Use of Vaccinia Immune Globulin (VIG) For Treatment of vaccinia vaccine complications and for prophylaxis of unvaccinated individuals exposed to Orthopoxviruses responsive to VIG

Investigational New Drug (IND) Proposal

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INVESTIGATOR'S BROCHURE

INTRODUCTION

This Investigational New Drug Application is being filed in order to make existing stocks of Vaccinia Immune Globulin available for treatment of complications of vaccinia vaccination or exposure to vaccinia or related pox viruses. Vaccinia Immune Globulin (VIG) (Human) is an isotonic sterile solution of the immunoglobulin fraction of plasma from persons vaccinated with vaccinia vaccine. The current lot, 0448A101A, was released as a licensed product by Baxter Healthcare Corporation in 1995. In 1998 a slight discoloration was noted in this product and the FDA placed a hold on its release. Consequently, VIG can no longer be entered into interstate commerce under terms of the approved license and must therefore revert to IND (investigational new drug) status.

CDC follows the June 22, 2001 Recommendations of the Immunization Practices Advisory Committee (ACIP) for Vaccinia (Smallpox) Vaccine. Since 1983 CDC has provided vaccinia vaccine for laboratory workers directly involved with smallpox or closely related orthopox viruses (e.g., monkeypox and vaccinia). Due to clinical trials involving recombinant vaccinia virus vaccines, health-care workers (e.g., physicians and nurses) may now be exposed to vaccinia and recombinant vaccinia viruses and may be considered for vaccinia vaccination. This protocol will establish a mechanism to make VIG lot 0448A101A available to physicians to treat or prevent:

1. Signs and symptoms of vaccinia resulting from injection of the vaccinia virus vaccine.
2. Signs and symptoms of vaccinia or related diseases resulting from exposure to vaccinia or related orthopox virus infection.

Treatment with VIG shall be secondary to clinical supportive care in cases of exposure to vaccinia and/or related orthopox virus which result in moderate or severe complications; i.e Generalized Vaccinia, Eczema Vaccinatum, Progressive Vaccinia, and Postvaccinial Encephalitis.
A secondary objective is to collect additional safety and efficacy data on this product by performing pre and post physicals. The physicals would include HIV, HBV and HCV testing, liver function tests, including serum alanine aminotransferase (ALT), serum creatinine, and complete blood count (CBC).

There are no specific indications that are to be investigated under this IND. The protocol enclosed with this IND lists no research questions to be answered or data analyses to be conducted. Nevertheless, should it become necessary for VIG to be used under this IND, data on the clinical course and outcome of the volunteer patient will be obtained from the treating physician as described in the enclosed protocol. These treating physician reports will be forwarded to the agency as part of the annual report for this IND.

Use of this intramuscularly administered product is proposed as a short-term solution to the problem presented by a lack of a licensed immune globulin to treat vaccinial infections. Work is under way to develop, test and license an intravenously administered vaccinia immune globulin. This intravenous product is intended to fulfill the longer-term need for availability of an immune globulin to support vaccinia vaccine trials. Plans for development of this intravenous product were discussed with the agency at a pre-IND meeting on 22 March 1999. The projected date for filing of an IND and availability of the intravenously administered immune globulin, as an investigational product, is late this year.

Background

VIG was first used to treat complications of smallpox vaccinations in the early 1950s. Kempe et al. (1956) described the production and harvest of VIG obtained from the sera of hyperimmunized U.S. Army recruits. With the eradication of smallpox in 1980, the use of vaccinia vaccine was nearly eliminated. Laboratory workers and others whose duties brought them into potential contact with an orthopox virus and select members of the Armed Forces were the only groups that continued to be routinely vaccinated. Currently (that is, prior to FDA hold on VIG lot 0448A101A) vaccinia virus vaccine is administered to persons at risk of exposure (e.g., laboratory workers) to vaccinia or related orthopox viruses. In addition, research is ongoing to develop a new smallpox vaccine using vaccinia virus. The virus is also being considered for use as a vector for vaccines against other infectious agents. These two areas of research could potentially expose individuals to complications resulting from vaccinia vaccination that would require treatment with VIG.

Description of Vaccinia Complications

The Immunization Practices Advisory Committee (ACIP) of the Centers for Disease Control and Prevention (CDC) has defined vaccinia complications as follows:

A Generalized Vaccinia: Among persons without underlying illnesses, a vesicular rash of varying extent characterizes generalized vaccinia. The rash is generally self-limiting and requires little or no therapy except among patients whose condition appears toxic or who have serious underlying illnesses.

A Eczema vaccinatum: This complication is a localized or systemic dissemination of vaccinia virus among individuals who have eczema or a history of eczema and other chronic or exfoliative skin conditions (e.g., acne, atopic dermatitis). The illness is usually mild and self-limiting, but may be severe and occasionally fatal. The most serious cases occur among primary vaccinees and appear to be independent of the activity of the underlying eczema. Severe cases have also been observed after contact infection.

A Progressive vaccinia (Vaccinia necrosum): This is a severe, potentially fatal illness characterized by progressive necrosis in the area of vaccination, often with metastatic lesions. It occurs almost exclusively among individuals with cellular immunodeficiency.

A Postvaccinal encephalitis: This is the rarest, but most serious complication and most frequently affects primary vaccinees <1 year of

age. From 15% to 25% of affected vaccinees with this complication die, and 25% have permanent neurologic sequelae.

EFFECTS IN HUMANS

Safety

General Precautions

When therapeutic proteins prepared from human blood or plasma are administered, the potential for the transmission of infectious agents cannot be totally excluded. This applies also to infectious agents that may not have been discovered or characterized when the current lot of VIG was formulated.

To reduce the risk of transmission of infectious agents, stringent controls were applied in the selection of blood and plasma donors. In addition, prescribed manufacturing standards were used at plasma collection centers, plasma testing laboratories, and fractionation facilities. Although the heat treatment step in the manufacturing process has been shown to reduce the level of Bovine Viral Diarrhea virus, a model for Hepatitis C virus, by more than 50,000 fold, its effectiveness toward other known or unknown infectious agents has not been determined.

Adverse Events Related to VIG

There is a paucity of published studies investigating the safety of VIG. This may be, in part, because the product was developed prior to current regulatory requirements for well-controlled safety trials of investigational products. Also, the circumstances under which VIG has been utilized, both pre- and post-licensure, tend to cause the researcher or clinician to focus on the ability of the product to prevent or cure the clinical manifestations of vaccinal infection rather than on possible adverse events.

The following is a direct quote from the Adverse Reactions section of the approved labeling of Vaccinia Immune Globulin (Human) - Baxter Healthcare Corporation (1995):

A few instances of allergic or anaphylactoid systemic reactions have been reported following intramuscular injection of human immunoglobulin preparations. It is advisable that epinephrine or other suitable medication be available for treating such reactions should they occur.

Occasionally local tenderness and stiffness occur, persisting from a few hours to 1 to 2 days following injection. (When the dosage is 10 ml or more, it should be divided and injected at two or more sites in order to reduce the trauma of injection).

Efficacy/Marketing Experience

Various forms of VIG have been used to treat complications of vaccinia vaccinations since the early 1950s. The following descriptions are based on the limited literature available on the efficacy of VIG.

Early Anecdotal Reports of VIG Usage as Prophylaxis and Treatment

Kempe et al. (1956) provided the following anecdotal reports on the use of hyper immune gamma globulin in the prophylaxis and therapy of serious dermal complications of smallpox vaccination.

- Eight eczematous children were administered 0.6 ml/kg of hyper immune vaccinal gamma globulin and then vaccinated. All eight children demonstrated vaccine "take" but none experienced complications.

- Six eczematous infants less than 18 months of age with known exposures to smallpox were given hyper immune globulin at 0.6 ml/kg. None of the infants developed eczema vaccinatum.

- Fourteen infants with eczema vaccinatum were treated with 0.6 ml/kg of hyper immune globulin. Two of these infants died. In both cases, therapy was delayed until 5 days after onset. In the remaining cases, no new lesions appeared after treatment, and clinical improvement was characterized as "striking."

- In eight cases of generalized vaccinia resulting from administration of vaccinia vaccine, no further lesions developed once the patients were treated with hyper immune globulin.

Clinical Trial of VIG in Prevention of Smallpox in Non-immune Contacts of Smallpox Patients

A more structured experimental design was used to assess the value of VIG as prophylaxis for unvaccinated family members and other close contacts of smallpox victims (Kempe et al., 1961). This clinical trial was conducted in Madras, India. Vaccinia-naive, healthy

household contacts of confirmed smallpox cases were divided into two groups. The control group received vaccinia vaccine. The treatment group was vaccinated and injected with VIG. Contacts who refused VIG or were not located until after the probable incubation period for the disease were evaluated as part of the control group. VIG used in this study came from three different manufacturers, all of which used immune globulin harvested from recently vaccinated adult donors.

Among the 326 subjects who received VIG, only 5 cases of smallpox were reported. Among the 379 control subjects, 21 cases of smallpox were recorded. The authors identified this difference as statistically significant although no probability value or description of statistical analytical method was presented in the published report.

Experience of VIG Treatment in the United Kingdom, 1967-1971

The experience of 661 persons given VIG in the United Kingdom between 1967 and 1971 was reviewed (Sharp & Fletcher, 1973). VIG was given to 431 patients considered at risk for developing complications from vaccinia vaccination. Of these, one 4-year-old child subsequently developed eczema vaccinatum that cleared without further treatment. Of the 22 pregnant women in this group, three who had been vaccinated during the first trimester of pregnancy spontaneously aborted their pregnancies. The other 427 patients remained free of complications.

In the remaining 230 patient experiences surveyed, VIG was given as a treatment for post-vaccination complications. The most common conditions being treated were generalized vaccinia and eczema vaccinatum. Lesions of the eyelid were also common among recent vaccinees who had accidentally self-inoculated the eye from the vaccination site. Ninety percent of these patients improved rapidly after VIG treatment. Of the five patients in this group who died, all had begun VIG treatment 20 or more days after vaccination or exposure to someone who had been vaccinated.

Case Report of VIG Treatment of Progressive Vaccinia in an Immunodeficient Infant

Seth et al. (1978) described the use of VIG to treat a case of progressive vaccinia after primary vaccination in a 7-month-old infant. The infant was the product of a full-term delivery but had a history of bronchopneumonia, recurrent upper and lower respiratory infections, and diarrhea. The infant had been hospitalized three times during the first 5 months of life. Because of these recurrent illnesses, vaccinia vaccination was postponed until the infant was 5½ months old. The infant subsequently presented with ulcerating lesions with marginal edema and induration at the primary vaccinia injection site. Satellite lesions were also found on the forehead, abdomen, and back. An immunologic work-up determined that the infant displayed no delayed hypersensitivity to common skin test antigens and had produced no vaccinia antibodies. Analysis of immunoglobulin isotypes revealed no IgA and low levels of both IgM and IgG. The infant was diagnosed as having progressive vaccinia secondary to congenital immunodeficiency. After treatment with 0.5 ml/kg VIG by intramuscular injection every 2 weeks for four total doses, the infant was completely healed of local as well as metastatic vaccinal lesions.

Review of Recent Use of VIG under the Auspices of the Centers for Disease Control and Prevention

With the declaration of the eradication of smallpox in 1980, the use of vaccinia vaccine came to a virtual halt. Laboratory workers and others whose duties brought them into potential contact with an orthopox virus and select members of the Armed Forces were the only groups that continued to be routinely vaccinated. Because VIG was the only product available to treat complications of vaccinia vaccination, there continued to be a need to have stocks of VIG available. The Centers for Disease Control and Prevention (CDC) was identified as the central source for VIG. Table 1 lists the incidents for which CDC has supplied VIG since 1991 and, where available, the treating physician's report of patient outcome.

In the past when VIG was a licensed product each release for protection of individuals was reviewed by a CDC staff person familiar with the indications for VIG. They were directly involved in consultation with the requesting physician, and in the opinion of the CDC consultant, it was felt that VIG could offer some protection against possible severe reactions after exposure to an Orthopoxvirus or recombinant vaccinia vectored virus.

Currently, there is no published clinical data to support the idea that vaccinia immune globulin is protective in the treatment of exposures to orthopox viruses other than variola and vaccinia. However the existence of shared serologic cross reactivity between the orthopoxviruses (which led to their grouping as a genus), and the ability of neutralizing antibodies to one orthopoxvirus to partially neutralize the infectivity of other members of the genus orthopoxvirus (Downie, AW and McCarthy K. 1950. The viruses of variola, vaccinia, cowpox, and ectromelia. Neutralization tests on the chick chorioallantois with unabsorbed and absorbed sera. Br. J. Exp. Pathol. 31:789-796.) permits speculation that some clinical benefit may be achieved by the use of VIG if an occupational exposure to an orthopoxvirus other than variola and vaccinia occurs. The fact that VIG is at all protective against variola may indicate that VIG may have a more clinically beneficial effect against an orthopoxvirus less virulent to humans.

This immune globulin generalized protection was reviewed by Kempe, et.al. in his 1956 paper "Hyperimmune Vaccinal Gamma Globulin - Source, Evaluation, and Use in Prophylaxis and Therapy" it showed hyperimmune vaccinal immune globulin would neutralize the smallpox virus and suppress or diminish viremia and thereby suppress or diminish infection of skin epithelium. The clinical expression of the disease would thus be modified or aborted, even though infection might still occur. This IND stipulates that after

consultation with the attending physician each request will be reviewed by the primary and/or co-investigator prior to release. Each case will be evaluated in terms of virus(es) involved and concentration of virus at time of exposure. **VIG therapy is effective for treatment of eczema vaccinatum and certain cases of progressive vaccinia; it might be useful also in the treatment of ocular vaccinia resulting from inadvertent implantation. However, VIG is contraindicated for the treatment of vaccinial keratitis. Patient should have opthalmologic esamination to rule out keratitis before administration of VIG for ocular implantation. VIG is recommended for severe generalized vaccinia if the patient is extremely ill or has a serious underlying disease. VIG provides no benefit in the treatment of postvaccinial encephalitis and has no role in the treatment of smallpox**.

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Table 1. CDC Experiences with Distribution of VIG

Date	Description of Patient	Clinical Presentation	VIG Use and Outcome
2 Jul 91	36 y.o., 188 kg, male maintenance worker	Generalized vaccinia on neck, back, legs, and scalp, beginning 10 days after vaccination	5 vials VIG released and administered; 3 days later fever resolved; few new lesions observed; no additional VIG given; patient fully recovered no adverse sequelae
6 Nov 92	Unvaccinated laboratory worker	Severe local reaction subsequent to needle stick with recombinant vaccinia virus	Not certain if VIG was administered; no outcome report provided
16 Mar 94	Female laboratory worker	Post vaccinal vaccine reaction, preliminary diagnosis of generalized vaccinia	6 vials of VIG released; no follow-up report on whether VIG was used or patient outcome
9 Jul 94	Male post-doctoral fellow	Recombinant vaccinia virus eye splash	6 vials of VIG released, no follow up report on whether VIG was used or patient outcome
2 Aug 94	19 y.o., male, military recruit with keratosis follicularis	7 days post-vaccination developed vesicular rash on right forehead, severe edema right orbital region, facial vesicles 0.5 cm	10 vials VIG released but not used; treated with Zovirax because of suspicion of herpes zoster infection, also given antibiotics to control for secondary infection; improvement noted and VIG withheld by local health authorities
6 Jan 95	Researcher with chronic lymphocytic leukemia	Gangrenous lesion developed at vaccination site	10 vials VIG released. No follow- up report
5 May 95	27 y.o., 70 kg, male, military recruit	Eczema vaccinatum of face, neck and arms beginning 9 days after vaccinia vaccination	18 vials VIG released; no follow-up report
31 Jul 95	19 y.o., 80 kg, male, military recruit	Eczema vaccinatum of face and neck beginning 10 days after vaccinia vaccination	20 vials VIG sent; no follow-up report
7 Mar 98	36 y.o., 65 kg, healthy, immunocompetent researcher , vaccinated in childhood verified via history and scar	Recombinant vaccinia virus splashed into both eyes, face, and mouth	10 vials VIG sent, 19 ml (<4 vials) given; patient refused additional VIG; no adverse sequelae reported; eyes washed 10 minutes immediately after accident; vidarabine ophthalmic ointment applied to eyes daily for 7 days; patient recovered

Nonclinical Studies

Baxter Healthcare Corporation performed the requisite nonclinical studies on VIG prior to its release as a licensed product in 1978. The current lot of VIG (0448A101A) also passed all safety tests prior to its release in 1995. With the exception of the slight discoloration in the vials, this lot continued to pass all other annual stability tests. In response to FDA's request, three genotoxicity studies, a subchronic study, and PCR tests for HBV, HCV, and HIV were conducted to assess the continued safety of the product. Results from these studies follow.

Genotoxicity Studies

A battery of genotoxicity studies was conducted by ---------- to determine the genotoxic potential of VIG both in vitro and in vivo. These studies consisted of a ----------, and ----------. A summary of the results of these studies is presented in Table 1.

Table 1. Summary of VIG Genotoxicity Studies

Test Type	***Route***	***Test System***	***Dose Levels***	***Results***	***Ref.***
----------	in vitro	----------	----------	Negative	2
----------			----------		
----------	in vitro	----------	----------	Negative	3

----------	IM	----------	----------	Negative	4

In vitro Mammalian ----------Test

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According to preliminary results from the definitive study, toxicity was observed using the vehicle, relative to the untreated control, in all treatment groups. However, relative to the vehicle control, no toxicity was observed at any dose level tested, regardless of treatment group.

The dose levels selected for analysis of ---------- in the treatment, vehicle control, and untreated control groups were ---------- Results from this phase of the study are not yet available.

The mutagenic potential of VIG was investigated by----------

Selection of dose levels for the ---------- was based on the toxicity and precipitation profile of VIG in a preliminary toxicity assay. The maximum dose tested was ---------. This dose was achieved using a concentration of --------- and a ------- aliquot. No precipitate and no toxicity were observed.

In the definitive assay, cells were exposed to concentrations of ---------- of VIG in the absence or presence of ----------. To demonstrate the sensitivity of the assay system, positive controls were used. They included ----------.

No positive responses were observed with test strains ----------in the absence of ----activation and with any of the test strains in the presence of --- activation. With test strain -------in the absence of--- activation, the revertant counts from the vehicle-treated plates were about one-third of the test article-treated and untreated control plate counts. This decrease in revertant count is inconsistent with the results of the preliminary toxicity assay. Because a dose-response was not observed, this response does

not qualify as a positive response; however, it does warrant further investigation.

Based on these results, test strain ------ in the absence of-- activation will be retested to resolve the unexpected decrease in revertant count with the vehicle control.

The potential for VIG to induce micronuclei in ----------was tested under in vivo conditions. ----
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No mortality, clinical signs, or significant decreases in animal body weights were observed in the pilot study. All animals appeared to be normal during the course of the study. Results from the definitive study are under review.

A 21-day Repeat Dose Study in Rabbits

A subchronic study was conducted by ----------to assess the toxicity of VIG following repeated intramuscular injections in ----------. Fifty-six (28/sex), 8-week old rabbits were randomized by body weight (~ 2 k) into 4 groups of 7 animals per sex. Group 1 was the vehicle control, Group 2 was the IgG control, Group 3 was the low dose (99 mg/kg) VIG, and Group 4 was the high-dose (495 mg/kg) VIG.

All study animals received seven intramuscular injections on Days 1, 3, 5, 7, 9, 11, and 13. The test article and control materials were administered in two doses on each side of the animals into the musculus longissimus dorsi. Different sites were injected on each dosing day. Three animals per sex and group were sacrificed on Day 14 and the remaining animals were sacrificed on Day 21.

Animals were weighed on Days 1, 8, 14, and 21 and were observed for clinical signs of toxicity prior to dosing, within 4 hours of the first dosing, and daily thereafter. The injection site was shaved and examined prior to dosing and daily thereafter. All surviving animals were bled from a marginal ear on Days 8, 14, and 21 for clinical pathology tests. Gross necropsy was performed on Days 14 and 21, and tissues from the high-dose VIG group and both control groups were examined microscopically.

Based on preliminary results, VIG appeared to have no effect on body weight. One female from the low-dose VIG group was euthanized on study Day 10, and one male from the IgG control group died accidentally on study Day 8. Study results are currently being analyzed.

----------Polymerase Chain Reaction Results

----------conducted a series of tests using PCR (polymerase chain reaction) to determine whether hepatitis B and C and human immunodeficiency viruses (HBV, HCV, HIV) are present in VIG lot 0448A101A. The three tests were conducted on material from three vials of VIG.

DNA was extracted from 3-ml samples of VIG, and 100 ml of purified DNA was subjected to HBV-specific amplification. RNA was extracted from 3-ml samples of VIG and reverse transcribed; and 100 ml cDNA was subjected to HCV-specific amplification. Finally, RNA was extracted from 3-ml samples of VIG and reverse transcribed; and 100 ml cDNA was subjected to HIV-specific amplification.

Results were negative, indicating that the target sequences for HBV, HCV, and HIV were not detected in the samples of VIG tested. However, HBV, HCV and HIV pre-post testing will be performed.

RATIONALE AND OBJECTIVES

Rationale for the Study

Baxter Healthcare Corporation, Hyland Division (Baxter Hyland) first received FDA approval to market VIG in 1978 after its safety and efficacy had been demonstrated in nonclinical and clinical studies. It has been used for nearly 20 years to treat symptoms of vaccinia infection in laboratory and health care workers who received vaccinia virus vaccine.

The current lot, 0448A101A, was released as a licensed product in 1995. Prior to being put on hold, Lot 0448A101A was used to successfully treat adverse reactions to vaccinia vaccinations. Because of a slight discoloration noted in vials of this lot in 1998, the FDA placed a hold on its release. As a consequence, VIG can no longer be entered into interstate commerce under terms of the approved

license and must revert to IND status for it to be used in humans.

Objectives

The primary objective this protocol is to provide Vaccinia Immune Globulin (Human) for the treatment of :

A vaccinia complications resulting from the use of vaccinia virus vaccine

A complications resulting from exposure to vaccinia or other related orthopox viruses

A secondary objective is to collect safety (adverse experiences) and efficacy (comparing the number of lesions prior to and after administration of VIG) data and pre/post test physicals, HIV, HCV, HBV and liver function tests will be performed.

RISK-BENEFIT ASSESSMENT

Risks

When therapeutic proteins prepared from human blood or plasma are administered, the potential for the transmission of infectious agents cannot be totally excluded. This applies also to infectious agents that may not have been discovered or characterized when the current lot of VIG was formulated. To reduce the risk of transmitting infectious agent, stringent controls were applied in the selection of blood and plasma donors, and prescribed standards were used at plasma collection centers, testing laboratories, and fractionation facilities.

There have been reports of local tenderness and stiffness, persisting from a few hours to 1 or 2 days following administration, and a few allergic or anaphylactoid systemic reactions have been reported following intramuscular injection of human immunoglobulin preparations.

The only experience of VIG being administered to pregnant women was noted by Sharp and Fletcher (1973). Among 431 patients considered at risk for developing complications of vaccinia vaccination were 22 pregnant women who received VIG 24 hours after vaccination. Of these, three who had been vaccinated during the first trimester of pregnancy aborted spontaneously. The benefit of treating a pregnant woman who has been exposed to vaccinia virus or a related orthopox virus is believed to outweigh the potential risk of adverse reactions that she and/or her fetus might experience as a result of having received the immune globulin.

The VIG product was made before the current FDA requirements for viral safety validation of licensed products were in effect, but retrospective analysis of the product support the conclusion that the product is safe. Therefore, pre/post physicals including testing for HIV, HBV and HCV, and liver functions tests will be included.

Benefits

The potential benefit from participation in this study is treatment and possible recovery from the complications of exposure to vaccinia virus or related orthopox viruses. Specifically, VIG has been shown to be effective in treating certain serious complications of vaccinia vaccination, including eczema vaccinatum, vaccinia necrosum, severe generalized vaccinia, vaccinia infections of the eyes or mouth, and vaccinia infections in the presence of other skin lesions such as burns, impetigo, varicella-zoster, or poison ivy. VIG has not been shown to be effective in the treatment of postvaccinal encephalitis.

Alternatives to VIG

At this time, there is no alternative to treating complications resulting from vaccinia vaccinations. In fact, Immunization Practices Advisory Committee (ACIP) recommends only vaccinia immune globulin for the treatment of complications resulting from vaccinia vaccination.

Risks to the Environment

There are no known risks to the environment other than those associated with the generation of biohazardous wastes attendant to injection of humans. All biohazardous wastes will be disposed of in compliance with hospital regulations and as stipulated by local, state, and Federal regulations.

STUDY DESIGN

Investigational Plan

This is a Phase 1, open-label, multi-site study of VIG. It is indicated for individuals who may experience adverse reactions to vaccinia virus vaccinations or to unprotected individuals (e.g., working in Biosafety Level 3 and 4 suites) who are exposed to vaccinia virus or related orthopox virus.

This IND application is being filed in order to make existing stocks of VIG available for treatment of complications of vaccinia or related pox virus infections. Such complications could arise from the vaccination of individuals at risk of developing vaccinia with the currently licensed live, viral vaccine. There are also plans to develop a "second-generation" smallpox vaccine. As the only product available for the treatment of vaccinia and other orthopox infections, VIG must be available to treat any volunteers in clinical trials of the new vaccine formulation who may develop signs and symptoms of vaccinia infection.

Use of this intramuscularly administered product is proposed as a short-term solution to the problem presented by a lack of a licensed immune globulin to treat vaccinal infections. Work is under way to develop, test, and license an intravenously administered vaccinia immune globulin that is intended to fulfill the longer-term need for availability of an immune globulin to support vaccinia vaccine trials.

Justification of Dose

The dose (0.6 ml/kg) is the one approved by FDA for treatment of postvaccinal complications when it issued the original license for VIG to Baxter Healthcare Corporation, Hyland Division in 1978.

Sample Size

Few subjects are expected to enroll in this protocol. This assumption is based, in part, on the VIG distribution records of CDC between 1991 and 1998. During this period, fewer than 100 vials of VIG were released to treat a total of nine patients. The number of vials of VIG actually used was not recorded.

Patient Assignment to Treatment Group

Because this is an open-label study, all patients consenting to participate will have the opportunity to receive VIG.

Planned Period of Study

The study period for the intramuscularly administered VIG is expected to extend until an intravenously administered vaccinia immune globulin becomes available as an Investigational New Drug.

Study Population

Inclusion Criteria

Subjects must meet the following inclusion criteria:

A Read and sign an approved informed consent form including consent for pre/post HIV counseling; if unable to sign consent form, one must be signed by next of kin, legal guardian, or attending physician (Subinvestigator) in an emergency situation

A Experience complications resulting from vaccinia virus vaccinations or be exposed to vaccinia virus or related orthopox viruses

Exclusion Criteria

Although there are no exclusion criteria per se in this study, patients should be asked if they have a history of acute allergic reaction to thimerosal (a mercury derivative used as a preservative in VIG). Precautions can be taken should they experience a reaction during administration of the VIG and this product should be used with caution in persons with a history os systemic allergic reactions following administration of human immune globulin products. In addition, a serum pregnancy test will be required of women of childbearing potential before administration of VIG.

Concomitant Medications Allowed

There are no restrictions on the use of concomitant medications during a course of treatment with VIG.

Subject Identification

Each patient will be identified by study identification number and study site. No personal data will be used in any communication or publication.

Withdrawal/Termination Criteria

A patient may refuse treatment at any point during the study.

The study may be terminated at any time or a patient's participation in the study may be terminated at any time without his/her consent if conditions are such that the patient's safety or health may be compromised by further participation. The medical monitor, principal investigator, or sponsor may make this determination.

Test Article - VIG

Composition

The test article, VIG, is covered under an Investigational New Drug (IND) application. It will be labeled for human administration and will include the following statement: "Caution: New Drug-Limited by Federal law to investigational use."

VIG is a sterile 16.5 (±1.5) percent solution of the immunoglobulin fraction of plasma from individuals who were immunized with vaccinia virus vaccine. The solution is isotonic and contains 0.3M glycine as a stabilizer. It contains 0.01% thimerosal (a mercury derivative) as a preservative, and 0.1% sodium chloride. The product meets the FDA potency requirements for vaccinia antibody (Baxter, 1995). It must not be frozen or used if turbid or after the expiration date.

Cold ethanol fractionation was used to prepare VIG lot 0448A101A. The manufacturing process included a bulk heat treatment step that has been shown to reduce virus burden in vitro studies. The studies were performed using ----------, which is a model for Hepatitis C virus. In three in vitro experiments using cold ethanol fractionation, the virus load was reduced from ------- to undetectable levels (<3.5 log10), with an average reduction factor of ----------. Samples from the current lot have also been tested for HBV, HCV, and HIV viruses.

Test Article Storage, Distribution, and Accountability

VIG shall be stored between 2º and 8ºC (36º-46ºF) in a monitored refrigerator at the CDC Drug Service and distributed on an as-needed basis to physicians (Subinvestigators) who will determine the number of vials needed after consultation with the CDC duty officer in the National Center for Infectious Diseases or his/her designee. The Principal Investigator is responsible for distribution of the test article and has ultimate responsibility for drug accountability. After receiving the vaccine, the Subinvestigator at each site will be responsible for and will maintain logs of test article receipt, temperature maintenance, and test article remaining until it is transferred back to the Sponsor or disposed of as biohazardous waste (see Pharmaceutical Accountability and Disposition Record). These documents will be maintained in the study file.

Test Article Preparation and Administration

VIG is available in 5-ml vials. The recommended dose of VIG for treatment of postvaccinal complications is 0.6 ml of a 16.5% solution/kg body mass (~100 mg/kg). For a 70-kg adult, this would amount to 42 ml for each course of therapy. VIG is to be administered intramuscularly, preferably in the buttock or the anterolateral aspect of the thigh. Doses greater than 10 ml should be divided and injected at two or more sites to reduce local pain and discomfort.

Study Procedures

CDC currently requires each physician that administered vaccinia vaccine to "at risk" individuals to enroll with the CDC Drug Service. CDC will notify enrolled vaccinia vaccine physicians of the existence of this protocol. If an individual associated with an institution requires treatment for complications from vaccinia virus vaccination or from exposure to vaccinia virus or related orthopox viruses, that individual's attending physician will notify the CDC Drug Service and/or the primary or co-investigator of this study in the National Center for Infectious Diseases. The decision to release VIG for clinical use will be made by the primary and/or co-investigator in the National Center for Infectious Diseases after consultation with the requesting physician (Subinvestigator). The decision to administer VIG will be made solely by the requesting physician. The patient if enrolled will be supplied a study ID number and it will be supplied by the Drug Service.

Information that will be requested prior to release of VIG:

- What virus(es) was patient exposed.
- Concentration of virus(es) if laboratory exposure and storage media.
- Type of exposure e.g. eye splash, mucocutanous, aerosol, etc.
- Time and place of exposure
- Process used to neutralize virus if laboratory accident
- Current patient history and physical exam including allergy history
- Ensure that medical facility that is to provide medical care for treatment of this reaction will be adequate to handle any adverse reactions and/or complications of treatment.

The Principal and/or co-investigator will authorize shipment of the VIG together with the protocol, investigator's brochure, case report forms, and informed consent form, as well as FDA Form 1572 (investigator and facility data), to be completed, signed, and returned to the sponsor for submission to the FDA. The physician will then be added to the list of Subinvestigators on the study and be subject to all regulations and reporting requirements applicable to the study. All data and forms collected will be stored at the CDC Drug Service. The CDC Drug Service will notify the FDA within two weeks of each release of VIG and will provide the FDA with the specific indication for which VIG was used, basic demographic information, and preliminary safety and efficacy information for each subject enrolled.

Following are the required procedures:
Prior to administration of the VIG and at 3 and 6 months following administration of the VIG:

- Routine physicals to include an evaluation of the number of lesions
- HIV, HCV and HBV testing
- Liver function tests to include serum alanine aminotransferase (ALT), serum creatinine, and a complete blood count (CBC).

Evaluation of lesions will be performed daily for five days following administration of VIG
VIG will be administered intra-muscularly (IM)
Multiple (IM) injections will be required, the number depending on body weight
Pre/and post test HIV counseling will be provided.

Adverse Events

Definitions

An ADVERSE EVENT (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE, therefore, can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

A SERIOUS ADVERSE EVENT is any untoward medical occurrence that at any dose:
1. results in death,
2. is life threatening,
3. requires in-patient hospitalization or prolongation of existing hospitalization,
4. results in persistent or significant disability/incapacitation, or
5. is a congenital anomaly/birth defect.

An UNEXPECTED ADVERSE EVENT is an adverse reaction, the nature or severity of which is not consistent with the applicable product information or any adverse event that has not been documented previously as an event to be expected, i.e., nature, frequency, or intensity, with administration of this test article (immune globulin).

Possible Adverse Events with the Administration of VIG

The following is a quotation regarding adverse reactions from the Package Insert for the previously licensed product:

A few instances of allergic or anaphylactoid systemic reactions have been reported following intramuscular injection of human immunoglobulin preparations. It is advisable that epinephrine or other suitable medication be available for treating such reactions should they occur.

Occasionally local tenderness and stiffness occur, persisting from a few hours to 1 to days following injection.

Assessing AEs
Volunteered, observed, and elicited AEs will be recorded. These include AEs that the patient reports spontaneously, those the investigator observes, and those the investigator elicits in response to open-ended questions.

Intensity
Regardless of the classification of an AE as serious or not, it severity must be assessed according to the following categories:
A Mild - Does not interfere with daily activities
A Moderate-Interferes with routine activities
A Severe-Unable to perform routine activities

Relationship to Test Article
The relationship between administration of the study vaccine and an AE must be assessed according to the categories defined in Table 2. The criteria to be used in making the assessment are:
A temporal relationship between administration of the test article and the AE
A known safety profile of the test article
A evidence of alternative cause(s)
Note: Only a physician can make this determination.

Recording AEs
The following information must be recorded for all AEs:
A Subject's Name A Investigator's name and name of medical treatment facility
A Subject's date of birth, gender, ethnicity A Study drug and dates of administration
A Date and time of onset A Signs, symptoms, and severity
A Continuous vs. intermittent reaction A Relationship to study drug
A Intervention/treatment
A Concomitant medication(s), including dose, route, frequency, and beginning and ending dates
A Date and time of resolution

Table 2. AE Causality Assessment Criteria

Category	Definition
Definite	Events occurring within a timely manner after administration of the test article that are known sequelae to the administration of the test article and follow a previously documented pattern of reaction but for which no other explanation is known. This category applies to those AEs that the investigator believes are incontrovertibly related to the study drug.
Probable	Any event occurring in a timely manner after administration of the study drug that follows a known pattern of reaction to the study drug and for which no other explanation is known. This category applies to those AEs that, after careful medical consideration at the time they are evaluated, are believed with a high degree of certainty to be related to the study drug.
Possible	Any event occurring in a timely manner after administration of the study drug that does not follow a known pattern of reaction and for which no other explanation is known. This category applies to those AEs that, after careful medical consideration at the time they are evaluated, are considered to be unlikely to be related but cannot be ruled out with certainty
Unlikely	In general, this category can be considered applicable to those AEs that, after careful medical consideration at the time they are evaluated, are considered to be unrelated to administration of the study drug.
Not related	Any AE for which there is evidence that an alternative etiology exists or for which no timely relationship exists to the administration of the study drug and the AE does not follow any previously documented pattern. This category applies to those AEs that, after careful medical consideration, are clearly and incontrovertibly due to causes other than the study drug.
Unclassifiable	There is insufficient information about the AE to allow for an assessment of causality.

Reporting Adverse Events

SERIOUS and UNEXPECTED AEs will be immediately telephoned and faxed to:

CDC Drug Service
Telephone: 404-639-3670 or 404-639-2888 during off-duty hours
Fax: 404-639-3717

A written follow-up report must be completed and submitted within 3 working days of the onset of the AE to:

CDC Drug Service (D-09)
1600 Clifton Road
Atlanta, GA 30333

Follow-up after an AE

All AEs will be followed to resolution regardless of whether the subjects are still participating in the study. Where appropriate, medical tests and examinations will be performed to document resolution of events. Outcomes may be classified as recovered, persists (i.e., chronic condition diagnosed), died, or lost to follow-up. CDC IRB will be notified of all severe adverse reactions.

Assessment of Safety and Efficacy

Safety will be assessed primarily by monitoring the number of AEs. Other safety criteria will include vital signs and other tests as needed.

Efficacy will be measured by comparing the number of lesions prior to and after treatment with VIG has been completed.

STATISTICAL PLAN AND EVALUATION

All patients enrolled in the study will be included in the evaluation of safety.

The change in the number of vaccinal lesions at baseline (prior to administration of VIG) to the end of the VIG treatment period will be the primary efficacy variable. As is customary for a Phase 1 study, no formal statistical hypotheses are planned.

PROTOCOL MODIFICATIONS

Any change or modification to the protocol that affects study patients, study objectives, study design, study procedures, or significant administrative aspects will require a formal amendment to the protocol. Such amendments will be agreed upon and approved by the Sponsor, the Principal Investigator, the CDC Institutional Review Board (IRB) prior to any implementation of said change or modification.

Administrative changes to the protocol include corrections and/or clarifications that have no effect on the way the study is conducted. These administrative changes will be agreed upon by the Sponsor and the Principal Investigator and will be documented in the study file. The CDC IRB will be notified in writing of all administrative changes prior to their implementation.

PROTOCOL DEVIATIONS

Deviations are defined as isolated occurrences involving a procedure that did not adhere to the study protocol or study-specific procedure. The Principal Investigator is responsible for identifying them. Each deviation is to be recorded on a Protocol Deviation Form and placed in the patient's case report form at the study site.

DATA MANAGEMENT

Recording Clinical Data

Case report forms, laboratory reports, hospital discharge summary, etc., will be used as source documentation. All original case report forms will be maintained in each patient's permanent study record.

Data Handling

Clinical data obtained during a patient's participation in the study will be entered into an individual study record and a database at CDC Drug Service..

ETHICAL, LEGAL, AND ADMINISTRATIVE REQUIREMENTS

Good Clinical Practices

The procedures set forth in this study are designed to ensure that the Sponsor and all study personnel abide by the U.S. Code of Federal Regulations (CFR) and the ICH/GCP guidelines. The Principal Investigator acknowledges this by the FDA Form 1572.

Informed Consent

Written informed consent in compliance with 21 CFR 50 will be obtained before any study-related procedures are initiated. The Principal Investigator or Subinvestigator will present the protocol in lay terms to the patients. Questions about the nature of the protocol, the means by which the study is to be conducted, and the risks to the patient will be solicited. The attending physician (Subinvestigator) will sign the form and submit it to the Principal or for those patients incapacitated to such an extent that they cannot sign the form themselves, and for whom the legal representative is not readily accessible.

STUDY MONITORING

A Sponsor-designated clinical monitor (CDC Drug Service) will monitor this study. Because of the nature and use of this product, clinical monitoring will be performed retrospectively (i.e., after administration of the VIG) and will involve a review of the case report forms, clinical outcome, and accountability records.

FINANCIAL REMUNERATION AND INSURANCE

The Centers for Disease Control and Prevention is funding this clinical study. Should a participant be injured as a direct result of participating in this study, he/she will not be entitled to medical care for that injury. The participant will not receive any injury compensation, only medical care. The patient should understand that this does not constitute a waiver or release of legal rights. This issue is addressed in the informed consent form and will be discussed with the patient by the investigator.

GUIDANCE FOR THE INVESTIGATOR

VIG should be given with caution to patients with a history of prior systemic allergic reactions following the administration of human immunoglobulin preparations.

VIG should be administered intramuscularly, and care should be taken to draw back on the plunger of the syringe before injection in order to be certain that the needle is not in a blood vessel. A separate sterile syringe and needle or single-use disposable unit must be used for each patient to prevent the possible transmission of hepatitis or other infectious agents.

Occasionally local tenderness and stiffness occur, persisting from a few hours to 1 to 2 days following injection. Consequently, doses $10 ml should be given in two or more sites to reduce the trauma of injection. Although systemic reactions to intramuscularly administered immunoglobulin preparations are rare, epinephrine or other suitable medication should be available for treatment of acute allergic reactions.

Antibodies to immune globulin preparations may interfere with the response to live viral vaccines. Therefore, administration of such vaccines should be deferred until approximately 3 months after administration of VIG. No interactions with other products are known.

REFERENCES

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