Efficacy of vaccine Ac NFU₁ (S⁻) MRC 5 given after an initial clinical episode in the prevention of herpes genitalis

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SUMMARY A subunit antigenoid vaccine, Ac NFU₁ (S⁻) MRC 5, was used in patients who had had a clinical episode of herpes genitalis. The rate of recurrence was compared with that in unvaccinated patients to determine the efficacy of vaccination in preventing recurrence and spread of the virus in the community. Seven of 22 (31%) vaccinated patients had eight recurrences after the initial clinical episode; in contrast there were 51 recurrences in 17 of 20 (85%) unvaccinated patients. Although further studies are needed, the results indicate that the vaccine may prevent recurrent episodes of herpes genitalis and thereby reduce the dissemination of this virus in the population.

Introduction

The incidence of herpes genitalis continues to rise with 10 801 new cases reported in 1980 by sexually transmitted disease (STD) clinics in England and Wales—a 50% increase over the preceding five years.¹ As this is a latent infection with a propensity to recur, it seems likely that the periodic shedding of virus will continually increase the genital reservoir of herpes simplex virus in the community.

The efficacy of vaccine Ac NFU₁ (S⁻) MRC 5 in preventing herpes genitalis in a group of patients considered to be at high risk of contracting this infection has been reported.² Several studies have investigated the possibility of modifying the pattern of recurrent disease by vaccination in patients with established herpes genitalis³⁻⁵; the results of these studies were possibly disappointing, although there was some evidence of a temporary clinical response. This encouraged us to investigate the possible modification of recurrent disease by vaccination after the initial clinical episode of herpes genitalis.

Patients and methods

PATIENT RECRUITMENT

Patients were referred to the herpes simplex virus (HSV) clinic at the Queen Elizabeth Medical Centre from the sexually transmitted disease (STD) clinic of the General Hospital, Birmingham, and from general practitioners and gynaecologists within the West Midlands region. A history of herpes labialis in the patient and the existence of a regular sexual partner with a history of herpes genitalis was sought. Patients were specifically asked whether orogenital contact had occurred in the week preceding the onset of lesions when a partner had oral cold sores.

The clinical outcome is presented in two groups of unvaccinated patients; those with an initial clinical episode of herpes genitalis attending the STD clinic at the General Hospital, Stoke on Trent, and a similar group who attended the Queen Elizabeth Medical Centre before the start of the vaccination programme.

The diagnosis of herpes genitalis was confirmed by virus isolation in all cases. When a patient was not seen at the HSV clinic during the acute period the isolate was obtained, if still available, from the regional reference laboratory for typing. Isolates

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Accepted for publication 19 February 1983

were typed by kinetic neutralisation tests and polyacrylamide gel electrophoresis.^{6,7}

VACCINATION SCHEDULE

Patients received three subcutaneous inoculations of vaccine Ac NFU₁ (S⁻) MRC 5 in the region of the deltoid muscle at monthly intervals. The vaccine dose of 5×10^7 cell equivalents was administered in sterile phosphate buffered saline without adjuvant. At each clinic visit after the initial vaccination any local reaction at the site of inoculation was recorded and specific inquiry made about the occurrence of any lower genital tract symptoms suggesting herpetic infection. Patients were seen at 1, 3, 6, and 12 months after the last vaccination. Any patient defaulting from their follow up visit was contacted by the responsible clinician, by telephone where possible. In addition, patients were asked to contact the clinic if they suspected a further episode of herpes genitalis.

VACCINE PREPARATION

Subunit antigenoid vaccine was prepared as previously described.² In brief, human embryo lung cells (MRC 5) obtained from the National Institute of Biological Standards were infected with herpes simplex virus type 1 strain (troisbell) and the infected cell extract treated with non-ionic detergent and formaldehyde. Virus particles were removed by ultracentrifugation and virus proteins constituting the final vaccine preparation were precipitated with cold acetone.

The safety, immunogenicity, and protective efficacy of vaccine preparations have been previously reported.^{2,8-10} Before inoculation into human subjects vaccine batches were tested by subcutaneous inoculation of 0.05 ml (5×10^6 cell equivalents) into the dorsal skin of newborn mice.

Results

The vaccinated group comprised 15 women and seven men with a mean age of 21 (range 17 to 31)

years. Five patients had a regular sexual partner who had a known history of recurrent herpes genitalis. Six patients reported orogenital contact with a partner who had had oral cold sores in the week preceding the initial clinical episode. The unvaccinated group comprised 16 women and four men with a mean age of 22 (range 18 to 36) years.

VIRUS TYPING

In vaccinated patients 15 of 22 isolates were available for typing,⁶ six of which were found to be type 1 and nine type 2. The virus isolates from five patients thought to have contracted the infection as a result of orogenital contact were found to be type 1. In unvaccinated patients 11 of 20 isolates were available for typing, four of which were found to be type 1 and seven type 2.

CLINICAL OUTCOME

The table indicates the frequency of recurrent disease in relation to virus type in vaccinated and unvaccinated patients. Seven of 22 patients vaccinated after the initial clinical episode had a total of eight recurrences after a mean follow up period of 12 (range 10 to 16) months. Two recurrences preceded the third vaccination and the remainder were at 1½, 2, 6, and 7 months after the final vaccination. Two of these episodes were confirmed by clinical assessment and the virus was isolated on one occasion; the remainder were reported by the patient at the next clinic visit. Seventeen of 20 unvaccinated patients reported a total of 51 recurrences of herpes genitalis within a mean period of eight months (range three to 16 months) after the initial clinical episode.

Discussion

In this study of the efficacy of a subunit antigenoid vaccine Ac NFU₁ (S⁻) MRC 5 in modifying recurrent herpes genitalis after the initial clinical episode 15 of 22 vaccinated patients remained free of disease after a mean follow up period of 12 months. In contrast 17 of 20 unvaccinated patients reported further episodes

TABLE Recurrent episodes of herpes genitalis in relation to virus type in vaccinated and unvaccinated patients

Virus type isolated	Vaccinated patients			Unvaccinated patients		
	Total No	No of patients developing recurrences	No of recurrent episodes	Total No	No of patients developing recurrences	No of recurrent episodes
HSV 1	6	2	3	4	3	9
HSV 2	9	2	2	7	6	19
Not typed	7	3	3	9	8	23
Total	22	7	8	20	17	51

HSV = herpes simplex virus

of recurrent disease after a mean follow up period of only eight months. The study was uncontrolled in the sense that the efficacy of a placebo preparation was not investigated and vaccine efficacy was compared with disease patterns in unvaccinated patients recorded after their initial clinical episode. Although this point will be scrutinised by a double blind placebo controlled trial, the role of a placebo vaccine in preventing recurrences in a group of patients yet to experience one is uncertain.

The role of virus type merits consideration. Although it has been suggested that genital infections with type 1 herpes simplex virus are less likely than those with type 2 virus to be followed by recurrent episodes, Mindell reported that seven of 15 patients in whom type 1 was isolated developed recurrences within six months (unpublished data, 31st General Assembly IUVDT, June 1982); this was confirmed by a recent study in which five of nine patients with recurrent herpes genitalis were found to have the type 1 infection.¹¹ While there were only four unvaccinated patients with type 1 initial infection in this study, three of these had a total of 9 recurrences. It is unlikely, therefore, that the favourable outcome in the vaccinated group can be attributed to the proportion of patients with type 1 herpes genitalis.

The interpretation of the immunological response to vaccination—an area of enormous interest—is complicated by the apparent variability of the immunological response after the initial clinical episode in unvaccinated subjects.¹² The clinical outcome in this study, however, indicates that vaccination not only considerably alleviates personal morbidity but in the long term will help to control the apparently irreversible dissemination of this virus in the community as a whole.

This work was supported by the Herpes Vaccine Research Trust and the West Midland Health Authority.

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