INVESTIGATION

Adverse effects of alternative therapy (minocycline, ofloxacin, and clofazimine) in multibacillary leprosy patients in a recognized health care unit in Manaus, Amazonas, Brazil*

Efeitos adversos das drogas (minociclina, ofloxacina e clofazimina) utilizadas no esquema alternativo para pacientes com hanseníase multibacilar, em unidade de referência, Manaus, Amazonas, Brasil

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Abstract: BACKGROUND: After the introduction of the multidrug therapy, there was a decline in the coefficients of prevalence and detection of new cases of leprosy. However, the records of drug resistance and relapses are threatening factors in leprosy control. Hence, new alternative schemes and monitoring of adverse effects to avoid treatment abandonment are important considerations. OBJECTIVE: Describe the side effects of a multidrug regimen containing minocycline, ofloxacin, and clofazimine in multibacillary leprosy patients.
METHODS: We conducted a prospective, descriptive, and observational study with multibacillary patients, including cases of intolerance to standard MDT and relapses. The study was carried out at Fundação Alfredo da Matta (Alfredo da Matta Foundation), in Manaus, Amazonas, from April 2010 to January 2012. The patients received alternative therapy, which consisted of daily self-administered doses of 100mg of minocycline, 400 mg of ofloxacin, and 50mg of clofazimine and a supervised monthly dose of 300mg of clofazimine for six months, followed by eighteen months of daily doses of ofloxacin 400mg, clofazimine 50mg, and a supervised monthly dose of clofazimine 300mg. Results: Twenty-one cases were included. Mild and transitory side effects occurred in 33.3% of patients. Of the total episodes, 45.9% were attributed to ofloxacin and they included abdominal pain, nausea, vomiting, headache, and insomnia; 21.6% were due to clofazimine, with 100% of patients presenting skin pigmentation. The mean time for the development of adverse effects after beginning the therapy was 15.2 days. CONCLUSION: All patients tolerated the drugs well, and compliance was satisfactory, with no serious events. Unlike other standard MDT studies had shown, no treatment was stopped due to side effects. Nevertheless, patient follow-up and studies with bigger samples are necessary to guarantee the efficacy and safety of the alternative regimen as a second-line scheme in multidrug therapy.
Keywords: Adverse drug reaction reporting systems; Drug therapy, combination; Leprosy; No-observed-adverse-effect level

Resumo: FUNDAMENTOS: Após introdução do esquema poliquimioterápico padrão, houve declínio nos coeficientes de prevalência e detecção de casos novos; entretanto, os registros de resistência medicamentosa e recidivas representam ameaça para o controle da hanseníase. Dessa forma, a proposição de novos esquemas alternativos e a necessidade de monitorar efeitos adversos são importantes para evitar o abandono do tratamento. OBJETIVO: Descrever efeitos adversos do esquema alternativo contendo clofazimina, ofloxacina e minociclina em pacientes com hanseníase multibacilar. MÉTODOS: Estudo prospectivo, descritivo e observacional de casos multibacilares, incluindo recidivas ou intolerância à poliquimioterapia padrão, realizado na Fundação Alfredo da Matta, Manaus, Amazonas, de abril de 2010 a janeiro de 2012. Os indivíduos receberam a terapia composta de doses diárias auto-administradas de 100mg de minociclina, 400mg de ofloxacina e 50mg de clofazimina e mensais supervisionadas de 300mg de clofazimina por seis meses, seguidas de 18 meses de doses diárias de ofloxacina 400mg, clofazimina 50 mg e supervisionadas mensais de clofazimina 300mg. Resultados: 21 pacientes foram incluídos. Efeitos adversos leves e transitórios foram observados em 33,3% dos pacientes; 45,9% foram atribuídos à ofloxacina, como dor abdominal, náuseas, vômitos, cefaléia e insônia; 21,6% foram associados à clofazimina, com relatos e observação em 100% dos pacientes de hiperpigmentação cutânea. O tempo médio de desenvolvimento das reações adversas a partir do início do esquema foi de 15,2 dias. CONCLUSÃO: A adesão e regularidade ao esquema foram satisfatórias, com boa tolerabilidade, sem casos de interrupção ao tratamento. Todavia, há necessidade de acompanhamento dos indivíduos e aumento do número amostral para garantir a eficácia e segurança em longo prazo.
Palavras-chave: Hanseníase; Nível de efeito adverso não observado; Quimioterapia combinada; Sistemas de notificação de reações adversas a medicamentos

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INTRODUCTION

Multidrug therapy (MDT) was responsible for a decline in leprosy cases in Brazil in the last decades. However, the emergence of specific first-line drug resistance is associated with occurrence of relapses, bacillus persistence, and maintenance of the leprosy chain of transmission.[1]

Since there is no primary prevention of leprosy, it is currently known that multidrug therapy and organized health services constitute important strategies for interrupting the bacillus chain of transmission and eradicating the disease. Therefore, it is necessary to monitor the adverse effects of anti-leprosy drugs to diagnose and prevent their occurrence.[2]

The scarcity of studies proposing criteria for alternative drug schemes and the effectiveness and tolerability of second-line drugs in comparison with standard MDT (MDT/WHO) contributed to the development of this study. There is research involving isolated drugs and a combination of drugs with bactericidal activity. However, there is no research involving these three components: ofloxacin, minocycline, and clofazimine. Four to 8% of the adverse reactions observed in a review were related to ofloxacin and minocycline. Most of these events involved the gastrointestinal system (nausea, vomiting, abdominal pain, and diarrhea).[3]

OBJECTIVE

This study aims at describing the side effects of a multidrug regimen consisting of minocycline, ofloxacin, and clofazimine in multibacillary (MB) leprosy patients.

MATERIALS AND METHODS

Patients

A prospective, observational study with multibacillary leprosy patients, including cases of intolerance to standard MDT and relapse cases, was carried out at Alfredo da Matta Foundation, in Manaus, Amazonas, from April 2010 to January 2012. During this time period, 21 patients were registered and followed. Inclusion criteria were either gender; age ≥18 years; individuals diagnosed with leprosy clinically classified as borderline-borderline (BB), borderline-lepromatous (BL), and lepromatous (LL), following the classification criteria by Ridley and Jopling (1966); bacterial index ≥ 3+ somewhere. Exclusion criteria were individuals with any other chronic diseases, age ≥ 65 years, pregnant or breastfeeding women, and indigenous people. All patients signed the consent form.

Chemotherapy

Self-administered daily doses of 100mg of minocycline, 400 mg of ofloxacin, and 50mg of clofazimine and a supervised monthly dose of 300mg of clofazimine for six months, followed by eighteen months of self-administered daily doses of ofloxacin 400mg and clofazimine 50mg and a supervised monthly dose of clofazimine 300mg.

Examinations before and during trial

The patients were submitted to dermatological examination, skin biopsy, and harvesting of material for smear to determine bacterial index (BI), and histopathological tests. Physical disability evaluation was performed at baseline through neuromotor assessment, during which peripheral nerve involvement (thickened and/or painful), areas of hypo/anesthesia detected by the technique of Semmes-Weinstein monofilaments, trophism, muscle strength detected by VMT (Voluntary Muscle Testing), and corneal sensitivity were recorded. The changes found were recorded based on disability grade, corresponding to the disability grade before treatment (DGBT).

During treatment, patients were seen monthly by a dermatologist in the outpatient department, and every adverse effect, therapeutic decision, and leprosy classification was added to their personal record. All other diagnoses were based on clinical signs and symptoms. Laboratory assessments were done before starting the alternative scheme and on the 30th, 60th, and 90th days of treatment. Tests included full blood count, blood biochemistry, and coprological studies. Gastrointestinal manifestations were defined as presence of one or more of these findings: nausea, diarrhea, vomiting, dysphagia or dyspepsia. Liver abnormalities were defined as any alteration in liver function tests with or without clinical evidence of jaundice, malaise, and other symptoms. One or more of these had to be present: serum aminotransferases (N: 10-40U/L), gama-glutamyltranspeptidase (N: 10-55 for male and 5-53 U/L for female), and alkaline phosphatase (N: 40-125 U/L) were taken as abnormal when they were twice the upper limit of normal. Total bilirubin levels greater than 1.2 mg/dL were considered abnormal. Dizziness was defined as one or more of these symptoms: faintness, light-headedness, loss of balance, sense of "spinning", and a vague "spaced-out" feeling. Hypersensitivity reaction was defined as one or more of these symptoms: runny nose, rashes, itchy skin, watery and itchy eyes, and angioedema. Skin reactions were defined as the following: skin rashes or exanthematous eruption, either localized or generalized, discoloration, and ichthyosis. Constitutional symptoms were fever, malaise, headache, insomnia, and no hunger.

Statistical analysis

We performed preliminary standard descriptive analyses by calculating measures of location, dispersion, and structure of tables and graphs, in addition to tests to verify data adherence to normal distribution. Quantitative variables were compared using the Student's t-test and Mann-Whitney test. The relationship between qualitative variables was observed based on the difference between proportions, calculated using the Fisher's exact test.

For statistical analysis, the software packages used were SPSS (Statistical Package for the Social Sciences), version 16.0; Epi Info, version 3.5.3; and the program R 2.11. The significance level (alpha) was 0.05, and confidence coefficient was 95%.

A limiting factor was the insufficient supply of minocycline by the Ministry of Health aggravated by its unavailability for purchase in the city from April to December 2011, which led to minocycline manipulation in pharmacies.

RESULTS

Preliminary results demonstrated promising effects. Twenty-one patients were included and analyzed for adverse effects, 17 (80.9%) were males and 04 (19.1%) were females. Of the patients undergoing an alternative regimen, 03 (14.3%) corresponded to cases of intolerance to standard MDT and 18 (85.7%) to cases of relapse.

The reasons for recommending the alternative regimen, regarding cases of drug intolerance, were the following: 01 case (4.7%) of intolerance to dapsone, 01 case (4.7%) of flu-like syndrome due to rifampicin, and 01 case (4.7%) of intolerance to dapsone and rifampicin, with drug-induced hepatitis, gastrointestinal manifestations, and enzymatic changes in liver function, which may increase up to twice the normal value.

As for adverse effects, all of the patients (100%) showed cutaneous hyperpigmentation, 07 patients (33.3%) had mild and transitory effects, including constitutional, gastrointestinal, hematological, liver, and renal/bladder symptoms or signs. The mean (+/- SD) time for the development of adverse effects after starting therapy was 15.2 + 25.6 days, except for skin pigmentation. There were no records of moderate or severe laboratory abnormalities indicating that treatment should be discontinued. Mild and transitory adverse effects, of low clinical significance, were resolved with administration of symptomatic drugs such as antiemetics, analgesics, and antihistamines.

Although discoloration and ichthyosis caused by clofazimine are the most common adverse effects of alternative schemes, like the MDT, some adverse effects could be attributed to two or even three drugs.

Considering these three drugs together, a total of 37 adverse effects were found. Twelve (32.4%) of these adverse effects corresponded to constitutional complaints: 03 reports of fatigue, 02 reports of myalgia, 03 reports of arthralgia, 01 report of headache, 03 reports of insomnia; 10 (27%) were recorded as cutaneous and ocular changes: 02 reports of rash, 06 cases of xeroderma, and 02 reports of burning eyes; 04 (10.8%) corresponded to haematological disorders: 04 cases of eosinophilia; 02 (5.4%) were related to liver changes: 02 cases of increase in transaminases (AST and ALT); 08 (21.6%) consisted of gastrointestinal disorders: 03 cases of abdominal pain, 02 reports of nausea, 01 case of vomiting, 01 case of diarrhea, 01 case of weight loss; 01 (2.7 %) corresponded to urinary/renal disorder: 01 case of increase in urea and creatinine levels; as shown in Chart 1.

Leprosy reactions, type 1 (reversal) and type 2 (erythema nodosum leprosum), were diagnosed in 05 patients (23.8%) during treatment, 04 (80%) of whom had erythema nodosum leprosum, and 01 (20%) had reversal reaction and acute varicella infection concomitantly. Onset of reactional leprosy occurred 6 months after initiating the alternative scheme. The reactions

CHART 1: Side-effects of the alternative scheme in leprosy patients

System	Side-Effects		Total
General	Fatigue	3	12
	Myalgia	2	
	Arthralgia	3	
	Headache	1	
	Insomnia	3	
	Itching	2	
Cutaneous and Mucosal	Xerosis	6	10
	Burning eyes	2	
Hematologic	Eosinophilia	4	4
Liver	Increase transaminases	2	2
Gastrointestinal	Abdominal pain	3	8
	Nausea	2	
	Vomiting	1	
	Diarrhea	1	
	Hyporexia	1	
Renal	Increased Urea and Creatinine levels	1	1
TOTAL			**37**

were varied and not included as adverse effects, because of the excellent response to corticosteroids.

Other 03 cases (14.2%) were confounding in the frame of side effects. They included concomitant treatment for tuberculosis in 01 case (4.7%); 01 case (4.7%) of erythema multiforme, caused by amoxicillin used to treat an upper respiratory tract infection; and 01 case (4.7%) of scabies, for which ivermectin was used. As the constitutional and gastrointestinal symptoms presented by such patients improved, they were not considered cases of reactions to alternative medication.

Leprosy reactions were observed and treated in 23.8% of patients during the alternative treatment. There was a good clinical response after administration of prednisone and thalidomide. It should be noted that the proportion of reactive episodes should increase with expansion of the sample size. These reactions range from mild to very severe and may compromise therapeutic response, mainly because of overlapping clinical manifestations.

Among the patients, 05 individuals (23.8%) completed treatment, only 01 was still using minocycline at the time of data consolidation. The mean follow-up time was 13.7 + 7 months, ranging from 4 to 24 months. Sixteen patients (76.2%) are still undergoing the alternative treatment and being monitored for leprosy reactions, primary and secondary drug resistance, and side effects.

Regarding compliance with the alternative scheme, it was found that 14 patients (66.6%) had at least 12 doses in 12 months and that 50% of the individuals had already completed 16 of the 24 recommended doses. Only 01 patient abandoned treatment in the 9th month, due to change of address to an inner city. The patient was located and brought back six months later. This patient restarted the alternative regimen during a reactional episode of erythema nodosum leprosum and is currently being treated with thalidomide and receiving the 8th dose of the alternative scheme, showing clinical improvement and bacterial index (BI) reduction.

DISCUSSION

Concerning the adverse effects of the standard regimen, although the WHO defends that there are no toxic effects or that these effects are very rare and can be overcome with minor adjustments to medication, we found that several authors reported cases of rash, thrombocytopenic purpura, hepatitis, flu-like syndrome, hemolytic anemia, shock, respiratory failure and acute renal failure after rifampin, psychotic reactions, Dapsone syndrome, jaundice, agranulocytosis and methemoglobinemia after dapsone, and especially skin changes associated with clofazimine.[2,3,4,5]

In our study, we found that 07 (33.3%) patients presented adverse effects to the alternative drug scheme: a total of 37 signs, symptoms and/or abnormalities in laboratory tests. Analysis of 37 clinical and secondary manifestations to alternative drugs revealed that 17 (45.9%) complaints and laboratory abnormalities were probably caused by ofloxacin, mainly gastrointestinal, liver, and constitutional symptoms; 08 (21.6%) corresponded to itching and ichthyosis due to clofazimine; and skin hyperpigmentation, the most frequent alteration, was attributed to clofazimine and present in all of the patients (100%). Other 12 (32.4%) non-specific manifestations could not be isolated or associated with only one drug of the regimen, being common to the three drugs. There was no specific complaint that could be associated with minocycline. Also, there were no reports of adverse effects leading to interruption of the alternative treatment.

Data on the adverse effects of alternative antibacterial agents of the fluoroquinolone class, such as ofloxacin, varied from 4 to 8% in a sample of 30,000 records. It was necessary to discontinue therapy in 1 to 2.6% of patients. The main events involved the gastrointestinal tract (nausea, vomiting, diarrhea, abdominal pain) in 1-5% of patients, followed by events involving the central nervous system (dizziness, headache, and insomnia) in 0.1 to 0.3% of patients, and the skin in 0.5 to 2.2%. Liver enzyme elevation occurred in 1.8 to 2.5% of patients, eosinophilia in 0.2 to 2%. Most of the adverse effects were mild and temporary. It was necessary to interrupt treatment with the drug in a few cases.[5,6,7,8]

In other studies, it was found that most of the adverse events were classified as constitutional, cutaneous, and gastrointestinal disorders, in a descending order.[4,6,7,8,9]

Regarding the use of minocycline, pigmentary skin changes are the main effects and they include erythema multiforme; the bluish appearance of pigmented lesions in the skin and oral mucosa; soft-tissue pigmentation; and stains on primary and permanent teeth, skin, nails, bones, thyroid, mucosa, and sclera. Prolonged use, for over a year, can cause drug-induced hepatitis. Although the hepatotoxicity of tetracyclines was described shortly after their introduction in 1950, fewer than 200 cases have been reported in the literature.[6,10,11]

Clofazimine, a dye known to cause skin pigmentation, which is aggravated by sun exposure and ichthyosis, caused side effects in 100% of patients. It may also cause gastrointestinal symptoms, but no major effects at a dosage of 50 to 100mg/day.[2,12,13,14]

The time of onset of signs and symptoms secondary to drugs, usually two weeks after starting the alternative treatment, is corroborated by studies and clinical trials on ofloxacin and minocycline. During a

six-month study on minocycline carried out with patients with lepromatous leprosy, it was found that side effects such as vertigo, abdominal pain, and diarrhea were experienced only in the first week of treatment in a few patients, in addition to generalized light brown and blue pigmentation around old lesions.[6,10]

Thus, an alternative regimen combining clofazimine, minocycline, and ofloxacin may be an effective treatment for leprosy in these situations, especially in cases of resistance to MB-MDT drugs. The good tolerability of the regimen, observed in these twenty-one patients with no record of adverse effects leading to discontinuation of treatment, but only of limited and mild adverse effects, provides better compliance with treatment.

It should be noted that seven patients had a second relapse after completing two prior therapeutic regimens. Of these patients, three were treated with two cycles of 24 doses of MB-MDT. Nine patients (50%) had at least one previous cycle of 24 doses of MB-MDT. This can be explained by the severity of the disease, possibly associated with bacteria persistence, the patient's specific degree of immunity, drug resistance or reinfection.

Regarding costs and operationalization, minocycline and ofloxacin are high-cost antimicrobials, which is a limiting factor for expansion and use of the scheme. Its operationalization proved to be very similar to the standard regimen, with daily and monthly supervised doses. Supervised administration is still very important to ensure treatment, prevent disability, and control possible adverse effects, avoiding treatment abandonment or even helping patients who had interrupted treatment to resume it in a timely manner.[15,16,17]

Manifestation of drug-induced skin reactions and reversal reactions can generate diagnostic difficulties, even in referral centers. Thus, cases are undiagnosed and treated incorrectly, with maintenance of corticosteroids unnecessarily or, in severe cases, with a delay in introducing corticosteroids when they are indicated, causing serious changes, deformities and disabilities. It should be noted that even when appropriate treatment is adopted timely and strict follow-up is performed, disabilities may emerge, for clinical, therapeutic, and laboratory response is idiosyncratic, depending on each individual's immunity against the bacillus.[16]

The current multidrug regimens containing bactericidal drugs against *M. leprae* cause early destruction of most bacilli. However, complete removal of fragments of bacilli depends on cellular immunity, which is depressed or absent in multibacillary leprosy patients, causing risk of erythema nodosum leprosum and manifestation of disability.[15,17]

Leprosy can cause great physical and psychological suffering in affected patients; therefore, a multidisciplinary approach with measures to prevent disabilities, encourage adherence to treatment, and to fight social stigma is fundamental.[16,18]

CONCLUSION

The scarcity of controlled studies on the adverse effects of a combination of these three drugs - clofazimine, ofloxacin, and minocycline - demonstrates the importance of monitoring patients undergoing alternative therapies to treat leprosy. If patients are properly informed about the common adverse reactions (ADRs) and advised to report to their health care provider if and when ADRs occur, and if they are properly informed about the benefits of the alternative scheme, ADRs may be managed with supportive treatment only, with no need for replacing the suspected drug.

Ofloxacin caused most of the adverse effects, and clofazimine was associated with 100% of the cases of skin pigmentation. The alternative therapy showed similar feasibility and operationalization when compared with MB/MDT. There was good tolerability and compliance.

Relapse cases after two courses of MB/MDT lead to suspected drug resistance, severity and complexity of the disease. Nevertheless, patient follow-up and new studies are necessary to guarantee the efficacy and safety of the alternative regimen as a second-line drug scheme. ❑

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