Cost-Effectiveness of Recombinant Activated Factor VII in the Treatment of Intracerebral Hemorrhage: A US Managed Care Perspective

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Background

- Intracerebral hemorrhage (ICH) is the deadliest form of stroke[1] resulting in mortality and severe disability among survivors.
- ICH events impose a significant economic burden due to intense medical resource use during acute treatment as well as the cost of long-term management of survivors.[2-6]
- Currently, no drug therapies have been proven effective in the treatment of acute ICH.
- Recombinant activated factor VII (rFVIIa) is currently indicated for treatment of bleeding episodes and for the prevention of bleeding in surgical interventions/invasive procedures in hemophilia patients with factor VIII inhibitors and patients with congenital FVII deficiency.
- A recent Phase IIb clinical trial showed that administration of rFVIIa within 4 hours of ICH onset reduced mortality and improved 90-day functional outcome compared to standard care.[7]

Objective

To determine cost-effectiveness of rFVIIa compared to current standard of care in patients with acute ICH from a US managed care perspective.

Methods

Patient Population

Patients enter the hospital emergency room presenting with acute ICH within 3 hours of symptom-onset. Specific patient characteristics include:

- Age distribution typical of published patient populations with ICH.[5,8]
- Characteristics (ICH severity, disease history, time of arrival after onset of ICH event) similar to those observed in the clinical trial.[7]
- Patient weight of 75 kilograms.

Study Design

- A decision-analytic model was created to estimate the cost-effectiveness of rFVIIa for acute ICH (Figure 1).
- Model takes a US managed care perspective.
- Patients entering the model receive rFVIIa 40 µg/kg, 80 µg/kg, or 160 µg/kg (three dose arms in the Phase IIb trial), or standard care within 4 hours of ICH onset . Drug costs are based on wholesale acquisition costs (WAC).[9]
- Patients are followed for the first 90 days after ICH onset and annually thereafter for the remainder of lifetime.
- Functional status, measured by modified Rankin Score (mRS), is estimated at 90 days after ICH onset based on clinical trial data (Table 1).[7]
- Short-term cost calculations (90 days after ICH onset) are based on:
  - Treatment-related clinical efficacy (Table 1)
  - Length of stay in hospitals from clinical trial data (Table 2)
  - Analysis of managed care claims data (Table 3)
  - Costs include: drug cost, inpatient stay, skilled nursing facility costs, and any additional medical management costs.
- Long-term Annual Calculations:
  - Post-90 day costs and outcomes are estimated annually based on mRS score, using mRS-specific multipliers obtained from published literature (Table 4).
- Utility weights specific to each mRS score are obtained from published literature (Table 4).
- Costs and outcomes are presented in 2005 US $ and discounted at a rate of 3% per annum.

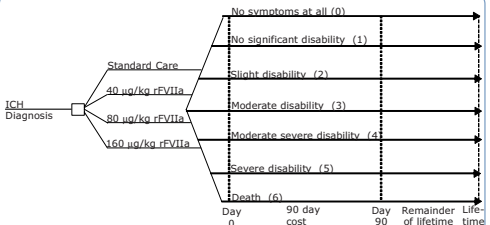
Sensitivity Analysis

- One-way sensitivity analyses were performed on key input parameters.
- Parameters were varied by +/- 20% or based on plausible range data provided in the literature.[10]

Modified Rankin Score (mRS)

mRS 0 = no disability
mRS 1 = no significant disability
mRS 2 = slight disability
mRS 3 = moderate disability
mRS 4 = moderate to severe disability
mRS 5 = severe disability
mRS 6 = death

Figure 1. Model structure



Model Assumptions
- The model assumes a permanent functional status after 90 days based on published literature.[8,10]
- Long-term cost multipliers and death hazard ratios are based on ischemic stroke model.[11] The model assumes that long-term costs and outcomes are based on functional status as defined by mRS.

Table 1. Distribution of Patients by Functional Status after 90 Days

Functional Status	Patients in mRS State (%)* Standard Care	rFVIIa 40 µg/kg	rFVIIa 80 µg/kg	rFVIIa 160 µg/kg
mRS 0	2.1	0.0	9.8	7.8
mRS 1	6.3	16.7	10.9	16.5
mRS 2	9.4	13.9	14.1	9.7
mRS 3	13.5	14.8	15.2	11.7
mRS 4	24.0	22.2	23.9	24.3
mRS 5	15.6	14.8	6.5	10.7
mRS 6	29.2	17.6	18.5	19.4

*Distribution of functional status was estimated 90 days after initial onset of ICH. Distribution of functional status was obtained from a phase IIb clinical trial.[7]

Table 2. Initial Hospital Length of Stay by Functional Status

Functional Status	Initial Hospital LOS (days)* Standard Care	rFVIIa 40 µg/kg	rFVIIa 80 µg/kg	rFVIIa 160 µg/kg
mRS 0	11.0	12.1	12.1	10.9
mRS 1	14.3	21.7	14.9	16.8
mRS 2	14.3	20.3	13.6	13.9
mRS 3	14.7	17.3	14.3	15.9
mRS 4	18.8	19.5	18.5	20.1
mRS 5	21.2	26.0	12.7	33.3
mRS 6	13.5	12.8	14.4	11.3

*Initial hospital length of stay was obtained from a phase IIb clinical trial.[7]

Table 3. Short-term Cost Estimates by Treatment Options

Functional Status	Standard Care	rFVIIa 40 µg/kg	rFVIIa 80 µg/kg	rFVIIa 160 µg/kg
mRS 0	$27,922	$30,659	$30,659	$27,674
mRS 1	$36,132	$54,541	$37,624	$42,351
mRS 2	$36,132	$51,058	$34,390	$35,137
mRS 3	$37,127	$43,595	$36,132	$40,112
mRS 4	$59,875	$61,493	$59,181	$62,880
mRS 5	$65,422	$76,518	$45,775	$93,391
mRS 6	$28,138	$26,679	$30,014	$23,553

Costs were estimated based on initial hospital length-of-stay and costs of initial hospitalization as estimated from a managed care claims data analysis.[4] Additionally, patients in mRS 4-5 were assumed to transition to a skilled nursing facility (SNF) after hospital discharge. The daily SNF costs were obtained from the MetLife market survey.[11]

Table 4. Long-term Costs and Outcomes

Functional Status	Long-term Annual Medical Costs	Long-term Mortality Hazard[11]	Utility Values[12]
mRS 0	$9,228	1.00	0.85
mRS 1	$9,228	1.00	0.85
mRS 2	$11,720	1.11	0.85
mRS 3	$17,902	1.27	0.51
mRS 4	$36,727	1.71	0.15
mRS 5	$55,460	2.37	0.15
mRS 6	$0	0.00	0.00

Long-term annual costs estimated from a managed care claims data analysis.[4] Costs for patients with no or minimal disability (mRS 0-1) were estimated, and then cost multipliers[11] were applied to estimate the annual costs for patients in each mRS state.[10] Note: these costs and outcomes are based on functional status (mRS score) after 90-days from ICH onset, and are thus irrespective of treatment arm.

Results

- Expected lifetime costs per ICH patient were calculated for each treatment arm (Figure 2). Treatment with 160 µg/kg rFVIIa resulted in the highest cost, while treatment with 80 µg/kg rFVIIa resulted in the lowest cost (Figure 2).
- Cost of rFVIIa is low relative to total expected medical costs (Figure 2).
- Expected gain in life-years and QALYs were higher for all treatment groups compared to patients who did not receive rFVIIa (Figure 3).
- Results are robust to realistic parameter variation (Table 5).

Figure 2. Expected Life-time Costs per ICH Patient by Treatment

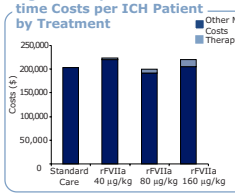


Figure 3. Expected Lifetime Outcomes per ICH Patient by Treatment

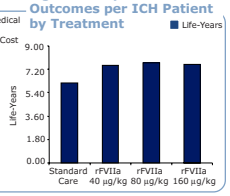


Table 5. One-way Sensitivity Analysis: Effect of Parameter Variation on the Incremental Cost per Life-Year for rFVIIa Compared to Standard Care

Model Parameter	rFVIIa 40 µg/kg vs Standard Care	rFVIIa 80 µg/kg vs Standard Care	rFVIIa 160 µg/kg vs Standard Care
Base-Case Analysis			
ICER ($/Life-Year)	$14,920	Dominant	$8,780
Sensitivity Analysis			
Cost Multiplier			
Lower Bound	$16,821	$8,237	$18,548
Baseline	$14,920	Dominant	$11,204
Upper Bound	$12,938	Dominant	$4,056
Death Hazard Ratio			
Lower Bound	$13,669	Dominant	$6,573
Baseline	$14,920	Dominant	$11,204
Upper Bound	$16,002	$4,145	$14,540
Clinical Efficacy 40 µg/kg			
Lower Bound	$31,323	--	--
Baseline	$14,920	--	--
Upper Bound	$4,677	--	--
Clinical Efficacy 80 µg/kg			
Lower Bound	--	$9,077	--
Baseline	--	Dominant	--
Upper Bound	--	Dominant	--
Clinical Efficacy 160 µg/kg			
Lower Bound	--	--	$28,208
Baseline	--	--	$11,204
Upper Bound	--	--	$2677

The table illustrates the effect on the incremental cost-effectiveness ratio (ICER)($/Life-Year) comparing rFVIIa 40 µg/kg, 80 µg/kg, and 160 µg/kg to standard care when input parameter values are varied. Baseline ICER for rFVIIa 40 µg/kg, 80 µg/kg, and 160 µg/kg are $14,920, -$2,296, and $11,204, respectively. Lower bound for the input parameter is an actual lower bound or 20% decrease in the input parameter. Upper bound is an actual upper bound or 20% increase in the input value.
Dominant means that the comparator (rFVIIa) is both more effective and less expensive than standard care.

Conclusions

- Treatment with rFVIIa 40 µg/kg and 160 µg/kg are cost-effective compared to standard care.
- Treatment with rFVIIa 80 µg/kg is not only cost-effective but is cost-saving compared to the current standard of care.

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