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ORIGINAL ARTICLE

A Clinical Trial of Progesterone for Severe Traumatic Brain Injury

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ABSTRACT

BACKGROUND

Progesterone has been associated with robust positive effects in animal models of traumatic brain injury (TBI) and with clinical benefits in two phase 2 randomized, controlled trials. We investigated the efficacy and safety of progesterone in a large, prospective, phase 3 randomized clinical trial.

METHODS

We conducted a multinational placebo-controlled trial, in which 1195 patients, 16 to 70 years of age, with severe TBI (Glasgow Coma Scale score, ≤8 [on a scale of 3 to 15, with lower scores indicating a reduced level of consciousness] and at least one reactive pupil) were randomly assigned to receive progesterone or placebo. Dosing began within 8 hours after injury and continued for 120 hours. The primary efficacy end point was the Glasgow Outcome Scale score at 6 months after the injury.

RESULTS

Proportional-odds analysis with covariate adjustment showed no treatment effect of progesterone as compared with placebo (odds ratio, 0.96; confidence interval, 0.77 to 1.18). The proportion of patients with a favorable outcome on the Glasgow Outcome Scale (good recovery or moderate disability) was 50.4% with progesterone, as compared with 50.5% with placebo. Mortality was similar in the two groups. No relevant safety differences were noted between progesterone and placebo.

CONCLUSIONS

Primary and secondary efficacy analyses showed no clinical benefit of progesterone in patients with severe TBI. These data stand in contrast to the robust preclinical data and results of early single-center trials that provided the impetus to initiate phase 3 trials. (Funded by BHR Pharma; SYNAPSE ClinicalTrials.gov number, NCT01143064.)

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Traumatic brain injury (TBI) is a major cause of death and disability, with large direct and indirect costs to society. In the United States, more than 1.7 million persons have a TBI annually,[1] and the annual burden of TBI has been estimated at more than $76 billion.[2] Globally, the incidence of TBI is increasing, particularly in developing countries.[3] Although in recent years there has been a heightened interest in mild TBI and concussion, the problem of more severe TBI remains substantial, despite improvements in trauma systems and critical care. Mortality rates of approximately 40% have been reported in a review of unselected observational studies.[4]

TBI is a progressive disorder, in which the primary injury initiates a complex sequence of biochemical and metabolic changes that lead to progressive tissue damage and cell death. These secondary events offer opportunities for therapeutic intervention. Multiple pathophysiological mechanisms are active in this complex disorder, with contusions, diffuse axonal injury, hemorrhage, and systemic insults occurring to varying degrees.[5,6] Potential therapeutic agents may need to target multiple mechanisms in order to be clinically effective.

Progesterone has been shown to have broad neuroprotective properties in multiple animal species and in a variety of models of neurologic injury. Multifactorial effects of progesterone include inhibition of inflammatory cytokines, reduced levels of inflammation-related factors, prevention of excitotoxicity, reduction of apoptosis, and control of vasogenic edema.[7-10] The progesterone receptor plays a key role in these neuroprotective effects.[11] A total of 20 research groups working with four species and 22 different models have found neuroprotective effects of progesterone in more than 180 experimental pharmacologic studies.[12] In addition, two phase 2 randomized, controlled clinical trials with progesterone showed a clinical benefit.[13,14] On the basis of these collective data, two phase 3 trials were initiated at around the same time: the Study of a Neuroprotective Agent, Progesterone, in Severe Traumatic Brain Injury (SYNAPSE) and the Progesterone for the Treatment of Traumatic Brain Injury (PROTECT III) trial.[15]

SYNAPSE, a trial sponsored by BHR Pharma, was designed to investigate the clinical effectiveness of progesterone, provided in a 6% soybean-oil emulsion as a ready-to-use formulation, under well-controlled conditions. The PROTECT III trial, funded by the National Institutes of Health, was conducted in parallel, but the study was halted on the basis of a futility analysis performed after 882 patients had undergone randomization. Here, we report the results of the completed SYNAPSE trial.

Methods

Study Design

We conducted a multinational, prospective, double-blind, parallel-group trial in which patients with severe TBI were randomly assigned to intravenous progesterone or placebo. Randomization was performed from July 2010 through September 2013. Patients were recruited at level 1 or equivalent trauma centers in 21 countries. The trial protocol (available with the full text of this article at NEJM.org) was approved by regulatory authorities in each country and by the local or regional ethics committee for each participating center. This report is consistent with the study design and procedures presented in the protocol.

Eligibility

A total of 10,519 male and female patients, 16 to 70 years of age, with severe nonpenetrating TBI were screened for eligibility at admission to the study hospitals. Eligibility criteria included a Glasgow Coma Scale (GCS) score, assessed after resuscitation, of 8 or less (on a scale from 3 to 15, with lower scores indicating a reduced level of consciousness), a Marshall classification score[16] of II or higher (on a scale from I to VI, with a score ≥II indicating visible pathologic changes or worse, as assessed on the basis of computed tomography [CT]), at least one reactive pupil, a body weight of 45 to 135 kg, initiation of treatment within 8 hours after injury, and a clinical indication for monitoring the intracranial pressure.

Patients were excluded if they had a GCS score of 3 and bilaterally fixed and dilated pupils, a life expectancy of less than 24 hours, prolonged or uncorrectable hypoxemia (partial pressure of arterial oxygen, <60 mm Hg), hypotension (systolic blood pressure, <90 mm Hg) at the time of randomization, spinal cord injury, pregnancy, only an isolated epidural hematoma, or coma that was suspected to be due primarily to other causes. A complete list of inclusion and exclusion criteria is provided in the Supplementary Appendix, available at NEJM.org.

Because all the potential participants were unconscious at the time of study entry, written informed consent was obtained from a legally acceptable representative before randomization, according to national regulations and ethics-committee requirements. In some countries, consent for participation was allowed to be provided by an independent physician.

STUDY PROCEDURES AND TREATMENTS

Randomization was implemented with the use of an interactive Web-based response system, with a block design of four stratified according to geographic region (Asia, Europe, North America, and South America). Patients were randomly assigned in a 1:1 ratio to receive progesterone or placebo. General treatment and the treatment of raised intracranial pressure were in accordance with published international guidelines.[17]

The study drugs (progesterone and placebo) were provided in 250-ml bottles with identical appearance, containing a lipid emulsion consisting of 6% soybean oil and 1.2% egg lecithin phospholipids, with the addition of 2.0 mg of progesterone per milliliter for the active treatment (BHR-100, Fresenius Kabi). Drug infusion was started intravenously with a loading dose of 0.71 mg per kilogram of body weight per hour for 1 hour, followed by 0.50 mg per kilogram per hour for 119 hours, through a dedicated peripheral intravenous catheter or dedicated lumen of a multilumen central catheter.

During the first 6 days, arterial blood gases, intracranial pressure, cerebral perfusion pressure, and therapeutic intensity levels (a score of all therapies used to control elevated intracranial pressure) were recorded. Standard laboratory assessments were performed on days 6 and 15, and a second CT study was scheduled to be performed on day 6. Patients were monitored for "neuroworsening," as defined by Morris et al.,[18] daily through day 15 (see the study protocol for definition of neuroworsening). Concurrent medications, surgeries, and adverse events were recorded for the first 15 days, and serious adverse events were recorded throughout the duration of the study; patients with such events were followed until resolution or for at least 6 months. Two follow-up visits were planned for 90 (±15) days and 180 (±30) days after injury, at which time the outcome measures were assessed.

Clinical data were collected through an electronic data-capture system with built-in data checks. All CT scans were reviewed and scored by a central reader.

OUTCOME MEASURES

The primary outcome measure was the Glasgow Outcome Scale (GOS) score at 6 months after the injury. The GOS and the Extended GOS (GOS-E) were administered with the use of a structured interview by a trained local staff member and were scored by the investigator according to the standardized approach.[19] The GOS captures information on the degree of recovery in terms of disability and handicap due to brain injury rather than impairment. The scale has five levels: death, vegetative state, severe disability, moderate disability, and good recovery; death and vegetative state were collapsed for the analysis in this study because they were considered to be equally undesirable.

Secondary outcome measures included the GOS score at 3 months, mortality at 1 month and 6 months, and the GOS-E score. The GOS-E differs from the GOS in that the three higher functional levels (severe disability, moderate disability, and good recovery) are each subdivided into a lower and upper category. Additional secondary outcome measures included changes in intracranial pressure, cerebral perfusion pressure, and therapeutic intensity levels, along with changes in intracranial pathologic findings as assessed on the CT scan obtained on day 6. The 36-Item Short-Form Health Survey (SF-36) scale was administered at 3 and 6 months to assess quality of life for those patients able to complete the scale.

STUDY OVERSIGHT

An independent data and safety monitoring board periodically reviewed blinded data. Staff from PRA Health Sciences and INC Research conducted onsite visits to assess protocol compliance and adherence to Good Clinical Practice guidelines and to perform data verification and query resolution. Medical monitors reviewed selected data centrally, and representatives of the sponsor regularly visited the study sites to monitor study compliance. The steering committee (see the Supplementary Appendix) assisted the sponsor with study design, data interpretation, and the development of the manuscript. Data management and statistical analysis was performed by PRA Health Sciences. Analyzable datasets were provided to the

steering committee for a check of analyses and further exploratory analyses. The decision to submit the manuscript for publication was made by the steering committee and was approved by the sponsor. The members of the steering committee vouch for the integrity of the data and analyses.

STATISTICAL ANALYSIS

We estimated that a sample of 1180 patients, with a 1:1 randomization ratio, would be required for the study to detect an odds ratio of 1.50, indicating an improvement in outcome (10% effect size) at the 1% significance level (two-sided). The sample-size estimation was based on the use of a proportional-odds model[20] to analyze the primary outcome variable (GOS score at 6 months after injury).

The analyses were performed on data from the modified intention-to-treat population, which excluded 16 patients who never received the study drug. This approach was agreed to by the Food and Drug Administration. In the proportional-odds analysis, covariate adjustment was performed for geographic region (Asia, Europe, North America, and South America) and the baseline values of age, GCS motor score (score of 1 or 2 vs. 3 vs. 4 vs. 5 or 6, on a scale from 1 to 6, with lower scores indicating a lower level of consciousness), pupillary response (bilateral response vs. unilateral response, no reactive pupils, or not testable), and Marshall classification (I or II vs. III vs. IV vs. V or VI).

As a secondary evaluation, efficacy was analyzed with the use of a sliding dichotomy[21] of the GOS outcome at 6 months. Baseline prognostic risk was calculated by means of the model developed by Hukkelhoven et al.,[22] and patients were then ranked according to prognostic risk and categorized into three groups on the basis of the prognosis (worst, intermediate, and best). The sliding dichotomy provides a means to assess each of the three prognostic groups individually instead of the entire group, increasing the sensitivity of the analysis. The analysis used a Cochran–Mantel–Haenszel chi-square test with adjustment for geographic region.

RESULTS

STUDY PARTICIPANTS AND DRUG LEVELS

Patients were recruited from July 2010 through September 2013, with the final 6-month visit occurring by the end of March 2014. A total of 1195 patients underwent randomization, with intravenous administration of progesterone initiated in 591 patients and placebo administered in 588 patients (the modified intention-to-treat population); 16 patients were excluded because they did not receive the assigned study drug. Of the 1179 patients in the modified intention-to-treat population, 96.0% were followed for 6 months or died before 6 months (Fig. 1). There were no meaningful protocol violations. After centralized assessment of CT scans, less than 1% of the patients who had undergone randomization were in Marshall classification I (i.e., no radiologically significant abnormality on baseline CT).

Baseline characteristics, including GCS overall score and motor score, Marshall classification, and pupillary reactivity, were similar in the two groups (Table 1). Drug-level assessment was performed 2 days after the initial dosing. Progesterone treatment resulted in a median progesterone level of 333.5 ng per milliliter (interquartile range, 268.9 to 405.7; 1061 nmol per liter [interquartile range, 855 to 1290]); this value was similar to the mean level obtained in the phase 2 PROTECT trial (347 ng per milliliter [1103 nmol per liter]), which provided the early support for the current trial. Drug levels in the cerebrospinal fluid were not monitored.

CLINICAL OUTCOMES

The primary end point, the GOS score at 6 months, did not differ significantly between the progesterone group and the placebo group (Table 2). The proportional-odds model revealed no effect of progesterone treatment in either unadjusted or adjusted analyses (adjusted odds ratio, 0.96; 95% confidence interval [CI], 0.77 to 1.18). The proportion of patients with an overall favorable outcome (good recovery or moderate disability) on the GOS was 50.4% in the progesterone group and 50.5% in the placebo group. The proportion of patients who were in a vegetative state or who died was also similar in the two groups: 22.2% in the progesterone group and 22.3% in the placebo group (Table S1 in the Supplementary Appendix). The GOS-E also did not reveal significant differences between the two study groups at 3 or 6 months.

SECONDARY OUTCOMES

The sliding dichotomy, which relates outcome to baseline prognostic risk, revealed no significant differences between progesterone treatment and

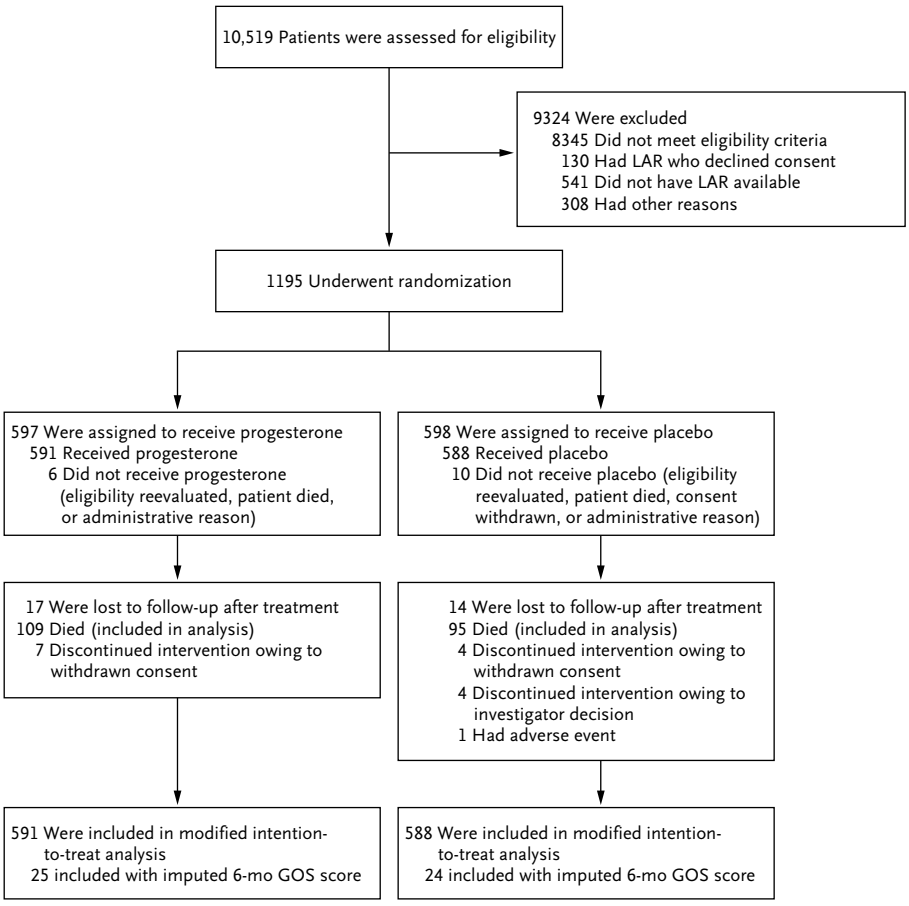

Figure 1. Study Enrollment, Randomization, and Follow-up of the Patients.

The modified intention-to-treat population excluded 16 patients (6 patients in the progesterone group and 10 in the placebo group) because they did not receive any study drug. A total of 31 patients (17 patients in the progesterone group and 14 in the placebo group) were lost to follow-up. A total of 204 patients (109 patients in the progesterone group and 95 in the placebo group) died before 6 months of follow-up. Data on 1179 patients were included in the efficacy analysis. Missing values were first imputed by carrying forward the Glasgow Outcome Scale (GOS) assessment at month 3. If a participant did not have a GOS score at 3 or 6 months, the missing value was imputed with the use of the proportional-odds model. LAR denotes legally acceptable representative.

placebo (Fig. 2). This approach showed no indication of efficacy in the groups based on prognosis (worst, intermediate, and best) (Table S2 in the Supplementary Appendix shows results of analyses of baseline prognostic factors). The subgroup analyses according to Marshall classification, decompressive craniectomy (yes vs. no), any other surgery (yes vs. no), and isolated head injury versus multiple trauma showed no significant odds ratios (Table 2). Cerebral perfusion pressure and therapeutic intensity levels did not differ significantly between the progesterone group and the placebo group (Tables S3 and S4 in the Supplementary Appendix). Data on the SF-36, which were available for a total of 723 patients at 6 months (74.2% of survivors), revealed no significant differences in physical or mental composite summary scores.

ADVERSE EVENTS

The distribution of adverse events is shown in Table 3. There were no significant differences in the rate of adverse events between progesterone treatment and placebo.

DISCUSSION

Our results do not support the hypothesized superiority of progesterone treatment over placebo in patients with severe TBI, as assessed by means of the GOS or mortality. TBI is a complex, heterogeneous disorder, in which the primary injury initiates a variety of secondary injury cascades. These cascades involve various processes that may not be responsive to monotherapy, as has been shown by the failure of previously studied monotherapies that have targeted single receptors or specific mechanisms,[23,24] despite considerable supportive experimental data. Systemic and extraneuronal effects of trauma also require consideration with respect to their effect on mortality

Table 1. Baseline Characteristics of the Modified Intention-to-Treat Population.*

Characteristic	Progesterone (N=591)	Placebo (N=588)
Age — yr		
Median	35	34
Interquartile range	23–51	24–50
Male sex — no. (%)	464 (78.5)	463 (78.7)
Geographic region†		
Asia	62 (10.5)	58 (9.9)
Europe	279 (47.2)	277 (47.1)
North America	219 (37.1)	220 (37.4)
South America	31 (5.2)	33 (5.6)
Cause of injury — no. (%)		
Motor vehicle or motorcycle accident	369 (62.4)	364 (61.9)
Fall	124 (21.0)	142 (24.1)
Sports or recreation accident or other event	98 (16.6)	82 (13.9)
Glasgow Coma Scale score — no. (%)‡		
Overall score		
3	52 (8.8)	64 (10.9)
4–6	262 (44.3)	276 (46.9)
7 or 8	276 (46.7)	248 (42.2)
Data missing	1 (0.2)	0
Motor score		
1–3	213 (36.0)	241 (41.0)
4–6	376 (63.6)	345 (58.7)
Data missing	2 (0.3)	2 (0.3)
Pupillary response — no. (%)		
Both reacting	480 (81.2)	475 (80.8)
One reacting	109 (18.4)	107 (18.2)
Other or untestable	2 (0.3)	6 (1.0)
Marshall classification — no. (%)§		
I	6 (1.0)	4 (0.7)
II	235 (39.8)	233 (39.6)
III or IV	213 (36.0)	199 (33.8)
V or VI	134 (22.7)	151 (25.7)
Data missing	3 (0.5)	1 (0.2)

Table 1. (Continued.)

Characteristic	Progesterone (N=591)	Placebo (N=588)
Traumatic subarachnoid hemorrhage — no. (%)¶	449 (76.0)	456 (77.6)
Confirmed or suspected hypoxemia — no. (%)‖	52 (8.8)	45 (7.7)
Confirmed or suspected hypotension — no. (%)**	93 (15.7)	78 (13.3)
Time from injury to first dose		
Median	7 hr 4 min	7 hr 2 min
Interquartile range	6 hr 0 min to 7 hr 45 min	5 hr 53 min to 7 hr 45 min

* There were no significant between-group differences at baseline.
† Geographic regions were defined as follows: Asia included China, Malaysia, Singapore, Taiwan, and Thailand; Europe included Austria, Belgium, the Czech Republic, Finland, France, Germany, Hungary, Israel, Italy, the Netherlands, and Romania; North America included the United States; and South America included Argentina.
‡ Overall scores on the Glasgow Coma Scale range from 3 to 15, with lower scores indicating a reduced level of consciousness. Motor scores range from 1 to 6, with lower scores indicating a reduced motor response.
§ The Marshall classification is based on a review of CT scans, with a score of I indicating normal findings, II indicating diffuse injury, III or IV indicating radiologic signs of elevated intracranial pressure, and V or VI indicating a mass lesion.
¶ Data were missing for 4 patients in the progesterone group and for 1 in the placebo group.
‖ Hypoxemia was defined as a partial pressure of arterial oxygen of less than 60 mm Hg. Data were missing for 16 patients in the progesterone group and for 22 in the placebo group.
** Hypotension as defined as a systolic blood pressure of less than 90 mm Hg. Data were missing for 14 patients in the progesterone group and for 12 in the placebo group.

among patients with TBI.[25] These complex injury mechanisms suggest that a successful therapeutic agent should influence several mechanisms rather than a single cascade.

On the basis of the experimental data, progesterone would appear to be an appropriate candidate for this pluripotential role, having been shown to prevent inflammation by inhibiting the production of inflammatory cytokines (e.g., tumor necrosis factor α), as well as by reducing levels of inflammation-related factors such as complement factor C3 fragments and inhibiting the activation of microglial cells. In addition, progesterone has been shown to prevent excitotoxicity and limit apoptosis by preventing biochemical insults, such as calcium (Ca^{2+}) flux and nitric oxide production, and by decreasing levels of caspase 3. Finally, progesterone has also been shown to limit vasogenic edema through reconstitution of the blood–brain barrier and modulation of the aquaporin-4 water transporter.[26]

Preliminary clinical data obtained with the use of various progesterone formulations and routes of delivery, combined with experimental data showing adequate brain penetration, provided initial support for a neuroprotective role of progesterone in TBI. The initial PROTECT trial[13] recruited 100 patients from a single site who had a GCS score of 4 to 12. Treatment was initiated within 11 hours after injury, with a 72-hour treatment duration, and was associated with a reduction in the rate of death from any cause, as compared with placebo (13.0% vs. 30.4%; relative risk, 0.43; 95% CI, 0.18 to 0.99). A similar single-site trial[14] in China recruited 159 patients who had a GCS score of 8 or lower. Progesterone treatment, which was initiated within 8 hours after injury by means of intramuscular injection, with a 120-hour treatment duration, was associated with reduced mortality, as compared with placebo (18% vs. 32%, P=0.04). The time windows and duration of treatment in SYNAPSE were based largely on these two studies.

The long history of failed TBI trials, including the current trial, is probably due to several factors, including the complexity and variability of the injury and the fact that multiple direct and indirect injury mechanisms are at work simultaneously. There may also be insensitivity of the available outcome measures. The lack of mechanistic early end points and the absence of reliable biomarkers to guide clinical development and inform clinical-trial design may be considered to be major obstacles to the development of neuroprotective agents for TBI. In addition, current approaches to the characterization of TBI are mainly unidimensional (based on GCS scores or Marshall classification) and do not permit

Table 2. Results of Efficacy Analysis in the Modified Intention-to-Treat Population.*

Outcome	Progesterone (N = 591)	Placebo (N = 588)	Odds Ratio (95% CI)
Primary efficacy analysis — no. (%)†			0.96 (0.77–1.18)
Dead or vegetative state	131 (22.2)	131 (22.3)	
Severe disability	162 (27.4)	160 (27.2)	
Moderate disability	109 (18.4)	114 (19.4)	
Good recovery	189 (32.0)	183 (31.1)	
Subgroup analyses — no.‡			
Geographic region			
Asia	61	56	1.35 (0.65–2.80)
Europe	267	265	0.81 (0.58–1.14)
North America	208	210	1.36 (0.93–2.00)
South America	30	32	0.46 (0.17–1.27)
Marshall classification			
I or II	221	222	1.01 (0.69–1.49)
III or IV	205	192	0.95 (0.64–1.41)
V or VI	130	145	0.94 (0.58–1.53)
Decompressive craniectomy			
Yes	132	97	0.86 (0.50–1.48)
No	434	466	1.10 (0.84–1.42)
Surgery			
Yes	401	377	0.93 (0.70–1.23)
No	175	186	1.11 (0.73–1.69)
Injury			
Head injury alone	77	65	0.81 (0.42–1.57)
Multiple trauma	489	498	1.04 (0.81–1.33)
Time to first dose			
≤6 hr	144	157	1.31 (0.83–2.07)
>6 hr	422	406	0.92 (0.70–1.21)

* CI denotes confidence interval.
† The primary analysis was performed as a proportional-odds analysis with adjustment for the following baseline variables: geographic region, age, Glasgow Coma Scale motor score, pupillary response, and Marshall classification. The unadjusted analysis yielded similar results (odds ratio, 0.98; 95% CI: 0.79 to 1.21).
‡ Subgroup analyses were restricted to patients with complete outcome data at 6 months, and treatment effects were analyzed according to the dichotomized Glasgow Outcome Scale (favorable vs. unfavorable). An odds ratio of more than 1.00 represents a benefit of active treatment; the results of the unadjusted analysis are presented.

appropriately targeted therapy. Multidimensional approaches are needed for better characterization of TBI in order to facilitate individualized treatment.[27]

Limitations in the ability to translate experimental data to the context of TBI in humans may also have contributed to the trial failures. A more systematic approach appears to be necessary to advance therapeutics in TBI. The basic science consortium approach currently under way, as a part of the Combat Casualty Care Research Program entitled Operation Brain Trauma Therapy Consortium, may be one improvement in drug-candidate selection.[28]

In conclusion, our data indicate that progesterone, as administered in this trial, had no clinical benefit in the treatment of severe TBI. The negative result of this study, combined with the results of

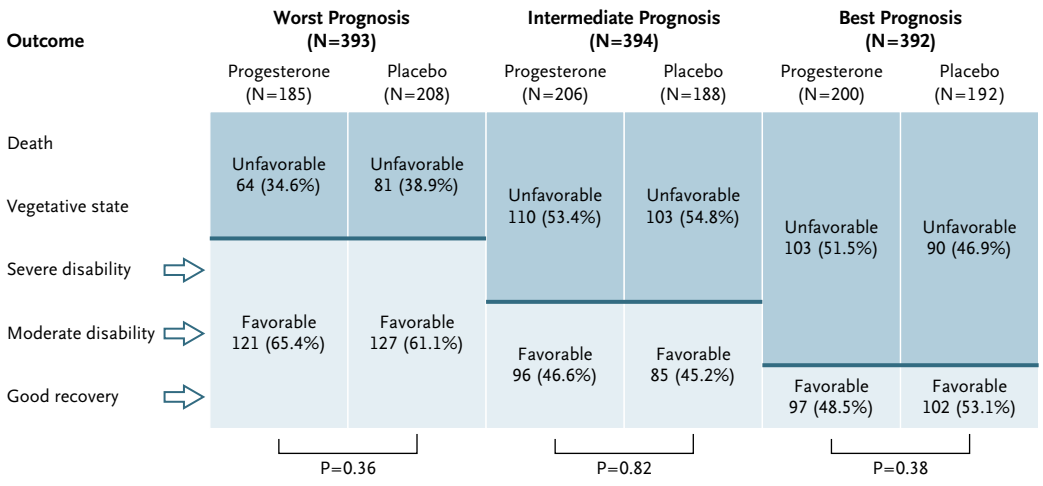

Figure 2. Efficacy Analysis with the Use of a Sliding Dichotomy Approach.

In the sliding dichotomy approach, the GOS was dichotomized for analysis, but the split for dichotomy was differentiated according to the baseline prognostic risk. Prognostic groups (based on worst, intermediate, and best prognosis)[22] were defined by baseline prognostic factors that included age, Glasgow Coma Scale motor score (1 or 2 vs. 3 vs. 4 vs. 5 or 6; scores range from 1 to 6, with lower scores indicating reduced motor response), pupillary response (bilateral response vs. unilateral response, no reactive pupils, or not testable), presence or absence of hypoxemia, presence or absence of hypotension, Marshall's classification (I or II vs. III vs. IV vs. V or VI), and presence or absence of traumatic subarachnoid hemorrhage. The Marshall classification is based on a review of CT scans; scores range from I to VI, with a score of II or higher indicating visible pathologic changes or worse. The arrow indicates the split for sliding dichotomy differentiated according to prognostic risk. P values were based on a Cochran–Mantel–Haenszel chi-square test with adjustment for geographic region (Asia, Europe, North America, and South America).

Table 3. Adverse Events in the Safety Population, According to Organ Class and Preferred Term.*

Event	Progesterone (N=596)		Placebo (N=583)	
	no. of patients (%)	*no. of events*	*no. of patients (%)*	*no. of events*
Any event	582 (97.7)	4025	570 (97.8)	4018
Blood or lymphatic system disorder	194 (32.6)	259	211 (36.2)	282
Cardiac disorder	133 (22.3)	159	129 (22.1)	157
Endocrine disorder	44 (7.4)	45	52 (8.9)	54
Gastrointestinal disorder	184 (30.9)	235	186 (31.9)	254
Infection or infestation	389 (65.3)	599	400 (68.6)	604
Pneumonia	208 (34.9)	221	222 (38.1)	239
Sepsis	46 (7.7)	48	40 (6.9)	40
Urinary tract infection	28 (4.7)	30	36 (6.2)	36
Nervous system disorder	266 (44.6)	450	246 (42.2)	389
Brain edema	32 (5.4)	34	28 (4.8)	30
Intracranial pressure increased	130 (21.8)	196	137 (23.5)	163

* The safety population included all participants who underwent randomization and received at least one dose of the study drug. The specific adverse events listed are those that occurred during treatment in more than 5% of all the study patients.

the PROTECT III trial,[15] should stimulate a rethinking of procedures for drug development and testing in TBI.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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