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Short Communication

Adverse events in patients with leprosy on treatment with thalidomide

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Abstract

Introduction: Thalidomide, used to treat erythema nodosum leprosum (ENL), is associated with severe adverse events (AEs) and is highly teratogenic. **Methods:** A cross-sectional study was conducted on thalidomide-treated patients with ENL. AEs and selected variables were investigated through interviews and assessment of medical records. Odds ratios with 95% confidence intervals were estimated via logistic regression. **Results:** Peripheral neuropathy symptoms and deep vein thrombosis (DVT) were the most common AEs reported. Although women of reproductive age used contraceptives, <50% of patients reported using condoms. Polypharmacy was associated with all endpoints, except DVT. **Conclusions:** Pharmacovigilance is crucial to prevent harmful thalidomide-associated AEs.

Keywords: Thalidomide. Leprosy. Adverse events. Pharmacovigilance. Drug safety.

Thalidomide was used as a sedative, hypnotic, and antiemetic in pregnant women with nausea. After a few years of use, approximately 10,000 teratogenicity cases associated with thalidomide use during pregnancy were reported in 46 countries, resulting in its withdrawal in the early 1960s[1]. Despite this tragedy, in 1969, Sheskin[2] prescribed thalidomide as a sedative to a patient with erythema nodosum leprosum (ENL), and reported a rapid and dramatic clinical response. The efficacy of thalidomide in ENL was confirmed in a double-blind clinical trial carried out by the World Health Organization (WHO)[3]. In 2015, there were 174,608 cases of leprosy in the world, of which 23,995 were in Brazil, making it the country with the second highest prevalence after India. Of the new cases registered, approximately 70% were multibacillary leprosy, which may manifest as ENL, or type 2 reaction, and require thalidomide treatment[4].

After sedation, peripheral neuropathy is the most frequently reported thalidomide-associated adverse event (AE). Teratogenic effects are characterized by severe fetal limb defects and internal organ deformities[5,6]. After the phocomelia epidemic caused by thalidomide in Europe in the 1960s, several countries recommended drug vigilance, as part of the WHO Programme for International Drug Monitoring, based on the spontaneous reporting of AEs. Nevertheless, underreporting is a well-known problem of this method which may therefore fail to ensure drug safety[7]. In Brazil, few studies focusing on thalidomide safety have been conducted. The aim of this study was therefore to estimate the frequency of AEs in thalidomide-treated patients with ENL and to determine associated factors.

This cross-sectional study was conducted in a public referral hospital for infectious diseases in Minas Gerais State, Brazil. All patients (≥18 years) treated for ENL with thalidomide between July and October 2016 were invited to participate. Interviews were conducted once with each patient using a previously tested standardized questionnaire and medical records were reviewed to supplement the interview information. Data were collected until 12 months preceding the interviews. Each AE was registered only once for each patient, regardless of the frequency it appeared in the medical record. An AE was defined as any undesirable event reported by the patient during the interview or registered in the medical records.

Seven key endpoints with clinical relevance in leprosy and thalidomide treatment, including paresthesia, weakness and

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cramps (peripheral neuropathy), permanent neuropathy, deep vein thrombosis (DVT), edema, and the number of AEs, were selected for analysis. Symptoms identified from neurological evaluation of the patients were also recorded. Exposure variables including sociodemographic (sex, age, city of origin, education, and family income) and clinical and therapeutic characteristics (comorbidities, use of other drugs/polypharmacy, and information regarding thalidomide treatment) were considered. Polypharmacy was defined as the concomitant use of ≥5 medications, including thalidomide.

Descriptive analysis of AEs and exposure variables was conducted through absolute and relative frequencies. Means were used as cutoff values to categorize continuous variables. Logistic regression was employed for both univariate and multivariate analyses. Peripheral neuropathy symptoms (paresthesia, weakness, and cramps), permanent neuropathy, DVT, edema, and the mean number of AEs per patient were compared with sociodemographic and clinical variables. The strength of the association between AEs and selected exposure variables was estimated using odds ratios (ORs) with 95% confidence interval (CI). The independent effect of selected variables on AEs was assessed via logistic multivariate analysis. Variables included in the initial model consisted of those statistically associated with an AE in the univariate analysis ($p < 0.20$). Modeling was initially done with all variables followed by sequential deletion to assess the statistical significance of each one, and only those with $p < 0.05$ were retained in the final model. A likelihood ratio test was used to compare models, and the goodness-of-fit was assessed via Hosmer-Lemeshow test. All analyses were performed using SAS software, version 9.4 (SAS Inc., Cary, NC, USA).

This study was approved by the Ethics Research Committees of the participating institutions (*Universidade Federal de Minas Gerais*: no. 54594916.4.0000.5149, and referral hospital: 54594916.4.3001.5124) and in keeping with the Helsinki Declaration of 1964, as revised in 1975, 1983, 1989, 1996, and 2000. Participation was voluntary, ensuring confidentiality concerning the information collected.

A total of 110 patients were interviewed. Patients presented between 2 and 20 AEs (mean = 11 events per patient). During the interviews, patients reported 1,356 AEs, whereas 1,278 were identified from medical records. The most frequent AEs reported during the interviews were dry skin, paresthesia, drowsiness, weight gain, and weakness, in this order. The most frequent AEs identified from medical records were pain, paresthesia, dry skin, infections, and lower limb edema (**Table 1**). No cases of teratogenicity were reported.

The most commonly reported neurological symptoms were loss of sensation in the lower (74.6%) and higher (53.6%) limbs, loss of strength in the lower (10.9%) and higher (40.9%) limbs, neuritis, and visual impairment.

Most patients were men (mean age = 47.8 years), and 10% of patients reported never having studied (illiterate group), 70% had an elementary education (some incomplete), 80% received up to two minimum wages as the monthly family income, 40% were retired, and 23.6% unemployed (**Table 2**).

The mean number of medical visits was nine per patient in the previous 12 months. The average length of treatment with thalidomide was 3 years and 76.4% of patients were treated for >1 year, which corresponds approximately to the duration of ENL. All patients had multibacillary leprosy and the most frequent comorbidities were arterial hypertension and diabetes mellitus. Two patients developed diabetes mellitus after starting thalidomide treatment. One case of diabetes secondary to corticosteroid use was identified from medical records.

Approximately 96% of patients had used other medications simultaneously with thalidomide, with a total of 680 prescription records. The most common drugs were prednisone (12.1%), antihypertensives (10.7%), medications for neuropathic pain (8.5%), antibiotics for multidrug therapy (MDT/WHO, 7.8%) used to treat leprosy, and anticoagulants (5.3%). The use of prednisone was recorded in 82 patients (74.6%). Polypharmacy was observed in 80 patients (72.7%).

Thalidomide dosage ranged from 100 mg twice weekly to 400 mg daily, according to the patients' needs. Approximately 37% of patients reported discontinuing thalidomide treatment for a period for some reason, leading to the reappearance of the characteristic ENL nodules. There were 36 hospitalizations recorded during the study period for ENL or necrotizing ENL and/or Lucio's phenomenon (52.8%), infection (19.4%), and DVT or suspected DVT (13.9%). Of 38 women, 23 (60.5%) reported using injectable contraceptives, seven (18.4%) had already undergone a sterilization procedure, and the rest did not use any contraceptive method as they were not of childbearing age. Only 34 (31.5%) patients, including men, reported using condoms.

The results of the univariate analysis are shown in **Table 2**. Age ≥47 years, family income <2 minimum wages, treatment duration of <1 year, comorbidities, and polypharmacy were associated with the AEs selected. The following were independently associated: sex with DVT, education up to elementary school and polypharmacy with ≥11 AEs, and polypharmacy with paresthesia, weakness, permanent neuropathy, and edema (**Table 3**). The goodness-of-fit of the final model was deemed satisfactory (p-value ≥0.05).

This study aimed to determine the frequency of AEs in thalidomide-treated patients with ENL based on data collected from the interviews and medical records of patients attending a referral public hospital for infectious diseases in Minas Gerais, Brazil. This hospital is the main health-service provider in this state, distributing approximately 14% of all thalidomide tablets annually destined to this state and accounting for approximately 5% of the national thalidomide production.

Our study revealed the large number and variability of AEs observed during thalidomide treatment ranging from nonspecific to specific events occurring more often within the first year of treatment. The frequency of AEs varied according to the source of information (self-report vs. medical records). In general, AEs recorded in medical charts were less frequent, which may result from underreporting of non-severe AEs. Therefore, the use of both sources may provide more accurate information regarding AEs.

TABLE 1: Main adverse events reported by patients and identified from medical records (≥10% in at least one source, n = 110).

Adverse event	Self-report n (%)	Medical record n (%)
Body as a whole		
Weight gain	73 (66.4)	1 (0.9)
Pain	61 (55.5)	93 (84.6)
Headache	42 (38.2)	12 (10.9)
Fever	36 (32.7)	52 (47.3)
Malaise	33 (30.0)	22 (20.0)
Tiredness	20 (18.2)	9 (8.2)
Infections	16 (14.6)	78 (70.9)
Weight loss	15 (13.6)	6 (5.5)
Nervous system		
Paresthesia	95 (86.4)	91 (82.7)
Drowsiness	85 (77.3)	5 (4.6)
Tremor	67 (60.9)	12 (10.9)
Anxiety/agitation	59 (53.6)	6 (5.5)
Dizziness	46 (41.8)	11 (10.0)
Insomnia	21 (19.1)	4 (3.6)
Fainting	15 (13.6)	1 (0.9)
Nervousness	14 (12.7)	3 (2.7)
Permanent neuropathy	0 (0.0)	42 (38.2)
Muscular skeletal system		
Weakness	68 (61.8)	27 (24.6)
Cramps	12 (10.9)	27 (24.6)
Skin and appendages		
Dry skin	105 (95.5)	88 (80.0)
Desquamation	54 (49.1)	31 (28.2)
Pruritus	25 (22.7)	25 (22.7)
Digestive system		
Constipation	40 (36.4)	6 (5.5)
Nausea	21 (19.1)	6 (5.5)
Increased appetite	12 (10.9)	0 (0.0)
Appetite loss	10 (9.1)	13 (11.8)
Cardiovascular system		
Tachycardia	34 (30.9)	4 (3.6)
Lower limb edema	25 (22.7)	70 (63.6)
Hypotension	19 (17.3)	2 (1.8)
Upper limb edema	11 (10.0)	27 (24.6)
Thrombosis†	7 (6.4)	10 (9.1)
Endocrine system		
Hyperglycemia	11 (10.0)	18 (16.4)
Special senses		
Loss of visual acuity	12 (10.9)	32 (29.1)
Cataract	2 (1.8)	27 (24.6)
Urogenital system		
Impotence	29 (26.4)	1 (0.9)
Teratogenicity†	0 (0.0)	0 (0.0)
Respiratory system		
Shortness of breath	3 (2.7)	12 (10.9)

†Thrombosis and teratogenicity were included because of their relevance as adverse events even though the frequencies observed were low.

TABLE 2: Univariate analysis for the comparison of adverse events and sociodemographic and clinical variables (n = 110).

Variables	n (%)	OR (95% CI)						
		Adverse events ≥11	Paresthesia	Weakness	Cramp	Permanent neuropathy	DVT	Edema
Sex								
Male	72 (65.5)	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Female	38 (34.6)	1.1	0.5	1.0	1.8	1.0	3.0	0.9
		(0.5–2.4)	(0.1–2.6)	(0.5–2.3)	(0.8–4.2)***	(0.5–2.4)	(0.9–10.3)**	(0.4-2.3)
Age (years)								
<47	55 (50.0)	1.0	1.0	1.0	1.0	1.0	1.0	1.0
≥47	55 (50.0)	2.8	5.4	1.9	1.0	2.6	2.2	2.3
		(1.3–6.1)*	(0.6–47.8)**	(0.9–4.3)***	(0.4–2.2)	(1.2–5.7)*	(0.7–7.7)	(1.0–5.4)**
Education								
HS + HE	22 (20.0)	1.0	1.0	1.0	1.0	1.0	1.0	1.0
NE + ES	88 (80.0)	3.5	0.8	1.1	1.2	2.5	1.3	1.6
		(1.3–9.8)***	(0.1–7.1)	(0.4–2.9)	(0.4–3.5)	(0.8–7.3)**	(0.3–6.3)	(0.6–4.4)
FI (min. wage)								
>2	19 (17.3)	1.0	1.0	1.0	1.0	1.0	1.0	1.0
≤2	91 (82.7)	2.6	2.6	1.1	1.3	1.1	1.1	2.8
		(0.9–7.6)**	(0.4–15.1)	(0.4–3.2)	(0.4–4.0)	(0.4–3.0)	(0.2–5.2)	(1.0–7.8)*
LTT (months)								
>12	84 (76.4)	1.0	1.0	1.0	1.0	1.0	1.0	1.0
≤12	26 (23.6)	3.5	†	1.6	1.0	1.3	0.6	1.4
		(1.3–9.1)*		(0.6–4.2)	(0.4–2.6)	(0.5–3.1)	(0.1–3.0)	(0.5–3.9)
Comorbidities								
AH	33 (30.0)	2.5	2.2	2.5	1.4	2.7	1.8	2.2
		(1.1–5.9)*	(0.3–19.8)	(1.0–6.5)**	(0.6–3.4)	(1.2–6.1)*	(0.5–6.1)	(0.8–5.9)***
DM	17 (15.5)	2.7	†	1.9	0.6	5.0	1.1	3.4
		(0.9–8.2)**		(0.6–6.2)	(0.2–2.1)	(1.6–15.6)*	(0.2–5.6)	(0.7–15.8)**
Polypharmacy	80 (72.7)	29.1	15.8	4.5	1.3	5.9	4.6	5.0
		(6.4–131.5)*	(1.8–141.7)*	(1.9–10.9)*	(0.5–3.4)	(1.9–18.4)*	(0.6–37.5)***	(2.0–12.3)*

†Indeterminate values. **OR:** odds ratio; **CI:** confidence interval; **DVT:** deep vein thrombosis; **HS:** high school; **HE:** higher education; **NE:** never studied; **ES:** elementary school; **FI:** family income; **LTT:** length of treatment with thalidomide; **AH:** arterial hypertension; **DM:** diabetes mellitus. Min. wage = BRL 880.00. *p-value <0.05; **p-value <0.10; ***p-value <0.20

TABLE 3: Final model of the multivariate analysis for adverse events to thalidomide (n = 110).

Variables	OR 95% (CI)					
	Adverse events ≥11	Paresthesia	Weakness	Permanent neuropathy	DVT	Edema
Sex						
Male	–	–	–	–	1.0	–
Female	–	–	–	–	3.0 (0.9–10.3)	–
Education						
HS + HE	1.0	–	–	–	–	–
NE + ES	4.4 (1.4–14.0)	–	–	–	–	–
DM	–	–	–	3.4 (1.1–10.9)	–	–
Polypharmacy	32.4 (7.0–149.8)	15.8 (1.8–141.7)	4.5 (1.8–11.0)	4.6 (1.4–14.7)	–	5.0 (2.0–12.3)

OR: odds ratio; **CI:** confidence interval; **DVT:** deep vein thrombosis; **HS:** high school; **HE:** higher education; **NE:** never studied; **ES:** elementary school; **DM:** diabetes mellitus. p-value <0.05 for all combinations showing values.

Patients with ENL require long-term treatment with multiple drugs, usually resulting in polypharmacy. Some of the AEs observed may have been caused by more than one of the drugs used by leprosy patients. MDT/WHO (combination of rifampicin, dapsone, and clofazimine) may be administered in combination with thalidomide to ENL patients[8]. Prednisone is also commonly used concomitantly with thalidomide in patients with leprosy. In combination with certain chemotherapies and corticosteroids, thalidomide raises the risk of DVT[6].

In our study, DVT was responsible for 14% of hospitalization cases. DVT occurred in 10 patients, showing a borderline higher association in female than male patients, but was not associated with the use of contraceptives. In another study, five of 25 patients with different diseases and four patients with ENL using other drugs (e.g., corticosteroids) simultaneously with thalidomide discontinued thalidomide treatment because of DVT. However, in that series, DVT occurred even when thalidomide was administered alone[9]. In our study, only one patient with DVT had been using thalidomide alone, and the other nine had used prednisone concomitantly.

Although peripheral neuropathy was not recorded, associated symptoms were, including paresthesia, numbness, tingling, burning, weakness, and cramps, and these should be carefully monitored during thalidomide treatment. Few cases of peripheral neuropathy have been reported during ENL treatment despite long-term use, possibly because of pre-existing neuropathies in certain ENL patients. Neuropathy is more likely to occur with higher doses of thalidomide, longer administration periods, and in older patients[10]. In our study, it was difficult to distinguish neurological ENL symptoms from AEs. However, studies have reported the association between peripheral neuropathy and thalidomide use in patients with multiple myeloma, cutaneous lupus erythematosus, and other diseases treated with thalidomide[11,12], in which the symptoms cannot be confused with thalidomide-associated peripheral neuropathy.

Thalidomide-associated AEs may be similar to ENL and leprosy symptoms. The clinical manifestations of leprosy are largely confined to the skin, upper respiratory system, eyes, testicles, and peripheral nerves with subsequent physical deformities and nerve damage, especially present in lepromatous leprosy (in which ENL is most frequently observed)[13]. Progressive nerve damage may result in muscle weakness and insensitivity, which were observed in 61.8 and 86.4% of patients, respectively. ENL-associated orchitis causes impotence, which was reported by 26.3% of patients. Patients with ENL are, in general, chronically fatigued and suffer from chronic pain and insomnia, which were reported by 18.2, 55.5, and 19.1% of patients, respectively.

The lepromatous form of leprosy is more common in men[10], in accordance with the higher number of men using thalidomide and the contraindications of thalidomide use in women of childbearing age, unless they are using effective contraception[14]. All women of childbearing potential in this study were using medroxyprogesterone. However, <50% of patients, including men, reported using condoms. This finding is a reason for concern, as warnings regarding the teratogenic potential of thalidomide appear to be focused on women. Male patients taking thalidomide should use barrier contraception, as thalidomide was shown to be present in semen[10]. However, studies confirming the association between teratogenicity and the presence of thalidomide in semen are still required.

Despite strict control on the use of thalidomide in Brazil during the last years, several new cases of malformation associated with thalidomide were identified in children born after 1965[15]. Fortunately, in this study, teratogenicity was not observed.

This study has some limitations. Participants were not representative of all patients with ENL in Brazil. Because of the cross-sectional design, AEs observed in this study cannot be indisputably attributed to thalidomide use. Despite this, our data may provide general insight into the safety issues concerning leprosy treatment, thus highlighting the need for effective pharmacovigilance to prevent harmful adverse events in patients.

Peripheral neuropathy and DVT are severe AEs associated with the use of thalidomide in patients with ENL. Patients with leprosy face social vulnerability and treatment limitations associated with this neglected disease. Furthermore, there is a need for multidrug regimens, the associated AEs of which may worsen the patients' quality of life. Female and male patients should be counseled about contraception methods and the appropriate use of thalidomide. Thus, pharmacovigilance is crucial for monitoring severe AEs and preventing avoidable harmful adverse events such as teratogenicity.

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