Clinical Efficacy of Intramuscular Vaccinia Immune Globulin: A Literature Review

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Background. Numerous literature reports describe clinical efficacy of intramuscular vaccinia immune globulin (VIG) for complications of smallpox vaccination, prophylaxis of individuals with contraindications to vaccination, and prevention of smallpox among close contacts of patients with smallpox.

Methods. We reviewed the literature regarding VIG treatment and prophylaxis of smallpox vaccine complications and the use of VIG as a preventative measure for close contacts of patients with smallpox.

Results. Data regarding intramuscular administration of VIG for treatment of smallpox vaccine complications occurred in 16 articles, none of which reported formal controlled trials. The indications for treatment include generalized vaccinia, progressive vaccinia, eczema vaccinatum, and certain accidental implantations. Six publications suggest VIG efficacy for prophylaxis of vaccinial superinfection of eczema, burns, chickenpox, immunosuppression, pregnancy, or certain skin conditions. Prophylactic VIG has also been used in healthy military recruits to reduce the incidence of postvaccinial encephalitis. The use of intramuscular administration of VIG to prevent smallpox in contacts of patients with documented cases of smallpox is reported in 4 studies that compare contacts who received intramuscular administration of VIG with those who did not and in 1 observational study, with varying but promising results.

Conclusions. Although controlled clinical trials do not exist to support the use of VIG for treatment of vaccinia-related complications or prophylaxis among individuals with contraindications to smallpox vaccination, available data suggest that VIG reduces morbidity and mortality associated with progressive vaccinia (vaccinia necrosum) and eczema vaccinatum. Furthermore, VIG seems to prevent vaccinial superinfection in patients with inflammatory skin diseases or burns, given the low incidence of vaccina-related complications associated with these conditions.

Smallpox vaccination is currently recommended to protect at-risk individuals and military personnel. The 2003 vaccination campaign included ∼500,000 military recruits [1] and ∼40,000 first-time responders [2]. The US government is acquiring supplies of vaccinia immune globulin (VIG) to help reduce the impact of smallpox vaccine complications in future vaccination programs. The currently available product is a 16.5% solution of immunoglobulin manufactured from plasma from individuals immunized with vaccinia virus [3] and is for intramuscular use.

The original US Food and Drug Administration–approved indications for VIG included treatment of individuals exposed to smallpox in conjunction with vaccination; prophylaxis of accidental implantation in the eyes or mouth; prophylaxis of accidental vaccinia exposure of children with extensive skin lesions, such as eczema, burns, impetigo, or variella; prophylaxis of eczematous children; and treatment of eczema vaccinatum, progressive vaccinia, 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 those due to poison ivy [3]. No clinical data are provided in the package insert to support these indications.

Nevertheless, intramuscular VIG (VIGIM) is considered the current standard to which future treatments should be compared. We conducted a literature review to assess the evidence for efficacy of VIG in a variety of therapeutic and prophylactic indications.
METHODS

We conducted an electronic search of International Pharmaceutical Abstracts, limiting the search to humans, English language, and all years. The search term used was “vaccinia immune globulin.” This search found 3 citations [4–6]. An electronic search of the MEDLINE, Embase, and Biosis databases, limited to humans, English language, and all years and including all article types (clinical trials, review articles, and meta-analyses) resulted in 4 citations [7–10]. An electronic search of the Biosis, Agricola, Pascal, Scisearch, Japanese Information Center for Science and Technology, Derwent Biotech Resources, and Chemical Engineering and Biotechnical Abstracts databases, limited to humans, English language, and all years, resulted in 2 additional citations [11, 12]. Detailed searches of the Medline database, limited to humans, English language, and all years and using the term “vaccinia immune globulin t/u” (therapeutic use) resulted in 12 citations [11–23]. An additional MEDLINE search using the term “VIG-IM” and with the same limits as the first search resulted in 3 citations [24–26]. A third MEDLINE search using the term “vaccinia immune globulin” and with the same limits as the first search resulted in 19 citations [27–45]. These articles were reviewed to identify additional references about the use of VIG. All citations were reviewed to obtain information and supplementary references on smallpox vaccine complications without VIG treatment. This review processes yielded 31 additional citations [46–77].

RESULTS

Table 1 summarizes the reports with information on VIG efficacy for the treatment of established smallpox vaccine complications, prophylaxis of complications among at risk individuals, and prevention of smallpox among exposed individuals.

<table>
<thead>
<tr>
<th>Treatment or prophylaxis, study</th>
<th>Date of report</th>
<th>No. of subjects</th>
<th>Study design</th>
<th>Complications and conditions evaluated</th>
<th>Outcomes assessed</th>
<th>Treatment intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment of established smallpox vaccine complications</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Greenberg [53]</td>
<td>1948</td>
<td>90</td>
<td>O</td>
<td>VE, EV</td>
<td>M</td>
<td>NT</td>
</tr>
<tr>
<td>Kempe [59]</td>
<td>1960</td>
<td>256</td>
<td>O</td>
<td>GV, VE, EV, PV</td>
<td>M</td>
<td>VIG</td>
</tr>
<tr>
<td>Ellis and Winograd [75]</td>
<td>1962</td>
<td>6</td>
<td>O</td>
<td>A</td>
<td>CR</td>
<td>VIG</td>
</tr>
<tr>
<td>Copeman and Wallace [46]</td>
<td>1964</td>
<td>137</td>
<td>O</td>
<td>EV</td>
<td>M</td>
<td>VIG/NT</td>
</tr>
<tr>
<td>Neff et al. [65]</td>
<td>1967</td>
<td>433</td>
<td>O</td>
<td>GV, VE, EV, PV, A</td>
<td>M</td>
<td>VIG/NT</td>
</tr>
<tr>
<td>Lane et al. [28]</td>
<td>1969</td>
<td>572</td>
<td>O</td>
<td>GV, VE, EV, PV, A</td>
<td>M</td>
<td>VIG</td>
</tr>
<tr>
<td>Hallett [54]</td>
<td>1969</td>
<td>4</td>
<td>O</td>
<td>GV, EV</td>
<td>CR</td>
<td>VIG, NT</td>
</tr>
<tr>
<td>Sharp and Fletcher [67]</td>
<td>1973</td>
<td>230</td>
<td>O</td>
<td>GV, EV, PV, VE, A</td>
<td>CR, M</td>
<td>VIG</td>
</tr>
<tr>
<td>Feery [51]</td>
<td>1976</td>
<td>815</td>
<td>O</td>
<td>GV, EV, PV, VE, A</td>
<td>M</td>
<td>VIG</td>
</tr>
<tr>
<td>Seth et al. [16]</td>
<td>1978</td>
<td>1</td>
<td>CR</td>
<td>PV</td>
<td>CR</td>
<td>VIG</td>
</tr>
<tr>
<td>Redfield et al. [6]⁴</td>
<td>1987</td>
<td>1</td>
<td>CR</td>
<td>PV</td>
<td>CR</td>
<td>VIG</td>
</tr>
<tr>
<td>Kesson et al. [9]</td>
<td>1997</td>
<td>1</td>
<td>CR</td>
<td>PV</td>
<td>CR</td>
<td>VIG</td>
</tr>
<tr>
<td>Prophylaxis for smallpox vaccination</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kempe [59]</td>
<td>1960</td>
<td>44</td>
<td>O</td>
<td>Eczema</td>
<td>M</td>
<td>VIG</td>
</tr>
<tr>
<td>Nanning [64]</td>
<td>1962</td>
<td>106,634</td>
<td>PC</td>
<td>VE</td>
<td>CR, P</td>
<td>VIG</td>
</tr>
<tr>
<td>Lane et al. [28]</td>
<td>1969</td>
<td>64</td>
<td>O</td>
<td>Multiple conditions</td>
<td>M</td>
<td>VIG</td>
</tr>
<tr>
<td>Sharp and Fletcher [67]</td>
<td>1973</td>
<td>431</td>
<td>O</td>
<td>Multiple conditions</td>
<td>CR, M</td>
<td>VIG</td>
</tr>
<tr>
<td>Feery [51]</td>
<td>1976</td>
<td>870</td>
<td>O</td>
<td>Multiple conditions</td>
<td>CR, M</td>
<td>VIG</td>
</tr>
<tr>
<td>Prophylaxis of close contacts of smallpox cases</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kempe [59]</td>
<td>1960</td>
<td>131</td>
<td>CC</td>
<td>NA</td>
<td>NA</td>
<td>VIG, NT</td>
</tr>
<tr>
<td>Kempe et al. [60]</td>
<td>1961</td>
<td>706</td>
<td>CC</td>
<td>NA</td>
<td>NA</td>
<td>VIG, NT</td>
</tr>
<tr>
<td>Hobday [55]</td>
<td>1962</td>
<td>29</td>
<td>O</td>
<td>NA</td>
<td>NA</td>
<td>VIG</td>
</tr>
<tr>
<td>Marennikova [63]</td>
<td>1962</td>
<td>13</td>
<td>CC</td>
<td>NA</td>
<td>NA</td>
<td>VIG, NT</td>
</tr>
</tbody>
</table>

NOTE. A, accidental infection; CC, case-control study; CR, case report; CR, clinical response; EV, eczema vaccinatum; GV, generalized vaccinia; M, mortality; NA, not applicable; NT, no treatment; O, observational study; P, placebo; PC, placebo-controlled study; PV, progressive vaccina; R, review; VE, vaccinal encephalitis.⁴ The subject in this report was positive for HIV infection.
VIG Treatment of Established Vaccine Complications

Studies that provide information on VIG treatment of established vaccine complications (table 1) generally report efficacy with respect to morbidity or mortality rates for specific complications: generalized vaccinia, vaccinia encephalitis, eczema vaccinatum, progressive vaccinia, and accidental infection (usually ocular). None of these studies are formal controlled trials. Five references provide information on clinical response without using clearly defined end points. The majority of treated complications were identified through VIG distribution records, and untreated control subjects are not included. One report compares clinical response among VIG recipients who had an “infectious etiology” with clinical response among those with an “allergic etiology” [51] in an effort to provide an internal “control” using complications that might not be expected to respond to VIG treatment.

Comparison of mortality rates of patients with VIG treatment and of “historical controls” (consisting of untreated patients) are found in selected literature reports. Table 2 summarizes these reports.

**Progressive vaccinia.** Early studies acknowledge the importance of both cellular and humoral immunity in the development and treatment of progressive vaccinia. Kempe et al. [59] observed a normal vaccination response in 33 male children with agammaglobulinemia, and Fulginiti et al. [50] noted that progressive vaccinia was more common in patients with thymic alymphoplasia and less common in individuals with Bruton-type hypogammaglobulinemia and acquired immune defects. The lack of delayed hypersensitivity was universal among the 8 progressive vaccinia cases.

A recent literature review identified 56 cases reported from 1893 through 1997 [7]. We identified an additional 8 reports

### Table 2. Reports of vaccinia-related mortality in patients receiving and not receiving treatment with vaccinia immune globulin (VIG) administered intramuscularly (VIGIM), by type of smallpox vaccination–associated complication.

<table>
<thead>
<tr>
<th>Treatment, study</th>
<th>Date of report</th>
<th>Progressive vaccinia</th>
<th>Eczema vaccinatum</th>
<th>Generalized vaccinia</th>
<th>Vaccinia encephalitis</th>
<th>Accidental infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>No VIGIM treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Greenberg [53]b</td>
<td>1948</td>
<td>...</td>
<td>2/38</td>
<td>...</td>
<td>4/45</td>
<td>...</td>
</tr>
<tr>
<td>Kempe [59]</td>
<td>1960</td>
<td>7/7b</td>
<td>(30–40)c</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Lane [28]</td>
<td>1969</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>4/14d</td>
<td>...</td>
</tr>
<tr>
<td>Bray and Wright [7]</td>
<td>2003</td>
<td>6/9 (67); 5/6 (83)e</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>VIGIM treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kempe [59]</td>
<td>1960</td>
<td>0/2; 7/23b</td>
<td>9/132</td>
<td>0/62</td>
<td>3/12</td>
<td>0/27</td>
</tr>
<tr>
<td>Ellis [75]</td>
<td>1962</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>0/6f</td>
</tr>
<tr>
<td>Copeman [46]</td>
<td>1964</td>
<td>...</td>
<td>11/137g</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Fulginiti et al. [76]</td>
<td>1965</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>0/4</td>
</tr>
<tr>
<td>Sussman et al. [69]</td>
<td>1965</td>
<td>0/5h</td>
<td>1/37</td>
<td>0/134</td>
<td>1/5</td>
<td>0/48</td>
</tr>
<tr>
<td>Neff et al. [65]</td>
<td>1967</td>
<td>0/9</td>
<td>2/111</td>
<td>0/134</td>
<td>5/12</td>
<td>0/115</td>
</tr>
<tr>
<td>Lane [28]</td>
<td>1969</td>
<td>4/10</td>
<td>1/126</td>
<td>0/143</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Ruben and Lane [66]</td>
<td>1970</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>0/348</td>
<td>...</td>
</tr>
<tr>
<td>Pond [20]</td>
<td>1972</td>
<td>1/1</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Sharp and Fletcher [67]</td>
<td>1973</td>
<td>1/1</td>
<td>2/47</td>
<td>0/50</td>
<td>1/1</td>
<td>0/42</td>
</tr>
<tr>
<td>Feery [51]</td>
<td>1976</td>
<td>2/13</td>
<td>0/31</td>
<td>0/309</td>
<td>0/2</td>
<td>0/71</td>
</tr>
<tr>
<td>Seth et al. [16]</td>
<td>1978</td>
<td>0/1</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Bray and Wright [7]</td>
<td>2003</td>
<td>10/24 (41); 14/17 (82)°</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

**NOTE.** Data are no. of subjects who died/no. of subjects evaluated, unless otherwise indicated.

b In addition, this article references previous mortality rates from Europe of 30%–50% in subjects who did not receive therapy with VIG.

c In addition to the 23 new cases of progressive vaccinia, 9 previously reported cases were reported in the literature; however, specific references were not provided. Two of the 9 subjects survived after treatment with massive amounts of VIG.

d Data are range of mortality rates in percentages, based on historical information for children <2 years of age receiving supportive therapy alone. The reference for this data was not provided.

e Although not specifically referenced, none of these 14 patients were treated with VIGIM (J. M. L., personal communication).

f Data are proportion (%) of adults who died; proportion (%) of children who died.

g Among the 6 patients with ocular cases reported, 5 showed a good response to VIGIM. The single patient who did not respond was believed to have a specific defect in the ability to form antibodies against vaccinia virus, although the y-globulin fraction was normal.

h It is not clear from this report how many individuals were treated. The overall mortality rate was 8% (11 patients), and gravely ill persons were reported to have been treated with hyperimmune VIGIM.

i All 5 patients survived; however, 1 patient required thiosemicarbazone after a VIGIM-resistant infection. Only 1 of the 5 cases is included in [7].

The number of subjects receiving VIGIM treatment was not specified, but most cases were captured via VIG distribution systems.
Eczema vaccinatum. Eczema vaccinatum occurs as a result of either intended vaccination or accidental inoculation; however, disease is more often severe when it occurs as a result of accidental inoculation [28]. The pathogenesis in vaccinated individuals is thought to involve either transient viremia or direct inoculation, and it often involves areas of normal skin as well as areas of atopic dermatitis. In severe cases, the pathogenesis may also involve a modest immune deficit [78]. In one study, a mortality rate of 7% (9 of 132 patients with treated cases) was noted in individuals treated with VIG [59]. A measurable antibody response developed in 55 of 56 tested individuals who survived and failed to develop in the 5 patients with fatal cases [59].

Two studies report mortality rates associated with eczema vaccinatum without VIG treatment [53, 59]. In the first study [53], death was reported in 2 (5%) of 37 children with pre-existing eczema (aged 4 and 6 months). A 30%–40% mortality rate was reported in a subsequent study [59], but no detail (or reference) was provided. Although an overall low mortality rate of 4% (26 of 627 individuals) for VIG-treated individuals is observed across studies (table 2), the 2 populations (VIG-treated patients and historical control subjects) may not be comparable across studies with respect to case definitions, identification methods, and/or demographic characteristics. Only a controlled trial proves efficacy in this setting.

Generalized vaccinia. Most patients with cases of generalized vaccinia experience only a mild illness. In the 2 larger US surveys [27, 28], the number of individuals with generalized vaccinia who actually received VIG therapy was not reported. In these surveys, ∼50% and ∼30% of patients, respectively, were hospitalized. Many had satellite vesiculation around the vaccination site. A clear distinction between true generalized vaccinia with vesicular or pustular rashes and maculopapular or erythema-multiforme-like rashes is not made in these studies. Statements in the literature suggest that individuals with generalized vaccinia recover with little or no specific therapy [26], but no studies have quantified the clinical response of patients with true generalized vaccinia with or without therapy [1].

Postvaccinal encephalitis. Clinical data to support any form of specific treatment of postvaccinal encephalitis are lacking. This condition is rare; therefore, mortality rates, with or without treatment, are based on very few cases and are highly varied. The pathogenesis of postvaccinal encephalitis is poorly understood. In most cases, the pathogenesis is probably similar to that of other postviral encephalitides. In rare instances, vaccinia has been isolated from CNS tissue at necropsy [74], but generally there is no evidence of active infection of the brain [74]. DeVries [74] distinguished between encephalopathy, which is generally just swelling of the brain and is seen mostly in children <2 years old, and encephalitis, with the classical perivascular cuffing found in allergic or immune-mediated encephalitis. Treatment with VIG is not commonly used for post-vaccinal encephalitis, because it is probably an immune-mediated condition like other postviral encephalitides. However, there is no evidence to suggest that VIG treatment would worsen the outcome. If some way is found to determine which patients actually have vaccinal infection of the brain, such patients might benefit from VIG therapy.

Accidental infection. Accidental infection results in a normal vaccination lesion in an inappropriate site. As such, most such lesions will heal with no therapy. In the 8 reports with information regarding VIG treatment [51, 59, 65–67, 69, 75, 76], there were no fatalities. The most common and most worrisome site for accidental infection is the eye, with ocular vaccinia occurring approximately 10–20 times per 1 million primary vaccinations. In a large series of 348 patients with ocular vaccinia treated with VIG, only 22 had corneal involvement; 4 of these 22 patients had mild long-term residua [66]. Healing of vaccinal keratitis with VIG therapy has been reported [75], but 4 cases with corneal clouding after VIG therapy have also been reported [76]. These observations led Fulginiti et al. [50] to conduct controlled experiments of therapy of corneal vaccinia in rabbits; they found persistent and larger stellate scars among VIG-treated animals, compared with control animals [76]. Current recommendations suggest that treatment with VIG be considered in severe cases of ocular vaccinia (after careful evaluation to rule out keratitis) and that even the presence of keratitis is not an absolute contraindication if there is a comorbid condition that requires administration of VIG. Modern ophthalmic antiviral therapy should also be considered, even in the absence of controlled clinical trials [77].

VIG Prophylaxis of Smallpox Vaccine Complications among At-Risk Individuals

There are 5 reports [51, 28, 64, 59, 67] (table 3) that describe VIG use for prophylaxis of smallpox vaccine complications among at-risk individuals. Demonstration of efficacy in this setting is increasingly important, given the increasing prevalence of individuals with eczema (true atopic dermatitis) and of individuals who are immunocompromised by HIV infection, cancer, chemotherapy, or organ transplantation. Although it is interesting to note that VIG prophylaxis among at-risk populations has a very low incidence of complications, it is not possible to conclude that efficacy has been demonstrated in the absence of placebo-controlled trials.
Conditions for which VIG prophylaxis has been given include being <1 year old; having eczema, burns, or chickenpox; and having congenital or acquired immunosuppression. A large study was performed to evaluate VIG prophylaxis versus placebo control concurrently with smallpox vaccination among healthy Dutch military recruits [64]. This study [64] found 3 encephalitis cases among 53,630 individuals who were given VIG prophylaxis plus smallpox vaccine, and it found 13 cases of encephalitis among 53,044 recruits given placebo plus smallpox vaccine. Very few complications developed with VIG prophylaxis, regardless of the condition evaluated. The limited data regarding prophylaxis of various conditions preclude definitive recommendations, but prophylaxis of most of these conditions is probably warranted if vaccination is essential.

Prevention of Smallpox among Exposed Individuals

Four reports explore VIG as a preventative treatment among close contacts of patients with smallpox [55, 59, 60, 63] (table 4). Three reports were attempts at clinical studies that assessed the incidence of smallpox among close contacts who received vaccination alone versus among those who received vaccination plus VIG treatment [59, 60, 63]. The selection of smallpox contacts in the early 1960s did not meet modern standards of randomization. Nevertheless, these studies [55, 59, 60, 63] found differences in development of disease among treatment groups across studies. In the 2 studies by Kempe et al. [59, 60] in Madras, ~50% of contacts received VIG plus vaccination, and the other 50% of contacts received vaccination alone. The first study [59] was conducted in 1953 and demonstrated a reduction in smallpox cases among family contacts from 10% (8 of 75 contacts) to 3.4% (2 of 56 contacts) with VIG therapy. The second, larger, and more carefully controlled study [60], reported in 1961, demonstrated a statistically significant reduction in smallpox cases among exposed contacts, from 5.5% (21 of 379 contacts) to 1.5% (5 of 326 contacts), with VIG therapy. Nine infants exposed to smallpox infection in utero, at birth, or shortly thereafter all received 5 mL of VIG. Mild disease occurred in 3 of the 9 infants, all of whom likely contracted disease from their mothers. The authors felt that the development of clinical smallpox in only 3 infants was a significant finding given a high expected mortality rate among infants infected in utero or at birth. They argue for preventative treatment with VIG in situations in which smallpox is not endemic, especially for unvaccinated contacts of early cases in an outbreak setting (in an effort to limit spread).

An additional report describes 42 close contacts of patients with cases of smallpox who were under observation [63]. Prophylactic VIG (administered at a dose of 9 mL in adults and 6 mL in children) was given to 13 of these 42 contacts, none of whom developed the disease. All 13 individuals who received VIG had contact with patients who had smallpox in an infectious stage of the disease and for whom the clinical diagnosis of smallpox had been confirmed by direct virus isolation. Four contacts had been vaccinated in childhood or infancy, and all but 3 were not revaccinated until at least the fifth day after contact. Among the other 29 contacts who were not given VIG prophylaxis, all were family members or caregivers who had approximately the same degree of contact as did the treated group. The report does not state when these 29 individuals were vaccinated in relation to the time of smallpox exposure. Thirteen of those 29 contacts developed smallpox. This report also describes 2 patients who received VIG as treatment for smallpox during the prodrome of illness and 2 others who received VIG at the height of disease. VIG was administered
to the first 2 patients on the third and fourth day after onset of the prodrome, respectively. The clinical course was mild (smallpox without eruption in one patient and “variolioid” in the other). In the 2 patients who received VIG at the height of disease, an improvement in their general condition was noted, and a favorable effect on skin lesions was claimed.

A fourth report, from the United Kingdom, claimed success with VIG prophylaxis among contacts of 3 smallpox cases [55]. An index patient had received a diagnosis of smallpox 5 days after admission to a general hospital. There were 9 adult contacts and 15 children at serious risk. All were vaccinated and given VIG (1 g for adults and 0.5 g for children), and none developed smallpox. A second severe case of smallpox occurred in a vaccinia-naive boy as a result of a contact with an imported case from Bombay, India. The boy had 2 contacts: his grandmother, who had not been vaccinated since infancy, and his 6-year-old sister, who was vaccinia naive. Both contacts were vaccinated and given VIG. Both developed mild rashes, suggesting that VIG had afforded protection where infection had probably occurred (variola was isolated from the sister). Another moderately severe case of smallpox was diagnosed 5 days after the appearance of a rash. This patient had 3 close contacts, none of whom had been vaccinated for at least 38 years. All were vaccinated and developed primary reactions, and they were also treated with 1.5 g of VIG. None developed smallpox.

**DISCUSSION**

Vaccinia complications associated with smallpox vaccination mandate stockpiling VIG, which, in the event of a bioterrorist attack, could also be used with concomitant vaccination in contacts of actual smallpox patients. The US government has contracted to manufacture and license an intravenous preparation of VIG. Because smallpox vaccine complications are extremely rare, evaluation of the clinical efficacy of VIG is difficult. The literature supports VIG for treatment of progressive vaccinia, eczema vaccinatum, and severe generalized vaccinia, although there have been no controlled therapeutic trials. The varied results seen across studies may be due to a treatment effect of VIG but could also be due to differences in case definitions, concurrent treatments, or survey methods. For established complications, the risk-benefit decision favors the use of VIG treatment, especially because immunoglobulins are fairly well tolerated. This is especially true for cases of eczema vaccinatum and progressive vaccinia, in which death may result from untreated disease. The more difficult decisions involve the prophylactic use of VIG among at-risk individuals with skin conditions (such as eczema, burns, impetigo, or varicella), acquired immunodeficiency syndromes (including HIV infection and other immunodeficiency states), or pregnancy. The demonstrated safety profile of intravenous VIG, which yields serum-neutralizing antibody levels estimated to be at least as high or higher than those achieved with VIGIM [79], is likely to push the pendulum in favor of prophylaxis even though controlled studies do not exist.

One concern is that prophylactic VIG might prevent the development of active immunity after vaccination if used concurrently with smallpox vaccination. Early reports noted that it was frequently difficult to vaccinate young infants with passively acquired maternal antibody. These observations prompted the study of paired vaccinia antibody levels in mother-infant pairs [59]. Antivaccinia antibody titers in infants were found to be similar to or higher than those found in their mothers regardless of when maternal vaccination occurred. Revaccination studies in infants suggested that active immunization is achieved under the cover of transplacental passive immunity, and this led to the subsequent evaluation of VIG in the prophylaxis of smallpox after known exposure [59]. Immune serum globulin is also known to reduce seroconversions after receipt of measles vaccine, and rubella and varicella vaccines are not recommended immediately after immunization [80–82]. The success of smallpox vaccination given with VIG has been evaluated in 2 studies [52, 64], which were conducted in the 1950s and 1960s, respectively. In the first study [52], varied doses (1 mL, 2–3 mL, 6 mL, and 12 mL) were tested as to their effect on primary vaccination among 1010 vaccinia-naive individuals. Vaccinations were administered within 2 days after VIG administration. Only 14 “no takes” and 9 “accelerated reactions” were observed. In the second study [64], >50,000 Dutch military recruits were treated with 2 mL of VIGIM without any abnormality in the local vaccination reaction. A subgroup of 92 VIG-treated individuals and 113 individuals not receiving VIG were all successfully revaccinated after 2–4 years. Intravenous administration of VIG and doses of VIGIM as large as 0.3 mL/kg (indicated for prophylactic use for at-risk individuals) [3] have not been evaluated for their effect on smallpox vaccination. Doses in this range were routinely given.
before vaccination of at-risk individuals in the 1960s and early 1970s with no diminution of the response to the smallpox vaccine. There is no reason to believe that VIG prophylaxis at doses similar to those used in the past would cause an inadequate smallpox vaccination. Nevertheless, this area deserves further study to ensure that robust “takes” with solid humoral and cell-mediated immunity develop following vaccination when given concurrently with currently recommended doses of VIG.

Research conducted during the past 6 decades supports the use of VIG in a variety of clinical settings related to smallpox vaccination. Newer products should achieve vaccinia-specific neutralizing titers equal or superior to those for the intramuscular product that has historically been used.

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