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REVIEW

Vaccinia immune globulin: current policies, preparedness, and product safety and efficacy

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Summary In 1980 the World Health Organization declared that smallpox was eradicated from the world, and routine smallpox vaccination was discontinued. Nevertheless, samples of the smallpox virus (variola virus) were retained for research purposes, not least because of fears that terrorist groups or rogue states might also have kept samples in order to develop a bioweapon. Variola virus represents an effective bioweapon because it is associated with high morbidity and mortality and is highly contagious. Since September 11, 2001, countries around the world have begun to develop policies and preparedness programs to deal with a bioterror attack, including stockpiling of smallpox vaccine. Smallpox vaccine itself may be associated with a number of serious adverse events, which can often be managed with vaccinia immune globulin (VIG). VIG may also be needed as prophylaxis in patients for whom pre-exposure smallpox vaccine is contraindicated (such as those with eczema or pregnant women), although it is currently not licensed in these cases. Two intravenous formulations of VIG (VIGIV Cangene and VIGIV Dynport) have been licensed by the FDA for the management of patients with progressive vaccinia, eczema vaccinatum, severe generalized vaccinia, and extensive body surface involvement or periocular implantation following inadvertent inoculation.

Introduction

Following an intensive smallpox vaccination strategy initiated in 1967, smallpox was finally declared eradicated from the world by the World Health Organization (WHO) in 1980.[1,2] Routine smallpox vaccination of the general public was discontinued in the USA in 1972.[3,4] British and American armed forces continued smallpox vaccination for a number of years, but routine vaccination was eventually discontinued in the early 1980s in the UK,[5] and in 1990 in the USA.[6]

Prior to September 11, 2001, awareness of a potential biothreat existed but countermeasures were not considered an urgent matter. Following September 11, 2001, however, the bioterrorism threat was brought sharply into focus, particularly with the anthrax attacks via the US mail. A bioterrorist agent of particular concern is the smallpox virus (variola virus) which, for a variety of reasons (discussed below), constitutes an ideal terrorist weapon of mass destruction.[7,8] There remains a low but very real risk of variola virus release, whether intentional or accidental.[9]

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Despite eradication of smallpox in the wild, samples of variola virus were retained for research purposes (for example, to develop more effective vaccines), not least because of fears that terrorist groups or states might possess clandestine samples of the virus.[10] There are two official repositories of variola virus, located in the WHO collaborating centers in the USA (Centers for Disease Control and Prevention (CDC), Atlanta, GA) and Russia (State Research Centre of Virology and Biotechnology "VECTOR", Koltsovo, Novosibirsk region), but there is a belief amongst experts that other states or groups may also possess virus samples with the aim of pursuing biological weapons programs.[3] It has also been reported that the former Soviet Union stockpiled 20 tons of variola virus during the 1970s, and subsequently developed a plant capable of producing up to 100 tons of virus per year.[3,11] Of even greater concern are reports that Russian scientists bioengineered variola virus during the Cold War in order to make it even more dangerous, such as by increasing its pathogenicity by inserting genes for foreign toxins, or creating novel strains of the virus capable of degrading the human immune response.[12] US officials have also indicated their belief that other states may possess undisclosed stocks of variola virus.[10]

Smallpox represents an effective bioweapon for a number of reasons. First, smallpox is associated with very high morbidity and high overall mortality rates (approximately 30%).[9,13] Historically, smallpox has been reported as presenting in three different forms (ordinary, flat, and hemorrhagic), probably depending on host rather than viral factors.[4] The flat and hemorrhagic manifestations of the disease were nearly always fatal.[4] Patients who recover from smallpox may be left with serious sequelae, including extensive scarring of the skin,[13] hearing loss or blindness[14] or, more rarely, other organ damage.[13] Second, smallpox is a highly contagious disease that is spread easily from person to person, and infection invariably results in symptomatic disease.[7] Furthermore, it has been shown that aerosolized variola virus is capable of spreading over considerable distances, and that infection may result even at low viral doses.[7] In addition, unlike anthrax, smallpox carries a risk of secondary and further generations of infection.[15] Finally, smallpox vaccine is generally effective in preventing illness if it is given within 72 hours of exposure, and may prevent death if given within five days.[15] Unfortunately, people exposed to variola virus are usually asymptomatic for up to 17 days, given the 9–17-day incubation period of the disease,[3] by which time vaccination is almost certainly too late.

In a simulated smallpox attack on the USA (entitled 'Dark Winter'), it was calculated that 30 g of weaponized variola virus could infect 3000 individuals.[3] In a scenario in which 3000 persons were initially infected in attacks on three different US states, it was determined that 16 000 people would be infected in 25 states by day 22 following the attack, and that the virus would have spread to other countries by international travelers from the USA. Assuming worst-case conditions (i.e., in the absence of an effective vaccination and isolation strategy), it was calculated that as many as 3 million cases of smallpox may ultimately result, leading to 1 million deaths.[3]

Since vaccination would be the only viable protection against disease spread following a terrorist attack with variola virus, restoration of the US National Smallpox Vaccination Program was announced in December 2002, and President George W. Bush was among the first to be vaccinated.[16] In the UK, the Ministry of Defence announced that it would offer vaccination against smallpox to a small number of specialist military personnel, whose specialization means they face a greater risk of exposure to smallpox.[17]

Reinstatement of smallpox vaccination to the military and other individuals brings with it a number of responsibilities, including:

- Development of policies and strategic planning in the event of a bioterrorist attack.
- Stockpiling of vaccine supplies.
- The need to manage serious adverse events associated with the smallpox vaccine (including encephalitis, eczema vaccinatum, generalized vaccinia and myopericarditis), particularly in view of the increased prevalence of immune suppression from congenital or acquired illness, organ or bone marrow transplantation, cancer, eczema and other dermatological conditions, etc. compared to the 1960s.[9]
- The need for stockpiling of vaccinia immune globulin (VIG) supplies for management of serious adverse reactions to the vaccine, particularly as no international stockpile of VIG was maintained following certification of smallpox eradication.[2] Given the changing characteristics of the general population described above, the need for VIG is likely to be increased compared to the 1960s, and compared to controlled studies conducted by the Department of Defense (DoD),[18] for the management of, and possibly prophylaxis against, vaccine-related serious adverse events. It has also been suggested that VIG might even be life-saving in unvaccinated persons who have come into contact with people exposed to variola virus itself, and may help to limit the spread of disease,[19] although neither this nor prophylaxis against vaccine-related events are currently licensed indications for VIG.

Response and preparedness programs

The Global Outbreak Alert and Response Network (GOARN) was developed by the WHO's Department of Communicable Diseases, Surveillance and Response in 1997 in order to enhance the world's collaboration in containment of infectious diseases, but does not replace the need for increased national public health investment in preparedness for intentional outbreaks of diseases such as smallpox.[2] Since September 11, 2001, many countries have initiated their own preparedness programs.

In the USA, for example, the CDC initiated a Bioterrorism Preparedness and Response Program to assess and progress a combination of countermeasure strategies. This program includes a wide range of plans and policies, such as funding assigned specifically to deal with bioemergencies; local and regional response plans, communication and training; and disease detection, reporting, patient isolation and management. Specifically, in 2003, the CDC's Advisory Committee on Immunization Practices (ACIP) pre-event vaccination program made a series of recommendations:[20] (1) Smallpox vaccination should be carried out for persons designated by public health authorities to conduct investigation and follow-up of initial smallpox cases that might necessitate direct patient contact. (2) Each state and territory should establish and maintain at least one smallpox response team. (3) Pre-exposure vaccination is contraindicated for persons

with eczema or atopic dermatitis or other acute, chronic, or exfoliative skin conditions, conditions associated with immunosuppression, infants under 1 year of age, those with a serious allergy to any component of the vaccine, and pregnant or breastfeeding women.[20] More recently, myopericarditis has been added to the list of anticipated adverse reactions to smallpox vaccination,[21] and symptomatic or asymptomatic heart disease should now be considered a contraindication to pre-event vaccination.[22,23]

Smallpox vaccine stockpiles in the USA include two generations of vaccine:

(1) First generation — Dryvax® is a live-virus vaccine that was used during the global eradication program, and is a preparation of vaccinia virus derived from the New York City Board of Health vaccinia strain, prepared from calf lymph (Wyeth Pharmaceuticals Inc).[23] Aventis Pasteur in France have also supplied the USA with old stocks of a first-generation smallpox vaccine made from the same seed stock as Dryvax®.
(2) Second generation — ACAM2000 is a clonal smallpox vaccine derived from the Dryvax® vaccine and manufactured using modern, serum- and protein-free cell culture techniques (Acambis plc), the aim being to improve the safety profile compared to first generation vaccines while providing the same protection against infection.[24] ACAM2000 is currently available in the USA as an Investigational New Drug, although Acambis was due to file a Biologics License Application before the end of 2005.

With regard to adverse reactions to smallpox vaccines, the CDC has advised that vaccinated persons who develop progressive vaccinia, eczema vaccinatum, severe generalized vaccinia or those with inadvertent inoculation elsewhere from the vaccination site might benefit from therapy with VIG or cidofovir.[20] It should be noted that cidofovir has never been used to treat vaccinia virus infections in humans,[22] has not been approved by the FDA for this indication,[20] and is associated with a number of serious adverse effects, including potentially irreversible renal toxicity.[25] It is therefore reserved as second-line therapy after VIG in this setting.[25] VIG may also be needed as prophylaxis — for example, in persons for whom smallpox

Table 1 Serious complications of smallpox (vaccinia) vaccination and their clinical presentation (from Thorne et al.)[9]

Serious complication	Clinical presentation
Postvaccinial encephalitis	Symptom onset between 8 and 15 d after vaccination Symptoms include fever, headache, vomiting, and drowsiness and, less commonly, spastic paralysis, meningitic signs, coma, and convulsions
Progressive vaccinia (vaccinia gangrenosa, vaccinia necrosum)	Initially painless but progressive necrosis of tissue at site of vaccination; occasional metastatic spread to other areas of skin, bone, and viscera. High mortality, esp in infants with large areas of skin affected
Eczema vaccinatum	Extensive vesicular and pustular eruption with generalized lymphadenopathy on sites of the body with active or past eczema
Generalized vaccinia	Secondary generalized eruption of vesicles or pustules distant from the vaccination site, usually 6 to 9 d after vaccination
Inadvertent inoculation (accidental implantation)	Physical transfer of vaccinia virus with development of lesions at the secondary site. Common sites include face, eyelid, mouth, nose, genitalia and rectum
Vaccinia keratitis	Pain, photophobia, tearing, and blurred vision. Might lead to corneal scarring and visual impairment
Other rash (e.g. erythema multiforme, Stevens—Johnson Syndrome, roseola vaccinia, toxic erythema, and postvaccinia urticaria)	Varied rash characteristics. Usually flat, erythematous, macular, or urticarial lesions
Fetal vaccinia	Fetal loss. Premature birth with extensive skin lesions. High mortality in newborns. Greatest risk in 3rd trimester
Myopericarditis	Varied presentations, such as chest pain/discomfort, generalized malaise, and fever
Acute ischemic events	Varied presentations, such as chest pain/discomfort, shortness of breath, tachypnea, orthopnea, diaphoresis, weakness, nausea/vomiting, impaired mentation
Death	

vaccine is contraindicated (such as those with eczema or pregnant women),[26] although it is currently not licensed in these cases.[25]

As of January 31, 2003, enough VIG was available in the USA to treat the anticipated number of serious adverse reactions that would result from vaccination, based on a ratio of 1:10 000.[20,27] Two intravenous (IV) formulations of VIG have been licensed by the FDA for the management of a range of adverse reactions to smallpox vaccination (VIGIV Cangene and VIGIV Dynport), described in more detail below.[28,29] In August 2002, Cangene was awarded a contract by the CDC to provide up to 100 000 treatment doses of VIGIV. Cangene delivered an initial consignment of VIGIV to the Strategic National Stockpile in March 2004.

In the UK in 2002, the Department of Health issued Guidelines for Smallpox Response and Management in the Post-Eradication Era,[30] which include planning for a smallpox outbreak (e.g., alert levels, regional diagnosis and response groups, care centers, and vaccination strategy), assessment and management of initial and subsequent cases (e.g., isolation, management, and tracing of contacts), vaccination (including mass vaccination, assessment of efficacy, and awareness of contraindications and complications), use of VIG, and enhanced surveillance and communication strategies. UK smallpox vaccine stockpiles include first and second generation vaccines from different suppliers.

Many countries are stockpiling smallpox vaccine (first and/or second generation vaccines) and the WHO is also building new stocks to help countries without the resources to build their own.[31] There is currently no common stockpiling of smallpox vaccine at the level of the European Union (EU); most member states follow their own national strategy, with the aim of having at least one vaccine dose per inhabitant.[32] Next steps at EU level include increase in the availability of VIG, which is currently in very short supply.[32]

Complications of smallpox vaccine and guidelines for management

Range of adverse reactions

Complications of smallpox vaccination range from minor local and systemic reactions such as local pain, fever, and headache, which require no more than symptomatic management with non-prescription analgesics, through 'robust take' (a powerful response to the vaccine), to serious reactions such as encephalitis and progressive vaccinia (Table 1).[9]

Table 2 Incidence of serious adverse reactions to smallpox vaccine in worldwide reports from 1924 through the 1960s (data from Poland et al.)[6]

Adverse reaction	Incidence (per million vaccinations)
Encephalitis	2—1200
Encephalopathy	3—50
Eczema vaccinatum	8—80
Progressive vaccinia	1
Generalized vaccinia	1—70

Incidence of serious reactions

A review of worldwide reports of serious adverse reactions to various first-generation smallpox vaccines from 1924 through the 1960s suggested that encephalitis may be the most common, but probably strain-dependent, complication, with reported rates ranging from 2 to 1200 cases per million vaccinations, although encephalopathy, eczema vaccinatum, and generalized vaccinia were not infrequent in some reports (Table 2).[6] Reported rates of myopericarditis following vaccination with Dryvax® were generally low in these early studies.[6]

In the US smallpox vaccination program that followed September 11, 2001, the pattern of adverse events was somewhat different. As of January 2004, the US Department of Health and Human Services (DHHS) had vaccinated approximately 40 400 people, and as of January 2005, the Department of Defense (DoD) had vaccinated 730 580 service members.[6] There were no reported cases of eczema vaccinatum, progressive vaccinia, or fetal vaccinia, and only two cases of encephalitis among this total population of around 770 000 subjects (Table 3).[6] This reduced rate of adverse reactions compared to the civilian vaccination program of the 1950s and 1960s is very likely to be due to effective screening of potential vaccinees for contraindications. The rate of ocular complications was also relatively low, probably

Table 3 Anticipated adverse events in the US smallpox vaccination program from 2002 onwards (from Poland et al.)[6]

	DoD vaccines (n = 730 580)	DHHS vaccines (n = 40 422)
Preventable		
Eczema vaccinatum	0	0
Progressive vaccinia	0	0
Fetal vaccinia	0	0
Contact transmission — nosocomial	0	0
Contact transmission — not nosocomial	50 secondary, 2 tertiary	0
Auto-inoculation — non-ocular	62	20
Auto-inoculation — ocular	16	3
Not preventable		
Generalized vaccinia (all mild, no sequelae)	35 suspect, 8 probable	2 suspect, 1 confirmed
Post-vaccination encephalitis	1	1

Table 4 Unanticipated myopericarditis in the US smallpox vaccination program from 2002 onwards (from Poland et al.)[6]

	DoD vaccines (n = 730 580)	DHHS vaccines (n = 40 422)
Myopericarditis	86 (incidence ~1:8500)	21 (incidence ~1:2000)
Suspected	8	16
Probable	74	5
Confirmed	4	0

as a result of both careful screening of vaccinees and training prior to vaccination to prevent accidental inoculation. Rates of myopericarditis, however, were relatively high compared to the earlier reports (Table 4),[6] probably because the vaccine recipients had not been screened for cardiac risk factors,[21] in view of the apparently low risk in earlier reports. Myopericarditis is a smallpox vaccine class effect, regardless of strain or generation,[33,34] and it should be noted that most of the recently reported cases recovered rapidly and completely.[35] Nevertheless, as stated earlier, evidence of heart disease has now been added to the list of contraindications for smallpox vaccine in individuals not exposed to variola virus.

Management of serious complications

The USA has led the way in integrating VIG within preparedness policies. USA guidelines for the medical management of serious complications of smallpox vaccination are summarized in Table 5.[9] Historically, intramuscular (IM) VIG was the only formulation available. However, this has since been superseded by intravenous VIG (VIGIV), which is the only licensed product currently available from the CDC for the treatment of complications of vaccinia vaccination.[9,24]

VIGIV (Cangene) and VIGIV (Dynport) were both licensed by the FDA in 2005 for the management of patients with progressive vaccinia, eczema vaccinatum, severe generalized vaccinia, and extensive body surface involvement or periocular implantation following inadvertent inoculation. As described in more detail below, use of VIG has been demonstrated to be an effective strategy for the management of these adverse events. For example, one study indicated that the mortality rate associated with eczema vaccinatum was reduced from 30–40% to 7% after the introduction of VIG.[36] Progressive vaccinia has also been shown to resolve following administration of VIG in many cases of acquired immunodeficiency in adults and in eight of 14 subjects with isolated immunoglobulin defects.[37]

Although VIG is licensed for the management of periocular implantation of vaccinia virus, it is specifically contraindicated for isolated vaccinia keratitis, because of the risk of corneal scarring.[25] However, if there are comorbid conditions requiring VIG that outweigh this risk, the CDC has indicated that VIG should not be withheld.[25] So far, VIG has shown no benefit in postvaccinial encephalitis but the pathogenesis of this adverse reaction is not well understood.[37] As there is generally no evidence of active infection in the brain, it is believed that the encephalitis may result from an immune-mediated response.[37] However, there have been rare reports of vaccinia virus being isolated from central nervous system tissue post mortem; therefore, if it were possible to identify patients with active brain infection, VIG may prove to be of some benefit.[37] It is also theoretically possible that a higher dose of VIG may be required to allow for product breakdown as it crosses the blood–brain barrier.

The role of VIG in the management of smallpox vaccine-induced myopericarditis is unclear; however, as it is currently believed that this adverse reaction is immune-mediated rather than due to an active viral infection, VIG would probably be of no benefit.[35]

VIG prophylaxis in vaccinia vaccine adverse effects

As mentioned above, smallpox vaccination is contraindicated in some groups of people, including those with eczema or other skin conditions, immunosuppressed persons, infants under 1 year of age, and pregnant or breast-feeding women.[20,22] There is evidence that prophylactic VIG may be useful in some of these subjects, as described below.[37] However, in the absence of further evaluation, VIG is not currently recommended for prophylaxis when persons with contraindications to smallpox vaccination are inadvertently exposed to vaccinia and are otherwise well.[25] Following the ACIP meeting of February 2003, the consensus was to 'offer' VIG to women inadvertently vaccinated during pregnancy, or with newly diagnosed pregnancy after vaccination, but to avoid 'recommending' VIG use for this indication.[38]

Source and preparation of VIG

VIG was first obtained from the plasma of hyperimmunized US Army recruits in the 1950s and the IM form was used to treat complications of smallpox vaccination.[39] However, it was determined more recently that IV formulations would improve both tolerability and pharmacokinetic profile,[40] and better accommodate the large volume administered.

VIGIV (Cangene Corporation, US Civilian Stockpile) is a sterile solution containing the purified gamma globulin (IgG) fraction of plasma taken from healthy donors previously vaccinated with live vaccinia virus vaccine (Dryvax®), who demonstrate high titers of anti-vaccinia virus antibody.[41] The IgG fraction is purified by the anion-exchange column chromatography method. The solution is solvent/detergent-treated to sterilize it, and is stabilized with 10% maltose and 0.03% polysorbate 80 (pH 5.0–6.5). VIGIV contains no preservative, unlike IM VIG, which contained 0.01% thimerosol for this purpose, a potentially teratogenic mercury derivative.[42]

The VIGIV (Cangene) production process ensures that any risk of viral contamination is reduced to an absolute minimum.

Table 5 Guidelines for medical management of serious complications of smallpox (vaccinia) vaccination (from Thorne et al.)[9]

Serious complication	Medical management
Postvaccinial encephalitis	No definitive treatment available VIG *not* recommended Supportive care, anticonvulsants, and hospitalization in ICU should be considered
Progressive vaccinia (vaccinia gangrenosa, vaccinia necrosum)	VIG recommended: mortality has been prevented with prompt and adequate VIG treatment (consult CDC) No proven benefit of surgical debridement, or antiviral therapy
Eczema vaccinatum	VIG recommended Observe for secondary infections and hemodynamic compromise
Generalized vaccinia	VIG recommended in severe cases, especially if underlying immunodeficiency or recurrent
Inadvertent inoculation (accidental implantation)	Usually self-limited but more serious in immunocompromised patients VIG if extensive body surface involvement or periocular implantation (because of threat to eyesight)
Vaccinia keratitis	Immediate consultation with experienced ophthalmologist Topical antivirals in consultation with CDC VIG *contraindicated* in isolated keratitis (risk of corneal scarring), but should not be withheld in subjects with comorbidities requiring VIG where the risk outweighs that of corneal scarring
Other rash (e.g. erythema multiforme, Stevens–Johnson Syndrome, roseola vaccinia, toxic erythema, and postvaccinia urticaria)	Typically resolve spontaneously after 2–4 d but hospitalization and supportive care recommended for Stevens–Johnson Syndrome Treat symptoms
Fetal vaccinia	VIG efficacy unknown Antivirals not recommended
Myopericarditis	Rule out acute ischemic event and pericardial effusion NSAIDs or steroids might be indicated
Acute ischemic events	Standard of care for acute ischemic events

Every plasma donation is screened for the presence of hepatitis B virus (HBV) surface antigen (HBsAg) and antibodies to human immunodeficiency viruses (HIV-1/2) and hepatitis C virus (HCV) using FDA-licensed serologic tests.[41] The plasma is also tested by FDA-licensed nucleic acid testing (NAT) for HIV-1 and HCV. Although still an investigational tool, NAT for HBV is also performed on all source plasma used.[41]

The potency of VIGIV (Cangene) is determined by a plaque reduction neutralization test and expressed as arbitrary units by comparison to the FDA reference standard. Each vial contains approximately 40–70 mg/mL total protein and >50 000 units of vaccinia antibody neutralizing activity. Although VIGIV predominantly contains IgG, it has also been shown to contain a very small amount of immunoglobulin A (IgA) ($\leq$40 μg/mL).[41]

Efficacy and safety of VIG

Management of smallpox vaccine complications

The clinical efficacy of IM VIG has recently been reviewed by Hopkins and Lane based on reports in the literature.[37] The authors identified 16 articles that reported the use of IM VIG for the treatment of smallpox vaccine complications, although these did not include any formal controlled trials. Indications for treatment with IM VIG included generalized vaccinia, progressive vaccinia, eczema vaccinatum, and some accidental inoculations.

These uncontrolled studies generally reported reductions in morbidity and mortality with VIG compared to observed rates in untreated patients.[37] There were no fatalities among

over 800 VIG-treated subjects with generalized vaccinia and over 600 with accidental infection. Mortality was around 10% or less in cases of eczema vaccinatum treated with VIG, and around 25% in vaccinia encephalitis, although patient numbers were small in the latter case (ranging from 2 to 45 in various studies). There were also few reported cases of patients with progressive vaccinia treated with VIG (range 1 to 24 in different studies), with mortality ranging from 0/9 patients to 7/7 patients. Generally, there was a suggestion that mortality was reduced in these patients.

Prophylaxis of smallpox vaccine complications

Six publications reported the efficacy of IM VIG for the prophylaxis of vaccinial superinfection of eczema, burns, chickenpox, immunosuppression, pregnancy, or certain skin conditions, although these were not placebo-controlled studies.[37] The results showed that two of 810 eczema patients and none of 126 subjects with other skin conditions developed vaccine complications when pre-treated with VIG. Only one of 205 immunocompromised patients, three of 64 pregnant women and none of 18 with burns or chickenpox developed complications when VIG was used as prophylaxis prior to vaccination.

There has been one large controlled study in which healthy Dutch military recruits were given VIG or placebo together with smallpox vaccination with the aim of determining rates of vaccinia encephalitis.[37,43] The results showed only three cases of encephalitis among 53 630 individuals given VIG prophylaxis, compared to 13 cases of encephalitis among 53 044 recruits given placebo, and there were very few complications associated with VIG. While far from conclusive, these findings suggest that VIG had a prophylactic effect in these subjects.

Prevention of smallpox in exposed individuals

Four controlled studies and one observational study have reported the use of IM VIG to prevent smallpox in contacts of patients with documented cases of smallpox, with (in the words of Hopkins and Lane) ''varying but promising results'' (Table 6).[37]

Table 6 Prevention of smallpox with VIG among exposed individuals (from Hopkins and Lane)[37]

Study (year)	No. of close contacts with smallpox after exposure/no. of close contacts with exposure (%)	
	Vaccination + VIG	Vaccination alone
Kempe (1960)	2/56 (3.8)	8/75 (10)
Kempe (1961)	5/326 (1.5)	21/379 (5.5)
Hobday (1962)	2/56 (3.6)	8/75 (10.6)
Marennikova (1962)	0/13 (0)	13/29 (45)

Pharmacokinetics and safety of IM VIG and VIGIV

IM VIG appeared to be generally safe, although a few instances of allergic or anaphylactoid systemic reactions were reported, and occasional local tenderness and stiffness occurred, persisting from a few hours to 1–2 days following injection.[25,42] The IM VIG package insert recommended that ephedrine or other suitable medication be available for treating anaphylactoid reactions.[42]

VIGIV is a new product and therefore its efficacy has not yet been tested in clinical situations. There are, however, pharmacokinetic and safety data from studies in healthy volunteers. Hopkins et al. have recently reported on the safety and pharmacokinetics of two experimental IV formulations of VIG developed by the US military (one lyophilized and one liquid) in healthy volunteers.[40] The results showed that VIGIV at the target dose achieved plasma levels that were not inferior to predicted levels after IM VIG injection. Treatment-related adverse events typical of hyperimmune therapy were reported in 5–7% of subjects, including headache, injection-site reaction, and nausea, and there were no serious adverse events. The authors concluded that their studies suggest that IV administration of VIG is well tolerated and results in a more favorable pharmacokinetic profile than IM VIG.

The clinical pharmacology and pharmacodynamics of VIGIV (Cangene) have been assessed in two phase 1, randomized, double-blind studies.[41] The clinical pharmacology of VIGIV was assessed in 60 healthy volunteers randomized to receive either 6000 units/kg or 9000 units/kg VIGIV. A five-day time point was selected for assessment of results, as this is the approximate time of peak serum antibody levels following IM administration of other human immune globulin products. The results showed that the binding capacity and neutralizing antibody activity of anti-vaccinia antibody five days after VIGIV administration (at both dosages) were at least as high as the theoretical values that would be achieved with IM VIG (Table 7). It should be noted that no historical pharmacokinetic data are available for IM VIG.

Table 7 Clinical pharmacology of VIGIV: test of non-inferiority versus IM VIG[41]

Dose VIGIV, U/kg	Plasma levels[a] U/mL (CI)		Ratio of means % (97.5 lower CI bound)[b]
	VIGIV[c]	IM VIG[d]	
6000	60.1 (36.1–84.6)	66.2 (42.3–94.9)	90.82 (86.95)
9000	90.3 (63.4–133.8)	64.8 (47.6–87.2)	139.40 (135.27)

CI: confidence interval.
[a] Geometric mean (range).
[b] Expressed as a percentage relative to the geometric mean of the simulated concentrations at day 5 after 6000 U/kg IM administration.
[c] Observed levels.
[d] Simulated levels.

No serious adverse events were reported during the VIGIV (Cangene) clinical pharmacology study. Of the events reported, 85% were mild and 15% were moderate in severity. Headache was the most frequent adverse event, followed by rigors, dizziness and nausea. All adverse events that were considered related to VIGIV were typical of those expected following IV administration of protein.[44]

The pharmacodynamics of VIGIV (Cangene) were assessed in 32 healthy volunteers who were randomized to receive vaccinia vaccination with or without VIGIV.[41] The objectives were to assess the effects of VIGIV on local and immunological responses to vaccinia vaccination and to characterize further the safety of VIGIV. The results showed that concurrent administration of VIGIV and vaccinia vaccine does not alter the safety profile of VIGIV compared to the findings of the pharmacokinetic study.

The other FDA-licensed IV formulation of VIG (Dynport) has been tested clinically in healthy volunteers and was reported to be well tolerated.[45]

General comments on VIG safety

Serious adverse events with VIGIV are anticipated to be similar to those observed with other IV immune globulin products, and may include hypotension, anaphylaxis and anaphylactoid systemic reactions, renal dysfunction, and aseptic meningitis syndrome.[25] Persons administering VIGIV should be aware that persons with selective IgA deficiency might have anaphylactic reactions to blood products that contain IgA.[25] It is not known whether VIG causes fetal harm when administered during pregnancy, nor whether it is excreted in breast milk; therefore, VIG should only be offered to pregnant women if clearly needed, and caution should be exercised in breastfeeding women.[25] It may be noted that WinRho (Rh_0 (D) Immune Globulin (Human)), a passive immunizing agent used for the prevention of Rh immunization and treatment of idiopathic thrombocytopenic purpura, is produced by the same process as VIGIV (Cangene) and has been safely administered to pregnant women and infants.[46]

While still in use, IM VIG was specifically contraindicated by the FDA for use in pregnancy because of potentially teratogenic levels of mercury,[47] a risk that does not exist with VIGIV.

VIG products are solvent/detergent-treated and undergo size-exclusion based filtration steps to reduce the risk of contamination with viruses and other infectious agents. While a theoretical risk remains, donor screening and recent manufacturing processes have reduced this risk.[25]

Dosing and administration of VIGIV (Cangene)

The recommended dosage of VIGIV (Cangene) for the management of severe complications of smallpox (vaccinia) vaccination (indications listed above) is 6000 U/kg, to be given as soon as symptoms appear.[41] Repeat dosing may be considered if symptoms persist or are severe, although there are currently no clinical data on repeat doses. VIGIV should be given through a dedicated IV line at a maximum rate of 2 mL/min (max 0.04 mL/kg/min in individuals weighing <50 kg). In pediatric or geriatric patients, it is suggested that the product be infused more slowly in the event of a minor adverse reaction (e.g., flushing), or in the presence of risk factors for thrombosis/thromboembolism and/or renal insufficiency. All partially used vials of VIGIV should be discarded.

Conclusions

The reintroduction of smallpox vaccination in response to the risk of bioterrorism has brought with it a need to manage the adverse complications of smallpox vaccine, and consideration of alternative prophylaxis in persons for whom vaccination is contraindicated. VIG represents an important component of preparedness policies and is currently indicated for the management of a number of serious adverse reactions to smallpox (vaccinia) vaccination. Stockpiling of VIG is underway in the USA and on the agenda in the EU. Intravenous formulations of VIG are currently being manufactured and offer clinical advantages over IM VIG, including rapid distribution, lack of mercury derivatives, and ease of administration. Studies are needed to evaluate further the usefulness of VIG for prophylactic use in at-risk individuals and in post-exposure settings or treatment of smallpox in the clinical setting.

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