Recombinant Human Coagulation Factor VIIa for Intracerebral Hemorrhage: Miracle Drug or Irrational Exuberance?

Science Times Editorial

The human recombinant Factor VIIa (rF-VIIa), marketed as Novo Seven, was approved by the United States Food And Drug Administration (FDA) in 1999 for the treatment of bleeding episodes in patients with hemophilia A and B, and inhibitors to Factor VIII or Factor IX. These indications were expanded in 2005 for surgical procedures in patients with hemophilia A or B and inhibitors, and the treatment of bleeding episodes in patients with Factor VII deficiency. The use of the drug in hospitalized patients has increased steadily since its approval, from less than 350 cases in 2000, to more than 4500 cases in 2004. The International Classification of Diseases, Ninth Revision (ICD-9) codes associated with this use also expanded markedly from less than 20 diagnoses in 2000, to nearly 100 different diagnoses in 2004. Much of this expanded use has been for “off-label” indications including massive hemorrhagic complications in non-hemophiliacs, with or without associated coagulopathy. Yet little is known about the effectiveness or complications of the drug in those settings.

O’Connell and colleagues, from the Center of Biologics Evaluation and Research of the FDA in Rockville, Maryland recently analyzed serious thromboembolic events reported to the FDA in association with rF-VIIa since its approval in March 1999 through December 2004 (5). The voluntary reporting system identified 168 case reports of 185 thromboembolic events. Of these, only 17 events occurred in hemophilic patients (approved indications), 59 cases occurred in approved postlicensure trials (all non-hemophiliacs), and 151 reports in other off-label uses (115 with active bleeding). The complications included cerebrovascular accidents, myocardial infarctions, pulmonary embolism, and other arterial, venous, and device occlusions. The thromboembolic complications were the cause of death in 36 (72%) of 50 reported deaths. The authors emphasize that voluntary reporting often vastly underestimates the true prevalence of the problem. The clear implication of the article is a sober expression of concern about associations associated with the off-label use of the drug.

The use of rF-VIIa has been advocated as a compassionate intervention in life-threatening intracranial bleeds, resulting in dramatically rapid and effective correction of coagulopathy from Coumadin and other causes, where the outcome is dismal with currently available therapies (1–3). At our own institution, we currently use the drug in compassionate indications for rapid correction of coagulopathy (mostly Coumadin related) in patients with expanding intracranial bleeds associated with neurologic deterioration, or where urgent surgical intervention is indicated. Often, a single dose of 40 microg/Kg dramatically corrects the coagulopathy in minutes, allowing stabilization of clot expansion and safe neurosurgical intervention, while fresh frozen plasma, vitamin K and other products are administered for subacute maintenance of normal coagulation. Recent Phase II trial of rF-VIIa administered within 4 hours in noncoagulopathic patients with intracerebral hemorrhage, was terminated prematurely because of dramatic and significant benefits of the drug as compared to placebo (4). A Phase III trial for that indication is currently underway.

So what does the paper by O’Connell, et al. imply with regard to emerging uses in neurosurgical patients? Does the enthusiasm for rF-VIIa in intracranial hemorrhage reflect premature and irrational exuberance? As usual, the truth lies in the detailed analysis of data, and not in the broad headlines. The 168 cases of thromboembolic complications reported by O’Connell, et al, included only 24 cases with drug administration for intracranial bleeding. Of these, 19 cases were within a clinical trial setting. Among 115 cases of thromboembolic events after off-label rF-VIIa administration for active hemorrhage, only 5 cases (4%) were for intracranial bleeding. So any runaway administration of the drug and concern about serious complications, highlighted by O’Connell, et al., mostly reflected non-neurosurgical off-label uses. These consisted of bleeding in cardiac and liver surgery, other bleeding and trauma. The vulnerability of those patients to thromboembolic complications, systemic activation of procoagulants, and risk benefit considerations vis-a-vis other available options, are likely very different from patients with intracranial hemorrhage. We raise a caution in return, in interpreting the O’Connell study, against “throwing the baby out with the bath water.”

We still need to be concerned about thromboembolic complications in neurosurgical patients who may receive rF-VIIa. The O’Connell study did not report an incidence of complications. Complications are known in noncoagulopathic patients with intra-cerebral hemorrhage enrolled in the Phase II trial by Mayer, et al (4). In that blinded placebo controlled dose escalation trial, thromboembolic complications occurred in 2% of placebo cases and 7% of patients receiving rF-VIIa in doses of 40 to 160 microg/kg, with greater incidence in the higher dose strata. This adverse drug effect was offset by the powerful and statistically significant benefit reflected in 25% relative reduction in final intracerebral hematoma volume, and 35% relative reduction in mortality in treated patients. The O’Connell study did not address such critical risk benefit considerations (what would have happened if the drug was not given), nor did it distinguish between causation and association (if complications would have occurred in the setting of illness or reversal of coagulopathy, regardless of rF-VIIa use).

The prevalence of thromboembolic events may be higher in cases where the drug is used in coagulopathic patients, especially in cases on Coumadin, where there may be underlying disease predisposing to thromboembolic risk. We echo the strong caution about the use of this drug in patients at known high risk for thromboembolism (coronary, carotid or other severe arterial occlusive disease, cardiac thrombus, hypercoagulability, metal prosthetic values, etc). Off-label use, outside ongoing clinical trials, should continue to be reserved for truly compassionate indications, where the risk of not using the drug is known to be truly dire. A clinical trial may not be ethical in cases where the drug works so dramatically, and mortality is so high with other available alternative treatments. But registries or non-placebo controlled trials will still be possible, and are strongly urged to refine indications, confirm effectiveness, and to truly adjudicate complication rates.

References:

Break out the Magnesium Sulfate in Aneurysmal Subarachnoid Hemorrhage?

In contrast to thromboembolic stroke, the interval between initial hemorrhage and the onset of cerebral vasospasm provides an opportunity for preventative therapy with neuroprotective agents. Considering that hypomagnesemia occurs in roughly half of all patients with aneurysmal subarachnoid hemorrhage (aSAH), and that magnesium is readily available, inexpensive, and has a well-established pharmacological profile, demonstrating even a small absolute benefit of magnesium supplementation would lead to substantial cost saving for health care services and significantly impact postoperative management in this patient population. Magnesium inhibits the release of excitatory amino acids, blocks the NMDA glutamate receptor, and acts as a noncompetitive calcium antagonist with a dilatory effect on cerebral arteries. While magnesium has been shown to be neuroprotective in numerous animal stroke models by reversing vasospasm, lowering ischemic depolarization time, and reducing infarct volume, retrospective clinical investigations by Veyna and colleagues failed to detect a difference in the incidence of cerebral vasospasm between aSAH patients administered magnesium supplementation postoperatively with those who did not. As a result, there continues to be much uncertainty about the role of magnesium in the postoperative management of this condition.

Given the importance of cerebral vasospasm as a cause of morbidity and mortality after aSAH, van den Bergh and colleagues (and the MASH Study Group) conducted a randomized controlled trial to investigate the impact of magnesium sulfate in this patient population (Stroke 36:1011–1015, 2006). In this double-blind, placebo-controlled, multi-institutional clinical trial, patients with aSAH were randomized within four days of the initial ictus to receive either magnesium sulfate supplementation (goal serum level 1.0–2.0 mmol/L) or placebo therapy. Patients with aSAH were enrolled. The authors found magnesium therapy in post-aSAH patients. Further-outcome measures included “poor outcome” (Rankin >3) and “excellent outcome” (Rankin 0). A total of 283 patients were enrolled. The authors found magnesium treatment reduced the risk of DCI by 34% and lowered the risk of poor outcome at 3 months by 23%. At the time of trial completion, 18 patients in the treatment group and 6 in the placebo group had an excellent outcome (risk ratio, 3.4). Based on these findings, the authors state that although it appears magnesium may play a role in preventing DCI and subsequent poor outcome, their results are not yet definitive.

Interestingly, the recently published results of the Intravenous Magnesium Efficacy in Stroke (IMAGES) trial showed that magnesium given within 12 hours of acute stroke did not reduce the risk of poor outcomes (The Lancet 363:439–445, 2004). However, given the delayed course of cerebral ischemia following aSAH, it may be possible to prevent secondary ischemic damage with extended use of magnesium sulfate. It is also important to realize the beneficial effect of magnesium may overlap with that of the routinely administered calcium channel antagonist nimodipine. Since the biological activity of nimodipine and magnesium are similar, and nimodipine has already been shown to reduce the proportion of patients with poor outcome and ischemic neurological deficits following aSAH, the protective actions of magnesium by itself may have been underestimated in this study.

Regardless, the results of this trial have important clinical implications by suggesting a potential role for magnesium therapy in post-aSAH patients. Furthermore, this study emphasizes the importance of funding a highly powered phase III clinical trial with functional recovery as the primary endpoint, as prevention of DCI is only an indirect measure for the beneficial effects of magnesium supplementation.

Ricardo J. Komotar, M.D.
E. Sander Connolly, Jr., M.D.
Technical & Clinical Research

Flipping the Switch: Turning an Embryonic Stem Cell into a Functional Dopamine Neuron

The full-programmed sequence of events that leads to the generation of midbrain dopaminergic neurons has not previously been elucidated. Understanding the sequence of gene activations that lead to the production of dopaminergic neurons would be of tremendous utility in trying to engineer stem-cell based therapies for Parkinson’s disease. In the recent issue of Cell (124, 393–405, 2006) Andersson et al., from the Karolinska Institute in Sweden, report on two homeodomain (HD) proteins, Lmx1a and Mlx1, which function as determinants of midbrain dopamine neurons.

Early induction events in the ventral midbrain are known to involve the expression and signaling of Sonic hedgehog (Shh) by ventral midline cells and the activity of fibroblast growth factor 8 (FGF8). The elements downstream of Shh and upstream of transcription factors influencing the maturation of dopamine neurons until now were never identified. The authors utilized E10.5 mouse embryo cDNA as a template to screen for HD-encoding transcripts by PCR (polymerase chain reaction). This approach combined with a large-scale in situ hybridization screen identified Lmx1a and Mlx1as transcription factors with relevant expression patterns. They show that these transcripts were appropriately expressed both temporally and spatially and were dependent upon Shh signaling. Using a retroviral vector harboring Lmx1a cDNA, they induced ectopic dopamine neurons in the chick midbrain, and using siRNA were able to knock down expression in the midbrain and drastically reduce the number of post-mitotic dopamine neurons. The authors then inserted these genes into expression vectors that were transfected into mouse embryonic stem cells. While control vectors generated post-mitotic neurons without any tyrosine hydroxylase (TH) expression, transfection with the Lmx1a vector expressed TH after 8 days in culture. Embryonic stem cell derived dopamine neurons (Lmx1a(−)/Mlx1a(+)) may soon represent an important cell-based therapy for Parkinson’s disease, using a more focused and sophisticated approach than early attempts at neurotransplantation for this disease.

Jeffrey P. Greenfield, M.D., Ph.D.
John A. Bookvar, M.D.
Stem Cell Research

GABA Regulates Synaptic Integration of Newly Generated Neurons in the Adult Brain

While dentate gyrus neurogenesis is now well-recognized in the adult mammalian brain, the mechanisms by which newly generated neurons integrate into local brain circuitry are poorly understood. A recent study published in Nature (439: 589–593, 2006) provides insight into this process. Ge and colleagues at Johns Hopkins used a green fluorescent protein retroviral labeling strategy to identify and electrophysiologically record from newly generated dentate granule cell (DGC) neurons in the young adult rodent brain. The authors found that new DGCs require the presence of tonic levels of GABA (gamma-aminobutyric acid) that acts in depolarizing fashion to facilitate dendritic development. Following these initial effects of extracellular GABA, there is sequential development of GABAergic and then glutamatergic synaptic inputs onto the DGCs.

The initial depolarizing GABA response is due to the high intracellular chloride level found in the immature DGCs. This in turn results from high expression in early neuronal development of the Na+/K+/Cl- cotransporter, NKCC1. The authors used short hairpin RNAs generated against NKCC1 to inhibit the early GABA mediated hyperpolarizing response in newly generated DGCs. Subsequent dendritic arborization and GABAergic and glutamatergic synaptic activity were impaired.

These findings provide evidence that that newly generated DGCs respond to local ambient concentrations of GABA to initially develop the dendritic organization that is necessary for subsequent inhibitory and excitatory synaptic formation. These results are relevant for a number of human pathologies, particularly epilepsy. In animal models of limbic epilepsy, seizures strongly trigger DGC neurogenesis. The newly generated neurons both develop in the dentate gyrus and also migrate aberrantly into the dentate hilus, where they can form pathological synaptic connections with CA3 pyramidal neurons. Unraveling the mechanisms of DGC integration into the normal hippocampus may help understand the pathological neurogenic processes that occur in the epileptic hippocampus. This mechanism may be used to enhance integration of implanted stem cells in the human brain, or to modify local milieu for treatment of epilepsy and other disorders.

Guy M. McKhann II, M.D.
Epilepsy Research

STEM CELL RESEARCH

NEUROSURGERY’S Science Times

Continues N7
Clinical Practice Guidelines and Quality of Care for Older Patients With Multiple Morbid Diseases

Although supporting evidence is sparse, the use of clinical practice guidelines has been touted as a means to improve the quality of care for many patients. In addition, physician adherence to guidelines recommendations is the most commonly suggested mechanism for determining the quality of care in pay for performance schemes. Significant concerns have been raised about the applicability of clinical guidelines recommendations to surgical care. Boyd and colleagues now raise similar concerns about the applicability of guidelines in the care of elderly patients with multiple, chronic diseases (JAMA 294: 716–724, 2005).

The purpose of this study is to evaluate the applicability of patient care guidelines in such patients. The authors selected nine of the 15 most common chronic diseases (hypertension, heart failure, angina, atrial fibrillation, hypercholesterolemia, diabetes, osteoarthritis, chronic obstructive pulmonary disease and osteoporosis) and reviewed clinical practice guidelines published by national and international organizations for each of them. They evaluated whether or not published guidelines addressed applicability in older patients and patients with multiple medical problems and whether or not they considered the issues of goals of treatment, interactions among recommendations, burden to patients and caregivers, patient preference, life expectancy and quality of life. Finally, the investigators examined the feasibility of following published guidelines recommendations for a hypothetical 79 year old patient with chronic obstructive pulmonary disease, diabetes, osteoporosis, hypertension and osteoarthritis.

The authors found that most clinical guidelines did not consider the applicability of their recommendations for older patients with multiple diseases. Neither did they comment on the burden to patients and caregivers that adherence to guideline would entail, what short and long term treatment goals were to be achieved or how the guidelines recommendations would affect quality of life. Application of published guidelines recommendations for their hypothetical patient would have resulted in prescribing 12 medications with a very complex regimen of care. Their conclusion was that adhering to published guidelines recommendations for older patients with numerous medical problems would likely have many undesirable effects. Furthermore, determining the quality of care based on adherence to clinical guidelines would lead to inaccurate conclusions about the quality of care provided and would create perverse incentives that diminish the quality of care and quality of life for these patients.

The National Guidelines Clearinghouse now lists more than 1500 active clinical practice guidelines and it is somewhat troubling that there is a good deal of variability among guidelines recommendations when multiple guidelines exist for a given condition. Such variability limits the use of the recommendations from any one document as an indicator of quality of care. At their best, clinical guidelines enumerate potentially beneficial options for patient care and thus support rational clinical decision making. It has been difficult, however, to document improved outcomes from the application of clinical guidelines recommendations. The algorithm of evidence based medicine seems to work better in theory than in practice.

The evidence base on which clinical guidelines rest is determined by the quality and applicability of the clinical trials. Because of the profound limitations of many prospective, randomized trials in neurosurgery (non-representative patient and surgeon selection, cross-overs and non-blinded evaluation of unclear endpoints) 1 question whether any neurosurgical guidelines can be applied in a meaningful way to the majority of neurosurgical practices. Using clinical guidelines recommendations as quality indicators and holding physicians accountable for many, sometimes contradictory, process measures of quality based on these guidelines is unlikely to benefit anyone. I believe that the emphasis on such measures will divert attention from more clinically relevant issues, increase the cost and complexities of care, and decrease the quality of life for our patients.

ROBERT E. HARBAUGH, M.D. OUTCOMES SCIENCE

Federal Funding Opportunities for Collaborative Research in Stem Cell Biology

The field of stem cell research holds special promise to neurosurgeons. For example, the ability to restore function to the nervous system promises to expand the spectrum of treatment options of nervous system diseases beyond mere prevention of damage. In many institutions both in the United States and internationally, neurosurgeons are engaged in research aimed at understanding the basic elements of stem cell biology and strategies to encourage stem cells to behave in a therapeutically beneficial manner. In addition, neurosurgeons will continue to play a central role in the transplantation of stem cells through stereotactic methodologies and even in the harvesting of neural stem cells from surgical specimens and biopsies. These efforts in neurosurgery will clearly be aided by interaction with researchers across the entire spectrum of the stem cell field.

In addition to new robust funding venues for stem cells research in several states, the National Institute of Neurological Disorders and Stroke (NINDS) is now introducing a program (PAS-04-130) designed to promote this type of cross-disciplinary collaboration. The NINDS is interested in supporting research that combines the unique and complementary expertise of laboratories from the United States and abroad, applying different disciplines, techniques, model systems, or tissues to design, refine, and improve upon the use of stem cells for diagnostic or therapeutic applications for neurological disorders. This program, which promotes collaboration from different scientific areas, has obvious relevance to neurosurgery. More information about this program announcement (PAS-04-130) can be found at: http://grants.nih.gov/grants/ guide/ps-files/PAS-04-130.html

CHARLES LIU, M.D., Ph.D. RESEARCH FUNDING AND GRANTS

It’s All in the Curve: Surface Imaging for Measuring Scoliosis?

The diagnosis and management of patients with spinal scoliosis requires accurate and precise quantitative assessments of the spinal curves, which has traditionally been performed with the use of 36° AP and lateral spine X-rays. The degree of deformity as well as progression of curvatures is critical in developing a subsequent treatment plan and determining the need for operative intervention. However, radiographs are costly, expose the patient to radiation, and require expert interpretation. Thus, screening programs for scoliosis have relied on crude physical assessments performed by minimally trained personnel.

Optical imaging methods for assessing topographical anatomy have the potential to assist in the assessment of spinal deformities. Ramirez, et al., at the University of Alberta have published the results of a clinical study using a support vector machines analysis of topographic data to determine scoliotic and kyphotic deformities of the spine (IEEE Transactions on Information Technology in Biomedicine 10: 84–91, 2006). Using a laser scanner to assess the topography of the back, they studied 111 subjects with idiopathic adolescent thoracic scoliosis. The patients had not been treated with bracing or surgery but did have X-ray measurements of their scoliotic curvatures. Specific parameters analyzed included trunk twist, shoulder angle, scapular angle, and waist asymmetry (Figure). Data analysis was then performed using support vector machines to classify the curvatures in terms of severity, and the accuracy of the determinations were then made with the radiographic Cobb angle as the gold standard, yielding a 69–85% agreement.

The appeal of this technology lies in its ability to quickly screen large numbers of adolescents using objective criteria and without any risk of exposure to radiation. Furthermore, unlike plain radiographs, the data obtained gives a three-dimensional assessment of the spine. Ultimately, such technology, merged into large databases, may improve our ability to screen or track adolescents with scoliosis.

MICHAEL Y. WANG, M.D. TRANSLATIONAL SCIENCE