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Randomized study of filgrastim versus molgramostim after peripheral stem cell transplant in breast cancer

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ABSTRACT

Background and Objective. **The aim of this study was to compare the efficacy and toxicity of Filgrastrim (granulocyte colony-stimulating factor-G-CSF) versus molgramostim (granulomonocyte colony-stimulating factor-GM-CSF) after autologous peripheral blood stem cell transplant (PBSCT) in patients with breast cancer. To the best of our knowledge no randomized studies comparing filgrastrim and molgramostim have been published.**

Design and Methods. **Forty-two patients with breast cancer were randomized to receive filgrastrim versus molgramostim subcutaneous at a dose of 5 mcgr/kg starting on day 6 after PBSCT. PBSC were collected in all patients after stimulation with filgrastrim and infused following conditioning with cyclophosphamide, cisplatin and carmustine (n=25) or cyclophosphamide, carboplatin and thiotepa (n=17).**

Results. **The median days to reach > 0.5×10^9/L granulocytes was similar for patients receiving filgrastrim (10.5±0.8 days) and molgramostim (10.2±0.9 days). No significant differences were observed in time taken to reach 20×10^9/L platelets 10.8±2.2 vs 12±2.9 for filgrastrim and molgramostim, respectively, but in time to reach 50×10^9/L was slightly lower in the filgrastrim arm (15.1±2.9 vs 18.9±8.4, p=0.03). Nevertheless there were no differences in the number of platelets transfused. Time of discharge was two days earlier in the filgrastrim arm (15±4.2 vs 17.4±4.7, p = 0,04). Finally, the incidence of adverse side effects attributable to the cytokines (filgrastrim or molgramostim) was equivalent and only present in 19% of the patients.**

Interpretation and Conclusions. **This randomized study shows that filgrastrim and molgramostim yield quite similar toxicity and efficacy for early hematopoietic reconstitution after PBSCT in breast cancer patients.**

Key words: filgrastrim, molgramostim, peripheral stem ccell transplant, breast cancer

The speed of hematopoietic recovery after high dose chemotherapy correlates with transplant mortality and morbidity, mainly due to infectious complications. Because of this, one of the most important tasks of transplantation programs is to reduce, as much as possible, the duration of aplasia. Two major tools have contributed to the achievement of this aim: the use of peripheral blood stem cells (PBSC) and the use of colony stimulating factors (CSF). In different types of malignancies treated with high-dose chemotherapy it has been shown that rescue with PBSC produces a faster hematopoietic recovery compared to bone marrow (BM).[1-6] This has considerable advantages including duration of inpatient stay and financial savings.[7] Regarding CSF, its high cost and expanded use, occasionally for reasons not clearly supported by scientific evidence, make it necessary to carry out a careful evaluation of their efficacy and differences. It is apparently clear that both granulocytic (filgrastim)[8,9] and granulocyte-macrophage colony stimulating factors (molgramostin)[10,11] reduce the period of absolute leukopenia in bone marrow transplanted patients as well as after PBSC.[12-18] However, appropriate comparisons between filgrastim and molgramostin through randomized studies have not been carried out. Moreover, data derived from non-randomized studies following either bone marrow[19] or PBSC transplantation[20,21] are controversial.

Recently, in a sequential but non-randomized study Bregni *et al.*[22] compared the effects of filgrastim and molgramostim in 50 patients with NHL or breast cancer treated with high dose cyclophosphamide. They found that toxicity was higher after molgramostim and neutrophil recovery was faster with filgrastrim whereas platelet count recovered more rapidly with molgramostim. Furthermore, a higher toxicity after molgramostim was observed most likely due to their intravenous administration.

In a recent publication about clinical practice guidelines of hematopoietic growth factors from an expert panel of the *American Society of Clinical Oncology,* it was concluded that guidelines about equivalency of the two factors filgrastim and molgramostim cannot be proposed because there have been no prospective comparative trials. The panel encourages clinical investigation by addressing issues of comparative clinical activity, toxicity and cost-effectiveness.[23] In this report we present the results of a prospective randomized trial comparing the efficacy and toxicity of filgrastim versus molgramostim administered from day +6 post-transplant in a uniform cohort of patients with breast cancer transplanted with PBSC.

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Materials and Methods

Patients selection

Forty-two patients with proven histologically breast cancer, eligible for autologous stem cell transplant were randomized to receive granulocyte colony-stimulating factor (filgrastim)(Amgen, Thousand Oaks, CA, USA) or granulomonocyte colony stimulating factor (molgramostim)(Sandoz/Pharma, S.A.E. Basel, Switzerland) starting on day +6 after the stem cell infusion. Forty-two women entered in the trial: twenty-one on each arm. The characteristics of patients entered in the study are presented in Table 1. Ten patients (24%) were in stage II, 14 (33%) in stage III and 18 (43%) had metastatic disease at diagnosis.

CSF-priming and PBSC harvest and infusion

Peripheral blood stem cells (PBSC) were collected after stimulation with filgrastim at a dose of 5 μg/kg/day (median dose 300 μg/day) administered subcutaneously (s.c.). After leukocyte recovery (3×10^9/L) from the last cycle of chemotherapy patients received filgrastim for 4 days. Leukaphereses were started on the mornings after the forth dose of cytokine. Stem cell apheresis were performed using a continuous flow cell separator, CS 3000 Plus with a small-volume collection (50 mL) (Baxter). In most patients (68%) antecubital venous access was used; in the remaining patients (32%) a Quinton-Mahurkar double-lumen line was inserted in the femoral vein. Following collection the cells were suspended in 10% dimethylsulfoxide (DMSO) with autologous plasma, frozen in a controlled rate freezer at –1°C/min, and stored in liquid nitrogen at –196°C. A mean number of apheresis 2.5±0.9 (1-5) were performed per patient. Forty-eight hours after conditioning the cryopreserved cells were rapidly thawed at 37°C and reinfused via a right atrial catheter.

Preparative regimen

The first twenty-five patients included in the study received cyclophosphamide, cisplatin and carmustine. Cyclophosphamide was administered at a dose of 1875 mg/m^2/day for 3 days /days -6, -5, -4) as a daily 1 hour i.v. infusion (total dose 5625 mg/m^2). Cisplatin was given at 55 mg/m^2/day for 3 days (days -6 through -4) as a continuous i.v. infusion (total dose 165 mg/m^2). Carmustine 600 mg/m^2, was given as a 2 hour i.v. infusion at the end of the cisplatin infusion. The last seventeen patients were conditioned with carboplatin (200 mg/m^2/day), thiotepa (125 mg/m^2/day), and cyclophosphamide (1.5 mg/m^2/day), by continuous infusion on days -7, -6, -5 and -4. In all patients, mesna was administered after cyclophosphamide. Stem cells were infused on day 0.

Growth factors

The patients were randomized to receive filgrastim (21 patients) or molgramostim (21 patients) subcutaneously (sc) at a dose of 5 μg/kg/day starting on day +6 until absolute granulocyte count was greater than 1×10^9/L for three consecutive days. Growth factors were administered in the evening (8:00 PM) after acetaminophen premedication.

Table 2. Comparison engraftment and stem cell data between G-CSF and GM-CSF arms.

	G-CSF		GM-CSF		p
	Mean	Range	Mean	Range	
No. days with factor	6.9±1.2	5-10	7.1±1.7	5-11	ns
MNC $\times10^8$/kg	4.3±1.1	3-7.3	4.63±1.1	2.1-6.9	ns
CD34$^+$ $\times10^6$/kg	2.2±1.4	0.9-7.2	2.4±1.9	0.6-8.9	ns
CFU-GM $\times10^4$/kg	41.6±26	1.3-91.9	29.9±21	3-75.7	ns
Day to AGC > 0.1×10^9/L	9.3±0.7	8-10	9.3±1.1	7-11	ns
Day to AGC > 0.5×10^9/L	10.5±0.8	9-12	10.2±0.9	9-12	ns
Day to AGC > 1×10^9/L	10.8±0.8	10-13	11±1.1	9-13	ns
Day to platelets > 20×10^9/L	10.8±2.2	6-15	12±2.9	7-19	0.073
Day to platelets > 50×10^9/L	15.1±2.9	11-22	18.9±8.4	10-50	0.031
Days to discharge	15±4.2	12-33	17.4±4.7	13-30	0.040
No. of RBC transfusions	2±1.4	0-6	2±1.8	0-6	ns
No. of platelet transfusions	1.8±0.8	1-4	2.4±1.6	0-7	0.084
No. of febrile days with AGC < 500	2.3±2.2	0-7	2.8±2.2	0-8	ns
No. of febrile days with AGC > 5000	6±2.6	0-12	0.7±1.1	0-4	ns

MNC: mononuclear cells, CFU-GM: Colony forming units of granulocyte-macrophage, AGC: absolute granulocyte count, RBC: red blood cell.

Supportive care

Patients were housed in private rooms with inverse barrier isolation or with a high-efficiency particle air filtration system (HEPA).

Quinolones and fluconazole were used as bacterial and fungal prophilaxis respectively once chemotherapy was started; intravenous broad spectrum antibiotics were started for the first febrile episode. All blood products were irradiated. Patients were transfused to maintain Hb > 9 g/L or platelets > 10,000 if no fever or bleeding were present. Patients were discharged from the hospital if asymptomatic, granulocyte count > 1×10^9/L and platelet > 20×10^9/L.

Progenitor cells assays (CFU-GM and CD34)

CFU-GM assays

Samples from the leukaphereses were collected in sterile and preservative free heparin tubes and separat-

Table 1. Patient characteristics according to treatment group.

	G-CSF	GM-CSF
No. patients	21	21
Age (range)	44.3±9.4 (27-58)	43.5±7.3 (30-58)
Stage		
II	5	5
III	8	6
*IV**	8	10
Prior treatment		
CAF/sCAF	16	13
CMF/CAF	1	2
FEC	4	6
Conditioning		
CBP+Cy+Thio	9	8
Cy+CCDP+BCNN	12	13

*CAF: cyclophosphamide 500 mg/m², Doxorubicin 50 mg/m², 5-fluorouracil 500 mg/m². sCAF: cyclophosphamide 600 mg/m², Doxorubicin 60 mg/m², 5-fluorouracil 600 mg/m². FEC: 5- fluorouracil 500 mg/m², Etoposide, cyclophosphamide 500 mg/m². CMF: cyclophosphamide 500 mg/m² days 1,8. Methotrexate 40 mg/m² days 1,8.; 5-fluorouracil 600 mg/m² days 1,8. *Two patients in the filgrastim and 3 in the molgramostim arm had bone metastasis.*

ed by Ficoll-Hypaque (d=1070) gradient density centrifugation. The CFU-GM assay was performed using the method described by Iscove *et al*.[24] Briefly, 1×10^5 mononuclear cells/mL in Iscove's modified Dulbecco's medium (IMDM) were plated on 35 mm Petri dishes in 0.9% methylcellulose containing 10% PHA-leukocyte conditioned medium (PHA-LCM), 10% bovine serum albumin and 10% human AB serum. Cultures were incubated at 37°C in a fully humidified atmosphere with 5% CO_2 and scored at day 14 under an inverted microscope. Colonies were considered when aggregates with more than 40 cells and cluster aggregates with 4 to 40 cells were observed.

CD34 cells

Quantitation of CD34 cells was performed using direct inmunofluorescence technique with a phycoerythrin-conjugated anti-CD34 antibody (HPCA-2; Becton/Dickinson Immunocytometry Systems, San José, CA, USA). Data acquisition was carried out using the FACS flow cytometer and software in a two step procedure as previously described.[24]

Statistical analysis

Results are expressed as the mean ± s.e.m. or as median. Results were compared by the Student's unpaired t-test using the Statview program (Brain-Power, Inc., Calabasas, CA, USA).

Results

Both arms were well balanced in terms of the stage of the disease (Table 1), previous chemotherapy and transplant regimen. Median number of days with growth factors after the transplant was the same for filgrastim and molgramostim (7.5 and 7.2, respectively) (Table 2).

Table 3. Patients with adverse events related with growth factor administration.

	G–CSF (n=21)	GM–CSF (n=21)
Fever	1	–
Bone pain	–	2
Headache	2	
Hypotension	–	1
Cutaneous rash	–	1
Vaso–vagal simptoms	1	–

Engraftment

No differences were observed between either arm in the characteristics of the infusion product in terms of numbers on mononuclear cells, CFU-GM and number of CD34 cells infused (Table 2). All patients were engrafted (Table 2). Median days to reach an absolute granulocyte count (AGC) greater than 0.5×10^9/L was 10.5±0.8 (9-12) for patients receiving filgrastim and 10.2±0.9 days (9-12) for those receiving molgramostim. Patients achieved more than 20×10^9/L platelets on day 10.8±2.2 (6-15) and 12.0±2.9 (7-19) in the arms of filgrastim and molgramostim, respectively. Time to reach more than 50×10^9/L platelets was slightly inferior for patients receiving filgrastim (15.1±2.9) than for those with molgramostim (18.9±8.4) days, and this difference reached statistical significance (p=0.03). There were no differences between the numbers of blood cells and platelet transfused on number of febrile days. However, when we analyzed the time from the day of transplant to discharge, this was slightly lower for patients receiving filgrastim (15±4.2 vs 17.4±4.7 days) (p=0.04).

Transplant-related toxicity and side effects of filgrastim and molgramostim

Overall the regimens were well tolerated and the main toxicity according to the Bearman scale[23] was stomatitis present in 41 of the patients (97%); it was grade I in 16 patients, grade II in 20 and grade III in 5 patients. Gastrointestinal toxicity was present in 15 patients (grade I in 12 and grade II in 3 patiens), cardiac toxicity grade I was observed in two cases while one patient presented grade III central nervous system toxicity (Table 3). One patient (2%) died in the early post-transplant period (day +33) due to progressive disease and sepsis; she had been transplanted with active disease. Most of the patients (88%) had fever due to infection. No differences were observed between patients receiving filgrastim or molgramo-

Table 4. Adverse events related with the transplant procedure according Bearman scale.

Side effects	*G-CSF*	*GM-CSF*
Stomatitis		
I	9	7
II	11	9
III	1	4
Gastrointestinal		
I	5	7
II	2	1
Cardiac		
I	1	1
CNS		
III	–	1

CNS: Central nervous system.

stim. Side effects attributable to growth factors were recorded in only four patients in each arm (19%). Moreover, these side effects were moderate and reversible by supportive measures and reduction and/or suppression of cytokine administration was not required in any case. The side effects in the filgrastim arm included fever (1 patient), vaso-vagal symptoms (1 patient) and headache (2 patients) and in the molgramostim group, hypotension (1 patient); cutaneous rash (1 patient) and bone pain (2 patient).

Discussion

The use of priming PBSC to reconstitute the hematopoiesis after high-dose myeloablative therapy has been widely employed over the last years in patients with solid tumors and hematological malignancies.[1-6] Moreover, most centers have used CSF after priming PBSC and, although there is some discrepant data,[2,3] several studies comparing CSF vs placebo have demonstrated that both filgrastim and molgramostim induce a faster engraftment[17,18] and also reduce the duration of hospitalization and the number of days on antibiotics.[17] However, to the best of our knowledge, no randomized study has compared the efficacy of filgrastim versus molgramostim, either after bone marrow or after PBSC support. In a non-randomized analysis based on 115 patients with breast cancer and melanoma treated with filgrastim or molgramostim after high dose chemotherapy and bone marrow transplant Laughlin *et al.*[19] have shown that both factors produced a similar effect on myeloid recovery. In patients with breast cancer treated with high dose cyclophosphamide and doxorubicin, Mamounas *et al.*[21] carried out two sequential studies administering either filgrastim or molgramostim, and observed that both CSF permitted the administration of higher doses of chemotherapy but that a shorter granulocytopenic period resulted after filgrastim. In our randomized study, no major differences were observed in the early granulocyte or platelet engraftment. However, patients who received filgrastim reached more than 50,000 platelets two days earlier than patients receiving molgramostim although this does not translate into greater platelet transfusion. These results contrast with those published by Bregni *et al*.[22] in a recent study in patients treated with high dose cyclophosphamide prior to leukaphereses. In this paper, patients receiving molgramostim achieved a granulocyte count later but platelets earlier than patients receiving filgrastim. Nevertheless, it should be emphasized that these studies are not comparable because Bregni's study is not a randomized trial and they used non-myeloablative chemotherapy.

Upon comparing the side effects attributable to filgrastim and molgramostim, the low toxicity observed was outstanding in both arms. This is particularly relevant for molgramostim, since a higher incidence of side-effects have been reported with this cytokine.[22,28] Thus, Bregni *et al*.[22] described an incidence of side effects in the molgramostim arm of 41% compared to 17% in the filgrastim arm. As we have previously mentioned this was a non randomized study, patients with different malignancies were included and growth factors were administered intravenously and that could be the reason of the superior toxic effects observed in this paper. Moreover, patients received CSF for a mean of 15 days while in our study it was only administered for 7 days. A possible explanation for the low incidence of side effects observed in this trial is the time scheduled for the administration of the cytokine; all patients received the CSF late in the evening and it is conceivable that some side effects, such as fever or malaise, took place during sleep and were therefore undetectable for the patients.

Overall, our data suggest that the toxicity and efficacy of filgrastim and molgramostim in accelerating hemopoietic reconstitution is similar.

Contributions and Acknowledgments

MDC was the main investigator and designed the study. She performed the literature revision and wrote the article with JMB; he also managed the statistical data. MDC and LV followed the patients during the transplant. MJN and MC did the aphereses while JJC, AG and EF took care of the patients before the transplant. JFSM was the main co-ordinator and reviewed the article. The order tries to take into account the time work and specific contribution of all authors.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

Manuscript processing

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References

1. Reiffers J, Castaigne S, Tilly H. Hematopoietic reconstitution after autologous blood stem cell transplantation. A report of 46 cases. Plasma Ther Transfus Technol 1987; 8:360-2.
2. Lasky LC, Hurd DD, Smith JA, Haake R. Peripheral blood stem cell collection and use in Hodgkin's disease: comparison with marrow in autologous transplantation. Trasfusion 1989; 29:323-9.
3. Bensinger W, Singer J, Appelbaum F, et al. Autologous transplantation with peripheral blood mononuclear cells collected after administration of recombinant granulocyte stimulating factor. Blood 1993; 81:3158-63.
4. Schwartzberg L, Birch R, Blanco R, et al. Rapid and sustained hematopioetic reconstitution by peripheral blood stem cell infusion alone following high-dose chemotherapy. Bone Marrow Transplant 1993; 11:369-74.
5. Beyer J, Schwella N, Zingsem J, et al. Hematopoietic rescue after high dose chemotherapy using autologous peripheral-blood progenitor cells or bone marrow: A randomized comparison. J Clin Oncol 1995; 13:1328-35.
6. Langenmayer I, Weaver C, Buckner CD, et al. Engraftment of patients with lymphoid malignancies transplanted with autologous bone marrow, peripheral blood stem cells or both. Bone Marrow Transplant 1995; 15: 241-6.
7. Ager S, Scott MA, Mahendra P, et al. Peripheral blood stem cell transplantation after high-dose therapy in patients with malignant lymphoma: a retrospective comparison with autologous bone marrow transplantation. Bone Marrow Transplant1995; 16:79-83.
8. Stahel RA, Jost LM, Cerny T, et al. Randomized study of recombinant human granulocyte colony-stimulating factor after hight-dose chemotherapy and autologous bone marrow transplantation for hight-risk lymphoid malignancies. J Clin Oncol 1994; 12:1931-8.
9. Schmitz N, Dreger P, Zander A, et al. Results of a randomized, controlled, multicentre study of recombinant human granulocyte colony-stimulating factor (Filgastrim) in patients with Hodgkin´s disease and non-Hodgkin's lymphoma undergoing autologous bone-marrow transplantation. Bone Marrow Transplant 1995; 15:261-6.
10. Nemunaitis J, Rabinowe S, Singer J. Recombinant granulocyte macrophage colony-stimulating factor after autologous bone marrow transplantation for lymphoid cancer. N Engl J Med 1991; 324:1773-8.
11. Rabinowe SN, Neuberg D, Bierman PJ, et al. Long-term follow-up of a phase III study of recombinant human granulocyte-macrophage colony-stimulating factor after autologous bone marrow transplantation for lymphoid malignancies. Blood1993; 81:1903-8.
12. Gianni AM, Bregni M, Stern AC, et al. Granulocyte-macrophage colony-stimulating factor to harvest circulatory haemopoietic stem cell for autotransplantation. Lancet 1989; ii:580-4.
13. Sheridan WP, Begley CG, Juttner CA, et al. Effect of peripheral-blood progenitor cells mobilised by filgrastim (G-CSF) on platelet recovery after high-dose chemotherapy. Lancet 1992; 339:640-4.
14. Nademanee A, Sniecinski I, Schmidt GM, et al. High dose therapy followed by autologous peripheral-blood stem-cell transplantation for patients with Hodgkin's disease and non Hodgkin's lymphoma using unprimed and granulocyte colony-stimulating factor mobilized peripheral blood stem cells. J Clin Oncol 1994; 12:2176-86.
15. Brice P, Divine M, Marolleau JP, et al. Comparison of autografting using mobilized peripheral blood stem cells with and without granulocyte colony-stimulating factor in malignant lymphomas. Bone Marrow Transplant 1994; 14:51-5.
16. Ho AD, Gluck S, Germond C, et al. Optimal timing for collections of blood progenitor cells following induction chemotherapy and granulocyte-macrophage colony-stimulating factor for autologous transplantation in advanced breast cancer. Leukemia 1993; 7:1738-46.
17. Klumpp TR, Mangan KF, Goldberg SL, Pearlman ES, Macdonald JS. Granulocyte colony-stimulating factor acelerates neutrophil engratment following peripheral blood stem-cell transplantation: A prospective, randomized trial. J Clin Oncol 1995; 13:1323-7.
18. Colombat P, Gardembas M, Delwanie V. Randomized study of GM-CSF post peripheral blood stem cell (PBCS) transplant with PBSC collected with GM-CSF in lymphoma [abstract]. Blood 1996; 88:(suppl 1)300a.
19. Laughlin MJ, Kirkpatrick G, Sabiston N, Peters W, Kurtzberg J. Hematopoietic recovery following high-dose combined alkylating-agent chemotherapy and autologous bone marrow support in patients in phase-I clinical trials of colony-stimulating factors: G-CSF, GM-CSF, IL-1, IL-2, M-CSF. Ann Hematol 1993; 67:267-76.
20. Gianni AM, Bregni M, Siena S, et al. Granulocyte-macrophage colony-stimulating factor or granulocyte colony-stimulating factor infusion makes high-dose etoposide a safe outpatient regimen that is effective in lymphoma and myeloma patients. J Clin Oncol 1992; 10:1955-62.
21. Mamounas EP, Andreson S, Wickerham DL, et al. The efficacy of recombinant human granulocyte macrophage colony-stimulating factor in permitting the administration of higher doses of cyclophosphamide combination. Am J Clin Oncol 1994; 17:374-81.
22. Bregni M, Siena S, Di Nicola M, et al. Comparative effects of granulocyte-macrophage colony-stimulating factor after hinght-dose cyclophosphamide cancer therapy. J Clin Oncol 1996; 14:628-35.
23. American Society of Clinical Oncology. Recommendations for the use of hematopoietic colony-stimulating factors: evidence-based, clinical practice guidelines. J Clin Oncol 1994; 12:2471-508.
24. Iscove NN, Senn JS, Till JE, McCulloch EA. Colony formation by normal and leukemic human bone marrow cells in culture: effect of conditioned medium from human leukocytes. Blood 1971; 37:1-5.
25. Bearman SI, Appelbaum FR, Back A, et al. Regimen related toxicity and early postransplant survival in patients undergoing marrow transplantation for lymphoma. J Clin Oncol 1989; 7:1288-94.
26. Macedo A, Orfao A, Ciudad J, et al. Phenotypic analysis of CD34 subpopulatiions in normal human bone marrow and its application for the detection of minimal residual disease. Leukemia 1995; 9:1896-901.
27. Cortelazzo S, Viero P, Bellavita P, et al. Granulocyte colony-stimulating factor following peripheral-blood progenitor-cell transplant in non Hodgkin's lymphoma. J Clin Oncol 1995; 13:935-41.
28. Lieschke GJ, Burgess AW. Granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor(1)(2). N Engl J Med 1992; 327:28-35 and 99-106.