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PHARMACY COMMITTEE ... NOTES

THE MOSES H. CONE GROUP OF HEALTH CARE SERVICES

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HA-1A®

HA-1A® (nebacumab - Centocor), a monoclonal IgM antibody against endotoxin from gram-negative bacteria, is soon expected to be approved for marketing by the FDA. HA-1A® has been shown to be safe and effective as adjunct therapy for patients with sepsis due to gram-negative bacteremia.[1]

Septic shock, a shock syndrome resulting from systemic response to infection, is the most common cause of death in intensive care units.[2] Annually, it is estimated that there are 400,000 cases of sepsis and 200,000 episodes of septic shock, with an associated mortality of 100,000 patients.[2] Therapeutic strategies for treating sepsis, including antibiotics, hemodynamic support, and ancillary therapies such as corticosteroids and naloxone, have failed to decrease the mortality associated with septic shock.[3] Recent advances in biotechnology have led to the development of monoclonal antibodies against endotoxin and tumor necrosis factor (TNF), two important mediators of shock syndrome.

Rationale for Immunotherapy

Endotoxin is the lipopolysaccharide (LPS) component of the gram-negative bacterial cell wall that is believed to be responsible for tissue damage and serious sequelae observed in patients with gram-negative bacteremia.[2] The core regions of endotoxin have almost identical chemical structures among gram-negative bacterial species and contains lipid A, the toxic component of the molecule.[4] These structural and biological properties of the molecule led to the hypothesis that passive immunotherapy with antibody directed against core determinants of endotoxin should inhibit the biological effects of endotoxin, prevent endotoxin tissue damage, and reduce mortality in septic patients with gram-negative bacteremia.

Clinical Trials

Initial evaluation of this hypothesis made use of human antiserum to the endotoxin LPS core. The results showed that there was a reduction in mortality from gram-negative infections.[5-10] Preparation of human antiserum for widespread clinical use is not practical; many volunteers would have to be inoculated to produce sufficient antibody and the product could potentially carry blood-borne infectious agents. This lead to the concept of developing immunotherapy based on monoclonal antibody (Mab) technology.

There are currently two monoclonal antibodies against endotoxin available, for investigational use, in the United States; E5, a murine (mouse) Mab (Xomen® - Xoma) and nebacumab, a human Mab (HA-1A® - Centocor). Both antibodies have been shown to improve survival of patients with gram-negative baceremia in prospective, controlled multicenter trials.[1,11] E5 also provides survival benefit in patients with gram-negative infections, without bacteremia complicated by multi organ dysfunction.[11] HA-1A® offers protection in shock,[1] but E5, inexplicably, does not improve survival in patients with septic shock.[11] In analyzing all patients with presumed gram-negative sepsis enroled in either the HA-1A® or E5 studies, no reduction in morbidity or mortality was observed.[1,11] The E5 Mab is not expected to be approved in the near future.

To date there has only been one published study evaluating the efficacy and safety of HA-1A®.[1] The clinical trial by Ziegler et al, was a placebo-controlled, double-blind study with the analyses focusing on the subgroup of patients with confirmed gram-negative bacteremia (see table). It has been shown that this subgroup of patients has a high incidence of endotoxemia.[4] The study patients received optimal antibiotic and supportive care based on the standards for the hospital in which they were enrolled and were evaluated for 28-days after treatment. A single intravenous dose of 100 mg HA-1A® was administered, on an average of 14 hours from time of diagnosis of sepsis, to 262 patients while 281 received placebo. In all, 200 patients with gram-negative bacteremia were followed through day 28 or until death (37% of all study patients). There were 32 deaths among the 105 recipients of HA-1A® (30%) and 45 deaths among the 92 recipients of placebo (49%; $p = 0.014$). This reflected a 39% reduction in mortality. Treatment benefit also extended to the 101 patients with gram-negative bacteremia who were in shock (defined as a systolic blood pressure of < 90 mmHg or the use of vasopressors to maintain blood pressure) at study entry. In this subgroup there were 27 deaths among the 47 recipients of placebo (57%) and 18 deaths among the 54 recipients of HA-1A® (33%; $p = 0.017$), resulting in a 42% reduction in 28-day mortality.

(continued on next page)

Among patients with gram-negative bacteremia, HA-1A® provided a greater resolution of organ failure. All evidence of organ failure disappeared within 7 days in 38 of 61 patients given HA-1A® (62%) and in 26 of 36 patients given placebo (42%; $p = 0.024$).

However, it is important to note that treatment with HA-1A® was not shown to improve overall survival. For all 543 patients with sepsis who were treated, the mortality rate was 43% among recipients of placebo and 39% among those given HA-1A® ($p = 0.24$).

To summarize this study, HA-1A® reduced mortality by 39% in patients with sepsis and gram-negative bacteremia and resulted in a 42% reduction in mortality in patients with gram-negative bacteremia who were in shock. However, it is important to remember that there was no statistical difference in overall mortality between the two groups (placebo vs HA-1A®).

Baseline Characteristics and Outcome in Major Reported Subgroups

	HA-1A® (n=105)	Placebo (N=95)
Baseline characteristics:		
mean age (yrs)	58.0	62.3
mean weight (kg)	70.3	75.6
male (%)	59	58
mean APACHE II scores	23.6	25.7
confirmed bacteremia (%)	100	100
evidence of shock (%)	51	51
organ failure (%)		
acute renal failure	35	46
ARDS	9	13
acute hepatic failure	19	26
DIC	18	21
mortality – gram(−) bacteremia		
entire subgroup (%)	32	49
patients with shock (%)	33	57
resolution of organ failure (%) (post 7 days)	62	42

Adverse reactions:

The safety of HA-1A® has been evaluated in over 800 patients. Hypotension during the infusion has been seen in approximately 1.4% of the patients receiving HA-1A®.[12] Episodes of flushing, hypotension, edema, erythema and bronchospasm during infusion have been observed rarely (< 1% incidence).[12] The incidence of other adverse events was similar between the HA-1A® and placebo groups.[12]

Dosing and administration:

HA-1A® is administered as a single intravenous dose of 100 mg in 50 ml of normal saline infused over 15 to 30 minutes. It is important to remember that the drug must be filtered with a low protein binding filter prior to administration.

HA-1A® is incompatible with low ionic strength solutions (water, dextrose) and low pH solutions (pH < 5.0). Therefore, HA-1A® should be infused via a separate line and not mixed with any solutions or medications.

The preliminary pharmacokinetic data suggest that dosing adjustments for age, APACHE II score, renal or hepatic function are not necessary.[3]

Cost

At Moses Cone, a single dose of 100mg HA-1A® is estimated to cost the institution $4,000.

Therapeutic issues

Due to the high cost of this drug, it is necessary to try to select the most appropriate patients for treatment. Patients most likely to benefit from administration of HA-1A® are those with gram-negative bacteremia. In reality one tends to treat two to three times the number of patients than the subgroup of patients that have been shown to have some benefit, as positive confirmation of gram-negative bacteremia usually occurs after the sepsis syndrome appears. This was shown in the Ziegler study where only 37% of all patients treated with HA-1A® actually had gram-negative bacteremia.

Studies for HA-1A® use in pediatric patients, prophylaxis of surgical patients in high risk patients and retreatment of patients are currently underway. The hypothesis of retreatment is that a subgroup of patients who have high levels of circulating endotoxemia may show some benefit. In addition, it is believed that the administration of antibiotics can cause a rise in circulating endotoxemia. However, due to lack of data, currently only a single dose of HA-1A® is recommended.

In addition, it should be remembered that this is an adjunct therapy to sepsis and that it does not replace appropriate management of the sepsis syndrome. Prompt presumptive treatment for sepsis is the standard of care which assumes there is access to intensive supportive care, specific surgical procedures when indicated, and antibiotic therapy effective against suspected or identified organisms. The level of care required is most likely to be rendered in the intensive care setting.

Use at Moses Cone

Due to the high cost of this agent the Pharmacy Committee has established criteria for use, in the form of an order form (see appendix), to assure that those patients most likely to benefit from the drug will be the ones to receive it. These criteria are based on the study by Ziegler, et al.[1] The order form must be completed by a physician prior to the patient receiving HA-1A®. The drug will be concurrently monitored by the pharmacy department in order to define the most appropriate patient population.

Summary

HA-1A®Has been shown to be safe and effective in the treatment of sepsis for the subgroup of patientes with gram-negative bacteremia. However, there has been no reduction in overall mortality when one takes into consideration patients with gram-negative, gram-positive and fungal septicemia. It, therefore, should only be considered for use when there is a strong suspicion of gram-negative bacteremia. In addition it does not replace intense supportive care or appropriate antibiotic therapy.

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Pharmacy Resident

References

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APPENDIX I

HUMAN MONOCLONAL ANTI-ENDOTOXIN ANTIBODY (HA-1A®) (NEBACUMAB) REQUEST FORM

The new monoclonal antibody against gram-negative bacterial endotoxin, HA-1A®, will cost the institution approximately $4,000 for one treatment. (Actual costs have not been announced by the manufacturer.) Therefore, in order to promote appropriate use of HA-1A®, the Pharmacy Committee requests that the drug be given only to those patients that meet the following criteria. **This order form must be completed and signed by a physician prior to dispensing the drug. Telephone or verbal orders are not acceptable.**

Please check appropriate boxes:

☐ Known or suspected gram negative infection.

☐ Temperature >101°F or <96°F.

☐ Heart Rate >90 and Respiratory Rate >20 or mechanical ventilation.

And either:

☐ Hypotension (Systolic Blood Pressure < or = to 90 or a sustained decrease in blood pressure > or = to 40 mmHg despite attempts at fluid resuscitation).

Or at least two of the following:

☐ Unexplained metabolic acidosis (pH < or = 7.3, base deficit of >5 mmol/liter, or an elevated plasma lactate level).

☐ Arterial hypoxemia (p_aO_2 of 75 torr or less or p_aO_2/FIO_2 <250).

☐ Acute renal failure (urine output <0.5 ml/kg/hour).

☐ Evidence of DIC (increased PT or PTT or either a platelet count of less than 100,000 or a decrease in platelets of 50 percent under baseline values).

☐ Sudden decrease in mental acuity.

☐ Cardiac index >4.0 with SVR <800 dyn-sec-cm^{-5}.

Excluded are:

☐ Patients with conditions marked by irreversible, rapidly fatal outcomes.

☐ Patients with uncontrolled hemorrhage or cardiogenic shock.

If criteria are met, give HA-1A® 100 mg IV, per Pharmacy protocol unless physician has specified otherwise. Do not filter HA-1A® during administration.

Thrombolytic Therapy in Myocardial Infarction

Many studies and articles about thrombolysis in myocardial infarction have appeared in the medical literature in recent years. Several of these address the question of whether to use tissue plasminogen activator (TPA) or streptokinase (SK).[1-5] Neither these nor the preliminary reports of the recently completed ISIS-3 (International Study on Infarct Survival) study have conclusively pointed to a particular agent of choice. This article will discuss some of the points of interest in these studies, as well as present data from a recent drug usage evaluation (DUE) of TPA performed at the Moses H. Cone Memorial Hospital (MCH).

In comparisons of TPA and SK, the endpoints which have been used include reperfusion rate, mortality, left ventricular function, and incidence of side effects. The time from onset of chest pain to treatment ranged from 3-7 hours in the referenced studies.[1-3] Recent reports question the arbitrary cut off for time and age as excluding many patients which may benefit from thrombolysis.[6-7]

Sherry and Marder[5] dispute the use of a 90 minute patency or reperfusion rate as a measure of outcome in comparing TPA to SK. The Phase I Thrombolysis in myocardial infarction (TIMI-1) trial suggested that TPA was twice as effective as SK in opening occluded vessels. This was based on 90 minute reperfusion rates of 62% and 31% with TPA and SK, respectively.[1] White et al[2] showed essentially equal patency rates 3 weeks post infarction with both agents.

However, as Sherry and Marder point out, overall mortality with the two agents in TIMI-1 was not significantly different.[5] The larger GISSI-2 trial also failed to show a significant difference in mortality between the two agents.[3]

White et al[2] compared TPA and SK to assess left ventricular function as the primary endpoint. They concluded that left ventricular function was similar with TPA and SK three weeks post infarction. GISSI-2 did not show a significant difference in its combined endpoint of mortality or left ventricular function between TPA and SK.

Another point of comparision with TPA and SK is side effects. Bleeding complications are the primary side effects attributable to thrombolytic agents which cause concern.[8] Allergic reactions and hypotension are also potential side effects. The GISSI-2 trial showed a higher incidence of allergic reactions, hypotension, and major bleeding with SK versus TPA. The incidence of stroke was similar with both agents (TPA slightly higher – not statistically different).[3] The study by White et al showed minor bleeding with both agents. They also found a higher incidence of allergic reactions with SK. A small number of patients experienced severe bleeding and stroke with TPA in the White study as well.[2]

Whereas the comparitive studies do not point to a clear advantage of TPA or SK, one consideration not addressed is cost.[1-3] TPA costs MCH approximately $2100 for 100mg while SK costs approximately $80 for 1.5 million units (the dosage used in these studies).[1-3]

Recently, a retrospective DUE was conducted with examined all patients receiving TPA for myocardial infarction (MI) at MCH during fiscal year 1989 (October 1989 – September 1990). This accounted for 22 patients (Streptokinase was not concurrently studied since only 1 patient received it for MI during the same time period).

The data studied was collected from patients' medical records, management systems reports, and pharmacy records. The criteria for the DUE were approved by the DUE subcommittee of the Pharmacy and Therapeutics Committee.

The DUE criteria included appropriate indications, lack of absolute contraindications, proper concurrent therapy (i.e. heparin and lidocaine), concurrent monitoring for adverse effects, and evidence of efficacy (outcome).

All patients studied had ECG changes suggestive of MI. Eight-six percent (19/22 patients) presented to the emergency room within 6 hours of onset of chest pain (9 within 2 hours).

Only one patient treated had a reported absolute contraindication to treatment with TPA. This patient had undergone a root canal one week prior to TPA but failed to inform the physician of this fact.

Concurrent lidocaine and heparin therapies were administered to all but one patient (one patient received no lidocaine or a heparin load). Appropriate monitoring of patient data (lab, ECG, vital signs, etc.) was done throughout hospitalization with few exceptions.

Four patients had reported minor bleeding including bleeding gums, bruising, and nosebleeds. All of these episodes resolved without incident. No other major problems were reported.

Outcome was measured based on resolution of chest pain and ECG changes as well as possible reperfusion arrhythmias. Eight-two percent (18/22 patients) had acute resolution of their chest pain; however, it most be considered that many patients also received nitroglycerin and morphine which could positively skew this indicator. Fifty-five percent (12/22 patients) had resolution of ECG changes, and thirty-two percent (7/22 patients) had possible reperfusion arrhythmias.

In general, the patients studied received appropriate dosing and monitoring of TPA with relatively few side effects.

The results of the DUE on TPA were presented to the cardiac services committee for discussion and comments at the June meeting. The results were considered in conjunction with the committee's continuing work on the development of emergency room guidelines in the management of myocardial infarction. This data was then presented to the Pharmacy Committee where the following recommendations were made:

1. Present data indicates the most cost effective agent (streptokinase) should be utilized more often.
2. t-PA will remain the agent of choice for the following:
   a. Time of onset of symptoms cannot be clearly determined.
   b. Patients who seek treatment relatively late (>3-4 hours).
   c. Patients who have received streptokinase in the last 6 months.
   d. Patients relatively hypotensive with symptoms of acute myocardial infarction.
   e. Patients who recently had a streptococcal infection.
3. Delete apsac (Eminase® – Anistreplase) from MCH Formulary.

Robert Moye, Pharm.D.
Jackie Roh, R.Ph.

References available upon request.

1991 Top Twenty Pharmacy Items

1991	Product	Cost	Percentages	1990	Cost
1	Enteral Products	$312,438.50	4.80%	1	$315,939.20
2	Ondansetron	$196,863.00	3.02%	N/A	
3	Dobutamine	$187,438.00	2.88%	3	$168,651.00
4	Ceftriaxone	$147,298.52	2.26%	10	$109,042.00
5	Ranitidine	$144,977.00	2.23%	2	$173,461.11
6	Ceftizoxime	$138,974.00	2.13%	17	$ 90,632.74
7	Diabetic Supplies	$136,132.35	2.09%	4	$157,150.00
8	G-CSF (Neupogen)	$125,828.00	1.93%	N/A	
9	Midazolam	$125,516.00	1.93%	12	$107,927.00
10	Timentin®	$125,112.00	1.92%	11	$108,762.02
11	Etopside	$123,111.00	1.89%	7	$132,701.00
12	Heparin	$119,161.00	1.83%	13	$102,964.17
13	Vancomycin	$118,241.00	1.81%	8	$127,862.64
14	Lorazepam	$113,439.00	1.74%	6	$133,779.00
15	Cefuroxime	$112,254.00	1.72%	9	$117,568.92
16	Cefazolin	$111,184.00	1.71%	16	$ 92,248.56
17	Immune Globulin IV	$107,952.00	1.66%	N/A	
18	Ceftazidime	$107,507.00	1.65%	20	$ 85,117.32
19	Cisplatin	$106,691.00	1.64%	5	$141,921.00
20	Hetastarch	$101,664.00	1.56%	15	$ 93,881.00
	TOTAL TOP 20	$2,761,781.37	42.39% OF TOTAL PURCHASES		
	TOTAL OTHER	$3,753,262.56	57.61% OF TOTAL PURCHASES		
	TOTAL PHARMACY 1991	$6,515,043.93	100.00%		

% OF PURCHASES IS OF TOTAL PHARMACY PURCHASES
NA – THESE DID NOT RANK IN TOP 20 IN 1990.