2. Clinical Trials

2.1. Multi-centric study on the use of intradermal administration of tissue culture antirabies vaccines in India

Rationale:

Production of Nerve Tissue Rabies Vaccine (NTRV), commonly used for post-exposure treatment (PET) in India is discontinued. Tissue Culture Anti-rabies Vaccines (TCARV) and purified embryo vaccines are approved for use by intra-muscular route in India. However, due to high cost, TCARVs are not being used for all post-exposure treatment (PET) purposes in the country. The use of TCARV in small doses given by intra-dermal route reduces the cost of treatment considerably compared to TCARV administered intra-muscularly and many developing countries are using these vaccines intradermally as PET for animal bites. With this background, the Government of India asked the Indian Council of Medical Research to undertake a study to assess feasibility, safety and immunogenicity of indigenously manufactured TCARVs to be administered intra-dermally in healthy human volunteers.

Methods:

The study was carried out among healthy volunteers selected from five centres in the country. The TCARVs used for intradermal administration were Purified Vero cell Rabies vaccine (PVRV Abhayrab and Coonoor), Purified chicken embryo cell vaccine (PCEC Rabipur) and Purified duck embryo vaccine (PDEV Vaxirab) with a 2-2-2-0-1-1 regimen. Responses to intradermal TCARVs were compared with that of French PVRV (Aventis) administered intramuscularly on 0, 3, 7,14 and 28 days. Ten volunteers were recruited for each of the TCARV arm in each center as well as for control group receiving French PVRV. Vaccinated individuals were observed for immediate hypersensitivity reactions and their follow-up blood samples were collected on days 14, 28, 90 days and tested for anti-rabies antibody levels using Rapid Fluorescent Focus Inhibition Test at Pasteur Institute, Coonoor.

In order to assess the feasibility of introducing intra-dermal anti-rabies vaccination (IDRV) in government institutions, a survey was carried out to assess

a. Availability of different facilities (physical, cold chain, manpower and injection supplies) at the anti-rabies vaccination clinics at the district hospitals

b. Animal bite load

c. Skill for Intra-dermal injection and

d. Acceptability of IDRV among the patients receiving nerve tissue vaccine

Results:

A total of 257 volunteers from five centres were recruited in the study after obtaining their consent. On the scrutiny of the data, it was observed that two centres in Delhi experienced several operational problems. Hence the data from 104 individuals from these 2 centres were not considered for the purpose of analysis. From the remaining 3 centres, day zero blood samples were available from 153 individuals. Twenty seven individuals were excluded from the analysis as their sera samples had a pre-vaccination antibody concentration of > 0.5 IU/ml. Six individuals were withdrawn from the trial for various reasons at different follow-ups; four by day 14 and two by day 90. All the vaccines administered intradermally were well tolerated. No adverse drug reactions were reported from any of the vaccinated volunteers from the three participating centers and none of the volunteers was withdrawn from the trial on account of vaccine related reasons. Thus the primary analysis was restricted to 126 sero-negative individuals. Details of the sera samples collected at different follow-up visits (with respect to seronegative individuals recruited at day 0) in different vaccine arms are given in Table 1.

Table 2 shows the proportion of volunteers sero-protected (antibody titre 0.5 IU/ml), geometric mean for antibody titres (GMT) and 95% CI according to different vaccines at different follow-ups. Proportions of individuals sero-protected on days 14, 28 and 90 for the French PVRV vaccine (standard) were 100%, 100% and 95.7% respectively with the GMT of 6.73, 10.08 and 4.65 IU/ml. The sero-protection rate and GMT dropped to 40.8% and 0.80 IU/ml by day 180. All the volunteers who received Abhayrab PVRV were sero-protected on days 14, 28 and 90. Results were similar for the PVRV from Coonoor. For volunteers receiving Rabipur PCECV, the responses were on the lower level but the sero-conversions achieved was 100%. For the volunteers who received Vaxirab PDEV the responses were very much on the lower side, both in terms of GMT values and the sero-conversions over all the three periods of observation. Responses to various vaccines in terms of the geometric means are shown graphically in Fig.1.

The results of the study indicate that three TCARVs (Abhayrab PVRV, Coonoor PVRV and Rabipur PCECV) could be used for intradermal administration in India.

Table 1: Sera samples tested for anti-rabies antibodies at different follow-up visits according to different vaccines for day 0 sero-negatives for the three centres.

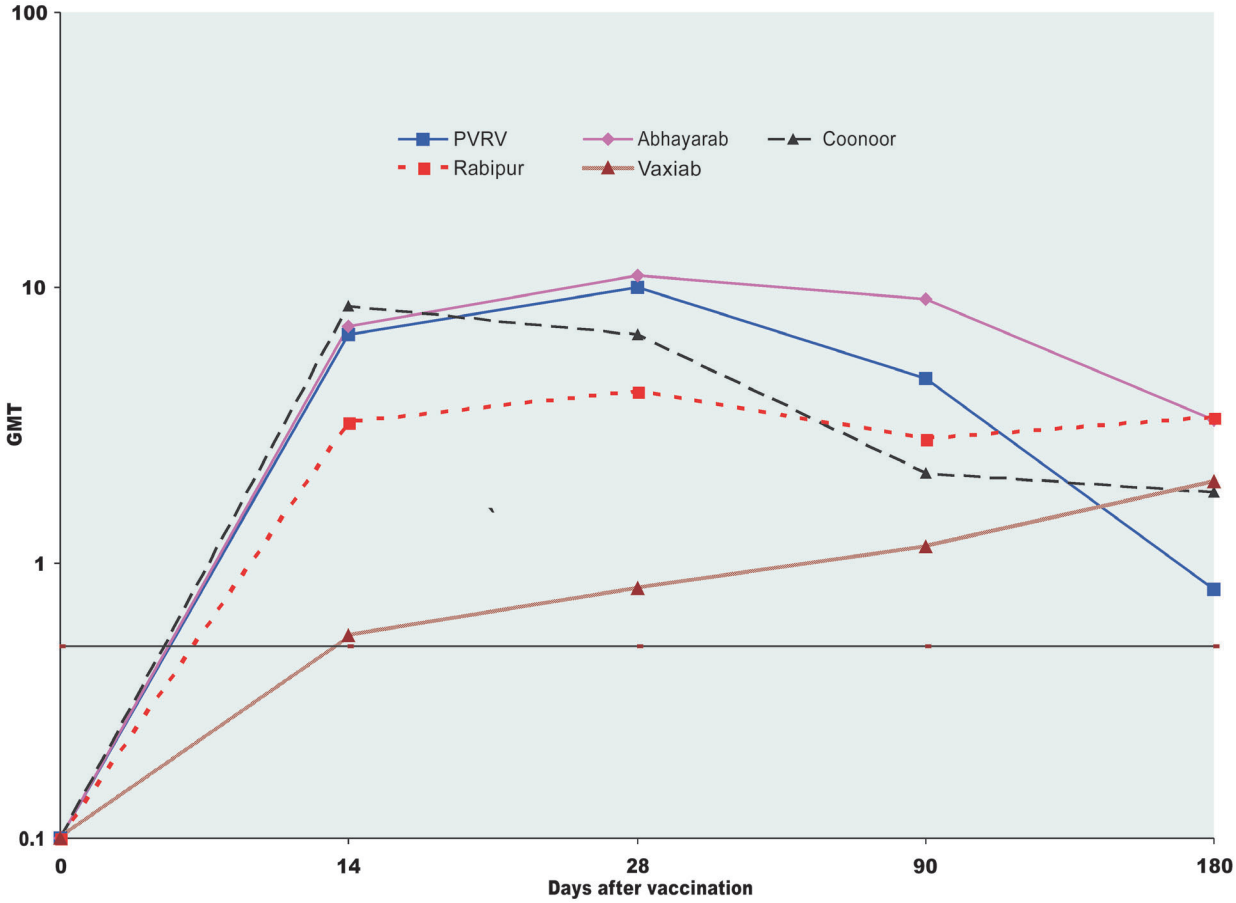
Vaccines	Day 0	Day 14	Day 28	Day 90	Day 180
French PVRV	25	24	24	23	22
Abhayrab	28	28	28	27	27
Coonoor	23	20	20	20	15
Rabipur	28	28	28	28	28
Vaxirab	22	22	22	22	19
Overall	126	122	122	120	111*

(*Eight samples from one participating centre are yet to be tested)

Table 2: Sero-protection rate, Geometric mean titres of anti-rabies antibodies and its 5% confidence limits among the volunteers receiving different vaccines

Vaccine	Day 14		Day 28		Day 90		Day 180	
	No. sero-protected/ No. tested (%)	GMT (95% CI)	No. sero-protected/ No. tested (%)	GMT (95% CI)	No. sero-protected/ No. tested (%)	GMT (95% CI)	No. sero-protected/ No. tested (%)	GMT (95% CI)
French PVRV	24/24 (100)	6.73 (3.64-12.42)	24/24 (100)	10.08 (5.77-17.62)	23/23 (100)	4.65 (2.45-8.81)	19/22 (86.4)	0.80 (0.47-1.37)
Abhayrab	28/28 (100)	7.25 (5.19-10.11)	28/28 (100)	11.04 (7.24-16.83)	27/27 (100)	9.10 (6.28-13.17)	26/27 (96.3)	3.31 (2.01-5.45)
Coonoor	20/20 (100)	8.57 (4.64-15.85)	20/20 (100)	6.73 (3.73-12.14)	19/20 (95)	2.12 (1.27-3.55)	14/15 (93.3)	1.80 (0.99-3.26)
Rabipur	27/28 (96.4)	3.26 (1.95-5.43)	28/28 (100)	4 (2.42-6.62)	28/28 (100)	2.83 (1.78-4.48)	28/28 (100)	3.36 (1.87-6.05)
Vaxirab	15/22 (68.2)	0.55 (0.31-0.97)	17/22 (77.3)	0.81 (0.4-1.63)	20/22 (90.9)	1.15 (0.71-1.84)	18/19 (94.7)	1.98 (1.08-3.63)

Fig. 1: Geometric mean antibody titres (GMT) to different TCARVs



2.2. Multicentric Study of Interferon-Glycyrrhizin Combination Therapy and interferon-Ribavirin Combination Therapy in the Management of Chronic Hepatitis C

Hepatitis C Virus (HCV) is an important cause for chronic liver disease in India. Studies indicate that one-fourth of chronic liver disease is HCV-related. There are about 10 million HCV carriers in our country and at least half of them are likely to develop chronic liver disease in the next 10 to 15 years. Recently in an ICMR Symposium on Interferon Therapy in chronic hepatitis, it was evident that 50-60% of Indian chronic hepatitis C patients, treated with Interferon showed a sustained viral clearance. Indigenous herbs and plants have been in use for many centuries in India for the treatment of liver disorders. The plant product Glycyrrhizin (Glycyrrhiza glabora) has been found to have antiviral properties through endogenous interferon induction as well as

hepatocytoprotective effect. Glycyrrhizin has also been shown to inhibit ribonucleic acid (RNA) viruses through a hitherto unknown mechanism. Glycyrrhizin is a safe drug with minimal side-effects. The modern medication available for the treatment of chronic hepatitis C (CHC) has known side-effects. Therefore, there is a need to explore the scope of plant products with minimal side-effect in the treatment of CHC. The combination of Interferon with Glycyrrhizin may have synergistic effect in achieving better virological clearance and histological improvement among patients with CHC. Hence, the Council has undertaken a multicentric trial of Interferon - Glycyrrhizin combination therapy and Interferon-Ribavirin combination therapy in the management of CHC. NIE is coordinating this trial.

Primary Objective

To assess whether the combination therapies of Interferon-Glycyrrhizin and Interferon-Ribavirin against Chronic Hepatitis C are effective to the tune of 70% in Indian patients.

Secondary Objective

To evaluate the side-effects / toxicity of the trial drugs;
To evaluate the cost effectiveness of the two combination therapies;
Study the role of certain identified factors, viz., genotype, viral load, some host factors in deciding the outcome of therapy.

Trial design

This is a multicentric double-blind randomized controlled equivalence trial in nine centers spread all over the country. Participating centers are PGI, Chandigarh; AIIMS, New Delhi; MAMC, New Delhi; GBPH, New Delhi; MCLDD, Noida; SGPGI, Lucknow; IPGMER, Kolkata; BHMRC, Mumbai and DCMSH, Hyderabad. All eligibles patients were randomly allocated in equal proportion to one of the following regimens for 48 weeks of treatment.

a. Interferon - 3 million units administered subcutaneously + Glycyrrhizin 250 mg daily
b. Interferon - 3 million units administered subcutaneously + Ribavirin 1000 mg daily

It was proposed to admit 270 patients (135 patients to Interferon-Glycyrrhizin regimen and 135 patients to Interferon-Ribavirin regimen) to the trial from all centers put together. The total duration of the trial is 2½ years. The intake to the trial was expected to be completed in 1½ years. The follow-up of all patients will be completed in the next 1 year.

The intake to the trial was stopped by 31st May 2004 and the treatment period was completed by November 2004.

Further the follow up period will be completed by May 2005. Completed study proformae are being received from the participating centers once a month. Forms were scrutinized and the inaccuracies and inconsistencies were rectified through correspondence. Trial drugs are being sent to the participating centers as and when the request comes from the Principal Investigator of the concerned centre. As on 31st March 2005, we have received a total of 131 forms of admission to the trial from various centers as follows: PGI - 20, AIIMS - 17, MAMC - 17, GBPH - 11, MCLDD - 21, SGPGI - 12, IPGMER - 13, BHMRC - 4 and DCMSH - 16

Progress reports are being sent to the ICMR Headquarters and to all Principal Investigators once in fortnight. Meetings of the experts and principal investigators had been organized periodically at ICMR Headquarters to review the progress of the trial. In one of the meetings, it was decided to reduce the treatment duration from 48 weeks to 24 weeks . Available data was analyzed without decoding of the treatment regimen. Results are encouraging in terms of virological and biochemical parameters.

In view of the encouraging results from the above study, ICMR decided to initiate two more trials viz. (a) Multicentric Open Labeled Clinical Trial Using Combination of Interferon and Ribavirin for 3 months among patients with Chronic Hepatitis C (b) Multicentric Open Randomized Controlled Clinical Trial of Combination Therapy with Ribavirin and Oral Glycyrrhizin in Decompensated HCV - Induced Cirrhosis. Details are given below.

(a) Multicentric Open Labeled Clinical Trial Using Combination of Interferon and Ribavirin for 3 months among patients with Chronic Hepatitis C

The objective of this study is to assess whether the combination therapy of Interferon and Ribavirin against Chronic Hepatitis C is effective to the tune of 70% in Indian patients with 3 months treatment duration. This study was initiated at 8 out of 9 above centers (except BHMRC, Mumbai) from June 2004 onwards.

As on 31st March 2005, 41 cases were admitted to the trial from various centers as follows: PGI - 5, AIIMS - 9, MAMC - 6, GBPH - 1, MCLDD - 10, SGPGI - 1, IPGMER - 4 and DCMSH - 5.

Trial is progressing in all centers. Results available so far indicate encouraging response in terms of virological and biochemical parameters.

(b) Multicentric Open Randomized Controlled Clinical Trial of Combination Therapy with Ribavirin and Oral Glycyrrhizin in Decompensated HCV - Induced Cirrhosis.

The objective of this trial is to assess whether a combination of oral Glycyrrhizin as an immunomodulator and hepato-protective drug and Ribavirin as an antiviral drug will improve the clinical, bio-chemical and virological outcome of HCV-induced cirrhosis of liver. Expected efficacy for this combination therapy is to the tune of 50% in Indian patients. This study is also being initiated at the above mentioned 8 centers from August 2004 onwards.

As on 31st March 2005, 25 cases were admitted to the trial from various centers.

2.3. Extended Multicentric Trial of Vijayasar (Pterocarpus Marsupium) in the management of type 2 diabetes mellitus

Aim : To assess the anti-diabetic effect of Vijayasar(Pterocarpus marsupium) in the management of the following two groups of mono therapy Type 2 diabetes mellitus patients.

1. Uncontrolled by allopathic oral hypoglycemic drugs (group 1)
2. Controlled, but opted for Vijayasar treatment (group2)

Methods: The study was carried out in four Diabetes Centres attached to teaching medical institutions in India representing different segments of the population.. The trial was initiated in July 2002 and the intake was stopped in July 2004. A total of 512 mono-therapy Type 2 diabetes patients (controlled or uncontrolled), whose fasting and post pyramidal blood glucose levels respectively did not exceed 200 mg% and 350 mg% were admitted to Vijayasar therapy. To avoid complications with multiple hypoglycemic agents, only mono therapy patients were included into the study. The duration of treatment was 20 weeks with 2 weekly clinic attendances up to 8 weeks and 4 weekly thereafter for review and drug collection. It was a flexible dose open trial, the dosage being 3g to 6g / day. If the blood glucose level of a patient was not controlled (fasting >126 mg% or postprandial >200 mg%) even after reaching the maximum dosage of 6g / day, the patient was withdrawn from the trial and labeled as "treatment failure". On the other

hand, if the blood glucose was controlled with any dosage less than 6g / day, that treatment dosage would be continued until 20 weeks from the commencement of the trial. Long-term control of blood glucose level was studied by using HbA1c. At any point of time during treatment, if the fasting blood glucose falls below 90 mg% or postprandial below 100 mg% or a patient develops overt hypoglycemia, the daily dosage will be reduced by 1g. All the patients who completed 20 weeks of treatment and those who were labeled as "treatment failure" were put on an appropriate hypoglycemic agent at the discretion of the Principal Investigator. Visits of social worker and dietician ensured drug and diet compliance. Excluding the 9 ineligible patients, there were 503 available for analysis.

Results: Among the 503 patients considered for analysis, there were 99 drop-outs. Seventy two of them had expressed that they were not satisfied with Vijayasar. There were 185 failures for not being controlled by the maximum dosage of 6g / day. One hundred and ninety six patients completed 20 weeks of treatment and among them 181 had their blood glucose control. On 55 occasions, the dosage of Vijayasar had to be reduced to maintain this fasting and post prandial blood glucose levels respectively above 90 mg% and 100 mg%. At week 8, there was significant fall in both fasting (23 mg%) and post prandial (32 mg%) glucose levels among cases uncontrolled by allopathic mono therapy (Group 1) patients, whereas the change (+5 mg%) was insignificant among those who were under control by other mono therapy (Group 2). Increase in HbA1c values were noticed at week 8 in both the groups. The increase in Group 1 was 0.3 units (95% C I ,0.1 to 0.5) from 7.0% and in Group 2 it was 0.2 units (95% C I, 0.04 to 0.3) from 6.7%. The optimum dosage of Vijayasar could be 3g to 4g / day. The Week 8 was chosen to analyse the blood glucose values as the course of change of the blood glucose values due to Vijayasar treatment was visible in majority of cases by then.

Conclusion: Treatment of Type 2 Diabetes with Vijayasar is safe upto 6 g of daily dosage. No side effect is attributable to Vijayasar nor were there any overt hypoglycemia. Among the group of diabetes controlled patients, majority continued as controlled with 3 g to 4 g by 8 weeks of treatment. There were no clinically significant changes in other biochemical parameters. There were 65 cases who could achieve blood glucose control out of 249 uncontrolled (group 1) mono therapy patients. The analysis is in progress.