Design of a Phase 4, Multicenter, Prospectively Defined, Observational Registry Study With Retrospective Data Collection Evaluating Premature & TNT Neonates With PH Receiving iNO Via Invasive or Non-invasive Ventilatory Support

Jim Potenziano, PhD, Vice President and Global Medical Lead, INOmax and Stannsoporfin
Mallinckrodt Pharmaceuticals, Bedminster, NJ

Mallinckrodt Pharmaceuticals

Background

- Severe hypoxic respiratory failure (HRF) affects about 2% of all neonates, and nearly 10% of these cases are associated with persistent pulmonary hypertension of the newborn (PPHN), which is characterized by vascular injury and elevated pulmonary vascular resistance, leading to severe hypoxemia.[1]
- Inhaled nitric oxide (iNO) is commonly used for the treatment of neonates with HRF associated with pulmonary hypertension (PH).
- iNO is FDA approved in conjunction with ventilation and other appropriate agents for use in term-near-term (TNT) neonates (≥34 weeks gestational age) with HRF associated with PH.[2]
- In TNT neonates, iNO administration results in a significant improvement in oxygenation and significant reduction in the need for extracorporeal membrane oxygenation (ECMO).[3-6]
- Definitive evidence regarding the effectiveness of iNO in preterm neonates with PH is lacking.
- A 2010 National Institutes of Health consensus report indicated that preterm neonates, including those with PH, may benefit from treatment with iNO in some situations; however, there was insufficient evidence to recommend its routine use.[7]
  - A systematic review and meta-analysis by Barrington and Finer found no clear indication for treatment with iNO in preterm infants with respiratory failure.[8]

Purpose

- The purpose of the multicenter, prospectively defined, observational Registry Evaluating Premature and Term-Near-Term Neonates With Pulmonary Hypertension Receiving Inhaled Nitric Oxide (PaTTerN) study (NCT03132428) is to obtain high-level evidence regarding use of iNO in preterm vs. TNT neonates with HRF associated with PH.

Objectives

- The primary objective of the multicenter PaTTerN study is to evaluate whether there is a difference in the degree of improvement in oxygenation between preterm and TNT neonates during up to 96 hours of iNO administration, as measured by oxygenation index (OI) or surrogate OI (SOI; in non-intubated neonates).
- A secondary objective is to evaluate the clinical time course of response to iNO during 96 hours of treatment in the preterm and TNT groups, considering the cause and severity of PH, and during safety follow-up through 7 days (for a total of up to 11 days) or to hospital discharge, whichever comes first.

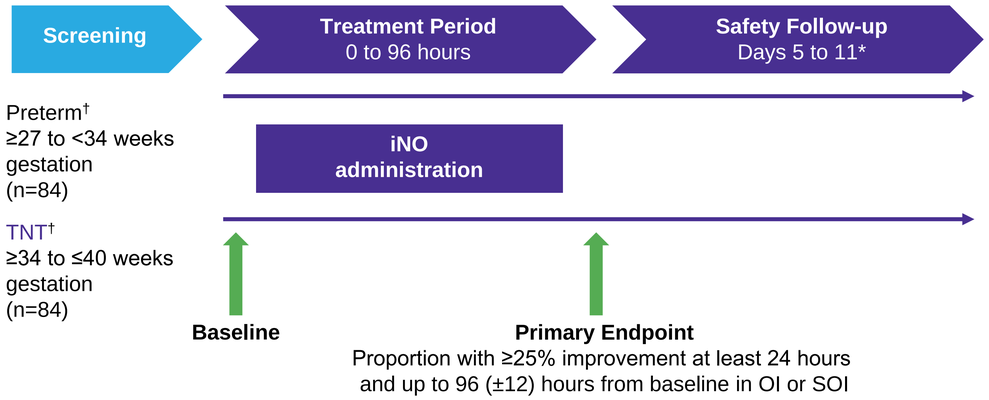
Study Population

- Preterm neonates born at ≥27 weeks to <34 weeks gestational age or TNT neonates born at ≥34 weeks to ≤40 weeks gestational age are being included in the study.
  - Neonates will be stratified by severity of PH (i.e., mild, moderate, or severe).
- Presence of PH must be confirmed by echocardiogram or a differential saturation gradient of ≥10%.
- Neonates must be administered iNO at 0 to 7 days of age via any route (i.e., invasive or non-invasive) for a treatment period of ≥24 hours up to 96 (±12) hours.
  - iNO must be administered as part of routine clinical practice in a Level III or higher neonatal intensive care unit in the United States.
- All relevant data for neonates must be available to calculate OI or SOI (i.e., baseline sample before treatment and 4 samples obtained during treatment).
- Neonates at risk for imminent death within 24 hours will be excluded, as will those with other clinical complications, including:
  - Resuscitation requiring chest compressions within 6 hours of receiving iNO.
  - Active uncontrolled bleeding, Grade IV bilateral intraventricular hemorrhage or periventricular leukomalacia, or disseminated intravascular coagulopathy.
  - Administration of ECMO.
  - Life-threatening, chromosomal, or congenital abnormality.

Study Design

- An overview of the registry study design is shown in the **Figure**.

Figure. The PaTTerN Study Design



*Safety data will be obtained during iNO administration up to 96 hours and up to 7 days later (for a total of up to 11 days) or to hospital discharge, whichever comes first. †Neonates aged 1 to 7 days with PH.

- The first registry patient was enrolled on August 1, 2017.[9]

Study Outcome Measures

Primary Efficacy Measure

- The primary efficacy outcome is the number and percentage of neonates in the preterm and TNT groups with ≥25% improvement at least 24 hours and up to 96 (±12) hours from baseline in OI or SOI during administration of iNO.

Secondary Efficacy Measures

- Secondary efficacy outcomes include:
  - PH severity in each group at ≥24 hours and up to 96 (±12) hours from baseline; 25% improvement in OI/SOI will be summarized for each severity group (i.e., mild, moderate, and severe) within each age group.
  - Time course of response to iNO up to 96 hours from baseline, stratified by baseline factors, including age group, severity group, disease subtype, weight, race, and gender.
  - Evaluation of 25% improvement in OI/SOI for up to 96 hours from baseline stratified by demographics, PH severity, and disease subtype.
  - Incidence of patients with <25% improvement in OI/SOI (i.e., partial responders).

References

1. Steinhorn RH. *Pediatr Crit Care Med*. 2010;11(2 Suppl):S79-S84.
2. INOmax [package insert]. Hazelwood, MO: INO Therapeutics; 2015.
3. Clark RH, et al. *N Engl J Med.* 2000;342:469-474.
4. Davidson D, et al. *Pediatrics.* 1998;101(3 Pt 1):325-334.
5. NINOS Study Group. *N Engl J Med.* 1997;336:597-604.
6. Roberts JD Jr, et al. *N Engl J Med*. 1997;336:605-610.
7. Cole FS, et al. *Pediatrics.* 2011;127:363-369.
8. Barrington KJ, Finer N. *Cochrane Database Syst Rev.* 2010: CD000509.
9. http://www.mallinckrodt.com/about/news-and-media/2290492.

INVESTOR DAY 2017 OCTOBER 4 NEW YORK, NY

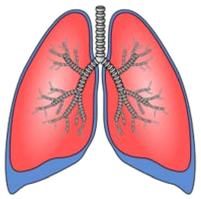
Investigation of Use of Gaseous Nitric Oxide (gNO) and a Toll-like Receptor 9 (TLR9) Antagonist in Improving the Viability of Organ Health and Increasing Ischemic Time (*Ex-Vivo* Time): The gNO and TLR9 Proof of Concept (PoC) Transplant Perfusate Trials

Mallinckrodt Pharmaceuticals

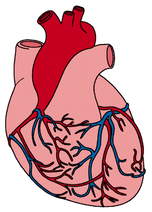
Background

- Organ shortage is the greatest challenge facing the field of organ transplantation.[1]
  - There is a high rejection of organs, especially with lungs and hearts; most of which do not meet the criteria for transplantation.[2,3]
  - Recent data shows only 15-20% of standard donor lungs are used in the US; for heart standard donors, only 35% are used.[2,3]
- There is a high unmet medical need and a need for increased organ supply worldwide.[1]

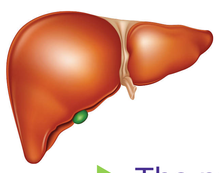
Lung, Heart, and Liver Transplants in the US



- In 2016, there were 2,327 lung transplants (6.9% of all transplants) performed in the US; this is 270 more than in 2015.[4,5]
- Lung transplantation remains limited by a shortage of suitable lung donors, resulting in long waiting times for listed patients and a substantial risk (10-15%) of dying before transplantation.[6]
- Donor lungs are subjected to a multitude of injuries during the brain death/organ donation process, as such, only 15-20% of donor lungs are currently utilized, with the majority (80-85%) being discarded and not utilized for transplant.[2]



- In 2016, there were 3,191 heart transplants (or 9.5% of all transplants) performed in the US; this is 387 more than in 2015.[4,5]
- In the past 2 decades the number patients who are waiting for heart transplants has increased, the use of stringent “donor criteria” has resulted in a deficit of available organs, contributing to extended waiting times and increased mortality while waiting.[3]
- Due to this severe donor shortage, recipient criteria is also stringent, limiting the number of patients placed on the waiting list to ~8,000 per year, though it has been estimated that at least 25,000 patients per year could benefit from the procedure.[3]
- Additionally, a significant number of donor hearts are not utilized; the “non-utilization rate” of suitable donors has been estimated to be as high as 65%.[3]



- In 2016, there were 7,841 liver transplants (or 23.3% of all transplants) performed in the US; this is 714 more than in 2015.[4,5]
- Currently 17,000 patients are waiting liver transplantation; more than 1,500 patients die each year while waiting for a transplant.[7]
- The proportion of livers not used reached a low of 14.8% in 2004, but since 2010, has increased to ~20%; had the rate of non-use remained stable at 14.8%, 328 more livers could have been transplanted.[8]

Hypothesis/Scientific Rationale

- Both gNO and TLR9 antagonist interrupt critical signaling pathways (eg, immune response/inflammation) and may improve the viability of organ health and increase ischemic time (time out of the body).[9,10]
- gNO and TLR9 antagonists will be added to the normothermic perfusion procedure to increase or improve
  - Ischemic time (time between organ donation and recipient transplant)
  - The health of an organ, this increasing the number of available organs
  - Clinical outcomes after transplantation

Overview of the Transplant Perfusate PoC Trials

Organ Perfusion Solutions

Organ Perfusion Systems

	gNO	TLR9 Antagonist
Compound/Agent Under Investigation:	gNO	TLR9 Antagonist
Trial Objective:	Ventilate and perfuse gNO to reduce ischemia-reperfusion injury (IRI)	Modulate the immune response
Model:	Human lungs	Animal
Clinical Status/ Anticipated Trial Completion Date:	Q3 2018	Q3 2018

References

1. Saidi RF, Hejazii Kenari SK. *Int J Organ Transplant Med*. 2014;5(3):88-96.
2. Makdisi G, Wozniak TC. *Ann Transl Med.* 2017;5(Suppl 1):S12. 10.21037/atm.2017.03.11
3. Wittwer T, Wahlers T. *Transplant International.* 2008;21(2):113-125.
4. 2016 annual report. UNOS™ (United Network for Organ Sharing) website. https://www.unos.org/about/annual-report/2016-annual-report/. Accessed September 5, 2017.
5. 2015 annual report. UNOS™ website. https://www.unos.org/about/annual-report/2015-annual-report/. Accessed September 5, 2017.
6. Van Raemdonck D, et al. *Proc Am Thorac Soc*. 2009;6(1):28-38.
7. Peyton A, Martin P. *Clin Liver Dis.* 2013;2(4):145-147.
8. Orman ES, et al. *Liver Transpl.* 2013;19(1):59-68.
9. Fukazawa K, Lang JD. *World J Hepatol.* 2016;8(34):1489-1496.
10. Howell J, et al. *Liver Transplantation.* 2014;20(3):270-280.

INVESTOR DAY 2017 OCTOBER 4 NEW YORK, NY

3080

Comparative Analysis of Length of Stay, Hospitalization Costs, Opioid Use, and Discharge Status among Spine Surgery Patients with Postoperative Pain Management including IV versus Oral Acetaminophen

Ryan N. Hansen[1], An Pham[2], Elaine A. Böing[2], Belinda Lovelace[2], George J. Wan[2], Timothy E. Miller[3]

[1]University of Washington, School of Pharmacy, Seattle, WA; [2]Mallinckrodt Pharmaceuticals, Health Economics and Outcomes Research Department, Hampton, NJ; [3]Duke University, School of Medicine, Durham, NC.

Mallinckrodt Pharmaceuticals

BACKGROUND

- Recovery from spine surgery is oriented toward restoring functional health outcomes while reducing hospital length of stay (LOS) and medical expenditures. Optimal pain management is a key to reaching these objectives.
- Prior research suggests that IV acetaminophen (IV APAP) for acute pain improves patient outcomes and reduces hospital resource use.
- We compared the outcomes of spine surgery patients who received standard pain management including either IV APAP or oral APAP.

METHODS

Data source, timeframe, and study cohort

- We performed a retrospective analysis of the Premier database (between January 2012 and September 2015) comparing inpatient spine surgery patients who received pain management with IV APAP to those who received oral APAP starting on the day of surgery and continuing up to the third postoperative day.
- Spine surgeries were identified using International Classification of Diseases version 9 procedure codes. Among those subjects, the receipt of IV APAP and oral APAP was identified using service records, with no exclusions based on additional pain management.

Outcomes

- We compared the groups on:
  - LOS from hospital admission to discharge day
  - Total hospitalization cost
  - Average morphine equivalent dose (MED)
  - Discharge to skilled nursing facilities (SNF)

Statistical analysis

- For adjusted analyses, we performed multivariable logistic regression for the binary outcomes and separate instrumental variable regressions comparing the LOS, hospitalization costs, and average MED. The quarterly rate of IV APAP use for all hospitalizations by hospital was used as an instrumental variable in two-stage least squares regressions with the following covariates:
  - Patient: Age, Gender, Race
  - Admission type
  - 3M APR-DRG severity of illness (SOI) and
  - Risk of mortality (ROM)
  - Hospital bed count
  - Indicators for whether the hospital was an academic center and whether it was urban or rural

RESULTS

Table 1. Baseline Demographic Characteristics of Spine Surgery Patients

	IV Acetaminophen* (n=51,835)	Oral Acetaminophen* (n=60,751)	p-value
Age, mean (SD)	57.2 (14.9)	58.7 (16.3)	<0.0001
Female, n (%)	26,835 (51.8)	33,224 (54.7)	<0.0001
Race, n (%)			<0.0001
White	41,411 (79.9)	44,455 (73.2)	
Black	4,781 (9.2)	5,345 (8.8)	
Other	5,600 (10.8)	10,872 (17.9)	
Unknown	43 (0.1)	79 (0.1)	
APR-DRG Severity of Illness, n (%)			<0.0001
Minor	29,496 (56.9)	26,609 (43.8)	
Moderate	17,465 (33.7)	23,351 (38.4)	
Severe	4,166 (8.0)	8,184 (13.5)	
Extreme	708 (1.4)	2,607 (4.3)	
APR-DRG Risk of Mortality, n (%)			<0.0001
Minor	43,291 (83.5)	44,742 (73.7)	
Moderate	6,449 (12.4)	10,141 (16.7)	
Severe	1,640 (3.2)	4,102 (6.8)	
Extreme	455 (0.9)	1,766 (2.9)	
Emergent Admission, n (%)	9,749 (18.8)	11,087 (18.3)	0.02
Urban Hospital, n (%)	46,423 (89.6)	56,664 (93.3)	<0.0001
Teaching Hospital, n (%)	24,814 (47.9)	35,308 (58.1)	<0.0001
Hospital Bed Count, mean (SD)	484.1 (252.3)	463.5 (254.0)	<0.0001
Year of Hospitalization, n (%)			<0.0001
2012	9,496 (18.3)	19,675 (32.4)	
2013	17,464 (33.7)	14,812 (24.4)	
2014	16,462 (31.8)	13,060 (21.5)	
2015	8,413 (16.2)	13,204 (21.7)	
Hospital Region, n (%)			<0.0001
Midwest	8,804 (17.0)	7,952 (13.1)	
Northeast	7,793 (15.0)	18,812 (31.0)	
South	30,958 (59.7)	24,291 (40.0)	
West	4,280 (8.3)	9,696 (16.0)	

*Subjects in each cohort were included regardless of additional pain management.

Table 2. Unadjusted Outcomes Comparing IV and Oral Acetaminophen

Outcome	IV Acetaminophen* (n=51,835)	Oral Acetaminophen* (n=60,751)	Difference (95% Confidence Interval)	p-value
LOS (days), mean (SD)	3.2 (3.8)	4.9 (6.5)	-1.6 (-1.7 to -1.6)	<0.0001
Hospitalization Cost ($), mean (SD)	24,800 (20,713)	29,366 (28,817)	-4,566 (-4,864 to -4,269)	<0.0001
MED (mg), mean (SD)	43.1 (55.2)	50.8 (66.6)	-7.7 (-8.4 to -7.0)	<0.0001
Discharge to SNF, n (%), odds ratio	3,386 (6.5)	7,193 (11.9)	0.52 (0.50 to 0.54)	<0.0001

*Subjects in each cohort were included regardless of additional pain management.

RESULTS

Patient demographics

- We identified 112,586 spine surgery patients with 51,835 (46%) who had received IV APAP (Table 1).
- Study subjects averaged 57 and 59 years of age and were predominantly non-Hispanic Caucasians (>70% both cohorts) and female (52% and 55%, respectively in the IV and oral APAP cohorts).
- The majority of subjects were in the minor or moderate category for both the APR-DRG SOI and ROM.

Unadjusted analysis

- The mean unadjusted LOS for IV APAP patients was 3.2 days (SD 3.8) compared to 4.9 days (SD 6.5) with oral APAP, a statistically significant difference of -1.6 days (p<0.0001) (Table 2).
- Average unadjusted hospitalization costs were $24,800 (SD $20,713) for IV APAP patients and $29,366 (SD $28,817) for oral APAP patients, also statistically significantly lower by $4,566 (p<0.0001).
- The average MED for IV APAP patients was 43.1 mg (SD 55.2) and 50.8 mg (SD 66.6) for oral APAP patients, a statistically significant difference of -7.7 mg (p<0.0001).
- IV APAP patients were 48% less likely to be discharged to a SNF (Table 2).
- IV APAP patients were 28% less likely to develop bowel obstruction, 27% less likely to develop nausea/vomiting, and 45% less likely to develop respiratory depression (Table 3).

Adjusted analysis

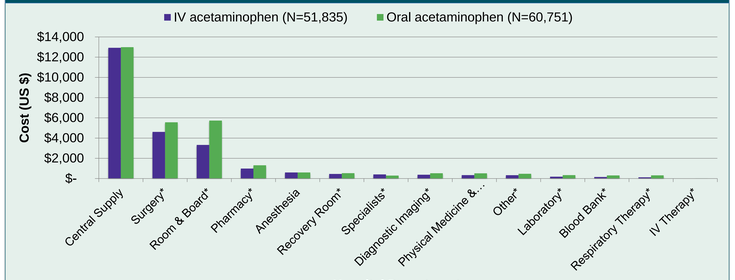
- In our adjusted models, IV APAP was associated with 0.7 days shorter hospitalization (95% CI: -0.8 to -0.6, p<0.0001), $1,175 lower hospitalization costs (95% CI: -$1,611 to -$739, p<0.0001), and 13 mg lower average MED (95% CI: -14 mg to -12 mg, p=<0.0001) (Table 4).

Table 3. Unadjusted Risk of Complications Comparing IV and Oral Acetaminophen Patients

Outcome	Odds Ratio*	95% Confidence Interval	p-value
Bowel Obstruction	0.72	0.69 to 0.76	<0.0001
Nausea/Vomiting	0.73	0.68 to 0.79	<0.0001
Respiratory Depression	0.55	0.53 to 0.58	<0.0001
Diagnosis	0.46	0.42 to 0.49	<0.0001
Mechanical Ventilation	0.28	0.23 to 0.34	<0.0001
Naloxone Administration	0.78	0.72 to 0.83	<0.0001

*Oral acetaminophen is the reference group.

Figure 1. Distribution of Unadjusted Costs of Spine Surgery Patients by Hospital Department Comparing IV and Oral Acetaminophen Patients



(* indicates p<0.0001 for difference between IV and oral acetaminophen)

Table 4. Adjusted Outcomes Comparing IV and Oral Acetaminophen Patients

Outcome	Difference/Odds Ratio (95% Confidence Interval)	p-value
LOS (days)	-0.68 (-0.76 to -0.59)	<0.0001
Hospitalization Cost ($)	-1,175 (-1,611 to -739)	<0.0001
Opioid MED (mg)	-13. 0 (-14.1 to -11.9)	<0.0001
Discharge to SNF (odds ratio)	0.66 (0.63 to 0.69)	<0.0001
Bowel Obstruction (odds ratio)	0.93 (0.88 to 0.98)	0.0041
Nausea/Vomiting (odds ratio)	0.79 (0.73 to 0.86)	<0.0001
Respiratory Depression (odds ratio)	0.91 (0.85 to 0.96)	0.0011

LIMITATIONS

- The differences observed between IV APAP and oral APAP patients could be explained by unmeasured confounders. Investigators attempted to account for this through the use of instrumental variable regression, adjusting models for potentially confounding variables, but unmeasured factors might still play a role in the associations reported.
- The medication use data in the Premier database reflects the amount and dose charged rather than what was administered. However, systematic differences in billing of other pain medications between patients who did or did not receive IV APAP is not suspected.
- The population of patients seen in Premier hospitals is not randomly sampled. Therefore these results may not be generalizable outside of Premier hospitals (20% of US hospitals).

CONCLUSION

- Compared to oral APAP in the adjusted models, managing post-spine surgery pain with IV APAP is associated with shorter LOS, decreased total hospitalization costs, lower doses of opioids, reduced risk of complications, and reduced risk of discharge to a skilled nursing facility.

DISCLOSURE

- The funding for this study was provided by Mallinckrodt Pharmaceuticals.

Estimating the effect of intravenous acetaminophen (IV-APAP) on length of stay and inpatient costs

E. Eve Shaffer, MS[1]; Robert L. Woldman, MA[1]; Andrew Spiegelman, PhD[1]; Scott A. Strassels, PharmD, PhD[2]; George J. Wan, PhD, MPH[3]; Thomas Zimmerman, MD[3]
[1]The Advisory Board Company, Washington DC; [2]Formerly with Mallinckrodt Pharmaceuticals, Hazelwood MO; [3]Mallinckrodt Pharmaceuticals, Hazelwood MO

Background

- Opioid analgesics are a mainstay for acute pain management, but their usage is associated with adverse events which may increase costs. Multi-modal analgesia has been shown to improve those factors, and intravenous acetaminophen (IV-APAP) can be incorporated as part of a multi-modal pain management strategy to help contribute to reduced costs and improved outcomes.
- The goal of this non-comparative study was to model length of stay (LOS), opioid-related complications, and costs for patients reducing opioid use and adding IV-APAP for management of post-operative pain.

Method

Data Source

- Data for this non-comparative, retrospective cohort study were derived from de-identified hospital data from the Advisory Board Company. This comprised inpatient encounters from 297 hospitals across 2012 – 2014, containing 2,238,433 encounters, with IV-APAP identified in 271,394 encounters (12.1%).

Inclusions & Exclusions

- Encounters for adults ≥ 18 years of age and admitted for cardiovascular, colorectal, general, OBGYN, orthopedics, or spine surgery based on the encounters All Patient Refined Diagnosis-Related Group (APRDRG) assignment, were included. Only data from acute care facilities with data available throughout the study period and having sufficient quality to identify drugs were included. Encounters with invalid age, gender or severity, without diagnoses, without drug utilization, with mortalities or with discharge to hospice were excluded.

Definition of Complications

- Potential opioid-related adverse drug events related to respiratory, gastrointestinal, central nervous system, urinary, and other events were defined using ICD-9-CM codes[1].

Modeling

- The effects of reducing opioid use and adding IV-APAP were estimated using hierarchical statistical models in SAS 9.4. Independent variables were: opioid use (none/low/medium/high), non-opioid use (none/low/medium/high) and IV-APAP use (none/used). Covariates included: age, gender, Elixhauser comorbidity index, All Patient Refined-Diagnosis Related Groups severity level, and admission type.
- Parameter estimates were applied to observed average LOS and complication rate baselines. Cost impact estimates were generated by multiplying modeled reductions in LOS or complication rates by observed average volumes (facilities designated AHA 100-399 beds), and by average cost per day of LOS or per complication (LOS: $2,383/day [HCUP-2013], complications: derived from observed charges).

Results

General

- In aggregate, including both LOS- and complications-related reductions, annual costs decreased by an estimated $4.7M for a medium-sized hospital.

Length Of Stay (Figure 1)

- Across all surgery types, LOS showed an average of 18.3% reduction at the category level for 1,898.75 cumulative total days reduced (categories ranging from 10.7% / 456.17 total days to 30.7% / 236.16 total days) for the modeled scenario of reducing opioid use by one level (high to medium, medium to low, or low to none) and adding IV-APAP, with an associated total LOS-related annual cost savings of $4.5M.
- At the category level, spine showed the largest percentage reduction in LOS (30.7% / 236.16 total days), while orthopedics, with much larger average case volume, showed the largest LOS-related cost reduction ($1,340,000). OBGYN showed the lowest percentage reduction in LOS (10.7% / 456.17 total days), while the general category, with lower average case volume, showed the smallest LOS-related cost reduction ($100,000).
- At the APRDRG level, knee and lower leg procedures showed the largest percentage reduction in LOS (39.0% / 84.00 total days), closely followed by dorsal and lumbar fusion (34.5% / 137.16 total days) and laparoscopic cholecystectomy (34.3% / 123.48 total days), while cesarean delivery, with much larger average case volume, showed the largest LOS-related cost reduction ($600,000), despite having a low percentage reduction in LOS (13.5% / 253.44 total days). Vaginal delivery showed the lowest percentage reduction in LOS (7.5% / 167.62 total days), while uterine and adnexa procedures, with lower average case volume, showed the smallest LOS-related cost reduction ($80,000).

Complications

- Complication rates showed similar improvements, averaging 28.5% (categories ranging from 5.4% to 44.0%) reduction in modeled opioid-related complication rate, with associated complications-related annual cost savings of $0.2M.
- At the category level, spine showed the largest percentage reduction in complications (44.0%), while colorectal showed the largest complications rate-related cost reduction ($70,000). The cardiovascular category showed the smallest percentage reduction in complications (5.4%), while the general category, with lower average case volumes, showed the smallest complications-related cost savings ($10,000), along with the cardiovascular and OBGYN categories.

Figure 1. LOS and Annual LOS-Related Costs After Dropping One Level of Opioid Use & Adding IV-APAP

Category	APRDRG Description	Estimated Avg. Admissions for a Medium-Sized Facility	Observed Avg. LOS *	Calculated LOS After Dropping One Level of Opioid Use & Adding IV APAP	Calculated LOS Reduction for Dropping One Level of Opioid Use & Adding IV APAP	% Change in LOS	Calculated Annual Impact for a Medium-Sized Facility **
Cardiovascular		276	4.01	3.00	1.01	25.2%	$ 660,000
	OTHER VASCULAR	73	5.57	3.96	1.61	28.9%	$ 280,000
	PERCUTANEOUS CARDIOVASCULAR PROCEDURES W/O AMI	85	3.39	2.80	0.59	17.4%	$ 120,000
	PERCUTANEOUS CARDIOVASCULAR W AMI	118	3.49	2.55	0.94	26.9%	$ 260,000
Colorectal		207	6.13	4.55	1.58	25.9%	$ 780,000
	BOWEL PROCEDURES	109	8.34	6.46	1.88	22.5%	$ 480,000
	LAPAROSCOPIC CHOLECYSTECTOMY	98	3.67	2.41	1.26	34.3%	$ 300,000
General		54	2.68	1.96	0.72	26.9%	$ 100,000
	APPENDECTOMY	54	2.68	1.96	0.72	26.9%	$ 100,000
OBGYN		1,573	2.70	2.41	0.29	10.7%	$ 1,080,000
	CESAREAN DELIVERY	528	3.55	3.07	0.48	13.5%	$ 600,000
	UTERINE & ADNEXA PROCEDURES FOR NON-MALIGNANCY EXCEPT LEIOMYOMA	59	2.23	1.67	0.56	25.1%	$ 80,000
	VAGINAL DELIVERY	986	2.27	2.10	0.17	7.5%	$ 400,000
Spine		246	3.13	2.17	0.96	30.7%	$ 560,000 ***
	CERVICAL SPINAL FUSION & OTHER BACK/NECK PROC EXC DISC EXCIS/DECOMP	80	2.43	1.86	0.57	23.5%	$ 100,000
	DORSAL & LUMBAR FUSION PROC EXCEPT FOR CURVATURE OF BACK	108	3.68	2.41	1.27	34.5%	$ 320,000
	INTERVERTEBRAL DISC EXCISION & DECOMPRESSION	58	3.07	2.14	0.93	30.3%	$ 120,000
Orthopedics		604	3.51	2.58	0.93	26.5%	$ 1,340,000 ***
	HIP & FEMUR PROCEDURES FOR TRAUMA EXCEPT JOINT REPLACEMENT	74	5.37	4.35	1.02	19.0%	$ 180,000
	HIP JOINT REPLACEMENT	174	3.48	2.58	0.90	25.9%	$ 380,000
	KNEE & LOWER LEG PROCEDURES	50	4.31	2.63	1.68	39.0%	$ 200,000
	KNEE REPLACEMENT	256	2.95	2.18	0.77	26.1%	$ 460,000
	SHOULDER UPPER ARM & FOREARM PROCEDURES	50	2.89	2.01	0.88	30.4%	$ 100,000

*Mean of all cases **Values are rounded to the nearest $ 20,000
***APRDRG values for this category just miss the rounding cut-off, causing a $20,000 gap between their sum and the category-level value

Discussion

- This investigation indicates that reducing opioid use and including IV-APAP during treatment can contribute to decreasing LOS, opioid-related complication rates and costs from a hospital perspective.

References

1. Oderda GM, Gan TJ, Johnson BH, Robinson SB. Effect of Opioid-Related Adverse Events on Outcomes in Selected Surgical Patients. Journal of Pain & Palliative Care Pharmacotherapy. 2013;27:62–70.

Disclosure

Funding for this project was provided by Mallinckrodt Pharmaceuticals.

Triple Aim as a Conceptual Framework for Conducting Comparative Effectiveness Research in Postoperative Pain

An Pham[1], Ryan Hansen[2], Elaine A. Böing[1], George J. Wan[1] , Belinda Lovelace[1], Timothy E. Miller[3]

[1]*Health Economics and Outcomes Research Department, Mallinckrodt Pharmaceuticals, Hampton, NJ;* [2]*School of Pharmacy, University of Washington, Seattle, WA;* [3]*School of Medicine, Duke University, Durham, NC*

Background

► The IHI Triple Aim framework for health care requires simultaneous pursuit of:
- – Reducing healthcare expenditures
- – Improving patient experience
- – Advancing population health

► Recovery from surgery is oriented toward restoring functional health outcomes while reducing hospital length of stay (LOS) and medical expenditures. Optimal pain management is a key to reaching these objectives.

► Pain management in the inpatient setting is commonly achieved through the utilization of opioid monotherapy. Practice guidelines recommend use of multi-modal analgesia (MMA) with increased adoption in clinical practice. There is a paucity of evidence on the comparative effectiveness of the route of administration of acetaminophen (APAP) as treatment strategies in this population.

Aim

We sought to utilize the Triple Aim as a conceptual framework to assess comparative effectiveness of treatment strategies for postoperative pain management.

Actions Taken

We performed a retrospective analysis of the Premier database (between January 2012 and September 2015) comparing total knee arthroplasty (TKA) patients with postoperative pain management including two treatment strategies, either IV APAP or oral APAP, used as part of multi-modal analgesia from the day of surgery up to the third postoperative day.

To compare IV and oral APAP groups, we organized outcome variables of interest as follows (although there is potential for overlap, we created mutually exclusive groups):

► **Reducing healthcare expenditures**: Hospital length of stay, total hospitalization costs;

► **Improving patient experience**: Potential opioid-related complications, opioid consumption; and

► **Advancing population health**: 30-day readmissions, discharge status (to home or to skilled nursing facility, SNF).

Results

► We identified 190,691 TKA patients with 56,475 (30%) who had received IV APAP.

► Study subjects averaged 66 and 67 years of age respectively in the IV APAP and oral APAP cohorts and were predominantly non-Hispanic Caucasians (>75% in both cohorts) and female (61% and 63%, respectively in the IV APAP and oral APAP cohorts).

► The majority of subjects ranked in the minor or moderate categories for both the APR-DRG Severity of Illness (SOI) and Risk of Mortality (ROM).

Unadjusted and Adjusted Differences in Outcomes Comparing IV and Oral Acetaminophen Patients[a]

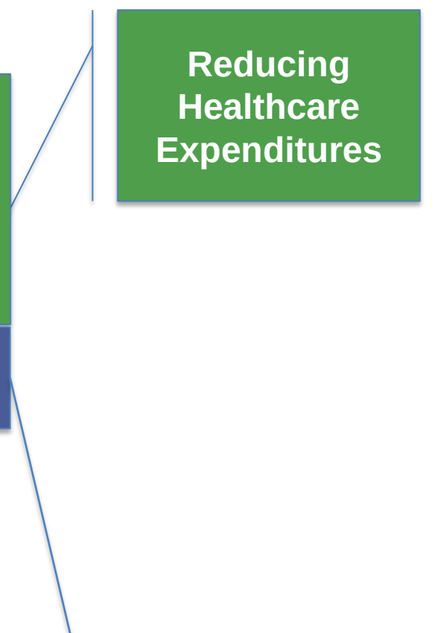
Outcomes	Unadjusted Analysis				Adjusted Analysis[b]	
	IV APAP* (n=56,475)	Oral APAP* (n=134,216)	Difference (95% Confidence Interval)	p-value	Difference	p-value
LOS (days), mean (SD)	2.8 (1.3)	3.0 (1.5)	-0.21 (-0.22 to -0.19)	<0.0001	-0.14	<0.0001
Hospitalization Cost ($), mean (SD)	16,214.6 (6,950.2)	16,750.4 (9,634.6)	-535.7 (-623.5 to -448.0)	<0.0001	-443.0	<0.0001
MED (mg), mean (SD)	47.2 (34.8)	49.0 (42.8)	-1.8 (-2.2 to -1.4)	<0.0001	-3.1	<0.0001

[a]Subjects in each cohort were included regardless of additional pain management. [b]Multivariable regression adjusted for patient age, gender, race, APR-DRG Severity of Illness and Risk of Mortality, year of admission, admitting physician type, hospital type (academic), hospital location (urban/rural), and number of beds. Oral APAP is the reference group. MED, morphine equivalent dose.

Unadjusted and Adjusted Odds Ratios Comparing IV and Oral Acetaminophen Patients[a]

Outcomes	Unadjusted Analysis			Adjusted Analysis[b]	
	Odds Ratio	95% Confidence Interval	p-value	Odds Ratio	p-value
Bowel Obstruction	0.96	0.91 to 1.02	0.2	1.00	0.1
Nausea/Vomiting	0.86	0.81 to 0.92	<0.0001	0.88	<0.0001
Respiratory Depression	0.67	0.63 to 0.72	<0.0001	0.76	<0.0001
Diagnosis	0.65	0.58 to 0.73	<0.0001	-	-
Naloxone Administration	0.69	0.64 to 0.74	<0.0001	-	-
Mechanical Ventilation	0.83	0.37 to 1.85	0.6	-	-
30-day Readmission	0.31	0.21 to 0.47	<0.0001	0.31	<0.0001
Discharge Home	1.32	1.29 to 1.35	<0.0001	1.22	<0.0001
Discharge to SNF	0.83	0.81 to 0.85	<0.0001	0.87	<0.0001

[a]Subjects in each cohort were included regardless of additional pain management. [b]Multivariable regression adjusted for patient age, gender, race, APR-DRG Severity of Illness and Risk of Mortality, year of admission, admitting physician type, hospital type (academic), hospital location (urban/rural), and number of beds. Oral APAP is the reference group. Dashes indicate that the model did not converge.



Conclusions

► Compared to oral APAP, managing TKA pain with IV APAP is associated with reduced healthcare expenditures, improved patient experience, and advanced population health.

► Use of the IHI Triple Aim as a research framework for policy and population health decision makers is a useful tool for assessing comparative effectiveness of treatment strategies in postoperative pain management and may also have broader applicability to other therapeutic areas.

28th Annual Forum on Quality Improvement in Health Care, December 4-7 2016, Orlando, FL

Single-Arm Study to Assess the Efficacy of UVADEX® (methoxsalen) Sterile Solution in Conjunction with the THERAKOS® CELLEX® Photopheresis System in Pediatric Patients with Steroid-Refractory Acute Graft-vs-host Disease (aGvHD)

Mallinckrodt Pharmaceuticals

Background

- Hematopoietic stem cell transplantation (HSCT) is a potentially curative option in children with high-risk malignancies.[1]
- GvHD and infections are the major causes of morbidity and mortality after allogeneic HSCT.[2] Systemic steroid treatment , 1st-line therapy for aGVHD, is associated with response rate of 30-60%.[2]
- Steroid-resistant patients have poor prognosis with high transplant-related mortality (TRM).[2] Several 2nd-line therapies have been proposed for management of unresponsive aGvHD, without proven beneficial effects on outcome or overall survival (OS).[2]
- While multiple second-line treatments have been proposed for management of unresponsive aGvHD, they have not affected patient outcomes or OS[2]
- Extracorporeal photopheresis (ECP) has been used in the treatment of steroid-resistant and steroid-refractory pediatric patients with aGvHD, with response rates ranging from 50-100% depending on organs involved [2]
- A recent study of ECP in patients with aGvHD found that the 5-year progression-free survival of primary disease was 72% for responders (79%) & nonresponders (30%) to ECP.[2]

Purpose

- The purpose of this ongoing prospective study (NCT02524847) is to evaluate clinical utility of ECP in treatment of steroid-refractory pediatric acute GvHD.

*Or fewer treatments if they discontinued treatment.

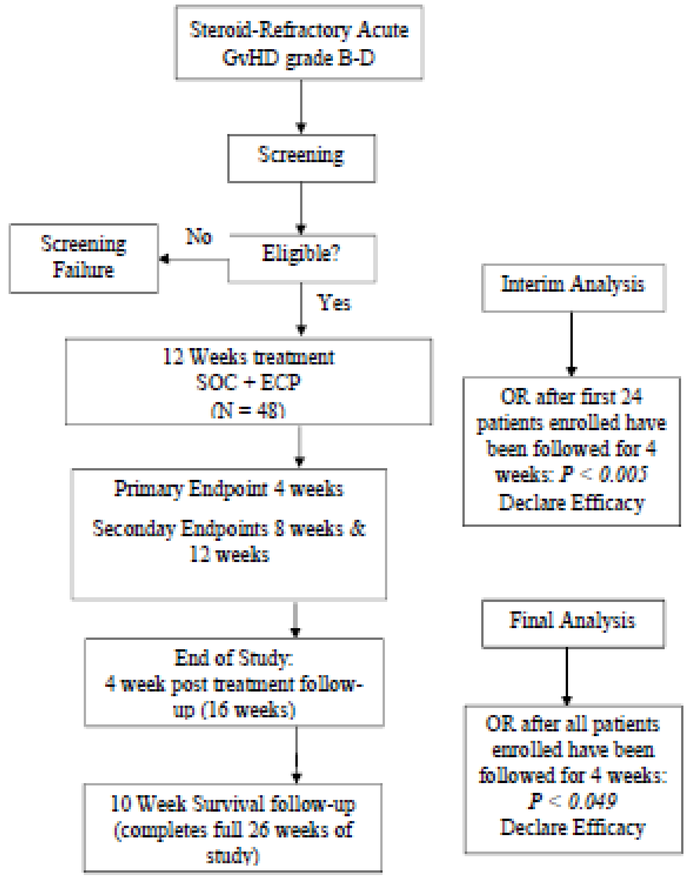
Objectives

- The primary objective of this study is to evaluate the efficacy of ECP in pediatric patients with steroid-refractory aGvHD.
- Secondary objectives are to access the:
  - Safety of ECP
  - Duration of response to ECP
  - Steroid-sparing effect of ECP, and
  - Organ-specific response to ECP therapy.

Study Population

- Male or female patients aged 1-21 who have steroid-refractory grade B-D aGvHD.
- Steroid-refractory is defined as a failure to respond to steroid treatment, with failure to respond defined as any grade B-D (International Bone Marrow Transplant Registry Database [IBMTR] grading) aGvHD that shows progression ≥3 days or no improvement by 5 days, of treatment with 2 mg/kg/day methylprednisolone or equivalent in patients with lower GI or liver disease, or skin disease associated with bullae. Grade D organ involvement will be limited to skin and liver.
- Steroid refractory may also be defined as a failure to respond to 1 mg/kg/day of methylprednisolone or equivalent in patients with disease confined to upper GI disease or lesser degrees of skin GvHD.

Study Design



Study Endpoints

Primary Endpoint

- Proportion of patients with an overall response (complete response [CR] + partial response [PR]) after 4 weeks (Day 28) of treatment with ECP*

Key Secondary Endpoints

- Safety parameters (vital signs, laboratory tests, and spontaneously reported adverse events [AEs] and serious adverse events [SAEs]).
- Proportion of patients with an overall response (OR) at 8 weeks (Day 56) and 12 weeks (Day 84) after initiation of treatment with ECP.
- Duration of response (defined as the length of time a patient maintains a response through Week 16 of the Follow-up Period on a per-patient basis).
- Proportion of patients with an OR after 4 weeks (Day 28), 8 weeks (Day 56), and 12 weeks (Day 84) of treatment with ECP according to the modified Glucksberg criteria.

References

1. Pulsipher MA, Peters C, Pui C-H *Biol Blood Marrow Transplant.* 2011;17(1 Suppl):S137-S148.
2. Calore E, et al. *Biol Blood Marrow Transplant.* 2015;21(11):1963-1972.

INVESTOR DAY 2017 OCTOBER 4 NEW YORK, NY

Extracorporeal Photopheresis (ECP) for the Management of Progressive Bronchiolitis Obliterans Syndrome (BOS) in Medicare-Eligible Recipients of Lung Allografts (ECP Registry) Investigator-Initiated Research

(George Despotis, MD; Washington University School of Medicine, St. Louis)

Mallinckrodt Pharmaceuticals

Background

- Lung transplantation has become the treatment of choice for selected patients with end-stage lung disease; however, long-term survival after transplantation remains disappointing.[1]
- Chronic rejection (BOS) has emerged as the leading obstacle to better long-term outcomes, and represents the leading cause of death beyond the first year after transplantation.[1-3]
- BOS is diagnosed by the decline in FEV_1, a pulmonary function test.[2,3]
- Management of BOS has been disappointing. BOS is treated by intensifying the immuno-suppressive regimen.[3] Despite treatment, most patients continue to show progressive decline in lung function resulting in worsening functional status, quality of life, and ultimately graft failure and death.[3]
- ECP has been used as a salvage treatment for refractory BOS with favorable clinical results in many cases.[4]
- On April 30, 2012, the Center for Medicare Services (CMS) issued a decision memo stating that ECP is covered for Medicare beneficiaries for the treatment of BOS following lung allograft transplantation only when the procedure is provided under a clinical research study (ie, coverage with evidence development [CED]).[5]
- What is not well understood currently is whether certain coexisting disease states or patient-related demographic, functional, treatment-related or diagnostic variables might have predictive value in identifying subsets of BOS patients that are likely, or unlikely, to experience reduced rate of decline or stabilization in FEV_1 following treatment with ECP.
- **Note: As this is an IIR, MNK is only funding this research and is not conducting or involved in this IIR**

Purpose

- The purpose of this ongoing, 1 year prospective, single-arm, cohort observational study (NCT02181257) is to determine if ECP is effective in the treatment of progressive BOS in patients after lung transplantation.

Objectives

- Registry study to enroll 160 patients from multiple US centers to
  - (1) confirm that ECP significantly reduces the rate of FEV_1 decline in BOS patients refractory to standard immunosuppressive drug therapy, and
  - (2) capture and assess specified patient demographic, treatment-related, diagnostic, functional and co-morbidity-related variables that may predict outcomes after ECP therapy.

Study Population

- Patients will be identified by physician investigators and co-investigators, study staff, and review of relevant administrative databases maintained for routine clinical care purposes (eg, lung transplantation division database, pulmonary function laboratory database, etc), subject to local Institutional Review Board (IRB) approval.

Study Design

- Following enrollment, patients will receive 24 ECP treatments over a 6-month period: 8 to 10 treatments (1st 30 days following treatment initiation); 8 to 10 treatments in the next 60 days (Months 2 and 3); 6 treatments in the next 90 days (Months 4 through 6) at a rate of 2 treatments/month.
- Patients will have spirometry the first week of treatment, and at Days 30, 60, 90, 120, 150, 180, 240, 300, and at 1 year; an improvement in FEV_1 will be used to assess success/benefit of ECP treatment.

Study Endpoints

Primary Outcome Measure

- Change in the rate of FEV_1 decline assessed by comparing the average rate of FEV_1 decline over the 6 months prior to ECP against the average rate of FEV_1 decline over the 6 months following initiation of ECP.

Secondary Outcome Measure

- Average rate of FEV_1 decline over the 12 months following initiation of ECP.

Other Outcome Measures

- All-cause mortality at 12 months following initiation of ECP (observational only)
- Proportion of patients with treatment related Serious Adverse Events (SAEs).*,†

Planned Protocol Amendment (pending WU IRB approval)

- The information presented is consistent with the current posting on clinicaltrials.gov (last updated November 22, 2016).
- As of the Fall 2016, CMS approved a protocol amendment which added early detection, through either more frequent laboratory spirometry or with a standardized home spirometry method, and a randomized controlled trial (RCT) cohort involving use of ECP as first line treatment compared with institutional standard of care; also included is a cohort involving patients with a current diagnosis of refractory BOS or patients randomized to control who become eligible for crossover ECP rescue therapy. The RCT will increase the scientific validity and definitively evaluate treatment efficacy. It'll enroll a total of 782 patients over 6 years, across 20 centers in the US.

*A SAE is any AE that results in death, a life-threatening adverse experience, a persistent or significant disability/incapacity, inpatient hospitalization or prolongation of existing hospitalization, emergency department visit or activation of an acute response team, pregnancy abortion, or a congenital anomaly, birth defect, or cancer in a neonate/infant born to a female patient. Medical events that do not strictly fulfill these criteria should be considered SAEs if they seriously jeopardize the patient or require aggressive medical or surgical intervention to prevent one of the above outcomes.

†Patients will be monitored and followed clinically according to each site's standard clinical practice. Sites should follow their local IRB's guidelines in terms of reporting AEs and SAEs to the local IRB.

References

1. Yusen RD, et al; International Society for Heart and Lung Transplantation. *J Heart Lung Transplant*. 2014;33(10):1009–1024. **2.** Gracon ASA, Wilkes DS. *Hum Immunol.* 2014;75(8):887-894. **3.** Spahr JE, Meyer KC. Chapter 9: Lung Transplantation. In: Hricik D, ed., American Society of Transplantation. *Primer on Transplantation*, 3rd ed. Medford, MA: Wiley-Blackwell; 2011:205-237. **4.** Morrell MR, et al. *J Heart Lung Transplant*. 2010;29:424-431. **5.** Decision Memo for Extracorporeal Photopheresis (ECP) (CAG-00324R2), Centers for Medicare & Medicaid Services (CMS.gov) website. https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=255. April 2012. Accessed August 29, 2017.

32-T

Estimating the Economic Impact of Reduced Total Surgery Time: An Analysis to Evaluate Potential Operating Room Cost Savings with a Novel Polyaldehyde-based Vascular Surgical Sealant

An Pham, PharmD, MBA, FAHA; George J. Wan, PhD, MPH; John Pribble, PharmD

Mallinckrodt Pharmaceuticals, Hazelwood, MO

PURPOSE

► The Triple Aim framework for health care requires simultaneous pursuit of (1) enhancing the patient experience, (2) improving the health of populations, and (3) reducing per capita costs of health care.[1]

► Time is regarded as the most expensive variable in the operating room (OR).[2] Suture line bleeding from vascular reconstructive surgeries can result in significantly increased surgery time, and subsequently increased costs.[3]

► A randomized, prospective, multi-institutional trial that evaluated the safety and effectiveness of a novel prophylactic vascular sealant in arterial surgery also revealed significantly reduced total surgery time (TST) when compared with the control group. Cost savings likely resulted from decreased TST, although no cost analysis was performed.[3]

► Objective: The goal of this analysis was to estimate the potential economic impact of shorter TST in a broad array of vascular procedures among patients treated with polyaldehyde-based vascular surgical sealant (PBS) compared with a commonly used topical agent, absorbable gelatin sponge (AGS).

METHODS

► Outcome of interest was potential OR cost savings with PBS when compared with AGS:

Potential OR cost savings =
OR cost per minute (USD) *x* reduced TST (minutes)

► Google searches identified online postings of OR charges and costs (keywords used: OR costs, OR charges, and OR cost estimates per minute).

METHODS

► Data on reduced TST comparing PBS with AGS was obtained from a prospective, multicenter, randomized, controlled study (NCT00759681).[3]

- TST was defined as the time from the initial incision to the time the dressings were placed.
- The prophylactic sealing of suture lines at the anastomosis between native vessels and synthetic vascular grafts or patches comparing the PBS sealant (PreveLeak, containing equal volumes of purified bovine serum albumin and polyaldehyde) versus the AGS (containing 125 units/mL human derived thrombin) showed a clinically meaningful and statistically significant difference of -0.7hr (95% CI: -1.2hr to -0.2hr, P=0.0085), equivalent to 42 minutes shorter TST [3.2±1.4hr (N=110) for PBS versus 3.8±2.2hr (N=106) for AGS].
- Vascular procedures included aortic, extremity bypass, carotid, hemodialysis access grafting, and other arterial surgical procedures.
- Patients were treated between October 2008 and December 2009 at 11 investigational sites.

► For this analysis, we focused on OR costs instead of a wider range of patient's OR charges to estimate a potentially closer actual cost at a surgical facility.

RESULTS

► While no formal data on actual OR costs at the facility level by the Healthcare Cost and Utilization Project or the American Hospital Association were published, OR time costing between $20-$65/minute was reported by OR Manager Inc. in 2014.[4]

RESULTS

► In contrast, a 2005 study of 100 US hospitals found that OR charges to patients averaged around $62/minute (range: $22-$133/minute), depending on a variety of factors including US region and surgical procedure based on complexity level (1-6) being performed. For example, OR time for major cardiac surgery costs more than that for an inguinal hernia repair.[5]

► At Akron General, a 532-bed hospital, a complexity level-1 case is billed at $28/minute whereas a complexity level-6 case is billed at $63/minute.[6]

► At University Hospitals Case Medical Center, with 1,032 beds, a level-1 case is billed at $64/minute whereas a level-6 case is billed at $128/minute.[7]

► From a $20-$65/minute cost perspective, a surgical facility could potentially save between $720-$2,340 per patient based on the absolute difference of 36 minutes in TST with PBS (Figure 1).

► We also performed a sensitivity analysis having as boundaries the lower and upper limits of the 95% CI around the mean difference in TST (42 minutes).

- Considering the lower limit (12 minutes), potential OR cost savings per patient could vary from $240-$780.
- At the upper limit (72 minutes), OR savings per patient could vary from $1,440-$4,680.

CONCLUSIONS

► Prophylactic sealing of suture lines at the anastomosis with PBS compared with AGS is associated with potential OR cost savings based on reduced TST.

► From a clinician's perspective, the inclusion of PBS to the vascular surgeon's armamentarium has the potential to assist in more cost-effective care.

CONCLUSIONS

► From a hospital administrator perspective, OR time is a significant variable in the total hospital operating cost structure. OR time efficiency may improve hospital gross margin or may provide an opportunity to increase incremental revenue generation.

► Furthermore, reduction of TST can lead to extra cases being performed. A range of common surgical procedures can be performed in 36 minutes[8], such as:

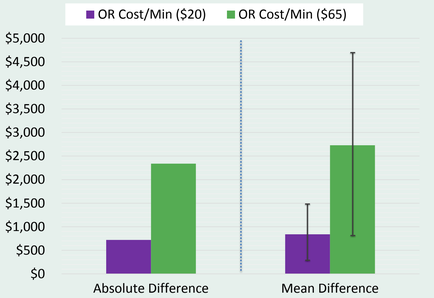
- **Gynecological surgery**: loop electrosurgical excision procedure (LEEP), tubal ligation, hernias, breast biopsy, dilation and curettage (D&C), hysteroscopy for abnormal uterine bleeding (endometrial ablation method), Caesarean section;
- **Abdominal surgery**: laparoscopic cholecystectomy and appendectomy;
- **Lung surgery**: video-assisted thoracoscopic surgery, laparoscopic lung biopsy;
- **Orthopedic surgery**: arthroscopy;
- **Hand surgery**: carpal tunnel release;
- **Ear, nose and throat procedures (ENT):** nasal cautery, tonsillectomy, myringotomy and ear tube placement, and laparoscopic ENT exams;
- **Circumcision**.

REFERENCES

1. Berwick DM, et al. The Triple Aim: Care, Health, and Cost. *Health Affairs*. 2008;3:759-769.
2. Saleh KJ, et al. "Operating-room throughput: strategies for improvement." *J Bone Joint Surg Am*. 2009;3:2028-2039.
3. Stone WM, Cull DL, and Money SR. A randomized prospective multicenter trial of novel vascular sealant. *Ann Vasc Surg*. 2012;26:1077-1084.
4. OR Manager. Firm policies and the right procedures tip the cost-benefit balance toward flip rooms. Vol 30, No 4, April 2014.
5. Macario A. What does one minute of operating room time cost? *Journal of Clinical Anesthesia* 2010;22: 233–236.
6. Cleveland Clinic. Akron General. Patient Price Information List. Available at: http://www.akrongeneral.org/portal/page/portal/AGMC_PAGEGROUP/Price_guide/PRICE_GUIDE5. Accessed March 6, 2016.
7. University Hospitals Case Medical Center. Patient Pricing Information. Available at: http://www.uhhospitals.org/ case/patients-and-visitors/billing-insurance-and-medical-records/patient-pricing-information. Accessed March 6, 2016.
8. Expert opinion from 10 practicing anesthesiologists attending the *Annual Congress of Enhanced Recovery and Perioperative Medicine Meeting*, April 20-22, 2016, Washington, DC.

Figure 1. Potential Economic Impact of Reduced Total Surgery Time (TST) – Cost Savings

Reduced TST	OR Cost/min: $20 Cost Savings (USD)	OR Cost/min: $65 Cost Savings (USD)
Absolute Difference (0.6 hours or 36 min.)	$720	$2,340
Mean Difference (0.7 hours or 42 min.)	$840	$2,730
95% Confidence Interval		
Lower Limit (0.2 hours or 12 min.)	$240	$780
Upper Limit (1.2 hours or 72 min.)	$1,440	$4,680



These values in 2014 USD would increase by 6% if adjusted to 2016 USD using the medical care component of the Consumer Price Index (Bureau of Labor Statistics data available at http://data.bls.gov/timeseries/CUUR0000SAM?output_view=pct_12mths).

ACKNOWLEDGMENT

► The authors would like to thank Ms. Elaine Boing, HEOR Research Associate, for assistance with poster preparation.

DISCLOSURE

► The funding for this study was provided by Mallinckrodt Pharmaceuticals.

200846

Recombinant human thrombin use in surgery: Systematic review of impact on clinical outcomes and costs

An T. Pham[1], PharmD, MBA, FAHA; Belinda Lovelace[1], PharmD; George J. Wan[1], PhD, MPH; Michael Baker[2], PhD

[1]Health Economics and Outcomes Research Department, Mallinckrodt Pharmaceuticals, Hampton, NJ; [2]Samorn Biosciences, Inc., San Diego, CA

BACKGROUND

► When surgical ligation of bleeding fails or is not possible, surgeons rely on a number of hemostatic aids, including topical thrombins (recombinant human thrombin [rhThrombin], pooled human plasma-derived thrombin, and bovine thrombin).

► Since the 1980s, the trend in vaccine and biologic drug development has been migrating toward either recombinant human or humanized technological platforms and away from animal-derived sources (ADS), given the well-documented potential immune reactions and safety concerns associated with the latter.

► Thrombin preparations have established efficacy in achieving hemostasis and are used in nearly 1 million patients each year in the United States across a broad range of surgical procedures (Lawson, 2006).

► **Objective**: The goal of this systematic review was to assess the impact of rhThrombin use during surgery on clinical outcomes and the potential for reductions in costs.

METHODS

► A literature survey was performed using BIOSIS, Embase, and Medline through May 2016 using the terms “recombinant human thrombin,” “rThrombin,” “rhThrombin,” and “Recothrom.”

► **Inclusion criteria**: Articles addressing rhThrombin use during surgery that evaluated costs and/or clinical outcomes such as time to hemostasis and incidence of adverse events were selected for inclusion in this review.

► **Exclusion criteria**: Evaluations of sealants, adhesives, glues, and hemostats that contain rhThrombin mixed with fibrinogen and other clotting factors were excluded.

RESULTS

► A total of 27 relevant articles were identified, comprising 9 reviews, 6 open-label and retrospective studies, 5 animal models of efficacy or immunogenicity, 3 prospective randomized controlled trials, 3 pooled analyses, and 1 case study (**Figure 1**).

► 10 articles reported on safety, immunogenicity, and efficacy (**Table 1**). Overall, rhThrombin use in multiple surgical settings was shown to be safe and well-tolerated, and was shown to achieve more rapid hemostasis than in patients not receiving rhThrombin.

RESULTS

► In a Phase 3 comparison of rhThrombin and bovine thrombin, the percentages of patients who achieved hemostasis within 10 minutes of application were comparable at 95.4% and 95.1%, respectively (0.3% difference in treatment effect, 95% CI, -3.7 to 5.0).

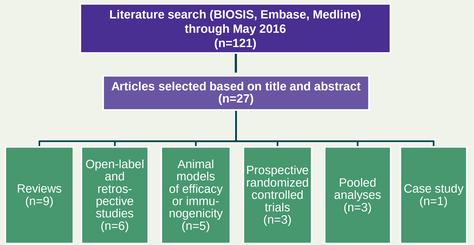
The incidence of antibody formation was 21.5% (43/200) in the bovine thrombin group and 1.5% (3/198) in the rhThrombin group (p<0.001). Patients with antibodies to bovine thrombin had numerically higher incidences of bleeding or thromboembolic events than did patients without these antibodies (19% vs 13%; p value not reported).

The study was not designed or powered to demonstrate an association of antibody formation with adverse clinical outcomes and the adverse events observed with the two products were similar (Chapman et al., 2007).

► In a randomized, double-blind, placebo-controlled, multicenter study, the hazard ratio of 1.3 estimated for the comparison of time to hemostasis for rhThrombin plus gelatin sponge versus placebo plus gelatin sponge suggests rhThrombin has a positive impact on hemostasis (Chapman et al., 2006).

► Adverse events and laboratory parameters reported in clinical trials of rhThrombin were found to be consistent with those commonly observed in surgical patients. Like all thrombins, rhThrombin has a potential risk of thrombosis if rhThrombin is absorbed systemically (Lew & Weaver, 2006).

Figure 1. Results of search strategy

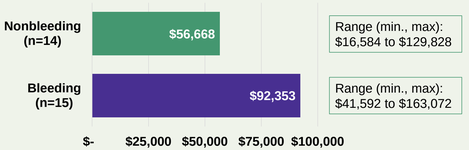


RESULTS

► No formal economic analyses for rhThrombin were identified. However, an economic impact model of costs related to cases of immune-mediated coagulopathy (IMC) was identified from published case reports of bovine thrombin-exposed patients (**Figure 2**) (Maxon et al., 2009).

Aggregate health care resource utilization was calculated for non-bleeding (n=14) and bleeding (n=15) cases based on established cost driver information. The estimated median total cost associated with managing bovine thrombin-associated IMC without bleeding complications was $56,668 as compared to $92,353 in cases with bleeding complications.

Figure 2. Estimated median cost associated with managing bovine thrombin-associated IMC complications*



*Maxon, M. S., Engley, G., Wisont, K., & Russell, T. (2009, October). *Impact of bovine thrombin-associated immune-mediated coagulopathy in the postoperative patient*. Poster presented at the American College of Clinical Pharmacy Annual Meeting, Anaheim, CA.

CONCLUSIONS

► Based upon a literature survey, rhThrombin use in multiple surgical settings was shown to be safe and well-tolerated, and was shown to result in more rapid hemostasis than in patients not receiving rhThrombin, but was no different than bovine thrombin.

► In addition, rhThrombin may be associated with lower antibody development than bovine thrombin (though clinical significance is unknown), and does not carry the risk of transmitting plasma-borne pathogens or prion diseases as with human plasma-derived thrombin.

► Whether the reductions in complications associated with use of rhThrombin during surgery directly reduce overall cost of care warrants further study.

ACKNOWLEDGEMENT AND DISCLOSURE

► The authors would like to thank Elaine A. Böing, HEOR Associate, for assistance with poster preparation.

► The funding for this study was provided by Mallinckrodt Pharmaceuticals.

Table 1. Recombinant human thrombin safety, immunogenicity, and efficacy data from included studies*

Author (Year) *Journal Name*	Safety	Immunogenicity	Efficacy
Chapman et al.[1] (2006) *J Thromb Haemost*	Compared with the placebo group (n=42), the rhThrombin group (n=88) had higher incidences of nausea (45% vs 26%), constipation (27% vs 12%), insomnia (19% vs 5%), and vomiting (13% vs 2%). Most AEs were mild or moderate in severity and none were assessed as related to study drug	One patient in each group developed anti-rhThrombin product antibodies, none of which were neutralizing or associated with bleeding complications	An estimated hazard ratio of 1.3 for the rhThrombin arm compared with placebo and the 95% effectiveness of open-label rhThrombin administered as rescue therapy suggest a positive impact on hemostasis
Chapman et al.[1] (2007) *J Am Coll Surg*	The most common AEs in the rhThrombin and bovine thrombin groups were incision site complication (63%, both groups), procedural pain (29% vs 34%, respectively), and nausea (28% vs 35%), respectively	In the rhThrombin group, 3 of 198 (1.5%) patients developed specific anti-rhThrombin product antibodies. In contrast, 43 of 200 (21.5%) patients treated with bovine thrombin developed specific anti-product antibodies (p<0.0001)	Hemostasis within 10 minutes was achieved in 95% of patients receiving either rhThrombin or bovine thrombin
Weaver et al.[1] (2008) *J Vasc Surg*	Adverse event profiles and laboratory findings were similar between groups (rhThrombin, n=82; bovine thrombin, n=82)	No patients in the rhThrombin group developed anti-rhThrombin product antibodies at day 29, whereas 27% of patients in the bovine thrombin group developed antibodies to bovine thrombin product (p<.0001)	A comparable incidence of anastomotic hemostasis was observed in both treatment groups at 10 minutes (94% bovine thrombin, 91% rhThrombin)
Greenhalgh et al.[2] (2009) *J Burn Care Res*	AEs occurring in ≥10% of the 72 patients treated with rhThrombin included procedural pain (35%), pruritus (25%), constipation (19%), insomnia (14%), anemia (11%), nausea (11%), and seroma (10%)	Of the 62 patients with antibody measurements at day 29, 1 (1.6%) developed anti-rhThrombin product antibodies following application of study drug. These antibodies did not neutralize native human thrombin	Following rhThrombin application, hemostasis at the burn wound excision site was achieved in 60.6% of patients within 15 minutes and 91.5% of patients within 20 minutes. Greater than 90% skin graft survival was observed in 88.9% of patients who completed the day 29 assessment
Singla et al.[2] (2009) *J Am Coll Surg*	AEs occurring in ≥10% of patients treated with rhThrombin included incision site pain (45%), procedural pain (39%), nausea (27%), constipation (20%), anemia (17%), muscle spasms (12%), hypotension (11%), and pyrexia (10%)	No subjects developed anti-rhThrombin product antibodies at day 29	Not reported
Ballard et al.[3] (2010) *J Am Coll Surg*	Adverse events reported for ≥10% patients treated with rhThrombin included incision site pain, procedural pain, nausea, constipation, pyrexia, anemia, insomnia, vomiting, and pruritus	Five of 552 patients developed antibodies to rhThrombin (0.9%; 95% CI, 0.3 to 2.1; day 29); antibodies did not neutralize the biologic activity of native human thrombin	Not reported
Foster et al.[2] (2011) *J Pediatr Surg*	AEs occurring in ≥10% of rhThrombin-treated patients included procedural pain, pruritus, anemia, skin graft failure, and pyrexia	None of the 27 pediatric patients for whom complete immunogenicity data were available developed anti-rhThrombin product antibodies at study day 29	Not reported
Kiani et al.[2] (2012) *Heart Surg Forum*	Not reported	Not reported	The hemostat group had significant reductions in RBC transfusion compared with controls whose port sites were untreated (24.2% vs 40.8% receiving blood; p=.026; 0.44 vs 1.39 U transfused postoperatively, p=.024)
Malgor et al.[2] (2012), *Vasc Endovascular Surg*	No distal embolization	No allergic reactions	Successful durable occlusion of the PDAs was achieved in 43 of 47 (91.5%) patients
Singla et al.[3] (2012) *Pharmacotherapy*	AEs reported for ≥10% of 644 patients included incision site pain (47.4%), procedural pain (33.4%), nausea (26.4%), constipation (21.3%), pyrexia (15.2%), anemia (14.4%), pruritus (11.8%), insomnia (10.7%), and vomiting (10.1%)	At day 29, 5 (0.8%) patients treated with rhThrombin developed anti-recombinant thrombin product antibodies; none of these antibodies neutralized native human thrombin	Not reported

*Select references on safety, immunogenicity, and efficacy; [1]Prospective randomized controlled trials; [2]Open-label and retrospective studies; [3]Pooled analyses.
AE, adverse event; RBC, red blood cell.