtain 2×10^6 $CD34^+$ cells/kg (known to constitute a graft of quality in the event of a cytapheresis) one vial per day of Granocyte was needed (on average 3.5 μg/kg/day if doses are given in μg/kg) compared to 10 μg/kg/day of Neupogen. Therefore almost 3 times as much Neupogen was needed for the same duration of treatment to achieve the same results.[22,23]

In the second case, using equal doses of the two products (10 μg/kg since it is a question of mobilizing without associated chemotherapy), the level of $CD34^+$ cells that can be obtained with Granocyte is 27% higher than that with Neupogen.[14,15] This is particularly important when one wants to perform a cytapheresis in patients who will undergo subsequent stem cell transplants. Indeed, having to perform one cytapheresis more or less during graft preparation has a lot of consequences in terms of cost if we consider that the cost of a cytapheresis is approximately equivalent to that of 20 vials of G-CSF, without taking into consideration the trauma caused to the patient.

In practice, hematologists prefer to plan and carry out two cytaphereses whatever the return. Either the return is average and it is necessary to carry out two cytaphereses anyway, or the return is good and to have more cells than necessary is an advantage because it has been shown that:[24] (i) The larger the graft to re-inject, the more quickly the graft is accepted; (ii) the larger the graft re-injected, the less risk there is of complications following transplantation (infections, thrombopenia, etc.); (iii) the greater the number of cells collected, the easier it is to carry out procedures to eliminate cancer cells (purge, positive selection, negative selection), procedures which unfortunately always result in a loss of normal $CD34^+$ cells; and (iv) the greater the number of cells collected, the easier it is to divide the graft with a view to carrying out several transplants without needing new leukapheresis (costly, trying for patients, sometimes difficult to carry out in patients who have had several courses of chemotherapy). Therefore it is important to consider the efficacy of the G-CSF that is used.

The superiority of Granocyte in producing 27% more $CD34^+$ cells than Neupogen is not surprising since there are 27% additional biological units in 1 μg of Granocyte as opposed to 1 μg of Neupogen.[14,15] This perfect correlation between the results obtained *in vitro* and the results obtained *in vivo* is significant and reassuring. Finally, from an experimental point of view, an important point that should be raised is that this study has been carried out with the only methodology that is acceptable: randomized cross-over study (each subject receiving each product alternatively and therefore becoming his own control) and in healthy subjects (no interference from underlying pathology or from prior potentially myelotoxic chemotherapy which could affect the validity of the study).[25] Another study, carried out in patients suffering from breast cancer, had similar results.[26] It compared the results obtained following treatment with Granocyte or Neupogen using identical doses in biological units/kg: 800 000 U/kg. In these conditions, the doses in μg/kg became 8 μg/kg for Neupogen and 6.2 μg/kg for Granocyte. The results were similar in each arm of the study. In a recent literature review[11] it was stated that to have a similar effect on the reduction of duration of neutropenia with chemotherapy, it was necessary to use 5 μg/kg of Neupogen compared to only 3.5–4 μg/kg of Granocyte.

Pharmaco-economic analysis

Very few comparative economic studies have been published to date.[11,27,28] In a recent study[27] it was noted that in the case of bone marrow transplantation, the recommended dose of Granocyte is 150 $\mu g/m^2$ (as for the reduction of chemotherapy-induced neutropenia), whereas that for Neupogen is 10 $\mu g/kg$ (twice the dosage required for the reduction of chemotherapy-induced neutropenia). As a result, in most cases, approximately 1 vial of Granocyte 34 is necessary while 2 vials of Neupogen 30 are approximately requested for identical efficacy. In these conditions, the overall cost of patient care is increased proportionally.

The first question one should ask oneself is: which economic criteria should be taken into consideration when choosing a G-CSF? As we have already seen, the two products available are not strictly identical. The fact that one compound is not glycosylated and has an additional amino acid means that they do not have the same molecular weight. As a result it is not logical to compare them by their price per microgram. Indeed nobody would compare aspirin to paracetamol on the basis of price per gram, thus the same reasoning applies to G-CSF.

So, which criteria should be used? It largely depends on the habits of people using G-CSF in the hospital.

In the first case, if they respect the prescribing information and administer the exact doses required (conserving the remains of the vial for subsequent use) or if the pharmacy has a central preparation unit (allowing to pool several vials: batching procedure), the most pertinent measure is the daily cost of treatment.[28]

We know from the French National Institute on Medical Research (INSERM) that the average patient receiving G-CSF weighs 65 kg and is 1.65 m tall for an average body surface area of 1.70 m^2.[28] When considering the indication 'reduction in the duration of chemotherapy-induced neutropenia', which represents the majority of G-CSF usage, the respective data sheets of the two products recommend that for an average patient, 325 μg (32.5 MU) of Neupogen be used per day (5 $\mu g/kg/day$ or 0.5 MU/kg/day) or 255 μg (32.5 MU) of Granocyte be used per day (150 $\mu g/m^2$/day or 19.2 MU/m^2/day). What we should compare therefore is the price of 325 μg of Neupogen and of 255 μg of Granocyte. However, the easiest way of doing this is to compare the price per million units (MU), since 32.5 MU are being considered in both cases for an average patient.

With a vial of Granocyte 34 (263 μg) or Neupogen 30 (300 μg) at about €100[28] [average price in France (€1=US$0.92)], the cost of 1 MU of Granocyte is €2.94 (€100 divided by 34 MU) against €3.33 (€100 divided by 30 MU) for Neupogen, while 1 μg of Granocyte is €0.38 (€100 divided by 263 μg) against €0.33 (€100 divided by 300 μg) for Neupogen.

From these figures, with the hypothesis of an average patient of 65 kg for a body surface area of 1.7 m^2, it is possible to calculate daily costs of treatment with each product as indicated in Table 4.

This simple calculation is made by using the recommendations in the prescribing information sheets of the two products. Two points should be mentioned.

First, the only measure which is meaningful in terms of therapeutic benefit for patients is the cost per active unit of the product. Usually the doses used in the prescribing information are based on an average patient, so it is logical that the same amount of active units is needed for each of the products to achieve the same results. This is both logical and reassuring.

Secondly, we should be cautious of users who, for reasons of simplification, use the two products at the same dosage of 5 $\mu g/kg/day$. If this dosage is correct for Neupogen, it corresponds to an overdose of 27%

Table 4. Daily costs of treatment (DCT) by Granocyte and Neupogen, according to indication, for an average patient of 65 kg and 1.7 m^2, with a price per vial of €100 for both Granocyte 34 (263 μg/vial) and Neuopgen 30 (300 μg/vial)[28]

Indications	Granocyte		Neupogen	
	Dosage	DCT (€)	Dosage	DCT (€)
Reduction in duration of chemotherapy-induced neutropenia	150 $\mu g/m^2$	96.9	5 $\mu g/kg$	108.3
Reduction in duration of neutropenia following auto- or allobone marrow transplantation	150 $\mu g/m^2$	96.9	5 or 10 $\mu g/kg$	108.3 or 214.5
Mobilization of hematopoetic stem cells in circulating blood associated with chemotherapy	150 $\mu g/m^2$	96.9	5 $\mu g/kg$	108.3
Mobilization of hematopoetic stem cells in circulating blood with G-CSF alone	10 $\mu g/kg$	247.1	10 $\mu g/kg$	214.5

for Granocyte (325 μg/255 μg=1.27, a ratio which is obviously identical to the ratio of number of active units of the two products per μg that we have already discussed). Unecessarily overdosing by 27% when taking into account the cost of this type of molecule is obviously a waste, at a time when physicians should rather be trying to reduce treatment costs. This is the reason why for Granocyte, the recommended dosage of 150 μg/m^2 should be strictly followed.

In the second case, if users prescribe 1 vial per day whatever the height and weight of the patient, there is a risk of harming patients by only taking into consideration the price per vial of each product.[28] Indeed if only the price per vial is considered, one loses sight of the benefit to the patient: one vial of Neupogen 30 does not contain the same number of active units as one vial of Granocyte 34. Two attitudes are possible. The first is to make a choice on the price per vial only. The second is to not only look at the price per vial, but also at the benefit to the patient and consider that for a price per vial more or less equal, the number of active units per vial being different, the potential therapeutic benefit for the patient is not the same. One could argue that for both products, being very active, treating a patient with a vial of one product or by a vial of the other should not make a big difference in terms of outcome. In fact we should consider G-CSFs as a kind of insurance against febrile neutropenia, which are rare but dramatic and difficult to predict events, with a very high risk of death for patients. In those conditions, at an equivalent price per vial, the difference in potential therapeutic benefit should be put into perspective and the product with the highest probability of preventing an accident (i.e. febrile neutropenia) be considered.

Conclusion

All the study results point in the same direction, demonstrating the significance of glycosylation as much in terms of efficacy as of quality of response. The results observed *in vitro* (which generally speaking must be considered with caution) confirm and, in part, explain the differences in efficacy observed in humans. It should be noted that the international studies published, which all support Granocyte, compare the two products in a therapeutic situation, and on criteria which are easily measurable and very standardized, and do not take into consideration criteria such as the duration of hospital stay, the incidence of neutropenia or the consumption of antibiotics.

In pharmaco-economical terms, the choice of G-CSF must be made according to the practices of individual hospitals. Either the hospital respects the recommended dosages (150 μg/m^2 or 19.2 MU/m^2 for Granocyte and 5 μg/kg or 0.5 MU/kg for Neupogen) and in this case the criteria taken should be the daily cost of treatment which, for an average patient, means comparing the price of 325 μg of Neupogen and of 255 μg of Granocyte. This is in fact equal to comparing the price per MU of each product. Alternatively the practices of the hospital are such that one vial per patient per day is used whatever their weight or body surface area, in those conditions the price per MU and the price per vial should be considered together, putting into perspective the potential therapeutic benefit for patients, one vial of Granocyte 34 containing more units of biological activity than one vial of Neupogen 30.

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