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Early stroke trial (EST): Study protocol and results of the adjudication process

A. Carolei, C. Fieschi, C. Argentino, G.L. Lenzi, E. Bottacchi, S. Muntoni, D. Inzitari, E. Ott, F. Gerstenbrand, J. Bogousslavsky, A. Portera-Sanchez, S. Horowitz, G.L. Brambilla, U. Senin, A. Bes, D. Gambi, G. Kraemer, K. Einhaeupl, A. Mamoli and R. Bruno

Istituto di Scienze Neurologiche, Università degli Studi di Siena, Siena, Italy

Introduction

GM1-Ganglioside is a complex glycolipid normally present in the cell membranes of mammalian nervous tissue. The parenteral administration of exogenous GM1 demonstrated a definite role in nervous tissue repair process, by means of its favorable influence on many functional, biochemical, and behavioural parameters after traumatic or ischemic lesions [1–7].

On the basis of these data we designed a clinical trial to evaluate safety and efficacy of GM1 in patients affected with acute ischemic stroke.

Patients and Methods

The Early Stroke Trial (EST) is a randomized, stratified, double-blind placebo-controlled trial to assess the effect of GM1-monosialotetraexosilganglioside in reducing the rate of mortality and change in the Canadian Neurological Scale (CNS) score at 4 months, in patients who have had an acute ischemic stroke in the carotid territory (within 5 h from the onset of symptoms).

The EST organization included 16 clinical centers (8 in Italy, 1 in the U.S.A., 2 in Germany, 2 in Austria, 1 in Switzerland, 1 in Spain and 1 in France), a coordinating and clinical monitoring center and appropriate policy, adjudication and monitoring committees.

The steering committee had overall responsibility for the study. A central adjudication committee was responsible for validating the eligibility of patients entered into the study and the outcome events reported by the investigators. An independent advisory-review and treatment effects monitoring committee (ARTEMC) with necessary expertise was responsible for ongoing monitoring of safety and efficacy.

Potentially eligible patients were those admitted to the emergency room of one of the participating centers because of a focal cerebral deficit of acute onset in the

carotid territory. A computed tomogram (CT) brain scan was required, primarily to rule out disease processes other than cerebral infarction.

Patients included were those evaluated, randomized and treated with the first dose of GM1 (or placebo) within 5 h from the onset of stroke. Excluded patients were the following: younger than 35 or older than 80 years; subjects with stupor or coma; with diseases which might interfere with the neurological assessment or with survival during the follow-up period; pregnant women; with clinical or CT evidence of intracerebral hemorrhage, brain tumor, subarachnoid hemorrhage or subtentorial lesion; involved in any other experimental trial; refusing participation in the trial or with a CNS score greater than 8.5.

GM1 was supplied in glass ampoules containing a 2-ml solution of 100 mg of monosialotetraexosilganglioside. The placebo ampoules were identical in appearance and packaging. The treatment regimen was two 100-mg ampoules, to be administered as a single intravenous dose no later than 5 h from the onset of stroke and a second intravenous dose of 100 mg, 12 h after the first. Afterwards the patients received a daily dose of 100 mg intravenously from day 2–10 and finally an intramuscular dose of 100 mg from day 11–21.

Eligible patients giving informed consent were allocated to either GM1 or placebo according to a randomization chart generated separately for each of the clinical centers.

The initial clinical assessment included a general physical and neurological examination, medical history and details of the qualifying stroke together with application of the Barthel Scale assessed by history, the Canadian Neurological Scale (CNS) and the Toronto Scale.

Clinical follow-up assessments were made daily by means of these scales, from day 1–15, at day 21 and at 2 and 4 months. At these follow-up visits general physical and neurological examinations, newly-observed signs and symptoms, concomitant therapies and adverse experiences were recorded.

Laboratory examinations, ECG and brain CT scan were performed on admission (within 5 h from the onset of stroke) and during the follow-up period. Compliance was assessed by the responsible physician. Cerebral angiography of the symptomatic carotid district was performed following brain CT scan, within 5 h from the onset of stroke. When angiography could not be performed or was contraindicated, Doppler sonography of neck arteries and transcranial Doppler (TCD) were performed.

The primary analysis of efficacy was based on mortality rate and changes in the CNS score at 4 months.

Results

The study lasted 40 months, from May 1987 to August 1990. A screening of 8,781 patients was performed. The main characteristics of these patients were recorded in the stroke registry. Only 833 subjects (9.4%) were eligible for the study. Twenty-

Table 1. Accrual by center of randomized patients (n = 805)

Center	Pts. (n)	Center	Pts. (n)
Rome	121	Lausanne	37
Cagliari	114	Madrid	37
Perugia	103	Mainz	34
Bergamo	67	Florence	26
Aosta	56	Toulouse	25
New York	54	Munich	20
Chieti	54	Graz	9
Innsbruck	42	Pavia	6

eight of them refused to be included. As a consequence, the 16 participating centers enrolled a total of 805 patients (Table 1). At entry 13 of these 805 randomized patients (1.6%) were ruled truly ineligible (without the disease of interest) and 22 (2.7%) technically ineligible (with minor protocol violations).

Seventeen patients (2.1%) did not complete the treatment (early discontinuation), 44 (5.5%) lacked one or more of the requested examinations but were alive at 4 months (incomplete data) while 5 patients (0.6%) were definitely lost at 2–4 months follow-up.

The demographic characteristics of the enrolled patients, with the expected sex differences for myocardial infarction, smoking and alcohol abuse are reported in Table 2.

The final distribution of patients, according to the assumed stratification factors (age, sex and severity of the neurological deficit, assessed by means of the CNS at entry) is reported Table 3.

One hundred and sixty-three patients (20.2%) have died. The highest mortality rates were reached in the OFS (39.2%) and OMS (27.0%) strata. The 30-day mortality represented 69% of the total rate. Sixty-nine (42.4%) patients had a

Table 2. Demographic characteristics and risk factors at entry

	Female	Male
Sex (%)	44.5	55.5
Mean age (yrs)	69.5	66.2
Severity (CNS score)	5.1	5.5
Diabetes (%)	10.1	9.6
Hypertension (%)	29.1	28.3
Previous TIA-RIND (%)	9.7	12.5
Congestive heart failure (%)	2.5	2.4
Myocardial infarction (%)	3.5	6.9
Atrial fibrillation (%)	12.2	11.1
Smoking (%)	5.2	27.8
Alcohol abuse (%)	0.7	7.2

Table 3. Patient distribution (%) according to stratification factors

Female	44.5	>65 years	65.8	CNS >5	53.5
Male	55.5	≤65 years	34.2	CNS ≤5	46.5
Y= ≤65 years		F = Female		L (Less severe)	= CNS >5
O= >65 years		M= Male		S (Severe)	= CNS ≤5

cerebral cause of death, 39 (23.9%) a cardiac or sudden death, 53 (32.5%) a non-vascular death and 2 (1.2%) an unknown cause of death.

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Study organization

Chairman: Cesare Fieschi (Rome)

Participating centers: C. Argentino (Rome), E. Bottacchi (Aosta), S. Muntoni (Cagliari), D. Inzitari (Florence), E. Ott (Graz), F. Gerstenbrand (Innsbruck), J. Bogousslavsky (Lausanne), A. Portera-Sanchez (Madrid), S. Horowitz (New York), G.L. Brambilla (Pavia), U. Senin (Perugia), A. Bes (Toulouse), D. Gambi (Chieti), G. Kraemer (Mainz), K. Einhaeupl (Munich) and A. Mamoli (Bergamo).

Steering committee: C. Fieschi (Chairman), G.L. Lenzi (Study Coordinator), R. Bruno, F. Dorsey and W. Rocca.

ARTEMC (Advisory-review and treatment effect monitoring committee): M. Walker (Chairman), J.D. Easton, M. Gent and R. Roberts.

Central adjudication committee: A. Carolei (Chairman), A. Ardia, C. Argentino, R. Bruno (Project Leader), G. Sancesario and E. Olivi.

Analysis center: F. Grigoletto (University of Padua)

Clinical monitoring: T. Alonso (1st year), F. Berni, A. Bianchetti, J. Klesing, C. Martinazzo, D. Poonian and G. Salvato.

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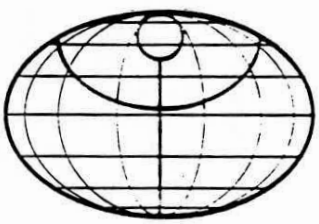

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