Short-term effect of miglustat in every day clinical use in treatment-naïve or previously treated patients with type 1 Gaucher's disease

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In a prospective, open-label study, 25 patients with mild-to-moderate type 1 Gaucher's disease (GD1) were treated with miglustat (Zavesca®), an oral glucosylceramide synthase inhibitor, over 12 months. Of the 25 patients, 10 were therapy-naïve and 15 had previously received enzyme replacement therapy (ERT). Clinical status, blood parameters, biomarkers, and organomegaly were assessed at baseline at 6 months and at 12 months. At 6 months the previously untreated patients showed a mean increase in hemoglobin of 0.77 g/dL, platelet counts improved or remaining stable, chitotriosidase and CCL18 decreased. These results were similar to those observed in 40 Spanish GD1 patients on ERT. Bone marrow infiltration cleared at 12 months. In the previously treated group, clinical and hematologic parameters and biomarkers were maintained/improved at 12 months. Miglustat was well tolerated. The efficacy of miglustat treatment after 6 months was comparable to that of ERT.

Key words: type 1 Gaucher's disease, oral therapy, safety and efficacy, real clinical setting.

Haematologica 2006; 91:703-706

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Enzyme replacement therapy (ERT) has been used extensively for type 1 Gaucher's disease (GD1), and is an effective treatment in the majority of patients.[1-3] Unfortunately, bone complications and other symptoms may remain refractory to therapy.[4,5] Furthermore, ERT must be administered by regular intravenous infusions, resulting in non-compliance in some patients. In some cases a decrease or interruption of ERT therapy increases the risk of bone crises, and hematologic deterioration.[6-8] In patients with type 3 Gaucher's disease, neurological progression continues despite maximal doses of ERT.[9,10]

Oral miglustat (N-butyldeoxynojirimycin, Zavesca®), an inhibitor of the ceramide-specific glucosyltransferase, decreases the formation of glucocerebroside and reduces the glycolipid burden acting as a substrate reduction therapy (SRT).[11] Miglustat has been proposed for clinical use in glycosphingolipid disorders.[12] In clinical trials following patients up to 36 months, substrate formation decreased and clinical features of GD1 improved.[12-14]

The Spanish GD Registry (SGDR), co-ordinated by the Spanish Foundation for study of Gaucher Disease (FEETEG), was established in 1993. This registry stores demographic, genetic, and clinical data from all GD patients whether or not they are receiving pharmacological therapy. The data in the registry are used to monitor the epidemiology and natural history of Gaucher's disease and the effectiveness of treatment. Following approval of miglustat for clinical use, a prospective observational study on GD1 was initiated by the FEETEG. This project, known as ZAGAL, is intended to evaluate the efficacy, safety, and tolerance of miglustat treatment in clinical practice over a 12-month period in patients with mild-to-moderate GD1.

Design and Methods

Twenty-six patients with mild-to-moderate GD1 were enrolled in the ZAGAL study between May 2004 and October 2005 although only 25 are evaluated here because one patient (who had switched from ERT) dropped out of the study after 2 months, due to poor compliance with therapy. The guidelines for miglustat therapy were devised by the FEETEG in order to optimize and standardize the use of this drug. The objectives were to establish a set of recommendations, to collect efficacy, safety, and quality of life data in a structured longitudinal manner, and to co-ordinate the use of miglustat for GD in a *real life* setting. Miglustat was used following the recommendations of the European Working Group on Gaucher Disease Advisory Council.[15]

Patients were classified as having mild or moderate disease according to Zimran's severity score index and divided into two groups: treatment-naïve(n=10) and those who had previously received ERT (*switched*, n=15). All patients received 100 mg *tid* miglustat orally. Instructions were given to patients prior to therapy regarding the correct administration of the drug and how to follow a lactose-free, low-carbohydrate diet, as recommended during the first weeks of treatment. The efficacy of therapy was evaluated using the following variables, assessed at baseline at 6 months and at 12 months: body weight, liver and spleen size quantified by MRI, blood parameters, chitotriosidase activity, and CCL-18/PARC, recently described as a surrogate marker for assessing therapeutic interventions.[16] Bone marrow infiltration was evaluated according to a score of the MRI pattern: homogeneous-4; non-homogeneous diffuse-3; non-homoge-

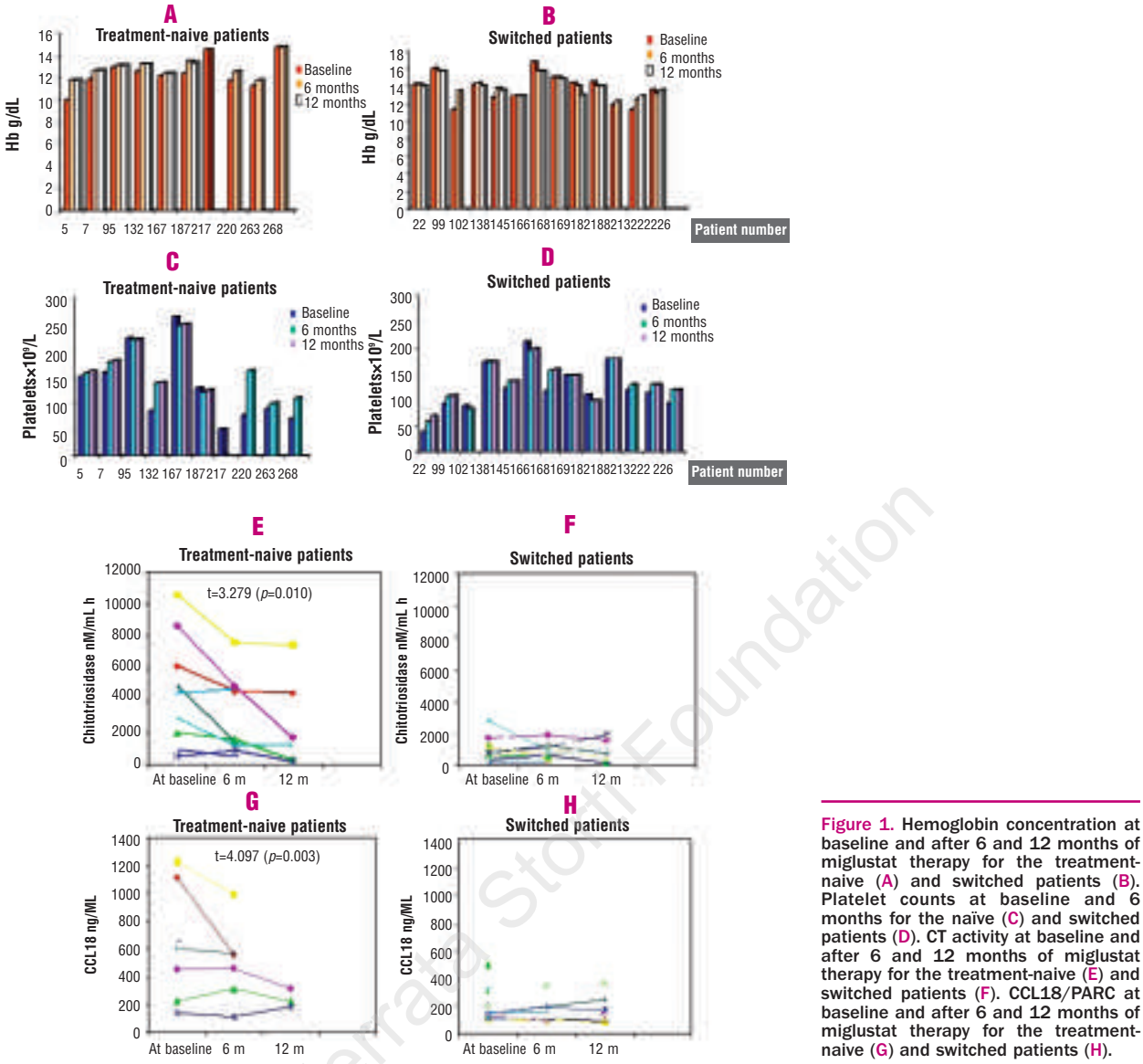

Figure 1. Hemoglobin concentration at baseline and after 6 and 12 months of miglustat therapy for the treatment-naive (A) and switched patients (B). Platelet counts at baseline and 6 months for the naïve (C) and switched patients (D). CT activity at baseline and after 6 and 12 months of miglustat therapy for the treatment-naive (E) and switched patients (F). CCL18/PARC at baseline and after 6 and 12 months of miglustat therapy for the treatment-naive (G) and switched patients (H).

neous mottled-2; non-homogeneous reticular-1; normal-0. Complications undetectable on plain X-ray added a value of 4 to the preceding score. The final score was calculated by adding the values computed for the different bone areas. The safety and tolerance of therapy were evaluated using specifically designed neurological and cognitive assessments. The neurological examination was performed by the same specialist and included both a neurophysiological study and a Memory Impairment Screen. Quality of life was evaluated using the SF-36 questionnaire. Data from 40 symptomatic adult patients from the SGDR with mild/moderate disease, without previous skeletal symptoms, and who had received ERT were analyzed retrospectively. These patients were matched to the miglustat-treated population according to the Severity Score Index, gender, and genotype. The results after 6 months of ERT in these patients were compared with the results of miglustat therapy in treatment-naïve patients.

Statistical analyses were performed using the SPSS database and included descriptive and frequency analysis, parametric ANOVA tests and the non-parametric Mann-Whitney U test for comparison of means.

Results and Discussion

The patients' baseline characteristics are detailed in Table 1. All patients had normal levels of vitamin B12 and normal neurological/cognitive function. By October 2005, nine naïve patients had received SRT for 6 months, six of them had reached 12 months of therapy and all were continuing with miglustat. Patients with anemia or thrombocytopenia showed satisfactory responses. After 6 months, both hemoglobin concentrations and platelet counts had increased by a mean of 0.77g/dL and 1.5×10⁹/L, respectively. Twelve patients who had switched from ERT to SRT had received 12 months' treatment with miglustat: hemoglobin increased or remained in the normal range and platelet counts remained within normal values. After 12

Table 1. Baseline characteristics of the patients in the treatment-naïve and switched groups.

Patient	Age (years)	Gender	Genotype	Age at diagnosis	SSI	Dose ERT U/kg/2w	Years on ERT	Start SRT
220	**45**	**female**	**N370S/N370S**	**42**	**9**	**–**	**–**	**May 04**
132	**74**	**female**	**N370S/N370S**	**40**	**7**	**–**	**–**	**May 04**
187	**59**	**female**	**G377S/D409H**	**50**	**8**	**–**	**–**	**May 04**
05	**44**	**female**	**N370S/L444P**	**19**	**9**	**–**	**–**	**Jun 04**
07	**63**	**female**	**N370S/c.500insT**	**53**	**4**	**–**	**–**	**Jun 04**
167	**30**	**female**	**N370S/L444P**	**28**	**6**	**–**	**–**	**Sept 04**
268	**21**	**male**	**N370S/L444P**	**21**	**5**	**–**	**–**	**Apr 05**
263	**59**	**female**	**N370S/N370S**	**58**	**4**	**–**	**–**	**Apr 05**
95	**25**	**male**	**N370S/L444P**	**23**	**5**	**–**	**–**	**Apr 05**
217	**44**	**male**	**N370S/L444P**	**40**	**1**			**Oct 05**
226	25	female	N370S/R120W	20	4	40	5	May 04
188	43	female	G377S/D409H	39	7	45	4	May 04
182	49	male	G377S/D409H	38	7	40	4	May 04
99	24	male	N370S/T134P	12	9	60	4	May 04
168	45	male	N370S/C(86dell)	22	5	30	4	Sept 04
169	43	male	N370S/C(86dell)	38	2	30	4	Sept 04
166	36	female	N370S/L444P	30	7	30	3	Sept 04
145	47	female	N370S/N370S	34	5	30	2	Oct 04
138	29	male	N370S/R257X	20	6	30	5	Nov 04
222	36	female	N370S/L444P	34	7	30	2	Apr 05
22	46	female	G377S/D409H	39	6	30	11	Apr 05
213	42	male	G377S/D409H	39	1	30	2	Apr 05
102	39	female	N370S/R257Q	31	9	60	8	Apr 05
202	48	female	N370S/?	28	4	30	3	Oct 05
158	38	female	N370S/G195W	30	3	30	5	Oct 05

Treatment-naïve patients (in bold): mean age 46.40 years, mean age at diagnosis 37.40 years, mean SSI 5.8; switched patients (in plain text): mean age 39.33 years, mean age at diagnosis 30.26 years, mean SSI 5.53, mean dose ERT 52.66, mean years on ERT 4.26. SSI: severity score index; SRT: substrate reduction therapy.

Table 2. Comparison of data for the treatment-naïve SRT patients and ERT patients (reference group; Giraldo *et al*. Haematologica 2000) at baseline and following 6 months of therapy.

	Treatment naive SRT	ERT	p
Number	9	40	
Age (years)	46.7 (21-74)*	37.42(17-52)*	0.021
Gender M/F	2/7	19/21	
Severity score index	6.33 (4-9)	6.80 (1-10)	0.683
Genotype N370S or G377S (%)	100	100	–
Previous spleen removal	2	0	–
Mean decrease in spleen size at 6 months (cm)	9.23 (1.5-18)	4.22 (0-80)	0.308
Mean decrease in liver size at 6 months (cm)	0.22 (0-10)	4.29 (1.6-5.7)	0.014
Mean increase in Hb at 6 months (g/dL)	0.77 (0.2-1.8)	0.81 (0-4.0)	0.856
Mean increase in platelets at 6 months ($\times 10^9$/L)	41.5 (10-116)	32.7 (0-95)	0.324
Mean decrease in chitotriosidase activity at 6 months (%)#	38.2 (20.58-42.8)	42.8 (0-80.2)	0.136

Numbers in brackets indicate range. SRT: substrate reduction therapy; ERT: enzyme replacement therapy. #Chitotriosidase plasma activity must be compared individually because variability in the inherited chitotriosidase gene does not allow mean crude values to be compared (homozygotes have significantly more activity than heterozygotes) Giraldo et al. Haematologica 2001;86:977-84.

months of SRT, all patients' blood counts had improved or remained stable (Figure 1). The decrease of biomarkers at 6 months compared with baseline values (mean chitotriosidase activity: 1095 nM/mL.h, p=0.01; mean CCL18/PARC decrease: 103 ng/mL, p=0.003) in the treatment-naïve group was particularly relevant. The values of the biomarkers decreased further at 12 months (mean chitotriosidase: 1475 nM/mL.h, p=0.01; mean CCL18/PARC: 100 ng/mL). In the group of patients who switched therapy, chitotriosidase remained stable/decreased after 6 months (mean: 99nM/mL.h, p=0.42) and remained stable at 12 months (mean:51.0nM/mL.h, p=0.695), suggesting that the positive effects of previous ERT therapy are maintained by miglustat. CCL18/PARC levels remained similar before and after switching from ERT to SRT in the patients who changed treatment (mean decrease at 6 months 67ng/mL, and mean increase after 12 months 53 ng/mL) (Figure 1). At 6 months mean spleen and liver volumes had decreased in the treatment-naïve group by 1.2 cm and 0.2 cm, respectively (p=0.03, p=0.30): these data must be considered carefully because only three patients in the treatment-naïve group had hepatomegaly. Organ volumes were stable in the group that switched therapy (p=0.12, p=0.27). At 12 months, none of the patients had reported bone pain or new bone crises. Bone marrow infiltration was re-evaluated by MRI after 12 months. More clearance of vertebral infiltration was observed in the treatment-naïve group: the calculated MRI score improved by one or two points from baseline to follow-up after 12 months of miglustat therapy. Quality of life assessment in treatment-naïve patients indicated high satisfaction and well-being during therapy; analysis of patients who completed 12 months of therapy showed improvement in self-perception of global health, physical activity and social functioning; scores were satisfactory. With regard to safety and tolerance, only three out of 25 patients complained of mild gastrointestinal disturbances, which resolved after compliance with dietary recommendations. One patient had moderate weight loss (9%) and three had mild hand tremor, similar to that associated with caffeine intake. Data from the treatment-naïve patients were compared with historical data from 40 patients receiving ERT. Mean increases in blood parameters after 6 months on SRT were comparable to those observed after 6 months on ERT (p=0.08) (Table 2). In addition, there were no significant differences between the two groups with regard to the mean decrease in chitotriosidase activity or spleen size. Liver size decreased more in the historical ERT group than in the group receiving SRT, although it should be noted that only three patients in this latter group had hepatomegaly at baseline. Intravenous administration of ERT may be inconvenient for some patients, and could lead to non-compliance. Furthermore, long-term complications such as skeletal disease, fibrotic nodules, or multiple organ involvement may persist despite ERT. It has been suggested that miglustat could be an alternative for these patients. Biomarkers may be the most sensitive parameters for monitoring activity and recurrence of disease.[17] The efficacy of miglustat in Gaucher's disease has already been demonstrated.[12] Following 12 months on therapy, hematologic variables improved, spleen/liver enlargement and chitotriosidase activity decreased. In an extension study to examine the long-term efficacy and safety of miglustat, 14 patients completed 36 months of treatment: improvement was evident in all major efficacy end-points and tolerance was good.[14] Our data at 6 months reinforce

these findings, indicating that SRT in clinical practice is both effective and well tolerated in patients with mild/moderate disease also in the short-term.[12-14] In addition, improvements in organomegaly, blood parameters and chitotriosidase activity were significant, in accordance with the findings of an open-label, non-comparative study.[18] Furthermore, retrospective analysis of clinical and analytical data of the first 6 months of ERT in matched patients revealed no significant differences compared with results obtained in the treatment-naïve patients 6 months after starting SRT, apart from a variation of liver size recorded in the treatment-naïve patients receiving SRT. Our results with ERT are comparable to those reported by the International Gaucher Registry although patients in that report were not matched for Severity Score Index.[19] A speculative explanation of the potentially better liver response to ERT may be that a significant proportion of the intravenously administered enzyme is taken up by this organ. The changes in marrow infiltration in patients on short-term treatment and the known delay in skeletal response to ERT could be interpreted in the light of miglustat, a small molecule, being widely distributed and possibly having greater access to extra hepatic sites of tissue storage.

The relatively early clinical effect exhibited by miglustat may be result of dual mechanisms of action. Besides inhibiting substrate formation, miglustat may also accelerate destruction of the glycolipid complex by increasing glucocerebrosidase activity. Mutations such as N370S have residual enzyme activity; *in vitro* studies demonstrated that glucocerebrosidase activity was increased 2.5-fold in cells transfected with the N370S mutation when cultured in a medium containing miglustat.[20] It is worth noting that 74% of the patients in our series had at least one allele with the N370S mutation. Tolerance of miglustat was good. Although a minority of patients experienced gastrointestinal upset during treatment, changing to a lactose-free, low-carbohydrate diet resolved this adverse event. No cognitive impairment or neurological problems were observed after 12 months of SRT. In summary, miglustat represents an effective and well-tolerated treatment for mild-to-moderate Gaucher's disease. The 12-month assessment data will provide further indications as to whether the clinical outcomes of patients treated with miglustat are maintained in the medium-term. Miglustat is an oral therapy good for mild forms of Gaucher's disease and it is an option for maintenance therapy.

PG: responsible for the Spanish Registry of Gaucher Disease, conducted the study, analyzed and interpreted the data, and drafted the manuscript; PL: contributed to the statistical analysis and to the manuscript; PA: contributed to the enzymatic, genetic and serum biomarker investigation, and to the statistical analyses; DA, RF, AB, AA, AS, VR and SS: collected clinical, analytical and follow-up data of patients, contributed to the analysis; MP: helped to conduct the study, interpreted the data, and corrected the manuscript. All the authors are members of the Spanish Study Group on Gaucher Disease, a group supported by the Spanish Gaucher Disease Foundation (FEETEG). PG and some of the other authors are researchers at the Aragones Institute of Public Health.

The authors would like to thank Dr. Manuel Giralt, President of FEETEG, for technical support and all the members of the Spanish Gaucher Disease Group (SGDG) who provided clinical data and samples. The complete list of physicians of the SGDG who contributed is available at the web site: www.feeteg.org. The authors are also extremely grateful to the patients and their families whose participation made this work possible. The authors declare they have no potential conflicts of interest.

This study was partially supported by the grants: REDEMETH (G03/054), FIS 03/1290, FIS 04/2476 and RCESP C03/09.

Manuscript received October 23, 2005. Accepted February 13, 2006.

References

1. Barton NW, Brady RO, Dambrosia JM, Di Bisceglie AM, Doppelt SH, Hill SC, et al. Replacement therapy for inherited enzyme deficiency-macrophage-targeted glucocerebrosidase for Gaucher's disease. N Engl J Med 1991; 324:1464-70.
2. Pastores GM, Sibille AR, Grabowski GA. Enzyme therapy in Gaucher disease type 1: dosage efficacy and adverse effects in 33 patients treated for 6 to 24 months. Blood 1993;82: 408-16.
3. Zimran A, Elstein D, Kannai R, Zevin S, Hadas-Halpern I, Levy-Lahad E, et al. Low-dose enzyme replacement therapy for Gaucher's disease: effects of age, sex, genotype, and clinical features on response to treatment. Am J Med 1994;97:3-13.
4. Rosenthal DI, Doppelt SH, Mankin HJ, Dambrosia JM, Xavier RJ, McKusick KA, et al. Enzyme replacement therapy for Gaucher disease: skeletal responses to macrophage-targeted glucocerebrosidase. Pediatrics 1995; 96:629-37.
5. Elstein D, Hadas-Halpern I, Itzchaki M, Lahad A, Abrahamov A, Zimran A. Effect of low-dose enzyme replacement therapy on bones in Gaucher disease patients with severe skeletal involvement. Blood Cells Mol Dis 1996;22:104-11.
6. Beutler E, Demina A, Laubscher K, Garver P, Gelbart T, Balicki D, et al. The clinical course of treated and untreated Gaucher disease. A study of 45 patients. Blood Cells Mol Dis 1995; 21:86-108.
7. Grinzaid KA, Geller E, Hanna SL, Elsas LJ 2nd. Cessation of enzyme replacement therapy in Gaucher disease. Genet Med 2002;4:427-33.
8. Perez-Calvo J, Giraldo P, Pastores GM, Fernandez-Galan M, Martin-Nunez G, Pocovi M. Extended interval between enzyme therapy infusions for adult patients with Gaucher's disease type 1. J Postgrad Med 2003;49:127-31.
9. Altarescu G, Hill S, Wiggs E, Jeffries N, Kreps C, Parker CC, et al. The efficacy of enzyme replacement therapy in patients with chronic neuronopathic Gaucher's disease. J Pediatr 2001; 138:539-47.
10. Campbell PE, Harris CM, Vellodi A. Deterioration of the auditory brainstem response in children with type 3 Gaucher disease. Neurology 2004;63: 385-7.
11. Inokuchi J, Radin NS. Preparation of the active isomer of 1-phenyl-2-decanoylamino-3-morpholino-1-propanol, inhibitor of murine glucocerebroside synthetase. J Lipid Res 1987;28:565-71.
12. Cox T, Lachmann R, Hollak C, Aerts J, van Weely S, Hrebicek M, et al. Novel oral treatment of Gaucher disease with N-butyldeoxynojirimycin (OGT 918) to decrease substrate biosynthesis. Lancet 2000;355:1481-5.
13. Heitner R, Elstein D, Aerts J, Weely S, Zimran A. Low-dose N-butyldeoxynojirimycin (OGT 918) for type I Gaucher disease. Blood Cells Mol Dis 2002;28:127-33.
14. Elstein D, Hollak C, Aerts JM, van Weely S, Maas M, Cox TM, et al. Sustained therapeutic effects of oral miglustat (Zavesca, N-butyldeoxynojirimycin, OGT 918) in type I Gaucher disease. J Inherit Metab Dis 2004;27: 757-66.
15. Cox TM, Aerts JMFG, Andria G, Beck M, Belmatoug N, Bembi B, et al. The role of the iminosugar N-butyldeoxynojirimycin (miglustat) in the management of type I (non-neuronopathic) Gaucher disease: a position statement. Advisory Council to the European Working Group on Gaucher Disease. J Inherit Metab Dis 2003;26:513-26.
16. Boot RG, Verhoek M, de Fost M, Hollak CE, Maas M, Bleijlevens B, et al. Marked elevation of the chemokine CCL18/PARC in Gaucher disease: a novel surrogate marker for assessing therapeutic intervention. Blood 2004; 103:33-9.
17. vom Dahl S, Poll LW, Häussinger D. Clinical monitoring after cessation of enzyme replacement therapy in M. Gaucher. Br J Haematol 2001; 113:1084-6
18. Pastores GM, Barnett NL, Kolodny EH. An open-label, noncomparative study of miglustat in type I Gaucher disease: efficacy and tolerability over 24 months of treatment. Clin Ther 2005;27:1215-27.
19. Weinreb NJ, Charrow J, Andersson HC, Kaplan P, Kolodny EH, Mistry P, et al. Effectiveness of enzyme replacement therapy in 1028 patients with type 1 Gaucher disease after 2 to 5 years of treatment: a report from the Gaucher Registry. Am J Med 2002; 113:112-9.
20. Alfonso P, Pampin S, Estrada J, Rodriguez-Rey JC, Giraldo P, Sancho J, et al. Miglustat (NB-DNJ) works as a chaperone for mutated acid b-glucosidase in cells transfected with several Gaucher disease mutations. Blood Cells Mol Dis 2005;35:268-76.