THERAPEUTIC UPDATE

TUBERCULOSIS CHEMOTHERAPY A REVIEW OF CURRENT TREATMENT REGIMENS

S.K. Teo

SYNOPSIS

This paper gives a review of the current treatment regimens available for pulmonary and extra-pulmonary tuberculosis. The following diseases are discussed under extra-pulmonary tuberculosis:- tuberculosis of lymph nodes, abdomen, genito-urinary tract, bones and joints and tuberculous meningitis. Since the 1950s, many regimens have been developed which are of long duration (18 months), intermediate duration (12 months) or short duration (6-9 months). Drugs can be self administered or taken under full supervision; they can be given daily or intermittently for part of or fully throughout the duration of treatment. In recent years, short course regimens have attracted much attention. These regimens are discussed in relation to cost-effectiveness, adverse reactions and patient acceptance.

INTRODUCTION

1982 marks the centenary of the discovery of the tubercle bacillus by Robert Koch. It was an event of the greatest importance in the history of tuberculosis, for it established the bacterial cause of the disease and it opened the way for chemotherapeutic advances. In 1944, streptomycin was discovered and quickly used in the treatment of tuberculosis. In the wake of streptomycin, other antituberculosis drugs were tested and found to be effective, e.g. PAS (1946), and isoniazid (1952). By the 1950s, it was soon established that the combination of streptomycin, isoniazid and PAS in the initial phase, followed by PAS/INH in the continuation phase was very effective in curing tuberculosis and just as important, it was able to prevent the emergence of drug resistant organisms.

STANDARD 100% REGIMENS - PRACTICAL PROBLEMS

Since the 1950s, a standard regimen used commonly to treat pulmonary tuberculosis has been streptomycin, isoniazid and PAS (p-aminosalicylic acid) for 3 months, followed by PAS/INH for 15 months. Although this regimen is potentially able to give a cure rate of 100%, in practice under service conditions, especially when the treatment is self administered, the results often fell below the expected rate. There are two main reasons for this: (i) patients have difficulty in taking 20 tablets of PAS/INH as one dose or even in 2 divided doses, because of the bulk and unpalatable nature of the drugs; (ii) the duration of treatment is too long, being 18 or 24 months. Consequently, patients either stop their

**Department of Medicine IV,
Tan Tock Seng Hospital
Moulmein Road
Singapore 1130**

S.K. Teo, MBBS, MRCP (UK)
Physician

treatment prematurely, especially when their symptoms have improved, or they become irregular in taking their medication. When ethambutol and rifampicin became available in 1961 and 1966 respectively, they were soon substituted for PAS thereby making it easier for patients to take their medication. However, the problem of prolonged treatment still remained. It became obvious that alternative regimens had to be developed to ensure better patient compliance. The 2 main changes which followed were using intermittent regimens and shortening the period of treatment.

STANDARD INTERMITTENT REGIMENS OF 18 MONTHS' DURATION

Table 1 gives a list of standard daily and intermittent regimens. A standard intermittent regimen used in Singapore is SPH or SEH for 3 months, followed by twice weekly streptomycin and high dosage isoniazid (15 mg/kg) given for 15 months. It gave good results (1). The advantages of intermittent regimens are: reduced doses of drugs are given; chronic drug toxicity is reduced; cheaper costs; patients can be fully supervised i.e. they have to attend an out-patient clinic and be seen to swallow their drugs. Failure to attend for treatment will be noted immediately and appropriate action taken. This type of regimen is recommended for unreliable patients who are suspected of not taking their drugs regularly. Thiacetazone containing regimens are not used on a routine basis in Singapore, as a previous study (2) showed that local patients belonging to the 3 main ethnic groups tolerated the drug poorly. In the United States, the twice weekly ethambutol plus isoniazid regimen is favoured since injection is avoided thus making it more acceptable to their patients (3). When rifampicin is used in the initial phase, cost is increased.

Table 1

STANDARD 100% REGIMENS - DURATION 18 MONTHS

Rhythm	Initial daily phase (3 months)	Continuation phase (15 months)	Cost Index†
Daily	SEH	EH	100
regimens	SPH	PH	174
	STH	TH	—
Inter-	SEH	S_2H_2	75
mittent	SPH	S_2H_2	86
regimens	SEH	E_2H_2	84
	SRH	S_2H_2	115

† Cost index - based on index of 100 for SEH/EH regimen at 1981 price for public hospitals. Abbreviations: S = streptomycin; E = ethambutol; H = isoniazid; P = p-aminosalicylic acid; T = thiacetazone; R = rifampicin
Subscript after letters in continuation phase refers to number of doses per week.

SHORTER DURATION INTERMITTENT REGIMENS

The intermittent regimens mentioned earlier are of long duration. Therefore, efforts were made to shorten the treatment period and obtain better patient compliance. A study in Hong Kong (4) showed good results by using 3 drugs namely Streptomycin, isoniazid and pyrazinamide thrice weekly for 9 months. However, the results were less favourable when resistant organisms were present initially. The introduction of rifampicin in 1966 and experience gained in earlier clinical trials led to the use of rifampicin in intermittent regimens. A study in Singapore (5) compared 4 regimens with rifampicin and isoniazid given twice or once weekly for 50 weeks preceded by 2 weeks of daily streptomycin, rifampicin and isoniazid. The results are summarised in Table 2. In the twice or once weekly regimens, 2 dosages of rifampicin were used, either a high dosage (900 mg) or low dosage (600 mg). The total duration of treatment was 12 or 18 months. I have omitted the results of treatment for 18 months as good results were already obtained with the 12-month regimens. The twice weekly regimen gave a success rate of 98 to 100%, while the once weekly regimens were slightly less effective. Immunological reactions in the form of the 'flu' syndrome were more frequent with the once weekly regimen especially when the higher dosage of rifampicin was used. The best regimen therefore is the twice weekly regimen using 600 mg rifampicin. This regimen is more expensive than the standard intermittent regimens but cheaper than the SPH/PH regimen.

In Arkansas, a modified rifampicin and isoniazid containing regimen was used with a total duration of treatment of 9 months (6). Rifampicin and isoniazid were given daily for 1 month initially, followed by twice weekly rifampicin and isoniazid for 8 months. The regimen was 98% effective (7) and it costs less than the Singapore twice weekly regimen mentioned above. However, this regimen is not suitable for patients who may have isoniazid resistant organisms since rifampicin will be the only effective drug left.

SHORT COURSE REGIMENS (SCR)

In recent years, the trend is to develop regimens of short duration of from 6 to 9 months. Rifampicin, a highly potent drug, gave the impetus to the development of such regimens. The concept of SCR is to kill (i) the rapidly multiplying bacilli and (ii) those which are slow growing known as persistors (8, 9). The population of bacilli in cavities are rapidly growing and they are killed by isoniazid, rifampicin and streptomycin which are bactericidal drugs. Bacilli which are slow growing can only be killed by drugs with sterilising activity e.g. rifampicin and pyrazinamide and to a weaker extent isoniazid and streptomycin. Both the bactericidal and sterilising activity occurs from the start of treatment. One advantage that rifampicin has over isoniazid is that it starts to act within an hour of contact with bacilli while it takes about 24 hours for isoniazid to become active (8). This makes rifampicin effective against semi-dormant bacilli which can show intermittent spurts of growth. Unlike both isoniazid and rifampicin, pyrazinamide is active in an

Table 2

SINGAPORE/BMRC STUDY OF INTERMITTENT RIFAMPICIN PLUS ISONIAZID IN PATIENTS WITH DRUG SENSITIVE STRAINS PRETREATMENT (5)

Regimen	Dosage of rifampicin	Rhythm	Total duration (months)	Treatment failure	Relapse	Cost. Index
SHR/H_2R_2	900 mg (high dosage)	twice weekly	12	0%	2%	216
SHR/H_2R_2	600 mg (low dosage)	twice weekly	12	0%	0%	151
SHR/H_1R_1	900 mg (high dosage)	once weekly	12	3%	2%	118
SHR/H_1R_1	600 mg (low dosage)	once weekly	12	8%	0%	86

For meaning of abbreviation - see Table 1.

The letters preceding the symbol / represent drugs in the initial phase; letters following / represent drugs in continuation phase.

Duration of SHR was 2 weeks for all 4 regimens. Dosage of once or twice weekly isoniazid was 15 mg/kg body weight.

acid environment e.g. inside macrophages and this makes it a most valuable additional sterilising drug. Thus most SCR include 2 but often 3 or 4 of the above mentioned drugs. The high potency of SCR is shown by (i) the high percentage of sputum conversion at 2 months of treatment and (ii) the low relapse rates after treatment. These 2 findings are good indices of the sterilising action of SCR. Bacteriostatic drugs have no place in the initial intensive phase of SCR except when used to prevent the emergence of drug resistance e.g. ethambutol. Pyrazinamide appears to exert its maximal effect within the first 2 months of treatment or even within a shorter period (10). It is also believed that streptomycin does not play a major role in SCR (10).

ADVERSE REACTIONS

Adverse reactions in the form of rashes, gastro-intestinal upset and vestibular disturbance were mild and usually occurred in the first 2 months of treatment. The incidence of hepatitis ranged from 1-4% of patients on regimens containing both isoniazid and rifampicin (11) and 3% with the latter 2 drugs plus pyrazinamide (12). Transient increases in serum transminases occur during the early phase of treatment.

COMPARISON OF DIFFERENT REGIMENS

Table 3 gives a list of SCR (13-19) which are highly effective and the cost index for each regimen. The most expensive is the 9-month BTTA and French regimen and the cheapest is the Hong Kong 9-month $S_3H_3Z_3$ fully intermittent regimen (19). The cost index of the thiacetazone containing regimen (15) is not given as thiacetazone is not normally prescribed in Singapore. Regimens with drugs given intermittently either throughout or for part of the course are cheaper in costs, particularly when rifampicin is omitted. Regimens of 4 months' duration were investigated but found to have high relapse rates (12). However, recent studies indicated that a regimen of 18 weeks' duration could be highly effective when rifampicin, isoniazid, pyrazinamide and streptomycin were given for at least 3 months in the initial phase (20) or the above first 3 drugs given for 18 weeks with streptomycin given for 60 days (21).

CHOICE OF REGIMENS

Many factors influence the choice of a regimen for use under programme conditions. Some of these factors are:— cost of drugs, prevalence of tuberculosis, financial resources, type of community (urban or rural) and organization of health services. In developed countries with a low incidence of tuberculosis e.g. the United Kingdom, the choice is to use the 9-month 2ERH/RH regimen which has a success rate of 100%. The American Thoracic Society in 1979 has also approved the use of the 9-month regimen as an alternative to conventional regimens of 12 to 18 months used in the United States. However, it restricts the use of the 9 month regimen to patients with uncomplicated pulmonary tuberculosis and with no other associated diseases (22). The Singapore/BMRC 6-month regimen is highly effective, with good results reported up to 30 months of study. It is a good alternative to the 9-month regimen and it is also cheaper. The disadvantage is that daily streptomycin injection has to be given for 2 months in comparison with a fully oral regimen. Currently, a study in the United Kingdom compares 2 six-month regimens 2EHRZ/RH and 2SHRZ/RH with the 9 month ERH/RH regimen. For the developing countries, the choice appears to be to opt for intermittent regimens or thiacetazone containing regimens which are cheaper. In Singapore, cheaper 6-month intermittent regimens are currently under investiga-

Table 3

EFFECTIVENESS OF SOME SHORT COURSE REGIMENS

Study	Regimen	Duration (months)	Efficacy‡	Cost Index
BTTA(13)	2ERH/RH	9	100%	286
Brouet & Roussel (14)	2SRH/RH	9	100%	292
Singapore/ BMRC(12)	2SRHZ/RH	6	99%	221
East Africa/ BMRC(15)	2SRHZ/TH	8	100%	—
Madras (17)	2SHRZ/ $S_2H_2Z_2$	7	100%	152
East Africa/ BMRC(16)	2SHRZ/ $S_2H_2Z_2$	6	95%	139
East Africa/ BMRC(15)	1SHRZ/ $S_2H_2Z_2$	8	98%	110
Hong Kong/ BMRC(18)	$4S_3H_3R_3Z_3$/ $S_2H_2Z_2$	8 6	99% 95%	118 102
Hong Kong/ BMRC(19)	$S_3H_3Z_3$	9	95%	88
Arkansas (7)	$1RH/R_2H_2$	9	98%	121

† adapted from W Fox (23).

‡ efficacy applies to patient with drug sensitive infection. Number preceding abbreviations for regimens indicate duration (in months) of initial phase.

tion and the preliminary results appear to be promising. The final result is likely to influence decision-making on chemotherapy in the future.

ADVANTAGES OF SHORT COURSE REGIMENS

The advantages of SCR are well summarised by Fox (23). These are:— (i) short duration and fewer doses of drugs result in cheaper cost and reduced drug toxicity; (ii) since the treatment period is shortened, less demands are made on the time of health personnels and patients. Thus more attention can be devoted to ensure that patients attend regularly for treatment and persevere with their treatment. (iii) as treatment period is already short, patients are less likely to abscond and those who abscond are less likely to relapse because of the high potency of the regimens; (iv) patients who do in fact relapse are likely to have drug sensitive organisms; (v) patients can be discharged soon after completing treatment as the relapse rate is negligible. In addition, SCR are also useful in treating a group of patients who are usually uncooperative e.g. prisoners, addicts and psychiatric patients (24). They are also more likely to have drug resistant organisms which respond to regimens containing rifampicin, isoniazid, pyrazinamide and streptomycin followed by a rifampicin containing continuation phase (25). Resistance to rifampicin and pyrazinamide is fortunately still rare.

EXTRA-PULMONARY TUBERCULOSIS (EPTB)

Extra-pulmonary tuberculosis constitute 7.7% of all cases of tuberculosis notified in Singapore for the year 1980 (26). The diseases to be discussed are those commonly seen in Singapore. Of all cases of EPTB, 54% were tuberculosis of lymph nodes, 14% involved the abdomen, 11% - genitourinary tract, 9% - bones and joints and 4% - cental nervous system including meninges.

LYMPH NODE TUBERCULOSIS

The conventional standard treatment is SPH/PH or SEH/EH given for 18 months. A recent study showed no difference between the SEH/EH and SRH/RH regimens both given for 18 months (27). No benefit was demonstrated with initial complete excision of lymph nodes prior to chemotherapy.

TUBERCULOSIS OF ABDOMEN

Patients may present either surgically or medically. Operation is usually done for an abdominal mass or when there is evidence of intestinal obstruction. The standard treatment is SEH/EH or SPH/PH. Predniso-

lone should be given when there is ascites or chronic intestinal obstruction, to reduce strictures.

GENITOURINARY TUBERCULOSIS

Diagnosis is confirmed by positive urine culture for tubercle bacilli or by radiographic abnormality demonstrated by intravenous urogram. The standard treatment is SEH/EH or SPH/PH for 12 to 24 months depending on the extent of the disease. In affluent countries, the use of rifampicin in place of streptomycin allows treatment to be shortened to 9 months. Horne (28) advocates the use of prednisolone when ureteric obstruction is first noted and then repeating intravenous urogram at 6 weeks. If there is improvement, prednisolone should be continued for a further 6 weeks but if the stricture persists, surgical treatment to dilate the ureter or reimplant the ureter should be done. In recent years, Gow in Liverpool (29) has been treating his patients with rifampicin, isoniazid and pyrazinamide for 2 months followed by rifampicin and isoniazid 3 times a week for 2 months making a total of 4 months. He has reported good results after a follow up of one year.

It is argued (29, 30) that renal tuberculosis should respond well to SCR for the following reasons:— (i) since the kidney is a highly vascular organ, drugs can reach the kidney and be excreted in the urine in high concentrations. Penetration of isoniazid and rifampicin into renal cavities is good. The bacterial population in the kidney is small compared with the lungs.

TUBERCULOSIS OF BONES AND JOINTS

Chemotherapy is very effective for both spinal and other bone and joint tuberculosis. The standard treatment is SEH/EH or SPH/PH given for 18 months. The good penetration of rifampicin into bone has led to rifampicin being used initially with ethambutol and isoniazid for 3 months followed by rifampicin and ethambutol for 15 months (31). Good results for spinal tuberculosis were reported at 12 months at the Royal National Orthopaedic Hospital, England (31). In Algeria, favourable results were reported with 6 months chemotherapy for non spinal tuberculosis (32).

TUBERCULOUS MENINGITIS

The choice of drugs is based on the ability of the drugs to cross the blood/brain barrier Good therapeutic levels are achieved by pyrazinamide, isoniazid, and rifampicin. Streptomycin penetrates poorly into the cerebrospinal fluid unless the meninges is inflammed (33). Therefore, a highly effective combination to use is rifampicin, isoniazid, pyrazinamide and streptomycin. High dosage of isoniazid (600 mg) plus daily pyridoxine and rifampicin (15-20 mg/kg) should be used, as only 10% of rifampicin (which is not bound to protein) enters into the cerebrospinal fluid. The place of steroid in treatment is controversial but prednisolone appears to reduce adhesions which can give rise to neurological complications. The dosage of prednisolone should be increased when it is given with rifampicin because of enzyme induction by rifampicin (34). After the initial (2-month) phase of treatment when inflammation has been reduced, isoniazid and rifampicin should be continued for a total of 1 year in standard dosages.

CONCLUSION

Progress in the field of tuberculosis chemotherapy over the last 3 decades has been dramatic. The duration of chemotherapy for smear positive pulmonary tuberculosis has been shortened from 18 months to 6 months and there are indications that it can be reduced further.

In the case of patients with initial smear and culture negative pulmonary tuberculosis, an earlier report of a study in Hong Kong (35) had indicated that chemotherapy for 2 or 3 months could be sufficient but this was not confirmed by a recent report of the results up to 30 months after admission to the study (36).

The success of SCR has also prompted clinicians to embark on studies using SCR for extra-pulmonary tuberculosis and the results have been encouraging. The results of further studies are awaited with keen interest. In both standard duration and short course chemotherapy, good results can only be achieved by a well organized health service which can provide efficient ambulatory treatment to every patient.

Editor's Note

This is the first of a series of invited Therapeutic Update articles written by consultants. We hope this will further enhance the standard of medical treatment in Singapore. Future articles include common conditions like bronchial asthma, diabetes mellitus, thyrotoxicosis, hypertension and heart failure.

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