Induction of Immune Tolerance in Patients With Hemophilia A and Inhibitors Treated With Porcine VIIIC by Home Therapy

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Home therapy with porcine factor VIIIC was safe and effective when administered to five hemophilic patients over periods of 8 1/2, 6, 4, 3 1/2, and 2 years. No significant transfusion reactions occurred. Before treatment with porcine factor VIIIC, all five had high-level, high-responding anti-human VIIIC inhibitors initially lacking anti-porcine factor VIIIC activity. Although specific anti-porcine VIIIC inhibitors arose in all patients, these were generally transient, and only one patient became refractory to treatment. We believe that porcine factor VIIIC is the treatment of choice in patients whose inhibitors do not cross-react. All five patients lost their original anti-human VIIIC inhibitors after starting treatment with porcine VIIIC, permitting the reintroduction of human VIIIC in three of them. There has been no recurrence of anti-human VIIIC inhibitor activity during 2 to 3 years of regular treatment with human VIIIC in these patients. This suggests that tolerance to human VIIIC has arisen as a result of treatment with porcine VIIIC. Porcine VIIIC may have a role in the desensitization of some factor VIIIC inhibitor patients.

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PATIENTS AND METHODS

Anti-human factor VIIIC inhibitor activity was measured using the Bethesda Method and pooled normal plasma. Anti-porcine VIIIC inhibitor activity was measured using the Bethesda Method and a porcine concentrate (Hyate:C, Speywood Laboratories) reconstituted in hemophilic plasma.

Factor VIII clotting activity was measured using a one-stage method in three centers and a two-stage method in two, with a pooled normal human plasma standard calibrated against national standards.

Human immunodeficiency virus (HIV) antibody was detected in 1985 and 1986 by radioimmunoassay, but later by enzyme-linked immunoassay (ELISA) and confirmed by Western blotting. T-cell subsets were estimated by flow cytometry.

Five patients with severe hemophilia-A (VIIIC less than 0.01 U/mL) from centers in England and France were regularly treated with porcine VIIIC (Hyate:C, Speywood Laboratories) for between 2 and 8 1/2 years. These patients were selected for regular treatment with porcine VIIIC because they had all had high-responding VIIIC inhibitors precluding satisfactory replacement therapy with human VIIIC, and because their factor VIII inhibitors were found to lack measurable cross-reactivity to porcine VIIIC.

Porcine VIIIC was administered under close hospital supervision for the first few weeks or months. When no significant treatment-related problems were encountered, the treatment was given on an outpatient basis, and then as self-administered home therapy. The treatment regimen varied according to the frequency of hemorrhages and the personal preference of the clinician. The three patients with most frequent hemorrhages were treated with 20 to 60 U/kg every second day, and the two with less frequent hemorrhages with 20 U/kg on demand.

Patient 1. This 35-year-old patient developed a factor VIII inhibitor at the age of 4 years that reached a peak of 28 Bethesda Units (BU) during adolescence. He was subsequently treated with factor VIII concentrate combined with plasmapheresis, prothrombin complexes are less likely to cause an anamnestic response, but are costly and do not confer striking clinical benefit. The variety of treatments available is an indication that no single mode of therapy is entirely satisfactory. Although large doses of human factor VIIIC are effective in patients with low-level inhibitors, they can cause pronounced anamnestic reactions (PCC) and activated PCC, recombinant VIIa, and factor VIII:C activity. Although specific anti-porcine VIII:C was found to lack anti-porcine factor VIIIC activity. Although specific anti-porcine VIII:C inhibitors arise in all patients, these were generally transient, and only one patient became refractory to treatment. We believe that porcine factor VIIIC is the treatment of choice in patients whose inhibitors do not cross-react. All five patients lost their original anti-human VIII:C inhibitors after starting treatment with porcine VIIIC, permitting the reintroduction of human VIII:C in three of them. There has been no recurrence of anti-human VIII:C inhibitor activity during 2 to 3 years of regular treatment with human VIII:C in these patients. This suggests that tolerance to human VIII:C has arisen as a result of treatment with porcine VIIIC. Porcine VIII:C may have a role in the desensitization of some factor VIIIC inhibitor patients.

CIRCULATING ANTIBODIES to factor VIII:C (inhibitors) arise in about 10% of patients with hemophilia A. Such inhibitors render the patient refractory to treatment by rapidly neutralizing infused factor VIII:C. Alternative treatments used in these circumstances include larger than normal doses of VIII:C, prothrombin complex concentrates (PCC) and activated VIII:C, recombinant VIIIa, and porcine VIII:C (Hyate:C, Speywood Laboratories, Wrexham, Wales). The induction of immune tolerance by regular administration of factor VIII:C concentrate over a period of weeks or months, but this is often unsuccessful in patients with high-responding inhibitors.

Anti-human factor VIII:C inhibitors cross-react to a variable extent with VIII:C from other species. Their capacity to neutralize human VIII:C is usually greater than their capacity to neutralize nonhuman VIII:C, however, so that inhibitor patients may respond to porcine VIII:C even when refractory to human VIII:C. The degree of cross-reactivity between porcine VIII:C and anti-human factor VIII:C inhibitors is very variable and may change after treatment, but averages 15% to 25%. Reactions occur in only a small percentage of patients, and are usually minor. Thrombocytopenia rarely accompanies treatment.

The potential side effects of porcine factor VIII:C have discouraged clinicians from using it in a home-care setting, and it is usually used under hospital supervision. We present data from five patients which demonstrate that a subgroup of inhibitor patients can be identified in whom prolonged home therapy with porcine VIII:C is both successful and safe, and can result in apparent immune tolerance with loss of inhibitor to human factor VIII:C.

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complex concentrates, factor VIII in combination with anti-

fibrinolytic drugs, and immunosuppression with cyclophosphamide,

all with little success. He became disabled with severe painful
arthropathy of both knees, and arthropathy of his elbows compli-
cated by right ulnar nerve palsy.

Treatment with porcine VIIIC began in October 1980 when his
inhibitor was found to lack cross-reactivity to porcine VIIIC. He
has been treated almost exclusively with this product since that time, and
has used no blood products of human origin since 1984. He uses 20
U/kg every second day for prophylaxis, and 40 U/kg for hemar-
theses, and his clinical response has always been excellent. Conse-
quently, he has been able to have remedial surgery, resulting in a
considerable reduction in pain, and improvement in mobility and
work pattern. No significant reactions or thrombocytopenia have
been observed. He is anti-HIV seronegative on repeated testing.

**Patient 2.** This 32-year-old patient has been confined to a
wheelchair by hemophilic arthropathy from the age of 8. An
anti-human VIIIC inhibitor of 18 BU was detected when he was 15
years old. He was treated irregularly with human factor VIIIC until
1977 when regular treatment with FEIBA prothrombin complex
concentrate began. This treatment was ineffective.

In October 1980 his anti-human inhibitor increased to 10 BU after
the administration of 500 U of human VIIIC for an ankle bleed.
Because no cross-reactivity with porcine VIIIC could be demon-
strated at this time, treatment on demand with porcine VIIIC began.
His clinical response to 20 U/kg has been consistently excellent and
he continued on home therapy, treating his hemarthroses exclusively
with porcine VIIIC approximately twice a month over the next 6
years. His inhibitor having disappeared, regular treatment with
human VIIIC resumed in 1986. He remains anti-HIV seronegative
on repeated testing.

**Patient 3.** This 22-year-old patient developed an inhibitor at age
7. Treatment with human factor VIII continued intermittently, but
was not very effective. He became disabled with severe painful
arthropathy affecting his left hip, both knees, and both ankles, and
he began to abuse dihydrocodein. He became infected with HIV
during 1984.

In March 1985 he suffered a fractured femur requiring internal
fixation, and was treated for 10 days with human VIIIC. This was
associated with a rapid anamnestic increase of his anti-human VIIIC
inhibitor to 56 BU, with transfusion reactions to human factor VIII
concentrate of increasing severity culminating in a life-threatening
anaphylactic reaction on the 10th day of treatment. Therefore,
human VIIIC was discontinued, and he has been treated exclusively
with porcine VIIIC ever since.

Hemarthroses were initially treated with 50 U/kg of porcine
VIIIC because presentation to hospital was usually delayed. After 2
years without any treatment-related problems, home therapy was
established. Porcine VIIIC, 20 U/kg, has been found to be adequate,
now that his hemarthroses are treated promptly. Therefore, the
initiation of home therapy has resulted in considerable financial
savings. His joint pain has been much reduced, and he has become
fully mobile and far more independent. He no longer abuses
analgesics.

**Patient 4.** This 15-year-old patient developed a high-responding
anti-human VIIIC inhibitor increasing to 50 BU at age 5. Treatment
with both FEIBA and prothrombin complex concentrates were
relatively ineffective, and treatment with human factor VIIIC was
always associated with a brisk anamnestic response. By age 10 he
was largely confined to a wheelchair by severe hemophilic arthropa-
thy, and suffered knee hemarthroses three times a week. He was able
to attend school only 1 day in 3. Synoviorthesis of his knee with osmic
acid was attempted in 1983 with little success. He became HIV-
seropositive in 1983, shortly before starting porcine VIIIC.

In January 1984 regular prophylactic treatment with 50 to 60
U/kg porcine VIIIC every second day began in an attempt to
improve his quality of life. A 10-fold reduction in the frequency of
his hemarthroses resulted, and he was gradually able to regain

**Patient 5.** This 17-year-old patient was 6 years old when his
inhibitor was first detected. Factor VIIIC treatment continued
intermittently until the late 1970s when treatment with Autoplex
(Baxter Travenol, Glendale, CA) or FEIBA (Immuo, Vienna,
Austria) prothrombin complex concentrates in doses of up to 30,000
U/mo began. This failed to control his bleeding or halt the
progression of his arthropathy, and human VIIIC precipitated a
brisk anamnestic response. It was decided to try treatment with
porcine VIIIC.

Prophylaxis with 50 U/kg of porcine VIIIC every second day
began in November 1983. Although a specific anti-porcine inhibitor
arose soon after treatment with porcine VIIIC began, the clinical
response was good and the frequency of his hemarthroses decreased
from 52 in the year before to 13 in the year after prophylaxis began.
After 2 years, when the anti-porcine VIIIC inhibitor level reached 6
BU, the patient became refractory to treatment. Porcine VIIIC was
discontinued, and regular treatment with human VIIIC restarted.
The patient became HIV-seropositive in 1983, shortly before start-
ing porcine VIIIC.

**RESULTS**

No significant reactions were encountered with porcine VIIIC. Mild
pyrexial reactions and a transient modest decrease in platelet count of
between 30 and 40 x 10^9/L were experienced with occasional earlier batches of concen-
trate by patients 1 and 2. Thrombocytopenia was not observed.

The administration of porcine factor VIIIC did not cause
an anamnestic increase in anti-human VIIIC inhibitor activity
in any of our patients (Figs 1 through 5).

A rapid initial decline in anti-human VIIIC inhibitor activity was observed in all patients during the first few
months of therapy. A slower decrease in anti-human VIIIC
inhibitor followed, and the inhibitor was undetectable 1 to 4 years after the last treatment with human VIIIc. Patient one showed occasional anamnestic increases in inhibitor level associated with human VIIIc therapy until 1984. He has been treated exclusively with porcine VIIIc since this time, and his inhibitor has been undetectable since 1987.

Anti-porcine VIIIc inhibitor activity arose in all patients (Figs 1 through 5). This reached a maximum level of 0.5, 2, 0.6, and 1.3 BU in patients 1 through 4, respectively, and did not compromise their clinical responses. These inhibitors were transient in patients 1 and 3 but disappeared more slowly, over 2 to 3 years, in patients 3 and 4 despite continued therapy with porcine VIIIc. Remarkably, patient 5 developed an anti-porcine VIIIc inhibitor lacking cross-reactivity to human VIIIc soon after starting porcine VIIIc. This reached a maximum level of 6 BU after 2 years, causing him to become refractory to porcine VIIIc. Because he had lost his original anti-human VIIIc inhibitor it was possible to resume regular treatment with human VIIIc. This did not provoke an anamnestic response, and his anti-porcine VIIIc inhibitor gradually disappeared over the next 18 months.

Porcine factor VIIIc recovery and half-life, estimated in four patients (1, 2, 4, and 5), reflected inhibitor activity against porcine VIIIc. A half-life of 8 to 9 hours and
recovery of between 1.5% and 2%/U/kg was observed in all patients at the start of treatment. Recovery and half-life assessed serially in patients 4 and 5 declined to a minimum of 1%/U/kg and 4 hours in patient 4, and 0.3%/U/kg and 1 hour in patient 5. Recovery and half-life returned to normal in patient 4 when his anti-porcine VIIIC inhibitor could no longer be detected.

Regular home therapy with human VIIIC was re-established in three patients (2, 4, and 5), 1 to 3 years after their anti-human VIIIC inhibitor had last been detected. Regular treatment with human VIIIC has continued for between 2 and 3 years in these patients, without any recurrence of anti-human VIIIC inhibitor activity (Figs 2, 4, 5). Patients 4 and 5 are HIV-seropositive. Two patients (1 and 3) have not been rechallenged with human VIIIC because they refuse treatment with human factor VIIIC.

Two patients (1 and 2) have remained anti-HIV seronegative on repeated testing. Patients 3, 4, and 5 were infected with HIV before starting porcine VIIIC. Their T4-helper cell counts at the beginning of therapy with porcine VIIIC were 0.8, 1.04, and 0.85 × 10⁹/L respectively, and 0.15 and 0.65, in patients 4 and 5 when treatment with human VIIIC was resumed. Although patients 3 and 4 now have mild acquired immunodeficiency syndrome (AIDS)-related complex (ARC), this did not develop until 1988, and patient 5 is asymptomatic. All three maintain protective levels of hepatitis-B surface antibody (HBsAB).

DISCUSSION

Porcine factor VIIIC was well-tolerated by five patients with anti-human factor VIIIC inhibitors lacking measurable cross-reactivity. No significant reactions or thrombocytopeenia were observed. This concurs with the results of a recent multi-center trial that reported minor reactions only with 4% of infusions of porcine VIIIC. The low incidence of reactions reported in more recent series may reflect increasing product purity, specific activity having increased from less than 25 U/mg in 1981 to greater than 140 U/mg in 1989. We suspect that the risk of reactions with current preparations of porcine VIIIC has been overstated.

Although our patients all developed anti-porcine VIIIC inhibitors at some stage, these were transient in four, despite continued treatment with porcine VIIIC. This suggests that they had become tolerant of porcine VIIIC. The induction of immune tolerance in patients with anti-porcine VIIIC inhibitors probably follows the same principles as the induction of immune tolerance in patients with anti-human VIIIC inhibitors by repeated exposure to human factor VIIIC.

No measurable anamnestic increase in anti-human VIIIC inhibitor activity followed the use of porcine VIIIC during 2 to 8½ years of regular treatment, and the inhibitor disappeared in all patients. An anamnestic increase in anti-human VIIIC inhibitor is reported to follow between 20% and 27% of infusions of porcine VIIIC, but may be less likely to occur in 10% to 20% of patients reported to have inhibitors with little or no affinity for porcine VIIIC. The failure of three of these patients to mount an anamnestic response when rechallenged with human VIIIC suggests that they have become tolerant of human VIIIC. This state of immune tolerance, or specific immune unresponsiveness, has probably arisen as a result of treatment with porcine VIIIC, since these patients all had high-responding inhibitors before starting porcine VIIIC. Tolerance develops for specific antigenic determinants and not particular antigens. Therefore, tolerance to one antigen may be induced by administration of immunogenic doses of a second antigen sharing the epitope to which the subject had originally been sensitized. Porcine VIIIC may have induced tolerance to human VIIIC in this way, and may be a better tolerogen than human VIIIC in some patients because it is less immunogenic. Indeed, immune tolerance may have been difficult to achieve conventionally using human VIIIC in our patients, since tolerance is only achieved in between 30% and 50% of patients with high-responding inhibitors often after many months of treatment. Porcine VIIIC may have a limited role in the induction of tolerance in patients with high-responding factor VIIIC inhibitors lacking cross-reactivity.

Although the unit cost of porcine VIIIC is twice that of intermediate-purity human VIIIC and similar to that of immunoadfinity-purified VIIIC, it is a cost-effective alternative to the high doses of human factor VIIIC often used to treat inhibitor patients.

Inhibitor loss has been reported in occasional patients with marked abnormalities of B-cell function and AIDS. However, this is not a general observation. It appears to be a feature of full-blown AIDS or severe ARC and has not been reported in asymptomatic patients. Two of our patients have remained HIV-seronegative, and none of the three HIV-positive patients had AIDS or ARC when treatment with porcine VIIIC began or when human factor VIII was reintroduced. Continued B-cell competence in these three patients is suggested by the maintenance of protective levels of hepatitis-B surface antibody and the development of specific anti-porcine VIIIC inhibitors. Therefore, HIV infection is unlikely to account for the loss of inhibitor or development of immune tolerance in these patients.

A group of inhibitor patients can be identified by their lack of cross-reactivity to porcine VIIIIC in whom prolonged home therapy with this product is safe and effective and may be associated with inhibitor loss and the development of immune tolerance. Although close monitoring of the early phases of treatment is clearly desirable, we would consider porcine VIIIC to be the treatment of choice for inhibitor patients with little or no cross-reactivity.

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