Artigo de Revisão

Chemoprophylaxis in the prevention of tberculosis

NORMA I SOZA PINEDA, SUSAN M. PEREIRA, ELIANA DIAS MATOS, MAURICIO L BARRETO

Tuberculosis chemoprophylaxis is a therapeutic measure for the prevention of infection by *Mycobacterium tuberculosis* or to avoid development of the disease in individuals already infected with it. Isoniazid is the most commonly used therapy; however, the use of rifampicin and pyrazinamide has recently been introduced. The objectives of this study were to review the results of the principal studies evaluating the indications for chemoprophylaxis with isoniazid alone and in association with other drugs, its efficacy in the prevention of tuberculosis with respect to the different risk groups and the alternative regimens available. A systematic revision of the medical literature was carried out with particular emphasis on clinical trials and meta-analyses. Official records were also consulted. Those studies involving randomized clinical trials on the use of isoniazid, rifampicin or pyrazinamide in HIV-positive or negative patients were selected. Isoniazid continues to be effective for the prevention of tuberculosis in populations of both HIV-negative and HIV-positive individuals. The standard dose of 5-15 mg/kg/day has shown similar protection over treatment periods ranging from six to twelve months. The risk of developing hepatitis was less than 1%; however monitoring during treatment is recommended in patients over 35 years of age and in users of alcohol. Studies involving treatment regimens with other forms of medication were inconclusive and new studies would have to be performed to evaluate the efficacy of these regimens in populations at high risk of developing tuberculosis.

Key words: Tuberculosis. Chemoprophylaxis. Isoniazid.

INTRODUCTION

Tuberculosis (TB) chemoprophylaxis consists of the administration of isoniazid (INH) to individuals uninfected with *Mycobacterium tuberculosis* (Mtb) in order to prevent infection (primary chemoprophylaxis) or to infected individuals in order to avoid the development of the disease (secondary prophylaxis). However, other drugs, such as rifampin (RIF) and pyrazinamide (PZA), have recently been introduced.[1]

Since 1952, INH has been used for TB treatment in the USA and in Brazil. Since 1965, the American Thoracic Society (ATS) has recommended the use of INH for TB prophylaxis in individuals presenting positive reactions in tuberculin tests (tuberculin reactors). In the early 1970s, the use of INH was associated with severe hepatotoxicity, which can be fatal. From 1974 on, the ATS restricted the use of INH to tuberculin reactors younger than 35 and those older than 35 who presented a high risk for TB reactivation, providing that they had not been diagnosed with liver disease. Later, in 1983, it was suggested that patients in certain age brackets who were receiving INH be clinically monitored through periodic assessment of liver function. The use of INH should be discontinued if aminotransferase levels reach three to five times higher than normal.[2-4]

The objective of this study was to analyze and review the principal studies on secondary chemoprophylaxis with INH and its effectiveness in TB prevention. We specifically intended to review questions regarding preventive treatment for TB, identifying the effectiveness of INH in the various risk groups, including those infected with human immunodeficiency virus (HIV), as well as identifying alternative regimens, determining duration of treatment, evaluating supporting evidence, and assessing adverse effects.

Abbreviations used in this paper:
95% CI – 95% confidence interval
AIDS – Acquired immunodeficiency syndrome
ATS – American Thoracic Society
BCG – Bacillus Calmette-Guérin
BTS – British Thoracic Society
EMB – Ethambutol
HIV – Human immunodeficiency virus
INH – Isoniazid
Mtb – *Mycobacterium tuberculosis*
PAS – Para-aminosalicylic acid
PPD – Purified protein derivative
PZA – Pyrazinamide
RFB – Rifabutin
RIF – Rifampin
RR – Relative risk
TB – TuberculosisM

Preventive use of isoniazid in risk groups

Based on the sensitivity and specificity of purified protein derivative (PPD) tuberculin tests and TB prevalence in the various risk groups, several cutoff points have been recommended. An induration 5mm is considered positive in Mtb-infected individuals who are at high risk for developing active TB.[5] An induration 10 mm is considered positive in those who are likely to have had a recent infection or in those who present any type of clinical condition that increases their risk of developing the disease. In individuals at low risk, for whom tuberculin tests are not usually recommended, an induration 15mm should be considered positive.[4,5]

Chemoprophylaxis in non-infected individuals (primary)

In Brazil, the *Ministério da Saúde* (Health Ministry) recommends that newborns cohabiting with active TB individuals be treated with INH during the first three months of life and subsequently be submitted to tuberculin testing. If the results are positive (induration 10mm), chemoprophylaxis should be continued for an additional three months. If the results are negative, administration of the drug should be interrupted and the children vaccinated with the bacillus Calmette-Guérin (BCG) vaccine.[6] These recommendations are similar to those made by the ATS and BTS (*British Thoracic Society*).[4,7] However, American public health officials recommend that children born to mothers infected with HIV be submitted to annual tuberculin tests.[8]

Chemoprophylaxis in infected individuals (secondary)

It is recommended that INH be administered to children younger than 15 who have not vaccinated with BCG and have had contact with pulmonary TB patients, assuming that those children present no signs of active disease and have strong PPD reactions (induration 10mm). It is also recommended for those children who were vaccinated with BCG and have a PPD reaction 15 mm.[1] This recommendation is in

accordance with the findings of a controlled clinical study on contact with TB patients in the home, in which it was demonstrated that TB incidence was highest among children less than 5 years of age (12.9/1000). The occurrence of TB in this age group is always considered a recent infection, and INH has demonstrated high efficacy (87%) against such infections.[9]

The general consensus in the literature is that children younger than 5, teenagers and young adult tuberculin reactors constitute high-risk groups and should be advised to accept chemoprophylaxis.[5,7,10]

In an observational study comprising 2494 children, the incidence of TB among children receiving a 12-month course of INH chemoprophylaxis was 3.2/1000/year, compared with 30.2/1000/year in the placebo group. Administration of INH provided 90% protection and no deaths were reported among those with pulmonary TB. In addition, no disease reactivation was observed during adolescence, which suggests that the treatment provided long-term protection.[11]

Individuals who have recently (within the past 12 months) undergone tuberculin conversion (to 10 mm of induration) are also considered a high-risk group. Children younger than 4 who have positive reactions (10 mm) should be considered recent reactors.[4]

There is a high prevalence of active TB among indigenous populations. For example, among members of the Yanomami tribe, the rate is 6.4% of 625 individuals, which is approximately 100 times higher than the prevalence in the state of Amazonas in general (68/100,000).[12,13] This calls for specific prevention measures. In the USA, individuals from various ethnic groups (African Americans, Hispanic Americans, and Native Americans) that have limited access to health care services are considered high-risk groups, and preventive therapy is therefore recommended whenever these individuals become tuberculin reactors, even if there are no other risk factors for TB.[4]

Chemoprophylaxis, under strict medical supervision, is also recommended for those who may not have active TB but have severe reactions to tuberculin tests, as well as for those have not previously undergone chemotherapy and those who present other extraneous conditions that may be conducive to TB development. Such conditions include alcoholism, insulin-dependent *diabetes mellitus,* silicosis, severe kidney disease, sarcoidosis, lymphoma, long-term corticosteroid use (immunosuppression dose), cancer chemotherapy, use of immunosuppressants, and presenting radiographs compatible with latent TB. This recommendation is based on the fact that chronic diseases such as diabetes, lymphoma, and severe kidney disease all result in some level of immunosuppression or require the use of corticosteroids as part of the treatment, thereby increasing the risk of developing reactivation TB. Nevertheless, this risk has not been precisely determined. It is known that, due to its immunosuppression effect, a course of prednisone at doses higher than 15 mg for 2 or more weeks substantially reduces tuberculin reaction, increasing the risk for the development of TB. There is no evidence that chemoprophylaxis is recommended for individuals receiving less than 15 mg of prednisone or its equivalents. It is necessary to evaluate patient risk for liver injury.[3-5]

In developed countries, immigrants from regions where there is high prevalence of TB are also considered a high-risk group. In the USA, the incidence of TB in this population increased between 1986 (27.1/100,000) and 1993 (33.6/100,000), representing 21.6% of all TB cases in 1986 and 29.6% of all cases in 1993. At the end of an 8-year study, incidence among immigrants (30.6/100,000/year) was determined to be 4 times higher than among non-immigrants (8.1/100,000/year).[14] The Pan American Health Organization and the BTS also recommend that this group receive preventive therapy.[15,16]

Treatment for latent infection with Mtb during pregnancy should be delayed until after delivery and should be administered with extreme caution in high-risk cases.[16] The ATS recommends its implementation in pregnant women infected with HIV and recently exposed to active TB or having previously been tuberculin reactors.[4] National health care officials in the USA recommend the administration of INH after the first three months of pregnancy for women who are HIV-positive tuberculin reactors and have contact with active-TB patients.[8]

Other groups that have been considered high-risk include individuals whose body mass is higher or lower than the ideal and those submitted to transplants, as well as residents of or workers at certain institutions – such as hospitals, correctional centers, elderly homes or centers for patients with acquired immunodeficiency syndrome (AIDS).[4,5,7]

Clinical evaluation of the use of isoniazid in chemoprophylaxis

The effectiveness of INH use (at a dose of 5 mg/kg, maximum 300 mg/day) in chemoprophylaxis has been established in double-blind, placebo-controlled, randomized clinical trials carried out since the 1960s. In a study conducted in Alaska, estimated effectiveness for one-year treatment was 75% in the first 4 years of follow-up, and a long-lasting protective effect was shown: 70% after 15 years and 50% after 19 years.[10,17,18] In the USA, a clinical trial showed a decrease in TB incidence among individuals having contact with TB in the home and treated with INH, which prevented primary pulmonary TB and extrapulmonary TB in uninfected children. The same study showed a decrease in the number of pulmonary TB cases among adults.[19] The authors of these studies reported neither INH resistance nor significant side effects. Another study showed that, in a population of war veterans in San Francisco, USA, 60% were protected against TB reactivation.[20] A recent meta-analysis among HIV-negative individuals, including 11 controlled clinical trials, found a relative risk (RR) of 0.40 and a 95% confidence interval (95% CI) of 0.31-0.52. This corresponds to 60% protection in various known high-risk groups. Such groups include those having had contact with active-TB patients, those living in areas with a high TB prevalence, those institutionalized for chronic psychiatric disorders, those recently converted to tuberculin reactors, those with no previous history of chemotherapy whose X-rays are compatible with latent TB, those with pneumoconiosis due to silica exposure and those having had a kidney transplant. This finding is in accordance with those in the literature if we consider that the level of protection is adequate for populations at low risk for TB. In those at high risk, considering the duration of treatment, this protection would have only a minor impact on the prevention of new cases.

Individuals with severe reactions to PPD (induration 10 mm), ranging from 28 to 65 cases per 100,000 inhabitants, are known to be at high risk for contracting active TB. However, this risk decreases with the passage of time.[18]

Randomized controlled clinical trials involving patients with pulmonary fibrotic lesions have been used to compare the effectiveness of INH regimens ranging from 3 months to 2 years. These studies have shown that, after a follow-up period of 5 years, a 3-month regimen decreased TB incidence by 21%, a 6-month regimen by 65% and a 12-month regimen by 75%. In comparison to patients in the placebo group, the ratio between benefit and risk was 1.2 for the first regimen, 2.6 for the second and 2.1 for the third. In 2003, Smieja et al.,[21] in the previously mentioned meta-analysis, reported no significant differences between 6-month and 12-month INH regimes (RR = 0.44 and RR = 0.38, respectively; p = 0.08). However, this difference may be significant, depending on the risk of developing active TB. For example, it has been estimated that it would be necessary to treat 179 individuals for 6 months in order to prevent 1 TB case under low-risk conditions (in adult tuberculin reactors with normal chest X-rays and risk of developing hepatitis lower than 0.5%). Using the 12-month regimen, 161 individuals would have to be treated in order to prevent 1 case. In patients at high risk for TB infection (20%), it has been estimated that 1 case is prevented for every 8 or 9 patients treated.[21] Another aspect to be considered is that the shorter the duration of treatment, the higher the compliance, that is, more people will complete the treatment (78% in 6-month regimens and 68% in 12-month regimens).[22]

In a clinical trial in Canada, the effectiveness of INH alone and in combination with para-aminosalicylic acid (PAS) in the prevention of TB reactivation was estimated in individuals diagnosed with latent TB. After 18 months of treatment, the authors observed no benefits provided by the use of INH alone or in combination if the period of treatment was less than 6 months, with reactivation rates similar to those seen in the control group. The use of INH combined with PAS effected a 90% decrease in the reactivation rate, in comparison with a 70% decrease from the use of INH alone. They also reported an increase (from 30% to 60%) in the incidence of mild adverse effects with the combination of INH and PAS. These side effects caused noncompliance with treatment to increase from 19% to 42%, thereby limiting INH use.[23]

Chemoprophylaxis with other treatment regimens

Use of 6-month and 12-month INH regimes in TB chemoprophylaxis has been standard practice in the USA for 30 years. Later, this recommendation was revised since the decrease in the incidence of

TB was lower than expected, and mortality due to liver failure began to be related to the use of INH. Moreover, poor compliance with the treatment (due to its long duration) and the occurrence of co-infection with HIV/AIDS has motivated studies on the effectiveness of chemoprophylaxis using other drugs, which, of necessity, requires the study of their implementation. In 2000, the ATS released a series of recommendations on chemoprophylaxis, suggesting that a 2-month course of RIF or PZA be used as a substitute for INH. These findings were based on clinical trials and experiments in animals.[5]

In 1998, the BTS recommended that TB chemoprophylaxis consist of the use of INH for 6 months or the combination of INH and RIF for 3 months. Based on controlled clinical trials, the use of both drugs combined has shown similar effects to the use of INH alone, with no increase in the number of adverse effects.[15] In 2000, it was suggested that, when using both drugs in combination, the duration of treatment should be reduced to 2 months, and that INH alone should no longer be used for prevention since both regimens had proven to be similarly beneficial. Treatment of high-risk, HIV-negative patients with the INH and RIF regimen for 3 months proved to be as effective as the INH regimen for 6 months. The RIF and PZA regimen for 2 months is less well tolerated than regimens using INH or RIF alone. The combination of INH and RIF is well tolerated by children for periods equal to or greater than 3 months. However, the BTS still recommends the use of RIF combined with INH for 3 months as an alternative to the 6-month INH regimen.[7]

In an experimental study using guinea pigs vaccinated with BCG, the efficacy of a 6-month course of INH was compared to that of 2-month courses of RIF alone, RIF + PZA, and RIF + PZA + INH. Doses, in relation to serum levels, were equivalent to those used in human populations. Treatment started 2 weeks after infection. After 2 months of therapy using the various regimens, the study showed that the number of positive results in spleen culture was 100% in specimens from guinea pigs treated with the first regimen, 50% with the second regimen, 0% with the third, and 80% with the last. After the use of INH for 6 months, the percentage of positive spleen cultures was 38%. The study also tested the extreme effectiveness of the RIF + PZA regimen compared to the RIF regimen for 3 months. Using similar procedures, spleen cultures were 100% positive using the INH regimen for 6 months, compared to 20% using RIF for 3 months, 0% using RIF + PZA for 2 months, and 80% using the combination of the 3 drugs for 2 months. Six months after the end of the treatment, the proportion of positive results were 100%, 60%, 56%, and 95%, respectively. The 2-month RIF + PZA regimen and the 3-month RIF regimen proved to be more effective than the 6-month INH regimen.[24]

In another experimental study, the efficacy of RIF in various treatment regimens (RIF alone, RIF + PZA and RIF + INH + PZA) was evaluated. Infected guinea pigs were initially treated with INH + PZA for 7 weeks. Later, 4 groups comprising 47 guinea pigs each, received the various treatment regimens for 6 weeks. A fifth group consisting of 10 guinea pigs was the control group and received INH + PZA for 13 weeks. After a period of between 26 and 35 weeks, the animals were sacrificed so that spleen culture results could be evaluated. The percentage of positive results were 74% in the RIF-only group, 63% in the RIF + INH group, and 53% in the RIF + PZA + INH group. These differences were not statistically significant, so efficacy of the various regimens was determined to be quite similar.[25]

A placebo-controlled, double-blind clinical trial conducted in Hong Kong and involving male patients diagnosed with silicosis compared four treatment regimens (RIF for 3 months = 142 patients; INH + RIF for 3 months = 161 patients; INH for 6 months = 123 patients; placebo = 133 patients) over a follow-up period of 5 years. The probability of developing TB was 10% when RIF was used, 16% when the combination of INH and RIF was used, 17% when INH alone was used, and 27% when a placebo was used. Regimens including RIF proved less likely to cause hepatotoxicity. Regimens using INH alone or in combination showed higher aminotransferase concentrations in the serum of patients during the period of treatment ($p < 0.001$). The authors recommended that other studies be performed so that more effective and safer treatment regimens for patients diagnosed with silicosis could be found.[26]

In a placebo-controlled, double-blind randomized clinical trial carried out in South Africa, the effectiveness of two regimens in preventing TB in patients diagnosed with silicosis. Study

subjects received either 600 mg of RIF alone or 400 mg of INH combined with 1250 mg of PZA, the INH and PZA in accordance with recommended doses. After a follow-up period of 4 years, TB was diagnosed in 11 males who had received medication (annual incidence of 1480/100,000) and in 15 males of the placebo group (p = 0.40). The authors determined that the lack of treatment regimen efficacy was correlated with silicosis as well as with a high risk of reinfection due to the high incidence of TB in that community.[27]

Recently, the American entities the ATS and the CDC recommended that the combination of RIF and PZA not be used in any preventive TB treatment regimens. According to data from patient cohort studies conducted in the USA, high rates of severe liver impairment and mortality result from the use of the two drugs. Other treatment alternatives should be considered for TB prevention.[28]

Prevention of drug-resistant TB

In cases of INH resistance, the ATS recommends the use of RIF (10 mg/kg). They also recommend the use of ethambutol (EMB, 15 mg/kg) when the strain is proven to be susceptible. For both regimes, 6-month courses are recommended for adults and 9-month courses for children. If there is evidence of contact with multidrug-resistant TB, daily doses of the EMB + PZA combination (20 mg/kg and 25 mg/kg, respectively) for 6 months are recommended. Although there are limited data on the use of quinolones as therapeutic agents against TB when there is resistance to EMB, the use of PZA combined with a quinolone (400 mg/day ofloxacin or 750 mg/day ciprofloxacin) for 6 months has been recommended. It is recommended that 6- to 9-month courses of RIF, alone or in combination with EMB, be given to children and immunosuppressed adults who have had contact with patients infected with INH-resistant TB strains when strains are susceptible to the latter drug[4,7]

It has been recommended that HIV-positive patients who have had contact with INH-resistant active-TB patients be evaluated on a case-by-case basis. For such patients, the decision to use other drugs should be based on the results of susceptibility testing of the Mtb strain isolated, as well as on the guidelines established by the respective health care authorities.[1,5]

Tuberculosis prevention in HIV-positive patients

Individuals who are HIV positive are at high risk for becoming infected with TB. Two specific conditions should be taken into consideration for this group: reaction to tuberculin tests is poor in individuals with severe immunodeficiency, and chest X-rays of individuals with coinfection present atypical characteristics. These two aspects make it more difficult to distinguish between latent infection and active disease. However, the International Union Against Tuberculosis and Lung Disease and the World Health Organization recommend preventive therapy for patients with coinfection.[29]

It is recommended that HIV-positive patients, regardless of age, with no evidence of active TB or previous history of TB treatment whose reaction to tuberculin test is equal to or greater than 5 mm and whose chest X-rays are normal should be treated for latent Mtb infection. Among this population, the risk of acquiring TB has been estimated at between 1.7 and 7.9/100 people/year[30], which is why the identification of coinfection and the administration of preventive treatment are highly relevant. Efficacy of this therapy has not been confirmed in individuals with negative tuberculin test results (anergic individuals). Some clinical trials involving this group have shown that patients do not markedly benefit from preventive treatment with INH. Problems with drug absorption and severe immunosuppression are likely to interfere with therapy efficacy. However, the use of INH for 12 months is recommended for HIV-positive patients, even for those whose PPD results are negative, if they have had recent contact with individuals diagnosed with infectious pulmonary TB. For this group of patients, decisions on the use of chemoprophylaxis should be considered on a case-by-case basis.[4,6,8,29]

Isoniazid and tuberculosis prevention in HIV-positive patients

In Brazil, the TB chemoprophylaxis treatment of choice for HIV-positive patients is 5 to 10 mg/kg/day of INH (maximum dose: 300 mg/day) for 6 consecutive months.[6] In the USA, the drug of choice is also INH (at the same dose levels), but is administered either daily or twice weekly for 9 months. The ATS

recommends that adults should continue therapy for 12 months.[5,8] Nevertheless, the American Academy of Pediatrics recommends that, for children, the duration of such treatment be less than 9 months.[4]

Various controlled, randomized clinical trials have shown the effectiveness of INH in adult populations coinfected with HIV and TB. In five of these studies, the effectiveness of INH was assessed by comparing patients receiving INH to those receiving a placebo and to those receiving no treatment. Between 1986 and 1992, the incidence of TB in Haiti decreased 83% in tuberculin test reactors receiving daily doses of INH for 12 months. This protection continued throughout a four-year period of follow-up.[31]

A 6-month course of daily administration of INH in tuberculin reactors and nonreactors has been evaluated in various studies, with varying results. In a study carried out in Uganda, the authors reported 68% protection.[30] In Kenya, the rate of protection was lower (40%; 95% CI = 0.23 – 1.60).[33] In Zambia, protection provided by the use of INH twice a week for 6 months was considered low (38%; 95% CI = 0.38 – 0.99). Protection was higher (70%) in tuberculin reactors, but results were not statistically significant due to the small number of individuals in this group.[34] Whalem et al., in 1997, and Gordin et al., in 2000, also reported little protection provided by INH in anergic individuals.[32,35]

In a meta-analysis encompassing seven studies that comprised a total of 2367 people treated with INH and 2162 controls, the RR of developing TB was 0.58 in the treated group (95% CI = 0.43 – 0.80), corresponding to 42% efficacy. The RR among tuberculin reactors was 0.40 (95% CI = 0.24 – 0.65; 60% efficacy), compared with 0.84 among tuberculin nonreactors (95% CI = 0.54 – 1.30; 16% efficacy). Estimated RR for mortality prevention was 0.94 (95% CI = 0.83 – 1.07), corresponding to 6% protection. Among tuberculin reactors, the RR for mortality prevention was 0.79 (95% CI = 0.37 – 1.70) versus 1.0 for tuberculin nonreactors (95% CI = 0.90 – 1.17). The authors of this study concluded that administration of INH for 6 months in HIV-positive patients who are tuberculin reactors reduced TB incidence by 60%.[36]

In the USA, a study of the protective effect of a 24-month course of INH chemotherapy on the incidence of diseases caused by mycobacteria in HIV-positive, injection drug users showed that TB risk decreased in 83% of these individuals with the use of intermittent, twice-weekly doses.[35]

Use of other drugs for preventing active tuberculosis in HIV-positive individuals

Several controlled randomized clinical trials have been carried out in order to evaluate proper duration of treatment and the effects of combining other drugs with INH. The combined use of INH and RIF for 3 months in daily doses has been shown to provide 59% protection. It has also been shown that daily administration of a three-drug combination of INH, RIF and PZA provides 57% protection. These results were similar to those found for the use of INH alone for 6 months.[5,32]

The levels of protection provided by twice-weekly, 3-month treatment regimens using two drugs combined (INH + RIF) or three drugs combined (INH + RIF + PZA) were 59% and 57%, respectively. These results were similar to that regimen using INH twice a week for 6 months.[32] The combined use of RIF and PZA for 3 months provided 42% protection, similar to that provided by the use of INH alone, twice a week, for 6 months.[34] In Haiti, the level of protection provided by two regimens (2 months of RIF + PZA and 6 months of INH twice a week) was similar after a follow-up period of 12 months.[38] In another study carried out in the USA, Haiti, Brazil and Mexico, the authors reported that daily administration of RIF combined with PZA for 2 months provided the same level of protection against TB as the daily use of INH for 12 months.[35] In Hong Kong, a study with patients suffering from silicosis showed that daily administration of RIF for 3 months provided protection (90%) similar to that of the INH regimen for 6 months (86%).[26]

A study involving a cohort of HIV-positive tuberculin reactors was carried out in order to determine the contribution of chemoprophylaxis using INH alone for 12 months to the survival of these patients. The authors reported that this chemoprophylaxis regimen was related to decreased risk for active TB – annual incidence of 2% in the study group and 4.8% in the placebo group. These results suggest that chemoprophylaxis contributes to the survival of HIV-positive patients in areas where there is high TB prevalence.[39]

In a randomized clinical trial carried out in Spain and comprising 133 patients, the authors evaluated compliance with treatment and treatment

tolerance, as well as the efficacy of a 12-month course of chemoprophylaxis with INH alone in comparison to a 3-month course of RIF combined with INH. The authors reported that the incidence of active TB was 4.23/100 people/year in the INH-only group, and 2.08/100 people/year in the RIF + INH group. The RR of acquiring active TB with the RIF + INH regimen was 0.51 (95% CI = 0.09 – 2.08) when compared to the use of INH alone.[40]

It is recommended that regimens targeting HIV-positive patients not include PZA. Severe liver damage reported in relation to daily administration of the RIF-PZA combination to HIV-negative patients. In devising treatment strategies for latent TB infection in HIV-positive patients exposed to strains resistant to INH or RIF, the RR of exposure to resistant strains must be taken into consideration. Therefore, each case must be evaluated in consultation with local health care authorities.[4,8]

In the USA, other drugs have been used. One such drug is rifabutin (RFB), which has been used to prevent the dissemination of infection with *Mycobacterium avium.* For HIV-positive patients, American health care officials currently recommend the use of RFB for a period of 4 months or RFB combined with PZA for 2 months. If there is resistance to INH or RIF, the use of RFB must be based on the risk of exposure to resistant strains, so each case must be considered separately. Since RFB interacts with protease inhibitors and with non-nucleoside reverse transcriptase analogs, it is recommended that doses be reduced by half (from 300 mg/day to 150 mg/day). Prophylaxis with RIF should not be used as a routine preventive treatment since resistance may occur.[8]

Toxic effects of isoniazid

No adverse effects, such as hepatitis, were reported in the first studies of INH.[9] In 1972, the first evidence of adverse effects was reported in patients submitted to therapy with INH in the USA – increased transaminase levels and fatal hepatitis. During therapy, 19 of the 2321 patients treated (8.2 cases/1000 people/9 months) showed clinical signs of liver disease and the deaths of two patients were attributed to the medication.[41] A clinical trial carried out by public health care agencies in the USA showed that, in a group of 13,831 patients receiving INH, 1% developed hepatitis, and the incidence was higher (2.3%) in patients over the age of 50. In addition to age, alcoholism has been shown to correlate significantly with a higher risk of developing hepatitis.[42] In a study conducted in Hong Kong, similar results were found for a group comprising 679 silicosis patients, 1% of which developed liver damage. Of the 9 patients diagnosed with liver injury, 4 had received the INH regimen, and 5 had been given a placebo. Only one patient receiving the INH regimen developed signs of hepatitis.[26] Other authors have reported rates of risk for acquiring hepatitis from INH use ranging from 2% to 10%, with 5% to 10% estimated mortality rates. Clinical monitoring and cautious use of chemoprophylaxis are recommended for patients who frequently use alcohol, have pre-existing liver or kidney injury, or are simultaneously receiving other drugs that are toxic to the liver or pancreas.[43]

A study carried out in Spain involving HIV-positive patients compared two different treatment regimens (a 3-month course of 300 mg/day of INH + 600 mg/day of RIF versus a 12-month course of 300 mg/day of INH). The authors demonstrated that only 18% of patients receiving INH + RIF showed signs of hepatotoxicity, compared to 41% of patients receiving INH alone (RR = 2.22; 95% CI = 1.23 – 4.01).[38]

The fact that the population under study presented a high prevalence of hepatitis C may explain the high levels of transaminases. However, between patients who presented anti-hepatitis C antibodies and those who did not, there were no significant differences in relation to the incidence of adverse effects and hepatotoxicity with the regimen adopted. Duration of treatment correlated with the appearance of toxic effects, independently of the type of drug employed.[40]

A study comprising 28,000 pulmonary fibrosis patients presenting positive tuberculin results, selected from 115 dispensaries in various countries, showed that the incidence of hepatitis in those submitted to chemoprophylaxis with INH for 12, 24 or 52 weeks was 0.5%, compared with 0.1% in those receiving a placebo. Reducing the duration of treatment has been found to reduce the risk of acquiring hepatitis in 1.6/1000 people submitted to the 6-month regimen and in 2.7/1000 people submitted to the 3-month regimen.[22] In 1979, Kopanoff et al. reported an incidence of 92

probable and 82 possible cases of hepatitis among 13,838 people using INH.[42] In 1997, Salpeter et al.[44] identified two deaths attributable to the use of INH within a group of approximately 200,000 patients treated for 6 months, concluding that the incidence of INH-related mortality is low.

CONCLUSIONS AND RECOMMENDATIONS

The various studies reviewed have shown that INH continues to be effective in the prevention of active TB in both HIV-negative and HIV-positive populations. Our results are statistically significant and clinically relevant.

In the majority of studies, treatment regimes involving INH are typically 6 months or 12 months in duration, and the dosages used are 5–15 mg/kg/day (maximum, 300 mg/day). Similar protection has been achieved with both treatment durations. Protection is significantly less when regimens shorter than 6 months are employed, but there is no significant increase in protection if regimens longer than 12 months are used. The 12-month regimen should be recommended for very high-risk groups.

In using INH for TB chemoprophylaxis, the risk of toxic effects, especially hepatitis, appearing, although significant, is outweighed by the benefits of its use. Age (over 35) and alcohol use have been associated with higher risks of developing hepatitis than that presented by INH use.

Further studies are necessary in order to evaluate the effectiveness of these, and other, regimens that include INH when employed in populations at high risk of developing active TB.

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