

CONCISE REPORT

Efficacy of isoniazid prophylaxis in patients with systemic lupus erythematosus receiving long term steroid treatment

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Objective: To study the efficacy of isoniazid prophylaxis (INHP) in patients with systemic lupus erythematosus (SLE) receiving long term glucocorticosteroid treatment.

Patients and methods: Treatment with INHP (5 mg/kg/day, max 300 mg/day) together with pyridoxine 10 mg/day for one year was started in all patients with SLE seen between January 1994 and December 1999 and followed up thereafter. Clinical examination and chest radiography were carried out in all patients before the start of INHP treatment. A liver profile was obtained only if liver toxicity was suspected owing to nausea, loss of appetite, and icterus. Only the data of those patients who completed the INHP treatment or who were withdrawn owing to toxicity have been analysed. This was compared with the results of an earlier study of the incidence of tuberculosis (TB) in patients with SLE not receiving INHP.

Results: Ninety seven patients were included, of whom 95 completed one year's treatment with INHP. Treatment was discontinued in two owing to toxicity: hepatitis in one and peripheral neuropathy in one, at eight and 10 months, respectively. One patient developed TB within one month of starting INHP. Seventy patients were followed up further for at least one year (mean 26.4 months, range 12–60 months) after completion of the INHP treatment. During this period one patient developed TB after one month. No deaths due to TB or hepatitis occurred. In comparison with earlier series the incidence of TB decreased from 11% to 2%, a reduction of 82%. The cost of treatment for each case of TB prevented in the first year was 5800 rupees.

Conclusion: INHP is safe and effective in SLE.

Patients with systemic lupus erythematosus (SLE) are inherently susceptible to infections. This is aggravated by treatment with steroids and cytotoxic agents.¹ In India, tuberculosis (TB) is the most important infection. We and others have reported a prevalence of TB ranging from 5% to 13.7% in patients with SLE receiving steroids.^{1–2} TB in SLE carries a higher mortality,³ probably owing to the disseminated nature of the TB in these patients.⁴ Treatment with isoniazid prophylaxis (INHP) has been advocated in immunocompromised subjects. In this paper we report our experience with INHP in SLE.

PATIENTS AND METHODS

Since 1994 we have adopted the policy of treatment with INHP (5 mg/kg/day isoniazid, maximum 300 mg/day and 10 mg/day pyridoxine) for one year of all patients with SLE requiring long term steroids. Patients who started treatment with INHP between January 1994 and December 1999 were studied. At the start all patients underwent a thorough clinical evaluation and chest radiograph to rule out active TB. Patients were evaluated at three to six monthly intervals. Liver function tests

Table 1 Demographic, clinical, and treatment details of patients

Number of patients	97
F:M	89:8
Age (years), mean (range)	26.3 (10–62)
Major system involvement (No (%))	62 (64)
Renal	48 (49)
Cardiovascular	4 (4)
CNS	14 (14)
Other systems	16 (16)
Concurrent cytotoxic agents (No (%))	48 (49)
High dose prednisolone* (n)	58
Duration (months), mean (range)	3.17 (1–8)
Moderate dose prednisolone* (n)	94
Duration (months), mean (range)	3.67 (1–12)
Low dose prednisolone* (n)	91
Duration (months), mean (range)	6.9 (1–12)

*High dose prednisolone, >0.5 mg/kg/day; moderate dose, 0.25–0.5 mg/kg/day; low dose, <0.25 mg/kg/day.

(LFT) were carried out during prophylaxis only if liver toxicity was suspected owing to nausea, loss of appetite, and icterus. Only data of those patients who completed the INHP treatment or in whom the drug was withdrawn owing to toxicity have been analysed. The results were compared with the results of our earlier series of patients with SLE who had not received INHP.² The study is divided into two phases. Phase 1 was the period during which the patients received INHP. Patients who completed at least one year's follow up after INHP were included in the phase 2 analysis. The cost effectiveness of the INHP treatment was evaluated.

RESULTS

Ninety seven patients were included in phase 1. Of these, 95 completed one year of INHP. Seventy of these patients were followed up for one further year after completion of the INHP treatment (phase 2). Table 1 gives demographic, clinical, and treatment details.

Phase 1

The duration of lupus at entry into the study ranged from one month to 120 months. One patient developed pulmonary TB within one month of starting INHP. She was treated successfully with five drugs (isoniazid, rifampicin, ethambutol, pyrazinamide, ciprofloxacin). Acid fast bacilli (AFB) culture and sensitivity could not be done. Adverse effects were seen in two patients. One patient developed mild hepatitis after eight months of INHP, which resolved when the drug was discontinued. Another patient developed peripheral neuropathy after 10 months of INHP. In both INHP was discontinued.

Abbreviations: INH, isoniazid; INHP, isoniazid prophylaxis; LFT, liver function test; SLE, systemic lupus erythematosus; TB, tuberculosis

Phase 2

This group of 70 patients includes the two patients in whom INHP was discontinued. The mean duration of follow up after INHP treatment was 26.4 months (range 12–60). One patient developed pulmonary TB one month after completion of INHP. In this patient acid fast bacilli culture and sensitivity was not done. He was treated successfully with isoniazid, rifampicin, ethambutol, pyrazinamide, ethionamide, streptomycin, and ciprofloxacin.

DISCUSSION

Tuberculosis is common in India.^{2,5} Prevalence of radiological disease has been estimated to be 1.3–1.9%.⁵ A recent study showed an 80% prevalence of latent TB in urban India.⁶ An increased prevalence of active TB has been reported in patients receiving chronic steroid treatment for renal transplantation and asthma.^{7,8} We have reported an incidence of 11.6% of TB in patients with SLE receiving steroid treatment.² That study analysed data of 146 patients over a period of five years. Seventeen developed TB with one death. Nine of the 17 (53%) developed TB within the first year of steroid treatment. Four of these 146 patients had received INHP and one of these four patients had developed TB.

TB in adults is due either to reactivation of healed foci or reinfection from an exogenous source. INH prevents reactivation of TB by eradicating the small number of bacilli present in the “healed” foci. Although INHP has been found to be efficacious in AIDS, haematological malignancies,⁹ and renal transplants,¹⁰ there are few data on its use in SLE. A recent study showed that INHP treatment for six months may be effective in systemic rheumatic diseases in countries with a high prevalence of TB.¹¹

INHP has been deemed impractical in the developing countries owing to the already existing high prevalence of INH resistance and extended duration of treatment resulting in non-compliance.¹² There is also a fear of propagating INH resistance.

Despite these misgivings, in view of the high incidence of TB in our patients, we have instituted routine INHP in all patients with SLE requiring long term steroid treatment with or without cytotoxic treatment, with good results. Only 1/97 patients developed pulmonary TB when receiving prophylaxis within a month of starting INHP and this patient might have been harbouring active disease when treatment with INHP was started; it was a case of inappropriate selection. During further follow up one patient developed TB one month after completion of INHP. He required second line treatment in view of the incorrect treatment given when tuberculosis was diagnosed. There were no deaths due to tuberculosis. Thus in comparison with our previous study the incidence of TB decreased from 11% to 2%, an 82% reduction. Although these two studies were carried out at different times, the odds ratio obtained after combining the results suggests that the risk of TB is six times higher when INHP is not used.

The most important consideration that precludes routine use of INHP is the fear of development of INH resistance. Mycobacterial resistance to INH is linked to large bacterial populations such as those which exist in cavitary lesions.¹³ A healed tuberculous focus, the setting in which INHP is used, contains around 10^2 – 10^4 bacilli as against cavitary lesions which contain 10^7 – 10^9 bacilli. The only mechanism of development of INH resistance in mycobacteria is by spontaneous mutation.¹⁴ INH resistance occurs at a rate of 3.5 in 10^8 divisions. A healed focus is highly unlikely to contain INH resistant mutants. Further, INHP acts primarily by prevention of bacillary multiplication. Ferebee has shown that INHP does not result in INH resistance.¹⁵ Nolan *et al* studied South East Asian refugees in the United States¹⁶ and concluded that INH resistant TB in their patients receiving INHP was more likely to be due to primary drug resistance than due to acquisition of resistance during prophylaxis.

Another fear is that of toxicity, especially peripheral neuropathy and hepatic necrosis. INH induced hepatotoxicity can be fatal.¹⁷ The incidence of INH hepatotoxicity is higher in elderly female patients and close monitoring is advocated.¹⁷ In our series one patient had transient transaminitis. However, a routine LFT was not done in our patients and, possibly, some patients might have had subclinical hepatitis that did not warrant discontinuation of INHP.

To evaluate the cost-benefit ratio of INHP as related to our situation, we compared the present data with those for our series of patients who had not received INHP.² From our earlier data, it can be estimated that about 6% of patients with SLE receiving corticosteroid treatment would develop TB in the first year in the absence of INHP. The cost of drug treatment of TB for these six patients in a group of 100 patients with SLE would be 11 880 rupees (1980 rupees for each patient: HRZE for two months, HR for four months). The cost of provision of INHP to the same group is 36 500 rupees. Addition of the cost of treatment for one patient with presumed INH resistant TB (HRZE for two months, HRE for 10 months) would increase the cost to 40 945 rupees. Thus the cost of prevention of one case of TB in the first year of treatment for SLE is estimated to be around 5800 rupees. This cost is therefore about four times that of treatment of the disease. Though this appears to be high, especially for a developing country like India, it is justified when one considers the protection afforded by INHP in subsequent years. Moreover, it also prevents morbidity, mortality, and transmission of TB in the community.

To conclude, our experience shows that in a situation with a high incidence of TB:

- INHP is safe and effective in patients with SLE receiving steroid treatment
- The fear of INH resistance seems to be misplaced
- Patients chosen to receive INHP treatment should be evaluated carefully to rule out active disease.

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