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RESEARCH ARTICLE

Upgrading the evidence for the use of ambroxol in Gaucher disease and GBA related Parkinson: Investigator initiated registry based on real life data

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Abstract

Ambroxol hydrochloride is an oral mucolytic drug available over-the-counter for many years as cough medicine. In 2009 it was identified as a pharmacological chaperone for mutant glucocerebrosidase, albeit in a several-fold higher dose. Unfortunately, there have been no pharma-driven clinical trials to establish its use. Thus, real-world observational data are needed on the safety and efficacy of ambroxol for patients with Gaucher disease (GD) and GBA-Parkinson disease (GBA-PD). Clinicians treating patients with ambroxol for GD and GBA-PD were approached to collaborate in an investigator-initiated registry. Anonymized data were collected, including demographics, GD type, GD-specific therapy (when applicable), adverse events (AEs), and, when available, efficacy data. We report the data of the first 41 patients (25 females)

at a median (range) age 17 (1.5–74) from 13 centers; 11 with GD type 1(four diagnosed with PD), 27 with neuronopathic GD (nGD), and three GBA mutation carriers with PD. The median (range) treatment period and maximum dose of ambroxol were 19 (1–76) months and 435 (75-1485) mg/day, respectively. One patient with type 2 GD died of her disease. No other severe AEs were reported. Twelve patients experienced AE, including minor bowel discomfort, cough, allergic reaction, mild proteinuria, dizziness and disease progression. Clinical benefits were reported in 25 patients, including stable or improved neurological status, increased physical activity, and reduced fatigue. Until the approval of specific therapies for nGD and disease-modification for GBA-PD, these preliminary data may be encouraging to physicians and patients who consider an off-label use of ambroxol.

1 | INTRODUCTION

The three decades of success of enzyme replacement therapy (ERT) for patients with type 1 Gaucher disease (GD1) have been an only limited success to those patients with the more severe neuronopathic forms, particularly the children with myoclonic epilepsy or the infants with type 2 GD (GD2).[1] Perhaps the facts that the majority of the patients with neuronopathic GD (nGD) receive high-dose ERT,[2] and that the majority of them live in Arabic and Asian countries[3] with limited ability to pay for high-cost therapies, explain in part the consequent lack of attempts to develop specific medications, that will cross the blood-brain barrier (BBB) and impact on the neuronopathic features.

Ambroxol hydrochloride is an oral mucolytic drug available over-the-counter (OTC) for many years as a cough medicine. In 2009 it was found (in vitro) to also act as a pharmacological chaperone (PC) for mutant glucocerebrosidase (GCase), albeit in a several-fold higher dose (up to 25 mg/kg/day but not to exceed 1.3 g/day).[4,5] As a small molecule, it can cross the BBB,[5] thereby being suitable to impact nGD. Regrettably, the use patent for this drug was licensed to a small company, which has not been able to fund a clinical trial for its development as a drug for GD, including nGD. More prominent pharmaceutical companies have shown no interest either, in part due to the availability of so many generic forms that can be purchased online.

In an attempt to provide the proof of concept to the potential use of ambroxol as a PC for patients with GD, the Gaucher Unit at Shaare Zedek Medical Center in Jerusalem, Israel, conducted a pilot study wherein 12 adult patients with GD1, all untreated with ERT or substrate reduction therapy (SRT), received off-label ambroxol at the OTC dose of 150 mg/day for six months.[6] A single patient, the thinnest of the group with a body mass index (BMI) of 17.1, achieved a robust response relative to baseline [+16.2% hemoglobin; +32.9% platelets; −2.8% liver volume; and −14.4% spleen volume]. Three patients, including this good responder, were elected to continue on ambroxol for an additional six months: while the hemoglobin levels and liver volumes were relatively stable, the platelet counts further increased in the patient mentioned above (+52.6% from baseline, a truly remarkable response) and spleen volumes decreased further in all three patients (−6.4%, −18.6%, and−23.4% from baseline).[6] It was hoped that this preliminary report would lead to a formal clinical trial using higher doses of ambroxol, perhaps in a placebo-controlled design, but this has not been undertaken.

Fortunately, a group of pediatric neurologists in Japan prescribed high-dose ambroxol to a severely affected, bedridden 28 years old female patient with GD3.[5] This patient suffered from diverse neurological manifestations, including refractory myoclonic epilepsy and severe ataxia. The dramatic improvement in seizure activity and gait, allowing her independent walking and proceeding with daily life activities, led to a formal investigator-initiated research (IIR) by the same group. The publication of the first five patients in 2016 has confirmed the results in the index case.[5]

With no specific treatment for nGD, and with the above-mentioned encouraging reports rapidly spreading on the internet and social media, individual patients in many countries have started to receive off-label ambroxol, and few case reports have been published.[7,8] In addition, few IIRs have started in different countries, including Korea, UK, and Canada, using high-dose ambroxol in patients with nGD or GD1, in *GBA*-related Parkinson disease (PD), and more recently in non-GBA carriers with PD and/or dementia (PDD).[9-11]

As clinical trials take time, even IIRs, many patients, particularly those with severe nGD or PD, cannot wait for the completion of the trials. Hence, off-label administration of high-dose ambroxol (available OTC) has become a realistic option for the management of these patients, as an adjunct to ERT or for treatment naïve patients without access to ERT.

In an attempt to upscale the level of evidence from anecdotal reports to an observational study,[12] we have established an investigator-initiated registry (II-Reg) . This is our first report of real-life data (observational data), including safety information and some preliminary efficacy results, from a cohort of 41 subjects exposed to off-label ambroxol.

TABLE 1 Detailed data on the 41 patients included in the study

No.[REF]	Sex/Age/Type	GBA mutation(s)	PD	ERT (years)	Ambroxol therapy				
					Duration (mo.)	Max dose (mg/day)	Adverse effects	Discontinuation	Preliminary efficacy[a]
1	F/57/GD1 (SPX)	N370S/IVS2+1	+	Vela (11)	9	600	—	Yes, personal reasons	—
2	M/57/GD1	N370S/L444P	+	Vela (6)	9	1200	—	Yes, reimbursement issues	—
3	F/18/GD1	L444P/V352A	–	Vela (17)	15	1260	—	No	—
4	F/16/GD1	N370S/C342Y	–	Vela (10)	12	300	—	Yes, reimbursement issues	Improvement in well being
5	M/72/GD1	N370S/N370S	–	Vela (23)	41	900	Minor bowel discomfort and light cough	No	85% decrease in Lyso-Gb1 levels
6	M/5/GD1	N370S/I402T	–	Vela (1)	10	360	—	No	Neurological improvement*
7	F/52/GD1 (SPX)	N370S/R120Q	+	Tali (20)	60	750	—	No	No neurological deterioration
8	M/64/GD1	N370S/N370S	+	Untreated	52	1275	PD deterioration**	Yes, due to AE	Increased platelets count
9	M/73/GD1	N370S/RecNcil	–	Untreated	12	75	Atypical drug reaction, dizziness, imbalance	Yes, due to AE	—
10	M/74/GD1	N370S/N370S	–	Untreated	10	300	Dizziness	Yes, due to AE	Reduced pain and fatigue
11	F/68/GD1 (SPX)	N370S/del55	–	Imi (16)	2	75	Allergic reaction, skin rash and redness	Yes, due to AE	—
12	M/2/GD2	84GG/V394L	–	Vela (2)	1	150	Increased mucus and cough	Yes, due to AE	—
13	F/2/GD2	L444P/IVS2+1	–	Imi (2)	24	380	—	No	Neurological improvement*
14	F/1.5/GD2	L444P/c.680_681delinsGG	–	Untreated	5	180	Patient died	Yes, patient died	—
15	F/5/GD3	L444P/L444P	–	Vela (4)	17	250	—	No	No neurological deterioration*
16	F/20/GD3	E233D/L444P	–	Vela (19)	72	1300	—	No	Neurological improvement*
17	M/6/GD3	L444P/L444P	–	Vela (5)	20	435	—	No	No neurological deterioration
18	M/5/GD3	L444P/L444P	–	Vela (4)	20	388	—	No	No neurological deterioration
19	M/4/GD3	L444P/L444P	–	Vela (3)	1	150	Cough**	Yes, due to AE	—
20	F/5/GD3	L444P/L444P	–	Imi (3)	16	248	—	No	No neurological deterioration*
21	F/12/GD3	L444P/L444P	–	Imi (8)	12	150	—	No	No neurological deterioration*
22	F/7/GD3	L444P/F2123	–	Imi (4)	13	373	—	No	No neurological deterioration*
23	F/39/GD3 (SPX)	L444P/L444P	–	Imi (14)	48	225	—	No	Decreased pain
24[8]	F/39/GD3 (SPX)	L444P/L444P	–	Imi (20)	60	300	—	No	Neurological improvement*
25[13]	M/16/GD3	G377S/G195E	–	Imi (14)	36	1300	Neurological deterioration	Yes, due to AE	—
26[13]	F/22/GD3	N188S/R463H	–	Imi (18)	48	1300	—	No	—
27[10]	F/21/GD3	N188S/A257G	–	Imi (7)	76	1485	—	No	Neurological improvement*
28[10]	F/18/GD3	N188S/A257G	–	Imi (6)	76	1215	Increase in mucus production and cough	No	Neurological improvement*
29[10]	F/15/GD3	N188S/c.630delC	–	Imi (5)	76	1377	—	No	Neurological improvement*

(Continues)

TABLE 1 (Continued)

No.[REF]	Sex/Age/Type	GBA mutation(s)	PD	ERT (years)	Ambroxol therapy				
					Duration (mo.)	Max dose (mg/day)	Adverse effects	Discontinuation	Preliminary efficacy[a]
30[10]	F/18/GD3	F213I/L444P	–	Imi (15)	76	1300	Mild proteinuria	No	Neurological improvement*
31	M/19/GD3c	D409H/D409H	–	Imi (13)	10	600	—	Yes, due to reimbursement issues	—
32	F/17/GD3c	D409H/D409H	–	Imi (15)	10	600	—	Yes, due to reimbursement issues	—
33	F/5/GD3c	D409H/D409H	–	Imi (4)	48	360	—	No	—
34	F/12/GD3	H255Q/L444P	–	Imi (7)	49	1275	—	No	No neurological deterioration*
35	M/12/GD3	L444P/L444P	–	Imi (10)	19	1200	—	No	Increased physical activity, reduced fatigue
36	F/3/GD3c	D409H/D409H	–	Imi (3)	19	200	—	No	Not available
37	F/7/GD3	L444P/L444P	–	Imi (6)	48	660	—	No	Neurological improvement*
38	M/7/GD3	N188S/R120W	–	Imi (5)	55	420	—	No	Decreased levels of Lyso-Gb1 and neurological improvement*
39	M/70/Carrier	N370S	+	–	72	300	Cognitive problems slowly are worsening	No	—
40	M/46/Carrier	N370S	+	–	8	1275	—	No	Improvement in UPDRS
41	F/70/Carrier	N370S	+	–	15	1200	—	No	Not available

Abbreviations: AE, adverse event; ERT, enzyme replacement therapy; F, female; GBA, glucocerebrosidase; GD1, type 1 Gaucher Disease; GD2, type 2 Gaucher Disease; GD3, type 3 Gaucher Disease; Imi, Imiglucerase; M, Male; mo., months; No., number; PD, Parkinson Disease; SPX, splenectomized; Tali, Taliglucerase alfa; UPDRS, Unified Parkinson's Disease Rating Scale; Vela, Velaglucerase alfa.

[a]The efficacy information is based on subjective report and not on standardized assessment.

[a]*Expanded information on efficacy by patient number:

[b]#6: Reduction of seizures in terms of daily number and intensity.

[c]#13: Improved head movement and contact with her parents.

[d]#15: Eye movement anomalies persist.

[e]#16: Since increasing dose of ambroxol in 2017 to 30 mg/kg (1300 mg daily), tremor has largely resolved, she is using wheelchair less, walks with assistance having been unable to walk prior to starting ambroxol, improvement in weight gain (patient was losing weight when her tremor was at is worst a year earlier, and she was unable to eat without assistance). She now uses a knife and fork, able to hold a pen and writing has improved, speech clearer. Myoclonic seizures very rarely now since starting ambroxol; only has occasional stimulus-sensitive myoclonus of the hands.

[f]#20: Eye movement anomalies (slow horizontal saccadic movements).

[g]#21: Eye movement anomalies remain the same.

[h]#22: Gaze palsy remains the same.

#24: Decreased epileptic attacks.

#27, #28, #29 and #30: Seizures decreased, tremor decreased, balancing improved, deterioration of intellectual disability stopped.

#34: Stable to slow progression of neurological symptoms: supranuclear gaze palsy, fine motor skills impairment, clumsiness, no seizures whatsoever. No spasticity.

#37: No seizures for at least a year.

#38: Improvement in the frequency and intensity of the seizure activity.

**Expanded information on safety by patient number:

#8: PD symptoms have significantly worsened (bradykinesia, tremor, decreased right hand dexterity).

#19: Patient has confirmed GD-lung involvement.

2 | METHODS

Colleagues treating patients with ambroxol for GD1, nGD, and *GBA*-related PD were approached to collaborate in an investigator initiated registry II-Reg. Anonymized retrospective data were collected using a unified case report form (CRF), including demographics, GD type and GD-specific therapy (when applicable), history of splenectomy, and adverse events (AEs) during ambroxol therapy, and when available also preliminary efficacy data. This registry was initially approved by the Shaare Zedek Medical Center Institutional Review Board (Protocol ID: 0097-20-SZMC). It was then submitted and approved at each of the other centers that collaborated in this registry. As only retrospective, anonymized data were collected for this study, an exemption was received for individual consent. The study was registered on ClinicalTrial.gov (ID: NCT04388969). Currently, 13 centers from 13 different countries contributed data.

Seven of the 41 patients have been previously published,[8,10,13] but in this report, the individual information has been updated for the length of therapy, safety and efficacy.

3 | RESULTS

Forty-one patients (25 females) at a median age of 17 (range 1.5-74) years are included in this report; 11 with GD1 (four diagnosed with PD), 27 with nGD, and three GBA carriers with PD. Thirty-four patients with GD received ERT for a median of 7 years (range 1-23) at a median (range) monthly dosage of 115 (range 25-206) Units/Kg. Five patients were splenectomized. The median (range) treatment period and the dose of ambroxol were 19 (1-76) months and 435 (75-1485) mg/day, respectively. Table 1 presents the demographic data, genotype, ERT status, ambroxol dose, therapy length in the different cohorts, AEs, and causes for discontinuation for all 41 patients.

One patient (No.14 Table 1) with GD2 died of her disease (which was unrelated to ambroxol according to the treating physician). No other serious AEs were reported. Twelve of 41 patients experienced AEs, including minor bowel discomfort, cough, allergic reaction, mild proteinuria, dizziness and disease progression (Table 1). Twelve patients stopped ambroxol, eight due to AEs (including the unrelated death of the GD2 patient), four for reimbursement issues, and one for personal reasons. Clinical benefits were reported in 25 patients including, stable or improved neurological status, increased physical activity, and reduced fatigue (Table 1).

4 | DISCUSSION

Since 1991, GD has become a model of success in medicine and industry, following the introduction of safe and effective ERT; the results of the seminal clinical trial of alglucerase have revolutionized not just the way we treat GD but have opened the door to the development of other ERTs for other lysosomal storage diseases. The parallel unprecedented financial success of the manufacturers has led to a rapidly growing interest of the entire pharmaceutic industry to invest in the development of orphan drugs for rare diseases at large. Unfortunately, the enthusiasm around the success in GD1 has skipped the patients who suffer from nGD; due to the inability of all ERTs to cross the BBB and the failure of the SRT small molecules to impact the CNS (miglustat is capable of crossing the BBB but failed phase 2 clinical trials,[14] whereas eliglustat cannot penetrate the CNS[1]). This has left all patients with nGD without specific treatment for their neurological manifestation for almost 30 years.

There are currently several on-going clinical trials, using different treatment modalities and led by pharmaceutical companies, addressing this major unmet need. These studies include an SRT that crosses the BBB (venglustat),[15] a heat-shock protein amplifier (arimoclomol),[16] and AAV9-based gene therapy (NCT04411654). Since all these trials are still at early stages of development, and with the complexities associated with recruiting patients with rare diseases,[17] market authorization is not expected before 5 or 10 years from today. Under these circumstances, those patients with significant neuronopathic features will seek any possible solution even if it is unregistered treatment or any product derived from alternative and complementary medicine, even if based on testimonials only.

Off-label use of ambroxol has become popular following the above-mentioned pilot studies demonstrating the proof of concept for the ability of this OTC cough medication to act as a pharmacological chaperon for mutant GCase,[4] and the dramatic improvement, particularly in amelioration of myoclonic epilepsy, in some individual cases from around the world. However, many physicians, particularly in the well-developed countries, are reluctant to recommend an unapproved medicine, and therefore are raising concerns about safety, even when the drug itself is available OTC and relatively easy to get. Moreover, the two very large multi-center multi-national comprehensive GD-registries (the ICGG of Sanofi/Genzyme with over 6660 patients and 28 years of existence,[18] and the GOS of Takeda with over 3000 patients over ten years of data collection[19]) have disallowed the entry of ambroxol as an additional GD specific treatment to their database. Therefore, we felt it was important to establish an investigator-initiated registry (II-Reg) that will include as many patients as possible to fill the gap until a formal international registry is established. It is expected that in the near future such registry will be launched by the International Gaucher Alliance (IGA) in collaboration with a dedicated professional organization (* www.gaucheralliance.org). In the meantime, it is to be hoped that this II-reg would continue to serve as a platform for retrospective data collection of all patients world-wide receiving ambroxol. Monitoring safety and efficacy must be an ongoing process and should not be neglected only because ambroxol is an OTC drug and do not require a physician prescription.

The 41 patients reported herein, including GBA related PD, provide satisfactory safety information, which has been the priority of this II-Reg. Most of the AEs were mild and transient in nature. The fact that a relatively large number of patients have discontinued therapy[19] should not be regarded as an alarming sign since only eight of them stopped ambroxol because of the AEs. It should also be emphasized that all GD3 patients received ambroxol as an adjuvant to ERT, whereas six patients with GD1 and GBA PD got it as single therapy. We have not noted an impact of the combination versus single therapy on the AEs; however, this should await a larger number of cases. Finally, it should be noted that the profile of AEs among these eight patients is not different than those reported in the placebo arm of phase 3 eliglustat ENGAGE trial or with any of the ERT studies.[20,21]

The safety of ambroxol is further appreciated once we include an additional 70 patients from four different cohorts that have already been either presented or published, giving an overall reported cases to 105; 12 patients with GD1 from the pilot report of Zimran et al.,[6] 23 patients with nGD from the IIR of Dr. Narita (five published[5] plus additional 17 that have been presented in 2019 at the GES conference), 17 cases of PD recently published by Mulin et al. (eight had GBA-related PD and nine non-GBA related PD[9]), and 24 GD1 patients

(out of 40 planned; from the on-going IIR NCT03950050) were presented by Ms Istaiti in 2020 at the EWGGD meeting. Among the 41 patients in the current report, we have not been able to relate either safety or efficacy results with age, sex and the type of mutation (not among the GD patients nor among the GBA-carriers with PD). To reduce adverse events, it was suggested to increase the doses gradually; via different schedules (changing every several days or every week) until reaching the maximal dose (25 mg/kg or 1.2 g/day).

It should be noted that in the Japanese, Korean and British IIRs, the in-vitro efficacy of ambroxol on GCase levels was tested on skin fibroblasts as a pre-requisite for enrollment to the study.[9,10] In the majority of the cases in the II-Reg, in-vitro screening was not performed, mainly due to the existence of potential discrepancies between in vivo and in vitro, particularly with regards to the most common neuronopathic mutation L444P, for which conflicting results have been published by different laboratories.[5,22] Given the lack of alternative treatment and the safety profile of ambroxol, we justify this "blinded" approach (skipping the in vitro screening).

Even though ambroxol is indeed widely available and relatively affordable, in many countries there are still obstacles that may interfere with its administration even when there is an interest to receive it. The almost universal lack of reimbursement due to the fact that it is not a registered therapy, and despite its being a relatively inexpensive drug, compared to ERT and SRT, many families still cannot afford it, particularly in underdeveloped countries. In some countries ambroxol is not available, even as a cough medicine. Finally, because the doses needed for the PC effect are much higher than the OTC ones, the ambroxol formulations are limited to lower concentrations, causing adults to take many capsules and children to drink a large amount of syrup, every day.

The expansion of the database via this retrospective II-Reg or any other prospective registry (that would require patients' consent) will allow greater understanding of the potential safety and efficacy of this PC; when this happens, regulatory agencies may consider approval of high-dose ambroxol as a PC for nGD and GBA-related PD. Accordingly, the various manufacturers may compose the drug in higher concentrations for better compliance and to improve quality of life.

ETHICS STATEMENT

The study design was approved by institutional IRB. IRB institutional number: 0097-20-SZMC

DATA ACCESSIBILITY

The datasets during and/or analysed during the current study available from the corresponding author on reasonable request.

CONFLICT OF INTEREST

M.I., M.B.-C., T.D., A.C., P.R., C.- F.Y., and B.R., declare no conflict of interest.

S.R.-V. receives grant/research support, honoraria and advisory fee from Takeda, Pfizer, Sanofi/Genzyme and Prevail therapeutics. The SZMC Gaucher Unit receives support from Sanofi/Genzyme for participation in the ICGG Registry, from Takeda for the GOS Registry, and Pfizer for TALIAS. The Unit also receives research grants from Takeda, Pfizer, Sanofi/Genzyme and Centogene.

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DATA AVAILABILITY STATEMENT

Data available on request due to privacy/ethical restrictions

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