Original articles

A model for rational introduction of new and expensive medicines

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Summary

The reported impact of human monoclonal IgM antibody (HA1A) on the mortality rate from Gram-negative bacteraemia aroused considerable interest in its use in Glasgow Royal Infirmary. However, the commercial preparation of HA1A was extremely expensive. With this in mind, the Infirmary's Drugs and Therapeutics Committee introduced a system whereby the commercial preparation of HA1A could be introduced in a controlled fashion, thereby establishing a model which would encourage targeting the prescription of new, highly expensive treatments to appropriate patients. This model provides the clinician with a set of objective criteria to be met before prescribing such a preparation, thus preventing unnecessary increases in the hospital drug budget and justifying using expensive resources.

Keywords: human monoclonal IgM antibody, Gram-negative sepsis, prescribing

Introduction

In the USA approximately 175 000 deaths occur annually from sepsis; 50% of these are caused by Gram-negative bacteria.¹ Thus, the reported impact² of human monoclonal IgM antibody (HA1A) on the mortality rate from Gram-negative bacteria aroused considerable interest in its use in Glasgow Royal Infirmary.

HA1A has been shown in several studies to reduce mortality significantly in septic patients with proven Gram-negative bacteraemia and became commercially available in 1991. Studies also showed no significant difference in the incidence of adverse effects between patients with Gram-negative bacteraemia receiving HA1A and those receiving the placebo.^{2,3} There were some reports, however, that suggest patients with Gram-positive bacteraemia, given HA1A, have a higher mortality rate than those patients given a placebo.⁴

The mechanism of action of HA1A was thought to be related to its ability to either neutralise or enhance the clearance of endotoxin produced by Gram-negative bacteria. A component of this endotoxin, lipid A, stimulates the release of factors from macrophages and endothelial cells which may lead to multiple organ failure and death.

Nonetheless, the commercial preparation of

HA1A is extremely expensive. With this in mind, the Drugs and Therapeutics Committee of the Glasgow Royal Infirmary introduced a system whereby the commercial preparation of HA1A would be introduced in a controlled fashion and its effect monitored and compared with other available and less expensive treatments for Gram-negative sepsis. If this model proved effective in the evaluation of HA1A, it could serve as a framework for evaluating the costs and benefits of other new expensive drugs.

Methods

Patients were considered for HA1A if there was clinical evidence of serious sepsis with suspected or proven Gram-negative bacteraemia and failure to respond to conventional therapy such as intravenous antibiotics.

The consultant responsible for the patient was required initially to seek authorisation for use of HA1A from any one of four nominated senior clinicians. This senior clinician would discuss the individual case with the senior bacteriologist 'on call'. If both the independent clinician and the bacteriologist agreed, authorisation would be given to release the HA1A for administration. To facilitate uniformity of decision-making and ease of subsequent interpretation, the requesting consultant was required to complete a standardised HA1A request form giving details of the patient's demographic information together with clinical details including temperature, heart rate, blood pressure, oxygen therapy and saturation, urine output, serum creatinine, bilirubin, transaminases, coagulation screen, white cell count, C-reactive protein, mental state, blood culture and other bacteriology results, antibiotic therapy, date of request, date of administration of HA1A and names of the authorising doctors. A sepsis score⁵ was calculated for each patient based on a scoring system which quantified the local effects of tissue infection, oral temperature, secondary effects of sepsis and laboratory data (tables 1–4). At a later date, the outcome and date of hospital discharge or death were inserted. This provided an extensive database to analyse the outcome of this selection process. Whether or not HA1A was authorised, the completed form had to be returned to the senior bacteriologist who was co-ordinating the study. For convenience, a stock of HA1A together with the authorisation forms were kept in the hospital's Intensive Care Unit.

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Table 1 Scoring of local effects of tissue infection

Attribute	Score	Patient score
Wound infection with purulent discharge/enterocutaneous fistula:		
Requiring only light dressing changed not more than once daily	2	
Requiring to be dressed with a pack, dressing needing to be changed more than once daily, requiring application of a bag and/or requiring suction	4	
Peritonitis		
Localised	2	
Generalised	6	
Chest infection		
Clinical or radiological signs of chest infection (without productive cough)	2	
Clinical or radiological signs of chest infection (with a cough producing purulent sputum)	4	
Full clinical manifestations of lobar/bronchopneumonia	6	
Deep-seated infection (eg, subphrenic abscess, pelvic abscess, empyema thoracis, acute or chronic osteomyelitis)	6	
	Total	A

Table 2 Scoring of pyrexia (oral temperature)

Attribute	Score	Patient score
Maximum daily temperature (°C)		
36–37.4	0	
37.5–38.4	1	
38.5–39	2	
> 39	3	
< 36	3	
	Add	
Minimum daily temperature > 37.5°C	1	
Two or more temperature peaks above 38.4°C in one day	1	
Any rigors occur in a day	1	
	Total	B

Temperature should be recorded at least four times in 24 h. The record for the 24-h period is assessed as above and ‘pyrexia score’ computed.

Table 3 Scoring of secondary effect of sepsis

Attribute	Score	Patient score
Obvious jaundice (in the absence of established hepatobiliary disease)	2	
Metabolic acidosis		
Compensated	1	
Uncompensated	2	
Renal failure		
Serum creatinine > 300 µmol/l	3	
Gross disturbance of mental orientation level of consciousness (eg, delirium, coma) and/or other focal neurological manifestation of pyaemia/septicaemia (having excluded other causes)	3	
Bleeding diathesis (from disseminated intravascular coagulation)	3	
	Total	C

Results

There were 23 requests for authorisation to use HA1A between 1 July 1991 and 20 January 1993, the date when the commercial preparation of HA1A was recalled by the manufacturers. Of the 23 requests, HA1A was authorised and administered to 20 patients and refused for three patients. There were four survivors and 16 deaths in those patients receiving HA1A. The three patients for whom HA1A was not authorised all survived (table 5). The mean average sepsis score for the four survivors given HA1A was 16.5. The sepsis score for those given HA1A who died was 16.6. The mean average sepsis score for those patients refused HA1A was 9.0 (table 5). Sixteen of the patients given HA1A had definite bacteriological evidence of Gram-negative sepsis. Of the four cases with no definite bacteriological evidence, there was strong clinical suspicion of a Gram-negative bacteraemia. The three patients who were refused HA1A had neither sufficient clinical nor bacteriological evidence of Gram-negative bacteraemia or had not received a trial of conventional treatment. The clinical histories of three typical patients for whom authorisation for HA1A was requested are given (see boxes).

Example of patient authorised to receive HA1A

Case A

A 64-year-old male was admitted for a prostatic biopsy. That evening, he developed signs of peritonitis. He was initially treated with intravenous fluids and antibiotics and underwent laparotomy which revealed gross oedema of the abdominal wall and retroperitoneal exudate. Post-operatively, he developed cardiorespiratory failure, septic shock and renal failure and was transferred to the Intensive Care Unit. He required inotropic support and he received HA1A. At this stage, his sepsis score was 13 and blood and peritoneal cultures grew *Escherichia coli*. Thereafter he progressed slowly and was discharged home.

Example of patient authorised to receive HA1A

Case B

A 52-year-old male with a history of cardiomyopathy and cerebrovascular disease was admitted as an emergency to the Intensive Care Unit with septic shock, a perforated duodenal ulcer and peritonitis. Following resuscitation with intravenous fluids, antibiotics and inotropes, he went to theatre for oversewing of the ulcer. He remained unwell post-operatively and was transferred back to the Intensive Care Unit where antibiotics and inotropes were continued. HA1A was authorised and administered on the basis of failure of conventional antibiotics, a sepsis score of 11 and likelihood of Gram-negative sepsis. Within six hours of receiving HA1A, he developed asystole and died.

Table 4 Scoring of laboratory data

Attribute	Score	Patient score
Blood culture:		
Single + ve culture	1	
Two or more + ve cultures separated by 24 h	3	
Single + ve culture + history of invasive procedure	3	
Single + ve culture + cardiac murmur and/or tender enlarged spleen	3	
Leucocyte count (× 10 ⁶ /l)		
12–30	1	
> 30	2	
< 2.5	3	
Hb concentration in the absence of obvious bleeding (g/dl):		
7–10	1	
< 7	2	
Platelet count (× 10 ⁶ /l):		
100–150	1	
< 100	2	
Plasma albumin concentration (g/l):		
31–35	1	
25–30	2	
< 25	3	
Plasma total bilirubin concentration in absence of clinically obvious jaundice:	1	
> 25 µmol/l		
	Total	D

Total = A (table 1) + B (table 2) + C (table 3) + D (table 4) = patient’s sepsis score

Table 5 Mortality rates and outcomes (July 1991–January 1993)

	HA1A requests	Died	Survived
Authorised	20	16	4
Not authorised	3	0	3
Total	23	16	7

Table 6 Sepsis scores (mean average)

Patient status	Sepsis score
Patients given HA1A who survived	16.5
Patients given HA1A who died	16.6
Patients not given HA1A	9.0

higher mortality rate (from Gram-negative bacteraemia) to be given HA1A and excluded those patients less likely to have Gram-negative sepsis (and hence probably have a lower mortality rate).

Authorisation for the administration of HA1A in this model came from any one of four senior clinicians in conjunction with the senior microbiologist ‘on call’. This joint decision-making allowed both the clinical and bacteriological status of the patient to be taken into account. The fact that all clinicians were aware that such an ‘authorisation procedure’ existed perhaps encouraged them to think even more seriously as to whether a patient had sufficient evidence of a Gram-negative bacteraemia to merit consideration for HA1A. Furthermore, sufficient detail had to be provided to the authorising senior clinician and bacteriologist to convince them of the need for administration of HA1A.

This approach to the introduction of new, expensive, drugs to a hospital is not designed to be obstructive to clinicians in the treatment of their patients. Indeed, the fact that the three patients who were refused HA1A all survived suggests that this model does not adversely affect care (assuming that HA1A has a beneficial effect). We have no information, however, on the number of patients where this drug would have been considered, or actually administered, in the absence of any constraint as to its use.

On the evidence to date, this model provides the clinician with objective criteria to be met before prescribing a new, unproven, highly expensive medication into an emotive area of

Example of patient not authorised to receive HA1A

Case C

A 61-year-old female with a history of pulmonary thrombo-embolism was admitted with melaena, left iliac fossa peritonism, septicaemic shock and renal failure. Following a prolonged period of resuscitation, she underwent laparotomy and drainage of a retroperitoneal abscess, thought to be perinephric in origin. Her post-operative recovery was complicated and prolonged. However, she survived and was discharged home. During pre-operative resuscitation, a request was made for administration of HA1A. However, at this stage, her sepsis score was only eight, blood cultures were negative, and intravenous antibiotics had just been commenced. On these grounds, authorisation for administration of HA1A was refused.

Discussion

This uncontrolled study was not designed to evaluate the benefits of HA1A. Rather it was designed to assess the effects of a selection procedure which prevented prescribing new, highly expensive treatment for inappropriate patients. There was major mortality in those patients with suspected or proven Gram-negative bacteraemia who received treatment with HA1A, whereas no patient refused HA1A died. Thus the ‘authorisation procedure’ only allowed the group of patients thought to have a

Recommendations for introduction of new and expensive anti-microbial therapies

- produce objective criteria which must be met before prescribing is allowed
- joint decision-making by both clinician and microbiologist
- decide outcome measures before prescribing

patient care. Furthermore, the approach allows for extensive audit and assessment thereby both preventing unnecessary increases in the hospital drug budget and permitting justification in use of expensive resources where these are approved by independent clinicians (see box).

The study was terminated when HA1A was withdrawn from sale by the manufacturers as it had become apparent that the drug was not associated with a net overall benefit in everyday clinical use.

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