Neurol Sci
DOI 10.1007/s10072-015-2182-5

ORIGINAL ARTICLE

Tolerability and efficacy of erythropoietin (EPO) treatment in traumatic spinal cord injury: a preliminary randomized comparative trial vs. methylprednisolone (MP)

Davide Dalla Costa[1] · Ettore Beghi[2] · Paola Carignano[3] · Cristina Pagliacci[4] · Franco Faccioli[5] · Elisabetta Pupillo[2] · Paolo Messina[2] · Alfredo Gorio[6] · Tiziana Redaelli[1]

Received: 22 January 2015 / Accepted: 19 March 2015

Abstract The only available treatment of traumatic spinal cord injury (TSCI) is high-dose methylprednisolone (MP) administered acutely after injury. However, as the efficacy of MP is controversial, we assessed the superiority of erythropoietin (EPO) versus MP in improving clinical outcome of acute TSCI. Patients aged 18 to 65 years after C5–T12 injury, and grade A or B of the ASIA Impairment Scale (AIS), admitted within 8 h, hemodynamically stable, were randomized to MP according to the NASCIS III protocol or EPO iv (500 UI/kg, repeated at 24 and 48 h). Patients were assessed by an investigator blind to treatment assignment at baseline and at day 3, 7, 14, 30, 60 and 90. Primary end point: number of responders (reduction of at least one AIS grade). Secondary end points: treatment safety and the effects of drugs on a number of disability measures. Frequentistic and post hoc Bayesian analyses were performed. Eight patients were randomized to MP and 11 to EPO. Three patients (27.3 %) on EPO and no patients on MP reached the primary end point ($p = 0.17$). No significant differences were found for the other disability measures. No adverse events or serious adverse events were reported in both groups. The Bayesian analysis detected a 91.8 % chance of achieving higher success rates on the primary end point with EPO in the intention-to-treat population with a 95 % chance the difference between EPO and MP falling in the range (−0.10, 0.51) and a median value of 0.2. The results of Bayesian analysis favored the experimental treatment.

Keywords Spinal cord · Injury · Erythropoietin · Randomized trial · Drugs · Methylprednisolone

✉ Ettore Beghi
ettore.beghi@marionegri.it

[1] Spinal Unit, Niguarda Ca' Granda Hospital, Milan, Italy

[2] Laboratory of Neurological Disorders, IRCCS, Mario Negri Institute for Pharmacological Research, Via Giuseppe La Masa, 19, 20156 Milan, Italy

[3] C.T.O./C.R.F./M. Adelaide Hospital, Turin, Italy

[4] Spinal Unit of Umbria, Silvestrini Hospital, Perugia, Italy

[5] Spinal Neurosurgery, Civile Hospital, Verona, Italy

[6] Pharmacological Laboratories, Departments of Medicine, Surgery and Odontoiatry, Faculty of Medicine, Polo H. San Paolo, Milan, Italy

Introduction

Traumatic spinal cord injury (TSCI) is a devastating clinical condition.

Primary injury is the result of the direct action of mechanical force on the spinal cord [1]. Secondary injury is the result of a stroke-like ischemic insult with abnormal arterial flow, venous stasis, edema and vasospasm, all lowering spinal arterial perfusion to critical levels [2]. The combination of primary and secondary degeneration determines the extent of tissue damage beyond the limits of the mechanical impact. The degenerated tissues are enclosed in a cavity surrounded by reactive glia [2, 3].

The attenuation of both cellular and molecular abnormalities underlying the secondary injury may result in improvement of recovery from TSCI-derived disability [4, 5]. More than 90 % of the TSCI are incomplete, and a portion of the ventral axons is spared by the injury [6]. The degree of recovery depends on the extent of spared white matter at injury site [7]. An effective acute intervention is as yet unavailable. The pharmacological treatment currently in use is high-dose methylprednisolone (MP) administered acutely after injury [8, 9]. The mechanisms of

Published online: 28 March 2015

action of glucocorticoids remain unclear, although it has been shown that MP administration suppresses chemokine production and the inflammatory reaction in the spinal cord after injury [4, 10–12].

Acute administration of erythropoietin (EPO) can attenuate the effects of TSCI and accelerate neurological recovery after injury in the rat [4, 13–15]. Most of the difference in the recovery rate is established within the first 48–72 h and is correlated with a reduction in the post-traumatic cavity and enhanced sparing of ventral axons. Improved recovery was observed when treatment was performed within 24 h from lesion. The efficacy of EPO treatment is abolished by concomitant treatment with MP [4].

When used in experimental stroke, EPO limits the evolution of the ischemic penumbra, the area surrounding the central infarct and the main site of the secondary degeneration, and increases the recruitment of endogenous stem cells [16–19]. This might explain the effects of EPO on TSCI. Our preliminary results showed that EPO receptors are also expressed in endothelial and vascular smooth muscle cells, and the expression is particularly high in the white matter vessels (Alfredo Gorio, unpublished results). This action may be protective in the immediate period after injury. Yet the beneficial action of EPO on the vasculature may extend further by suppressing the expression of inducible nitric oxide synthase and promoting the production of neurotrophins such as brain-derived neurotrophic factor [15, 20].

Considering the mechanisms of action of EPO together with its beneficial effects in TSCI animal models, our primary objective was to assess whether EPO was better than MP in improving the clinical outcome of TSCI in a clinically relevant and measurable way during the acute phase after injury, a period in which the greatest degree of improvement is expected.

Materials and methods

The study design is in line with the guidelines for the conduction of clinical trials developed by the International Campaign for Cures of Spinal Cord Injury Paralysis [21] (http://www.clinicaltrial.gov—ClinicalTrials.gov Identifier: NCT00561067).

Study design and setting

This was a multicenter randomized single-blind, phase III, parallel group trial involving Italian Spinal Units (SU). In Italy, SU are competent health care facilities to take care of TSCI patients starting from the first aid management and diagnosis and ending with a comprehensive rehabilitation program. All centers involved were well trained as having participated in educational meetings, organized by the Coordinating Center, the SU of Niguarda Hospital in Milan, aimed at standardizing the acute and long-term assistance of TSCI.

Population

Included were consecutive patients with TSCI complicated by paraplegia or tetraplegia. The diagnosis at the time of hospital admission was made through neurological examination, in accordance with the latest version of the International Standards for Neurological Classification of SCI [22], to determine the neurologic level of injury and the extent of injury (ASIA Impairment Scale—AIS), and neuroimaging (spinal computerized tomography, CT). Only patients with TSCI and AIS grade A or B were enrolled. Other inclusion criteria were age 18–65 years, the time between the traumatic event and treatment (within 8 h), hemodynamic stability at treatment start (systolic blood pressure >90 mmHg for at least 1 h without massive infusion or vasopressor support), neurological level between C5 and T12, and written informed consent. Excluded were patients with SCI of non-traumatic origin, TSCI caused by edged weapons or firearms, time interval from trauma >8 h, neurological level above C5 or below T12, AIS grade C, D, E, uncontrollable arterial hypertension, past or current cerebrovascular disease or myocardial infarction, history of thrombotic events, other chronic cardiovascular disorders (cardiac arrhythmias, congestive heart failure), peripheral arterial disease, polycythemia, porphyria, active malignancy, previous or current neurological diseases with abnormal neurological examination, pregnancy or lactation (requiring βHCG confirmation), clinically relevant psychiatric disease, known allergy to EPO, hypersensitivity to human albumin, and acute or chronic renal failure.

Patients were also excluded when MP was administered by the emergency doctors prior to diagnosis of TSCI.

Treatment

Eligible patients were immediately randomized to one of the following treatment modalities: (1) MP 30 mg/Kg iv in the first hour, followed by 5.4 mg/kg/h for 23 h if treatment was started within 3 h after the spinal injury, or for 48 h if treatment was started between three and 8 h (protocol NASCIS III, National Acute Spinal Cord Injury Study) [23]; (2) EPO 500 IU/Kg diluted in 50 ml saline and infused in 30 min; treatment was started within 8 h after injury; the same drug dosage was infused at 24 and 48 h.

Study conduct and outcome assessment

Every patient with TSCI transferred by the Emergency Services to one of the participating SU was screened. After confirmation of a spinal cord lesion, patient's eligibility was assessed by verifying the inclusion/exclusion criteria. Eligible patients or, where indicated, the relatives or other legal representatives were asked to provide a written informed consent. Patients underwent venipuncture for the assessment of the laboratory parameters and, where not contraindicated, were randomized to receive MP or EPO. Randomization was performed through a password-protected centralized web database (located at the IRCCS-Mario Negri, Milan) after verifying the patient's eligibility criteria. Separate randomization lists were used for patients classified as AIS grade A and B. Random permuted blocks were used.

Patients were assessed by investigators blind to treatment assignment at baseline and at day 3, 7, 14, 30, 60 and 90.

Study monitoring

An electronic database was made available to each SU; the database included automatic measures of the accuracy of the data collection. A data manager located at the IRCCS-Mario Negri, checked at weekly intervals the quality and completeness of the data from each patient enrolled and contacted immediately the local investigator if a problem arose.

Data collection

Data collection included demographics (age, sex, injury's date and time, center), baseline clinical findings [site and extent of the spinal lesion with indication of the neurological level, ASIA motor/sensory level, AIS score and grade, Spinal Cord Independence Measure (SCIM version II) [24], Ashworth measure [25], Penn Spasm Frequency [26], VAS scores [27], CT signs of spinal cord injury, and laboratory values including blood cell count, standard coagulation tests, glucose, urea, ßHCG, serum electrolytes, transaminases, and bilirubin]. Follow-up data (collected at each visit) included ASIA motor/sensory level, AIS score and grade, SCIM version II, Ashworth, Penn, and VAS scores, MRI findings, somatosensory-evoked potentials (SSEP) from the pudendal and tibial nerve, and laboratory values.

Every patient (or legal representative) was informed about the possible benefits and risks of both treatments, without emphasis on the experimental treatment.

End points

Primary end point was the reduction of at least one AIS grade. This outcome measure has a good "face validity" [21]. Secondary end points were the number of treatment-emergent adverse events, serious adverse events, and events leading to treatment withdrawal, effects on the spinal motor and/or sensory functions (including the SSEP), on measures of functional autonomy (SCIM), spasticity and spasms (Ashworth and Penn Scales), and neurogenic pain.

Expected adverse events included drug-related events (hematocrit value $\geq$51 %) and disease-related events (acute myocardial infarction, thrombotic pulmonary embolism, deep venous thrombosis, acute hypertension, seizures, piastrinosis, hyperkalemia, hyperphosforemia, skin rash, hypercalcemia, and liver dysfunction).

Statistical analysis

Descriptive statistics were performed on patients' demographic and clinical features at baseline. Discrete and continuous variables were reported as count, percent, median and range. The primary end point was assessed using the Fisher exact test. Between-group comparisons by different scales used Mann–Whitney Test or the Fisher exact test, as appropriate. Given the low statistical power of the study (see "Results"), a parallel Bayesian analysis (see below) was performed (post hoc) on the primary outcome. Bayesian analysis is a statistical approach that does not base its estimates only on observed data, but also uses an a priori information. No literature or subjective information was used to perform this analysis (uninformative prior). We used the Gibbs sampling (a Markov Chain Monte Carlo MCMC algorithm) for obtaining a sequence of random samples (1000) from the multivariate probability distribution, the joint probability distribution of the uninformative prior and the binomial distribution (occurrence of successes and failures) of the data observed. All statistical analyses were performed in the intention-to-treat (ITT) and the completer (completer) populations. All tests are two tailed. Data were analyzed using the Statistical Analysis System (SAS Institute, Inc., Cary, NC, USA) package for PC (version 9.2) and the R (version 2.13) software.

Sample size and study power

Based on published reports and personal experience, patients with an improvement of the AIS grade with MP were estimated at 10 % [28, 29]. Estimating an increase of this percentage to 35 % for patients treated with EPO, 40 patients in each therapeutic arm were needed, with a power of

80 % and a level of significance of 5 %. Given the small sample enrolled, we simulated (post hoc) a two-stage sequential design situation under the planned hypotheses (35 vs. 10 %, alpha = 0.05 and beta = 0.8). This design required two different examinations (first and final stage). At the first and the final stages, a total of 18 (9 per arm) and 38 (19 per arm) patients, respectively, should have been enrolled. If a trial continues to the final stage, the null hypothesis is either rejected or accepted. As we enrolled 19 patients, the data collected up to that point were analyzed, and statistics were computed, in accordance with the requirements of the first stage. At that stage, the test statistic generated should have been compared with critical values generated from the sequential design, and the trial stopped or continued. The stopping boundaries for the first stage were selected according to the O'Brien & Fleming approach [30] (stop for futility $p > 0.31247$, stop for efficacy $p < 0.01044$, continue $0.01044 < p < 0.31247$).

Ethical approval

All procedures performed were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the Ethics Committees of the participating institutions.

Results

Due to the strict selection criteria, only 19 consecutive patients (18 men and 1 woman aged 20–65 years) from four SU entered the study between May 15, 2008 and July 19, 2010 (Table 1; Fig. 1). The causes of injury were motorcycle accidents (9 patients), downfalls (4 patients), strenuous physical activities or dives (2 patients each), car accident, bicycle accident, one crush by heavy object (1 each). Eight patients (42.1 %) aged 27–54 years were randomized to MP and 11 patients (57.9 %) aged 22–65 years to EPO. The ITT analysis revealed that 0 patients on MP and 3 patients (27.3 %) on EPO satisfied the primary end point by day 90 (one-tailed Exact Fisher p value = 0.1703) (Table 1). The Completer analysis, performed in 18 patients (one was withdrawn for missing the second treatment course), returned the same results ($p = 0.1471$). The assessment of secondary outcomes failed to show significant differences between the two treatment groups during follow-up (see Tables 1, 2). No adverse events were even reported in both groups throughout the study. Laboratory data

Table 1 General characteristics of the sample

Pt	Sex	Age (year)	Center	ASIA (baseline)	ASIA (day 90)	Treatment	Most caudal segment with normal sensory function						SSEP (baseline)	SSEP (day 90)
							T0	T1	T2	T3	T4	T5		
1	M	51	AO Niguarda, Milan	A	B	EPO	NA	T8	T8	T9	T10	T9	Neg	Neg
2	M	45	AO Niguarda, Milan	A	B	EPO	NA	T3	T3	T3	T3	T3	Neg	Neg
3	M	23	Osp. Civile, Verona	A	A	EPO	C6	C6	C7	T1	T1	T1	Neg	Neg
4	M	65	AO Niguarda, Milan	A	B	EPO	NA	NA	NA	NA	T2	T3	Neg	Neg
5	M	28	CTO Adelaide, Turin	A	A	EPO	–	–	–	–	–	–	–	–
6	M	22	CTO Adelaide, Turin	B	A	EPO	T12	T12	T9	T9	T9	T9	Neg	Neg
7	M	30	CTO Adelaide, Turin	A	A	EPO	T4	T4	T4	T5	T5	T5	Neg	Neg
8	M	22	CTO Adelaide, Turin	A	A	EPO	NA	C5	C5	T3	T3	T3	Neg	Neg
9	M	58	AO Niguarda, Milan	A	A	EPO	T7	T7	T7	T7	T6	T8	Neg	Neg
10	M	55	AO Niguarda, Milan	A	A	EPO	NA	NA	C4	C4	C3	C4	Neg	Neg
11	M	27	AO Niguarda, Milan	A	C	EPO	NA	T12	NA	T12	T6	T11	Pos	Pos
12	M	33	AO Niguarda, Milan	B	A	MP	T10	T9	T9	T10	T10	T10	Neg	Neg
13	M	27	AO Silvestrini, Perugia	A	A	MP	T6	T6	T6	T5	T9	T9	Neg	Neg
14	M	54	Osp. Civile, Verona	A	A	MP	C6	C6	C6	C7	C7	C7	Neg	Neg
15	M	35	AO Niguarda, Milan	A	A	MP	NA	T6	T6	T6	T5	T6	Neg	Neg
16	M	41	AO Niguarda, Milan	A	A	MP	NA	NA	T4	T3	T3	T3	Neg	Neg
17	M	32	AO Niguarda, Milan	A	A	MP	NA	C4	T4	T3	T2	T1	Neg	Neg
18	F	36	AO Niguarda, Milan	B	B	MP	C4	C4	C4	–	–	C4	Pos	NE
19	M	45	AO Niguarda, Milan	A	A	MP	NA	NA	T3	T3	T3	T3	Neg	Neg

M men, *W* women, *EPO* erythropoietin, *MP* methylprednisolone, *NA* not assessed, *SSEP* somatosensory-evoked potential, *Pos* positive, *Neg* negative, *NE* non-evaluated

differed significantly at visit 2 (leucocytes), at visit 3 (sodium, urea, hemoglobin and hematocrit), at visit 4 (sodium and urea), and at visit 6 (potassium). All values were higher in the MP group (except for the expected EPO-promoted increase in hemoglobin and hematocrit); however, all data fell in the normative bounds (see Fig. 2).

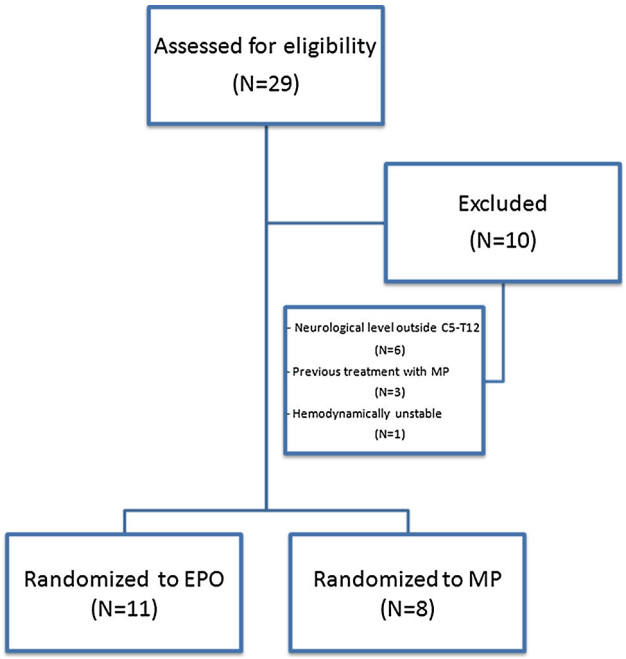

Fig. 1 Study flow diagram. *EPO* erythropoietin, *MP* methylprednisolone

In the Bayesian analysis, according to 1000 replications based on the observed data, there was a 91.8 % chance of achieving higher success rates on the primary end point with EPO in the ITT population, with a median value of 0.21 and a 95 % chance to range between −0.10 and 0.51 (Fig. 3). The same analysis repeated in the Completer population reported a 93.2 % chance of success with a median (range) of 0.23 (−0.09, 0.55) (Fig. 4). Figure 3 reports the acceptance (treatment ineffective) and rejection regions (treatment effective) according to the "simulated" two-stage sequential design. Our sample (19 patients) is comparable in size to that required for the 1st stage analysis ($n = 18$), and according to the results of our Fisher exact test on the primary end point ($p = 0.1703$) we are in the uncertainty region, that should suggest us to continue the recruitment to reach the planned size.

Discussion

In our small trial population, 3/11 cases receiving EPO and 0/8 cases receiving MP presented a significant clinical improvement, showing reduction of at least one AIS grade.

Table 2 Secondary end point

	Baseline		Day 90		*p* value
	EPO Med (min–max) or *n* (%)	MP Med (min–max) or *n* (%)	EPO Med (min–max) or *n* (%)	MP Med (min–max) or *n* (%)	
Asia total score					
Motor	49 (10–50)	45 (18–50)	50 (20–50)	50 (10–50)	0.9117
Pinprick	40 (12–76)	45 (21–72)	52 (18–83)	45 (12–69)	0.3862
Light touch	42 (12–76)	49 (38–75)	52 (22–97)	55 (34–80)	0.8954
Penn score					
0	10 (100)	8 (100)	5 (50.0)	3 (37.5)	0.6641*
1	–	–	1 (10.0)	1 (12.5)	
2	–	–	3 (30.0)	1 (12.5)	
3	–	–	1 (10.0)	3 (37.5)	
4	–	–	–	–	
Ashworth score					
0	8 (80.0)	8 (100)	4 (40.0)	4 (50.0)	1.0000*
1	2 (20.0)	–	4 (40.0)	1 (12.5)	
1+	–	–	1 (10.0)	–	
2	–	–	–	2 (25.0)	
3	–	–	1 (10.0)	1 (12.5)	
4	–	–	–	–	
VAS score	5 (0–9)	6 (0.8)	3 (0–6)	0 (0–7)	0.2327
SCIM score	6 (0–13)	7 (6–16)	46 (7–73)	43 (22–61)	0.8608

* The Fisher exact test compared the two groups across the categories (0 vs. ne 0) where ne = not equal

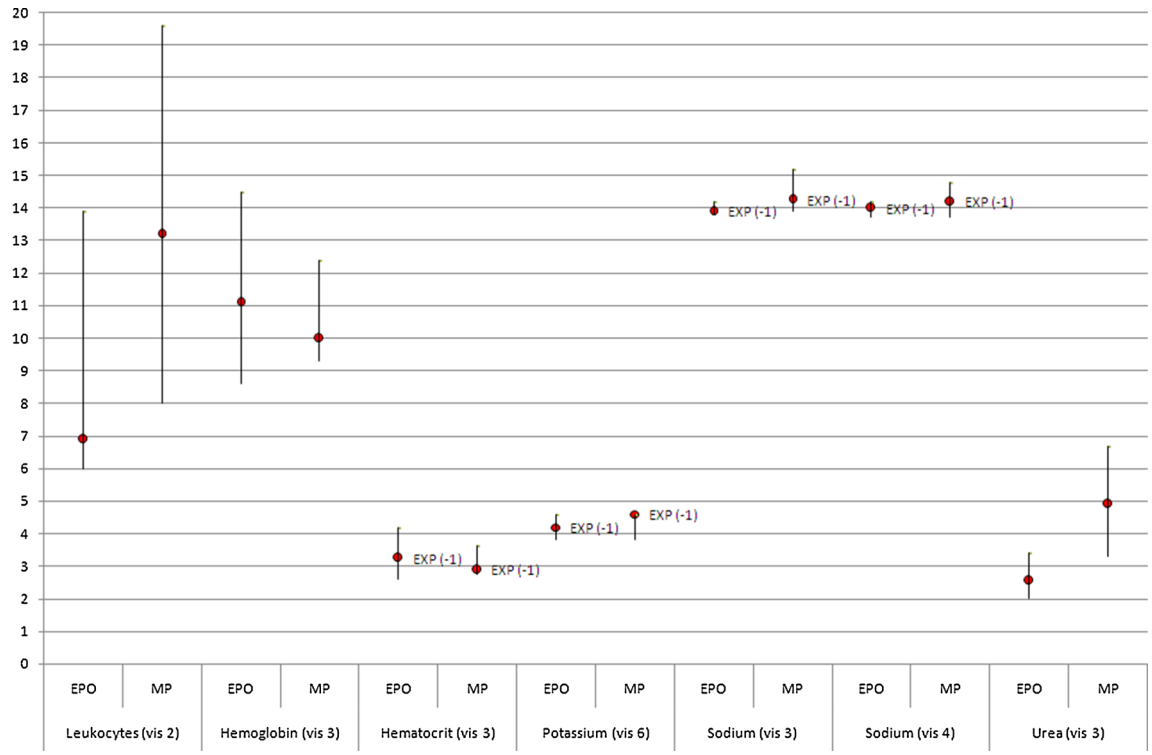

Fig. 2 Laboratory data with normative bounds

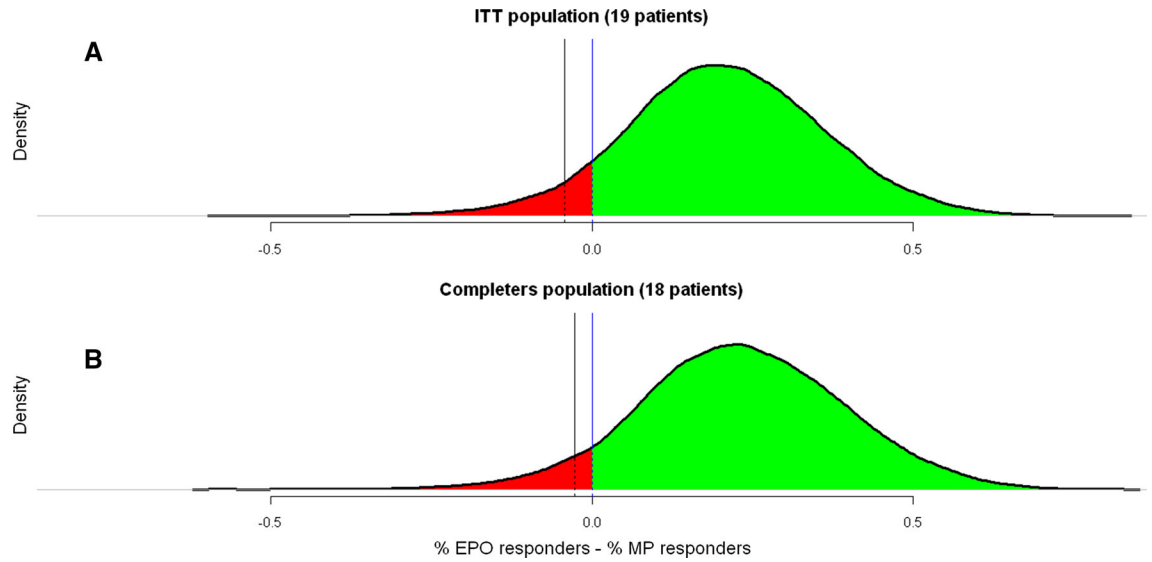

Fig. 3 Bayesian simulation on the primary end point. *Green area* EPO successes greater than MP successes, *red area* MP successes greater than EPO successes

Although the sample size was insufficient for the results to attain statistical significance, these results represent a 27 % absolute difference, in line with our power calculations. In addition, the Bayesian analysis confirmed a trend favoring EPO as an effective treatment.

The neuroprotective effects of EPO have been further confirmed by studies on various animal models [31]. The outcome of our study is positively supported by a recent phase II trial reporting beneficial effects of EPO treatment in the reduction of delayed ischemic deficits in patients with aneurysmal subarachnoid hemorrhage [32]. No safety concerns were identified also in this latter study.

To our knowledge, there is only one other randomized trial on the use of EPO in spinal cord injury. This study is

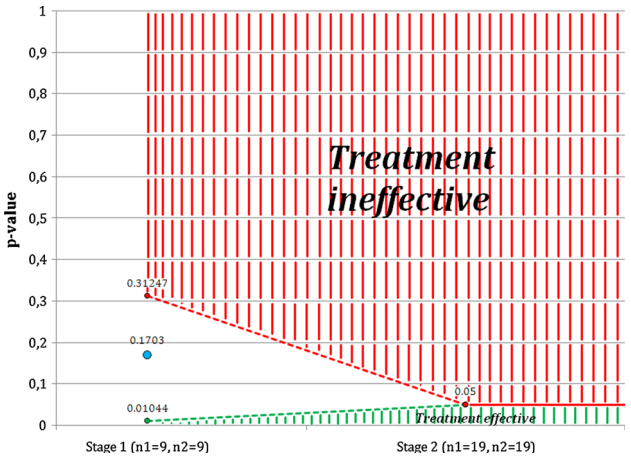

Fig. 4 Two-stage sequential design boundaries and regions of inefficacy (*red*) and efficacy (*green*). Our test statistic (*p* value Fisher exact test = 0.1703) fell in the uncertainty region. According to these results, if we had planned a two-stage sequential design, we would proceed till the end (2nd stage)

being conducted in Canada in patients with malignant spinal cord compression and paraparesis/paraplegia (http://www.clinicaltrial.gov—ClinicalTrials.gov Identifier: NCT00220675). The results of this study are pending.

Several preclinical studies have supported the neuroprotective effects of EPO treatment in various animal models of ischemic and non-ischemic injuries to CNS [33]. The extent of nerve fiber loss in spinal cord injury depends initially on the severity of the mechanical trauma, and is greatly amplified by a secondary phase (over days and weeks) of tissue injury involving fibers spared by the initial impact [34] and eventually leading to chronic demyelination [35].

The reported positive effects of EPO on recovery of function after experimental SCI are due to limitation of secondary damage, reduced inflammation, and axonal and myelin sparing with particular relevance to the monoaminergic pathways and reticulospinal system [36]. The observed recovery of function is likely secondary to plastic changes occurring in the cord below the injury contributing in an important manner in the re-expression of the locomotor ability, and spinal cord monoamines play an important role in such conditions [37].

Some limitations affect our study. First, patients' recruitment has not been completed, leaving the study insufficiently powered to attain statistically significant results with a frequentistic analysis, even in the presence of a clear difference between the two treatment groups on the primary end point. Selection criteria and therapeutic window were too restrictive to recruit a sizable sample within the time limits imposed. This problem must be considered if a new trial is implemented. Second, the benefit of treatments has been assessed over a 90-day period. This interval may also be critical as most patients may show spontaneous improvements and better rate of motor recovery during the first 3 months than at later time points [38]. Thus, a significant difference between the two treatment arms might have been later uncovered. Third, the validity of AIS within 8 h after injury can be questioned since this score may not provide an accurate detection of functional changes when the patient is still medically unstable as it occurs within the first 24 h after injury [39]. However, a measure of outcome at 72 h (as we did) may provide meaningful results. Although the psychometric properties of AIS are well defined [40], we did not test inter-rater agreement. However, a standardized outcome assessment was taught to the study participants during a pre-study meeting.

This was a single-blind trial, thus more positive attitudes of patients randomized to the experimental treatment might be expected. However, this bias was minimized by the use of concurrent controls receiving an active treatment. Even with these limitations, our study provides background and lessons for another confirmatory phase III trial comparing EPO to MP.

Acknowledgments The study was funded by the Italian Drug Agency (Agenzia Italiana del Farmaco), contract number FARM6Y35XMI.

Conflict of interest Ettore Beghi has received personal fees for board membership by VIROPHARMA and GSK; has received funding for travel and speaker honoraria from UCB-Pharma and GSK, for educational presentations from GSK; has received Grants for research activities from the Italian Drug Agency, Italian Ministry of Health, EISAI and the American ALS Association. Elisabetta Pupillo has received funding from the American ALS Association and Italian Ministry of Health for data management and data monitoring of an observational study protocol. She is receiving funding from Italian Drug Agency (AIFA) for data monitoring and study management of randomized clinical trial. Paolo Messina has received funding from Sanofi-Aventis, EISAI, Lombardy Region, and the American ALS Association for the data analysis and data management of RCT and observational study protocol. Paola Carignano, Davide Dalla Costa, Franco Faccioli, Alfredo Gorio, Cristina Pagliacci and Tiziana Redaelli: nothing to disclose.

References

1. Schwab ME (2002) Repairing the injured spinal cord. Science 295:1029–1031
2. Kakulas BA (2004) Neuropathology: the foundation for new treatments in spinal cord injuries. Spinal Cord 42:549–563
3. Faulkner JR, Herrmann JE, Woo MJ, Tansey KE, Doan NB, Sofroniew MV (2004) Reactive astrocytes protect tissue and preserve function after spinal cord injury. J Neurosci 24:2143–2155
4. Gorio A, Madaschi L, Di Stefano B et al (2005) Methylprednisolone neutralizes the beneficial effects of erythropoietin in experimental spinal cord injury. Proc Natl Acad Sci USA 102:16379–16384

5. Bottai D, Cigognini D, Madaschi L et al (2010) Embryonic stem cells promote motor recovery and affect inflammatory cell infiltration in spinal cord injured mice. Exp Neurol 223:452–463
6. Kakulas BA (1999) The applied neuropathology of human spinal cord injury. Spinal Cord 37:79–88
7. Windle WF, Clemente CD, Scott D Jr, Chambers WW (1952) Structural and functional regeneration in the central nervous system. AMA Arch Neurol Psychiatry 67:553–554
8. Fawcett J (2002) Repair of spinal cord injuries: where we are, where are we going? Spinal Cord 40:615–623
9. Pointillart V, Petitjean M, Wiart J, Lassie P, Thicoipe M, Dabadie P (2000) Pharmacological therapy of spinal cord injury during the acute fase. Spinal Cord 38:71–76
10. Coleman WP, Benzel E, Cahill D et al (2000) A critical appraisal of the reporting of the National Acute Spinal Cord Injury Studies (II and III) of methylprednisolone in Acute Spinal Cord Injury. J Spinal Cord 13:185–199
11. Bracken MB (2000) Pharmacological interventions for acute spinal cord injury. Cochrane Database Syst Rev 2000(2):CD001046
12. Hall ED, Braughler JM (1982) Glucocorticoid mechanisms in acute spinal cord injury: a review and therapeutic rationale. Surg Neurol 18:320–327
13. Gorio A, Gokman N, Erbayraktar S et al (2002) Recombinant human erythropoietin counteracts secondary injury and markedly enhances neurological recovery from experimental spinal cord trauma. Poc Natl Acad Sci USA 99:9450–9455
14. Vitellaro L, Mazzetti S, Maraschi L, Bosisio P, Gorio A, DeBiasi S (2007) Erythropoietin mediated preservation of the white matter in the spinal cord after traumatic injury. Neuroscience 144:865–877
15. Brines M, Cerami A (2006) Erythropoietin in spinal cord injury. Erythropoietin and the nervous system. Novel therapeutic options for neuroprotection. Springer, New York, pp 147–164
16. Bernaudin M, Marti HH, Roussel S et al (1999) A potential role for erythropoietin in focal permanent cerebral ischemia in mice. J Cereb Blood Flow Metab 19:643–651
17. Ehrenreich H, Weissenborn K, Prange H et al (2009) Recombinant human erythropoietin in the treatment of acute ischemic stroke. Stroke 40:e647–e656
18. Wang L, Chopp M, Gregg SR et al (2008) Neural progenitor cells treated with EPO induce angiogenesis through the production of VEGF. J Cereb Blood Flow Metab 28:1361–1368
19. Giese AK, Frahm J, Hübner R et al (2010) Erythropoietin and the effect of oxygen during proliferation and differentiation of human neural progenitor cells. BMC Cell Biol 11:94
20. Digicayloglu M, Lipton SA (2001) Erythropoietin mediated neuroprotection involves cross talk between jak-2 and NF-kB signaling 6 cascades. Nature 412:641–647
21. Lammertse D, Tuszynski MH, Steeves JD et al (2007) Guidelines for the conduct of clinical trials for spinal cord injury as developed by the ICCP panel: clinical trial design. Spinal Cord 45:232–242
22. American Spinal Injury Association, International Medical Society of Paraplegia (2002) International Standards for Neurological and Functional Classification of Spinal Cord Injury. American Spinal Injury Association, Chicago (Revised 2002)
23. Bracken MB, Shepard MJ, Holford TR et al (1997) Administration of methylprednisolone for 24 or 48 hours or tirilazad mesylate for 48 hours in the treatment of acute spinal cord injury. Results of the third national acute spinal cord injury randomized controlled trial. JAMA 277:1597–1604
24. Catz A, Hzkovich M, Agranov E, Ring H, Tamir A (1997) SCIM-Spinal Cord Independence Measure: a new disability scale for patients with spinal cord lesions. Spinal Cord 35:850–856
25. Bohannon RW, Smith MB (1987) Interrater reliability of modified Ashworth scale of muscle spasticity. Phys Ther 67:206–207
26. Penn RD, Savoy SM, Corcos D et al (1989) Intratecal baclofen for severe spinal spasticity. N Engl J Med 320:155–214
27. Wewers ME, Lowe NK (1990) A critical review of visual analogue scales in the measurement of clinical phenomena. Res Nurs Health 13:227–236
28. Marino RJ, Ditunno JF Jr, Donovan WH, Maynard F Jr (1999) Neurologic recovery after traumatic spinal cord injury: data from the Model Spinal Cord Injury Systems. Arch Phys Med Rehabil 80:1391–1396
29. Waters RL, Yakura JS, Adkins RH, Sie I (1992) Recovery following complete paraplegia. Arch Phys Med Rehabil 73:784–789
30. O'Brien PC, Fleming TR (1979) A multiple testing procedure for clinical trials. Biometrics 35:549–556
31. Sargin D, Friedrichs H, El-Kordi A, Ehrenreich H (2010) Erythropoietin as neuroprotective and neuroregenerative treatment strategy: comprehensive overview of 12 years of preclinical and clinical research. Best Pract Res Clin Anaesthesiol 24:573–594
32. My Tseng, Hutchinson PJ, Richards HK et al (2009) Acute systemic erythropoietin therapy to reduce delayed ischemic deficits following aneurysmal subarachnoid hemorrhage: a phase II randomized, double blind, placebo-controlled trial. J Neurosurg 111:171–180
33. Carelli S, Marfia G, Di Giulio AM, Ghilardi G, Gorio A (2011) Erythropoietin: recent developments in the treatment of spinal cord injury. Neurol Res Int 453179
34. Crowe MJ, Bresnahan JC, Shuman SL, Masters JN, Beattie MS (1997) Apoptosis and delayed degeneration after spinal cord injury in rats and monkeys. Nat Med 3:73–76
35. Totoiu MO, Keirstead HS (2005) Spinal cord injury is accompanied by chronic progressive demyelination. J Comp Neurol 486:373–383
36. Cerri G, Montagna M, Madaschi L et al (2012) Erythropoietin effect on sensorimotor recovery after contusive spinal cord injury: an electrophysiological study. Neuroscience 219:290–301
37. Rossignol S, Giroux N, Chau C, Marcoux J, Brustein E, Reader TA (2001) Pharmacological Aids to locomotor training after spinal cord injury in the cat. J Physiol 533:65–74
38. Fawcett JW, Curt A, Steeves JD et al (2007) Guidelines for the conduct of clinical trials for spinal cord injury as developed by the ICCP panel: spontaneous recovery after spinal cord injury and statistical power needed for therapeutic clinical trials. Spinal Cord 45:190–205
39. Steeves JD, Lammertse D, Curt A et al (2007) Guidelines for the conduct of clinical trials for spinal cord injury (SCI) as developed by the ICCP panel: clinical trial outcome measures. Spinal Cord 45:206–221
40. Furlan JC, Noonan V, Singh A, Fehlings MG (2011) Assessment of impairment in patients with acute traumatic spinal cord injury: a systematic review of the literature. J Neurotrauma 28:1445–1477