Review Article

Drug choice to lowering risk contiguity with Morbus Hansen disease: A review article

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ABSTRACT

Morbus Hansen is a chronic infectious disease caused by the bacteria Mycobacterium lepromatosis and Mycobacterium leprae. Mycobacterium lepromatosis was found as a Morbus Hansen pathogen in an endemic case that occurred in South America in the 20th century. In comparison with females, Morbus Hansen cases are more common in males. An increase in the incidence of Morbus Hansen occurs in people with household contacts with Morbus Hansen sufferers. The incidence rate is higher in contacts with multibacillary cases (MB) than in paucibacillary (PB) 5-14 times. Many studies have revealed that chemoprophylaxis administration or in combination with immunoprophylaxis in individuals who have come in contact with the Morbus Hansen patient is quite effective in the reduction of the detection rate of new Morbus Hansen cases in endemic areas. Various options of drugs can be utilized as prophylaxis in lowering risk contiguity with Morbus Hansen. Unfortunately, the effectiveness is low, because strains of M. leprae were resistant to various drug types. This article aims to review drug choice for high-risk contiguity with Morbus Hansen. Drug choice prophylaxis against Morbus Hansen is mainly given to those who had contacts with Morbus Hansen patients. Prophylaxis as dapsone, clofazimine, and rifampin is effective in lowering the risk of the incidence of Morbus Hansen disease in individuals had contiguity with Morbus Hansen patients. Furthermore, research needs to confirm drug prophylaxis for lowering risk who had contact with Morbus Hansen.

Keywords: Drug prophylaxis, Health risk, Morbus hansen disease, Illness

Introduction

Morbus Hansen is a chronic infectious disease caused by the bacteria Mycobacterium lepromatosis and Mycobacterium leprae. Mycobacterium lepromatosis was found as a Morbus Hansen pathogen in an endemic case that occurred in South America in the 20th century. In comparison with females, Morbus Hansen cases are more common in males. An increase in the incidence of Morbus Hansen occurs when people of the household come in contact with Morbus Hansen sufferers. The incidence rate is higher in contacts with multibacillary cases (MB) than in paucibacillary (PB) 5-14 times [1].

Morbus Hansen disease can occur at any age and children are more susceptible to contracting Mycobacterium leprae infection than adults. This disease is transmitted from one person to another through airborne droplets. The Mycobacterium leprae spread can also be influenced by several factors, including socioeconomic status, population density, nutrition, and immune response. The endemicity rate in a region also describes the degree of public health facilities and the BCG immunization attainment rate in a region [2].

Early detection of Morbus Hansen disease in individuals who have contact with Morbus Hansen patients and

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chemoprophylaxis is the main strategy in breaking the chain of the spread of Morbus Hansen's disease [3]. Various studies have shown that administration of chemoprophylaxis or in combination with immunoprophylaxis in individuals who have contact with the Morbus Hansen patient is quite effective in reducing the detection rate of new Morbus Hansen cases in endemic areas. Various drug options can be used as prophylaxis in lowering risk contiguity with Morbus Hansen [4]. Unfortunately, the effectiveness is low, because strains of M. leprae were resistant to various types of drugs. This article aims to review drug choice for high-risk contiguity with Morbus Hansen.

Results and Discussion

Dapsone

Dapsone is a sulfonamide class of antibiotics. Dapsone can be easily absorbed in the intestine and is widely distributed through body fluids and most body tissues with a peak plasma time of 4-8 hours after consumption. The half-life for dapsone is about 1 to 2 days, and dapsone tends to be deposited in the skin, muscles, liver, and kidneys. The mechanism of action of dapsone is to inhibit the action of para-aminobenzoic acid (PABA) from bacteria used for folic acid synthesis by acting as a competitive inhibitor of PABA. Dapsone has a bactericid and bacteriostatic effect on Mycobacterium leprae [5].

Dapsone is metabolized in the liver by CYP 3A4 as well as in the kidneys. This drug is then excreted into the bile and reabsorbed in the intestine. Dapsone is then excreted in the urine as metabolites (85%), and most of it is in acetylated form. Dapsone was the first sulfonamide class of drugs to be administered orally. Since 1940, dapsone has been the drug of choice for leprosy therapy, until the standard therapy for leprosy changed in the 1980s to multi-drug therapy with the dapsone-rifampin-clofazimine combination. Based on a meta-analysis conducted by the MILEP study group, dapsone also has chemoprophylactic properties with efficacy of around 60%. The disadvantages of dapsone as chemoprophylaxis are increased resistance to dapsone and poor patient adherence due to long-term therapy [6].

The usual dose of dapsone in adults with Morbus Hansen is 100 mg per day. While the dose for children depends on their body weight with a dose of 1-2 mg / kgBW. In patients with liver and kidney disorders, the dapsone dose should be adjusted. Dapsone is contraindicated in patients who are hypersensitive to the drug or this drug class [5].

Resistance to dapsone increased with the use of dapsone as a single therapy in the case of Morbus Hansen. This then became the basis for consideration of Morbus Hansen's standard change of therapy in the 1980s from single dapsone therapy to multidrug therapy consisting of dapsone, rifampin, and clofazimine. By administering MDT, it is hoped that the resistance rate of Mycobacterium leprae to existing therapy regimens, including dapsone, can be reduced [6].

Some patients have hemolytic conditions, especially those with G6PD deficiency. Gastrointestinal symptoms such as nausea and vomiting may occur. Fever, insomnia, headache, photosensitivity may also occur. Blood disorders in the form of anemia, leukopenia, and agranulocytosis were also found in some patients on dapsone therapy. Skin disorders such as exfoliative dermatitis, pruritus, toxic epidermal necrolysis (TEN), and several other dermatological reactions can occur. In some cases, erythema nodosum was also found, although it is sometimes difficult to distinguish between reactions due to dapsone and conditions caused by Morbus Hansen himself. Erythema Nodosum Leprosum can be treated with corticosteroids or thalidomide [7, 8].

Rifampin

Rifampin can be easily absorbed in oral administration, but food can slow down or reduce the peak plasma reach, so oral administration should be done on an empty stomach. Rifampin has a peak plasma time 2-4 hours after consumption. The half-life for rifampin is about 3 to 4 hours, which is prolonged in conditions of liver damage, and in patients with chronic renal failure, the half-life can be up to 11 hours [9].

Rifampin is a highly lipophilic drug, can easily cross the blood-brain barrier, and can provide relative diffusion from blood to cerebrospinal fluid with or without inflammation. The mechanism of action of rifampin is to inhibit DNA-dependent RNA polymerization by binding to the beta subunit thereby stopping RNA transcription. Rifampin also has the potent ability to induce enzyme action (CYP 3A4). Rifampin has a strong bactericidal effect against Mycobacterium leprae [10].

Rifampin is metabolized in the liver and then undergoes enterohepatic recirculation. This drug is then excreted through feces (60-65%) and urine (30%) in the form of a fixed compound. The usual dose of rifampin in adults with Morbus Hansen is 10 mg/kg/day with a maximum daily dose of 600 mg. While the dosage for children depends on their body weight with a dose of 10-20 mg / kgBW / day with a maximum daily dose of 600 mg. Rifampin bonds with protein by 80%, so in patients with hypoalbuminemia, the rifampin dose needs to be adjusted [11].

Rifampin is contraindicated in patients who have hypersensitivity to rifampin, in patients who are being given live vaccines, and also in patients who are taking drugs such as tenofovir, ritonavir, and saquinavir because they increase the risk of developing severe hepatocellular toxicity, and are taken with some antiviral drugs. other because rifampin can substantially reduce plasma concentrations of these antiviral drugs, thereby reducing the efficacy of treatment and can lead to the emergence of resistance to these antivirals [12].

Rifampin can also decrease the effectiveness of oral contraceptives because it increases the metabolism of these drugs. In patients on anticoagulant therapy, rifampicin administration can also decrease the effectiveness of this therapy by inducing hepatic enzymes so that anticoagulant metabolism occurs more quickly. The administration of rifampin to patients with a history of diabetes mellitus also needs to be watched out,

for because rifampin makes the management of diabetes mellitus more difficult [13].

Resistance to rifampin can occur when a spontaneous mutation in bacteria makes the bacterial RNA polymerase enzyme lose affinity for the antibiotic. In addition, resistance to rifampin can be influenced by the presence of an enzyme that deactivates rifampin by transferring the ADP-ribosil molecule to one of the hydroxyl groups on the aliphatic carbon chain in the antibiotic rifampin. Resistance via enzymes can be spread by horizontal spread via plasmids [14].

Rifampin generally causes an orange discoloration of urine and other body fluids such as sweat and tears, but this condition is temporary and will resolve completely with the discontinuation of drug administration. Some patients have increased hepatic function (increased AST / ALT) because rifampin is hepatotoxic. Some patients also present with skin rashes, epigastric pain, anorexia, nausea, vomiting, diarrhea, abdominal cramps, jaundice, and hepatitis. In addition, the administration of rifampin above the maximum daily dose can cause the flu-like syndrome, which is characterized by fever, chills, and myalgia, disruption of hematopoiesis resulting in anemia, leukemia, or thrombocytopenia. Rifampin therapy should be discontinued if the patient shows signs of liver damage, including hyperbilirubinemia [15].

Chlofazimine

This iminophenazine synthetic dye has been used as a therapeutic agent for leprosy for more than 3 decades. In 1962, Brown and Hogerzeil demonstrated clinical and bacteriological improvement in lepromatous patients using this therapy. This was immediately confirmed by a study conducted by the National Institute of Health (NIH), Bethesda, USA. This drug has mild bactericidal properties against the bacteria Mycobacterium leprae, with a slightly weaker effect than dapsone. Although it is not certain how this drug works, it is possible that this drug works by inhibiting the function of DNA prints. Numerous studies have shown that the accumulation of clofazimine in macrophages, the site of Mycobacterium leprae, causes the local emergence of superoxide and hydroxyl radicals. These products are inhibitors of the multiplication of Mycobacterium leprae [16].

This drug acts as an anti-inflammatory which may benefit type 2 reactions. Simulation of PGE2 synthesis and inhibition of neutrophil motility, together with selective suppression of Th-1 subtype T-helper cells, is thought to also increase the role of this drug in type 2 reactions. This drug is not water-soluble so the micronized crystal components included in gelatin capsules need to be dissolved in an oil-based vehicle and encapsulated into soft gelatin for oral consumption. Although it has been formulated in this form, the percentage of absorption of this drug in the intestine is 30-50%. Giving a dose of 50 mg will produce a serum level of 0.5 μg while giving a dose of 300 mg only increases serum concentration levels 2 times that of the 50 mg dose [17].

In humans, as in mice, the drug enters several organs and is stored in them in the form of needle-like crystals, mainly deposited in macrophages and cells of the reticuloendothelial system. Accumulation of this drug in macrophages can benefit patients and inhibit intracellular multiplication of Mycobacterium leprae [18].

This drug accumulates in large amounts in the skin, subcutaneous fat, liver, lungs, adrenals, kidneys, lymph nodes, and gastrointestinal tract. The accumulation of this drug in the tissues results in staining of the organs and skin. This drug is excreted very slowly from the body, usually taking an average of 6-12 months. Thus, it will take a long time for the patient to achieve normal skin color. Small amounts of the drug component can still be found even after 3 years after stopping the clofazimine treatment. Accumulation of clofazimine in macrophages likely affects the capacity of macrophages to process and present antigens thereby limiting their movement and activation, IL-2 release, and clonal expansion. In contrast to dapsone, this drug has a role in suppressing the release of cytokines (IL-1) causing decreased movement of lymphocytes to the type 1 reaction site or reversal reaction [19].

Due to the long half-life of this drug (about 2 months) and its tissue storage, it can maintain activity even when given intermittently, although intermittent administration is not as effective as regular daily administration or when given intermittently every 2 days. Clofazimine is equally able to play an active role against Mycobacterium leprae which is sensitive to dapsone and against Mycobacterium leprae which is resistant to dapsone [20].

The clinical response produced by administering a daily dose of clofazimine 50-100 mg is almost the same as that produced by administering 100 mg of dapsone, although the effect exerted by this drug is slightly slower. Nearly all types of leprosy respond well to this drug. However, it should not be given as a single drug or as a cheaper and more effective substitute for dapsone. This drug is indicated for patients with type 2 reactions even though the anti-inflammatory action it produces is very slow. This drug has a special role in the prevention and management of patients with chronic ENL reactions. Several investigators have shown that clofazimine can reduce the risk of hypersensitivity-type reactions [21].

Resistance to clofazimine is rare. However, when given as a single drug, Mycobacterium leprae tends to become resistant to this drug. Thus, like other antileprosies, clofazimine should be given only as part of MDT and not given as a single drug. Reddish-brown staining of the skin, due to deposition of clofazimine in the skin, is quite common. This discoloration is more pronounced in sun-exposed areas of the skin including the face and this is a factor in the disfavor of this drug among white individuals/races. Xerosis of the skin can be found and at a later stage ichthyosis acquired with a brownish color in the extensor area and localized in the area of the lesion (due to the ceroid-like pigment) is common. In some patients, hyper melanosis can be found [22].

Other side effects are frequently seen in patients with reactions, who receive a daily dose of 200-300 mg per day for a long period and an effect that results from the deposition of clofazimine in reticuloendothelial cells in several organs. In women, this can lead to abdominal problems, such as pain or diarrhea, which in

turn can lead to malabsorption and cachexia. In severe cases, hypokalemia and death may occur. Decreased volume of sweat and tears, possibly as a result of the anticholinergic action, including dryness of the skin and eyes, makes it more difficult for patients with leprosy. This can severely affect patients with corneal xerosis and lagophthalmos. The episclera may also experience discoloration. Findings of splenic infarction and ceroid congestion in the small intestine have also been reported, in addition to findings of reddish sputum due to excretion of clofazimine crystals in the respiratory tract - mimicking hemoptysis. It can also cross the placental barrier and affect fetal skin. Until now, it is still unknown the possible teratogenic effects that could result [23].

Research about chemoprohpylaxis drugs

Dapson

There are several studies evaluating the effectiveness of dapsone as chemoprophylaxis at a weekly or bi-weekly dose for two years. A study on 732 healthy children under 15 years of age with contact Morbus Hansen at home in **Table 1**. The study was conducted by giving dapsone 20-150 mg twice a week for the first 6 months and 10-75 mg as a maintenance dose until the end of the study period. Wardekar observed the effectiveness of dapsone as chemoprophylaxis in 27 villages compared to 27 other villages as controls. Dapsone appears to provide significant protection against Mycobacterium leprae infection by preventing the emergence of new cases of Morbus Hansen in the general population, especially in patients under the age of 25 years [24]. Another study conducted by Noorden and Neelan showed different results. Dapsone with common doses (75 mg) and low doses (50 mg) did not provide a significant difference when compared with control (placebo) in protecting individuals who had contact with MH lepromatous type patients. Meanwhile, dapsone with the general dose only gave a significant difference compared to controls in protecting individuals in contact with non-lepromatous MH-type patients. Several clinical investigations noted that in general the duration of dapsone as monotherapy for MH lepromatous in 5 years often results in a relapse of the disease after discontinuation of therapy. Consequently, life-long sulfone therapy in MH lepromatous is recommended [25].

The results of the meta-analysis regarding the use of dapsone as chemoprophylaxis show that giving dapsone for a long time provides effectiveness of 60%. The effectiveness of dapsone chemoprophylaxis in contact individuals who live at home with Morbus Hansen patients varies between 34% and 54%. Meanwhile, the mass effect of dapsone chemoprophylaxis in the population was 91%. The drawbacks of giving dapsone as chemoprophylaxis are the problem of drug resistance that often arises and the low level of adherence are low due to the long period of time [25].

Research evaluated the relative risk of developing secondary dapsone resistance in several countries and found across the surveyed regions that dapsone resistance was very frequent and mostly high-level resistance (0.01% in experimental mice equivalent to 100 mg in humans). In Ethiopia, Pearson reported that as many as 15% of patients with MH lepromatous experience a dapsone resistance relapse. When tested on these Ethiopian strains on mice, unlike in other regions, the majority had resistance to 0.0001% dapsone in mice and not to a higher degree [16]. In conclusion, the findings of the prevalence of relapses of secondary dapsone resistance were not high. However, it only occurs in special circumstances in the most ideal setting such as in Malaysia and does not occur in all patients [26].

Table 1. ***Randomized Controlled Trial*** **Dapson as Chemoprophylaxis of Morbus Hansen [19]**

No.	Year	Country Author reference	Duration of trial in years	Treated	Controls	Disease rate in treated group per 1000 population	Disease rate in control group per 1000 population	Rate of effiacy	NNT
1	1969	India, Wardekar	4.5	12754	12931	0.24	2.78	99%	393
2	1976	India, Noorden	3.5	1000	1000	109.00	0.24	34%	27

Acedapson

In 1967-1970, acedapsone was used intramuscularly as an effort to eliminate Morbus Hansen in the community as a chemoprophylaxis program in Micronesia. The research was conducted by Russel in the endemic area of Morbus Hansen in Micronesia where the Morbus Hansen rate reached 41/1000 population. Study subjects were given 225 mg of acedapsone every 75 days for 3 years and reported that the incidence of new cases decreased in the first year, and no new cases were found in the second and third years, it showed in **Table 2**. However, 5 years later, the number of new Morbus Hansen cases increased again. The failure of chemoprophylaxis is thought to be the result of inadequate therapy in the case of sulfone-resistant Morbus Hansen [27].

There were two studies conducted by Neelan, namely in 1983 and 1986 which evaluated the effectiveness of using acedapsone as chemoprophylaxis against MH type MB. The dose of acedapsone used is 150-225 mg every 10 weeks for 7 months. These two studies showed that acedapsone significantly prevented the emergence of new cases of Morbus Hansen within 3.5 years and 4.7 years. Noordeen in 1977 also conducted a similar study on 700 respondents with 350 respondents given intramuscular acedapson with the same dose. divided into 3 times giving every 10 weeks [28].

Table 2. *Randomized Controlled Trial* Acedapson as Chemoprophylaxis for Morbus Hansen [19]

No.	Year	Country Author reference	Duration of trial in years	Treated	Controls	Disease rate in treated group per 1000 population	Disease rate in control group per 1000 population	Rate of effiacy	NNT
1	1977	India, Noorden	2	350	350	51.40	91.43	44%	25
2	1986	India, Neelan	4	280	280	46.42	107.14	54%	17

Rifampin

Rifampicin is a strong bactericidal antibiotic against Mycobacterium leprae, which is the cause of Morbus Hansen, and a single dose of rifampin can prevent the occurrence of Morbus Hansen disease in people who come in contact with patients with Morbus Hansen. Single-dose rifampin provides fairly good effectiveness as chemoprophylaxis by protecting 60% for 2 years, based on research results in Bangladesh [28].

In a study conducted by COLEP, it was shown that chemoprophylaxis with SDR (single dose rifampicin) was most effective in relatively low-risk contact groups such as the contact group with paucibacillary patients, contacts with patients who did not live at home or who had no blood relations. It is estimated that the infected contacts in this group were exposed to less, resulting in a lower bacterial load than those who had closer contact with the patient, making therapy with single-dose rifampicin more successful [29].

The study was conducted on people who had contact with the newly diagnosed Morbus Hansen patient, where interventions were given in the form of a placebo in one group and a single dose of rifampin in the other group, and the study subjects were followed for up to 6 years. The results of the above study indicate that the preventive effect of rifampin was only seen in the first two years of chemoprophylaxis therapy, additional preventive effects were not obtained after year 4 and year 6. This intervention was found to be most effective in the contact group of female patients, especially in neighbors and social contacts, where a trend towards an increased risk of Morbus Hansen transmission was obtained, followed by an increase in the effectiveness of a single dose of rifampin. In addition, there were also indications of an increase in the effectiveness of single-dose rifampicin in the contact group in patients who were included in the cluster of two or more Morbus Hansen patients at the time of the intervention [30].

A study conducted by Cartel in 1988 showed that rifampin haS a protective efficacy of 40-50% **(Table 3)**. Based on an analysis of costs, the combined expenditures between Morbus Hansen treatment with standard MDT (Multidrug Therapy) regimens and chemoprophylaxis with rifampin were more effective than treatment expenditures. Morbus Hansen with standard MDT alone without prophylaxis [30].

Table 3. Number of New Hansen Morbus Cases (6 Years of Follow Up) in the Contact Group based on Gender and Relationship with Patients and with Prophylaxis [20]

		Distance of new case to original index patients			
		Not close		Close	
		n	N per 100 contact groups (95%)	n	n per 100 contact groups (95% CI)
Placebo prophylaxis Sex index patient (n)	Female (166)	41	24.7 (18.2-33.5)	12	7.2 (4.1-12.7)
	Male (342)	28	8.2 (5.7-11.9)	27	7.9 (5.4-11.5)
Total		69	13.6 (10.7-17.2)	39	7.7 (5.6-10.5)
Rifampicin prophylaxis Sex index patient (n)	Female (177)	14	7.9 (4.7-13.4)	9	5.1 (2.6-9.8)
	Male (317)	29	9.1 (6.4-13.2)	25	7.9 (5.3-11.7)
Total		43	13.6 (10.7-17.2)	34	6.9 (4.9-9.6)

Another study by Bakker and friends was carried out on five islands in Indonesia that are endemic to Morbus Hansen. A total of 3.965 individuals were given rifampin prophylaxis (600 mg rifampin in adults, 300 mg rifampin in children) twice at 3-month intervals and then followed for 6 years. All samples were divided into three groups, namely the contact group for Morbus Hansen patients, the risk group (blanket group), and anyone (the control group). After being followed for three years, the Morbus Hansen incidence rate in the blanket group was significantly lower than the control group, but there was no significant difference between the contact group and the control group). Rifampin administration in the blanket group was effective in preventing Hansen's Morbus with the effectiveness of 75% [30].

A study conducted on five hyperendemic Indonesian islands Morbus Hansen showed that chemoprophylaxis with rifampin in the entire population was more effective than interventions for close contact with patients only [31]. This approach could be considered in areas where Morbus Hansen is highly endemic with an increased risk of transmission and intervention. this can be done at the hamlet, village, or wider scope.

Conclusion

Prophylaxis against Morbus Hansen is mainly given to those who had contacts with Morbus Hansen patients. Prophylaxis as dapsone, clofazimine, and rifampin is effective in lowering the risk of the incidence of Morbus Hansen disease in individuals had

contiguity with Morbus Hansen patients. Furthermore, research needs to confirm drug prophylaxis for lowering risk who had contact with Morbus Hansen.

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