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Thalidomide control and use: are these appropriate to extend the use and mitigate the risk of teratogenicity in Brazil?

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Abstract *Drug utilization research to describe the control of thalidomide in Brazil and its use in Minas Gerais state. An online questionnaire was sent to the Brazilian federative units to collect data concerning distribution, dispensation, user registration, and thalidomide adverse events. Distribution (2011-2018) and dispensing (2015-2018) data in Minas Gerais were obtained through the pharmaceutical care management system. Analysis of variance and Tukey test were used for data comparisons. Of the 16 participating federative units, 100% and 50% used electronic distribution and dispensing systems, respectively, and about 43% registered users. Adverse event reporting systems were scarce. A 44% reduction was observed in the distribution in Minas Gerais for the period. Dispensing remained constant (mean 0.0004 DDD/1,000 inhabitants/day) and occurred mainly for erythema nodosum leprosum and multiple myeloma. Off-label use (2.2%) was increasing. Most users were male (mean age 56 years) and thirty percent of women were of childbearing age. Thalidomide surveillance is a public health challenge. Despite the increased use and mandatory control, there is no national standardization, and adverse event reporting is incipient.*

Key words *Thalidomide, Teratogens, Drug Utilization, Pharmacovigilance*

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Introduction

Thalidomide is a derivative of glutamic acid with analgesic, anti-inflammatory, immunomodulatory, and antiangiogenic properties. It was discovered in Germany, in 1953, and used mainly to relieve nausea in pregnant women[1]. In utero exposure to thalidomide led to the birth of babies with severe deformities, resulting in the withdrawal from the world market in 1961[2] and, in 1965, in Brazil[3].

In 1965, the physician Jacob Sheskin observed rapid clinical improvement in the lesions of patients with erythema nodosum leprosum (ENL) after the use of thalidomide[4]. A double-blind clinical trial conducted by the World Health Organization (WHO) in 1971 confirmed its effectiveness in ENL[5], and subsequent studies have shown promising results from the use of thalidomide for the treatment of infectious, autoimmune diseases and cancers[6]. In Brazil, its use is regulated by RDC 11/2011 of the National Health Surveillance Agency (ANVISA) for the treatment of ENL, idiopathic aphthous ulcers in people living with HIV, lupus, graft-versus-host disease (GVHD), multiple myeloma (MM) and myelodysplastic syndrome (MDS)[7]. Other indications of thalidomide are exceptionally provided for in the Resolution as off-label use[7], and its use has been observed in the country[8].

The thalidomide disaster in the 1950s and the increased use resulted in the adoption of strict measures to control access in some countries[9]. In 1998, the Food and Drug Administration (FDA) authorized the sale of thalidomide in the United States (U.S.), requiring the development of use monitoring programs[10]. The manufacturer established the Risk Evaluation and Mitigation Strategy - REMS®[9-12] program (initially System for Thalidomide Education and Prescribing Safety - STEPS®[9,10]), based on the isotretinoin and clozapine programs[9], to control prescription, dispensing, and use.

In Brazil, thalidomide is used mainly for the treatment of ENL and MM[13]. The country ranks second in the world for leprosy incidence (13%), with 67.7% of new cases can evolving to ENL[14]. The entire chain of production, distribution, dispensing, and notification of adverse thalidomide events is managed by the Unified Health System (SUS) and is regulated by RDC 11/2011, which determines, among others, control of dispensing centers and prescription, besides user registration[7].

The notification of thalidomide adverse events is mandatory[7] and must be carried out by VigiMed or the manufacturer's customer service. However, pharmacovigilance and control do not seem to be taking place properly. A study carried out in 2016 with patients undergoing ENL treatment in a sentinel hospital in Minas Gerais found essential discrepancies between the frequencies of medical records and (mandatory) notifications to ANVISA or the manufacturer in case of thrombosis and neuropathy associated with thalidomide[15]. Moreover, cases of fetal malformations with thalidomide embryopathy phenotype occurred after 1965[16-22].

The Ministry of Health is responsible for the planning and distribution of thalidomide to the federative units. However, there is a lack of studies describing thalidomide control systems and how the distribution, dispensing, and registration of users are effectively carried out. Moreover, in the scientific literature and official reports, no data concerning the number of users of the drug by therapeutic indication in the country have been released.

The study aimed to identify and describe the thalidomide control systems in the Brazilian federative units and characterize use in Minas Gerais, considering its teratogenic potential.

Methods

Study design

This is a descriptive study of drug utilization to evaluate Brazilian thalidomide control systems and use in Minas Gerais, consisting of: i) qualitative assessment of distribution, dispensation, organization of user registration and notification of adverse events in the 27 federative units and ii) qualitative and quantitative assessment of data on distribution, prescription and dispensing in Minas Gerais.

The Research Ethics Committee of the Federal University of Minas Gerais (COEP/UFMG) approved the study.

Data collection and variables

Management and control in Brazil

Data was collected using an online questionnaire (Google Forms), based on RDC 11/2011 and the pharmaceutical care management system in Minas Gerais. The questionnaire contained open-ended and closed-ended questions on user registration, distribution, and dispensation control (use of national or proprietary electronic sys-

tems, content, and data transmission) and system for notification of adverse events (e.g., content, monitoring and sending data to SUS entities).

The pilot study was carried out by sending the questionnaire to the Pharmaceutical Care Department of the State Health Department (SES) of Minas Gerais to test the instrument's adequacy and data collection procedures. Telephone contacts identified those responsible for Pharmaceutical Care in all SES, and the questionnaire was sent by e-mail. Up to six telephone contact attempts were made, and the questionnaire was sent up to three times.

Use in Minas Gerais

Thalidomide distribution and dispensing data from the pharmaceutical care management system were made available by the SES of Minas Gerais. Distribution data, representative of all dispensing units in the state, from January 2011 to November 2018, included the date of the medication request, the name of the regional health department, and the number of pills. Dispensing data were analyzed from January 2015 to December 2018 and contained the dispensation date; name, regional health department, and the municipality of the health unit; identification code, date of birth, gender and municipality of residence of the patient; International Classification of Diseases (ICD-10)/therapeutic indication; regional council and prescriber's specialty, and amount dispensed. Off-label use was characterized by the dispensation of thalidomide for treatment indications other than those approved by RDC 11/2011 (ENL, idiopathic aphthous ulcers, lupus, GVHD, MM, and MDS).

Distribution and dispensing data were expressed in Defined Daily Dose (DDD)[23] and DDD/1,000 inhabitants/day, calculated using the formula: DDD/1,000 inhabitants/day=CMA (mg)*1,000/DDD*population*365 days, with CMA=mean amount (milligrams) of thalidomide in the period; DDD=defined daily dose of thalidomide (100mg) in the primary indication in adults (ENL)[23]; population=population of Minas Gerais estimated by the IBGE for 2015 (20,648,978 inhabitants).

Data analysis

Descriptive analyses were performed to characterize the variables using absolute and relative frequencies. Mean, standard deviation, and 95% confidence interval (CI) were calculated for distribution and dispensation data. The analysis of variance (ANOVA) was used to compare differences between the mean dispensation by users between 2015 and 2018, and multiple comparisons were based on the Tukey test, considering a significance level of 0.05. Data management and analysis were performed using the Statistical Analysis System (SAS), version 9.4.

Results

Management and control in Brazil

Sixteen (59%) federative units answered the questionnaire (Table 1). The South and Southeast regions achieved 100% participation, while North, Midwest, and Northeast obtained 28.6% (n=2), 50% (n=2), and 55.6% (n=5), respectively.

Nine (56.3%) secretariats do not register users or did not provide information. All reported using electronic systems (National Pharmaceutical Care Management System [Hórus] or proprietary system) for distribution. Eight secretariats (50%) do not have dispensing control systems and use Excel spreadsheets and control books (n=3), or the system is unknown or nonexistent (n=5). The other half reported using electronic dispensing control systems (Hórus) [n=2], proprietary systems [n=5], Hórus together with proprietary system and manual dispensing [n=1]).

Only one secretariat has its proprietary notification system, which provides patient data (name, date of birth, gender, address, ICD, clinical data and clinical development, concomitant drugs, and diseases), medication (name and batch number) and adverse events (event, severity, and date of occurrence), and it is possible to monitor its development, send it to ANVISA and other SUS entities. Units without notification sending systems (n=14) informed that they sent notifications to one or more institutions such as ANVISA, Ministry of Health, or the manufacturer.

Use in Minas Gerais

Distribution and dispensing

A total of 3,493,230 thalidomide tablets were distributed between January 2011 and November 2018, equivalent to 3,493,230 DDD or a mean of 0.0006 DDD/1,000 inhabitants/day (Table 2). A 44.3% reduction in distribution was observed in the period. Four of the 28 health regions were responsible for approximately 50% of the distribution (Belo Horizonte, 31.4%; Uberlândia, 8.0%; Coronel Fabriciano, 6.0%; Uberaba, 5.6%). The

others individually represented 4.0% or less of total distribution in the state.

Dispensing has remained relatively constant since 2016 (p-value> 0.05). In the 2015-2018 period, it represented 83.0% of the quantity distributed, corresponding to a mean of 0.0004 DDD/1000 inhabitants/day.

Table 1. Use of thalidomide user registration systems, distribution and dispensation control, and the adverse event reporting system in Brazilian federative units (n=16).

Characteristics (n=16)	n (%)
User registration	
Registers	7 (43.8)
Does not register	1 (6.3)
Not informed	8 (50.0)
Registration system	
Hórus	1 (6.3)
Hórus and proprietary system	1 (6.3)
Hórus and Excel	1 (6.3)
Excel	2 (12.5)
Proprietary system	1 (6.3)
Proprietary system and Excel	1 (6.3)
Nonexistent	1 (6.3)
Not applicable	8 (50.0)
Forwards data to the Ministry of Health	6 (37.5)
Does not forward data to the Ministry of Health	1 (6.3)
Unknown process of forwarding data to the Ministry of Health	1 (6.3)
Not applicable	8 (50.0)
Distribution	
Control system in place (yes)	16 (100.0)
No control system (no)	0 (0.0)
Distribution system	
Hórus	7 (43.8)
Hórus and proprietary system	1 (6.3)
Proprietary system	8 (50.0)
Forwards data to the Ministry of Health	4 (25.0)
Dispensation (n=16)	
Control system in place (yes)	8 (50.0)
No control system (no)	8 (50.0)
Dispensation system	
Hórus	2 (12.5)
Hórus, proprietary system and manual	1 (6.3)
Proprietary system	5 (31.3)
Control books and Excel spreadsheet	3 (18.8)
Unknown or nonexistent	5 (31.3)
Forwards data to the Ministry of Health	7 (43.8)
Notification of adverse event (n=16)	
Notification system in place (yes)	1 (6.3)
No notification system (no)	14 (87.5)
Unknown notification process	1 (6.3)
Forwards adverse events to SUS entities	15 (93.8)
ANVISA	10 (66.7)
Ministry of Health	8 (53.3)
Manufacturer	3 (20.0)
Other SUS entities	3 (20.0)

Source: Elaborated by the authors.

Users

Most users were male, aged 50 years or over (mean 56 years), with a registered clinical diagnosis, and resided in Belo Horizonte. A total of 506 women (10% of participants and 30% of women) were of childbearing age (between 10 and 49 years) (Table 3).

Diagnoses

Of the total dispensations (n=29,212) in the four-year period, most were for the treatment of ENL (54.5%), MM (27.3%), lupus (6.0%) and off-label uses (2.2%). Dispensations for aphthous ulcers, MDS, and GVHD together accounted for <1% of records. An increased number of dispensations for MM (127.9%) was observed, followed by lupus (81.1%), off-label uses (76.3%), ENL (34.7%), and MDS (15.8%). An improvement in the recording of diagnoses was noted, with a 99% reduction in the number of unknown data (Figure 1).

Off-label use

A total of 642 thalidomide dispensing records were verified for 39 different off-label uses. Behçet's disease (n=113), stomatitis (n=83), lichen (n=79), nodular prurigo (n=75) and lung diseases (n=71) represented more than half of the records.

Table 3. Characteristics of thalidomide users seen at dispensing units in Minas Gerais, 2015-2018 (n=4,625).

Characteristics	n (%)
Gender	
Male	2,802 (60.6)
Female	1,823 (39.4)
Childbearing age*	506 (10.9)
Age (years)	
≤9	13 (0.3)
10-49	1,474 (31.9)
≥50	2,941 (63.6)
Unknown	197 (4.3)
Nº of diagnoses	
1	3,346 (72.3)
2 or more	1,279 (27.7)
Municipality of residence	
Belo Horizonte	423 (9.1)
Uberlândia	254 (5.5)
Uberaba	138 (3.0)
Contagem	108 (2.3)
Montes Claros	103 (2.2)
Other (n=579)	3,599 (77.8)

*Childbearing age: 10-49 years.

Source: Minas Gerais Pharmaceutical Care Management System (SIGAF).

Table 2. Thalidomide distribution and dispensation in Minas Gerais, 2011-2018.

Period	Distribution		Dispensation	
	DDD	Records (n)	DDD	DDD/user (mean)*
2011	582,090	---	---	---
2012	433,410	---	---	---
2013	468,540	---	---	---
2014	462,120	---	---	---
2015	403,050	7,402	333,722	171.0
2016	327,090	6,721	298,369	329.7
2017	492,450	7,421	330,424	358.0
2018	324,480#	7,668	320,879#	379.7
Mean (SD)	436,654 (85,905)	7,303 (406.5)	320,849 (15,945)	---
95CI%	364,836-508,472	230.3-1,516	295,476-346,221	---

DDD=Defined Daily Dose (1 DDD thalidomide=100mg); SD=Standard Deviation; 95%CI=Confidence Interval. *P-value<0.0001 - Anova/Tukey test (the observed difference between the means is due to 2015 compared to 2016, 2017, and 2018). #January to November 2018.

Source: Minas Gerais Pharmaceutical Care Management System (SIGAF).

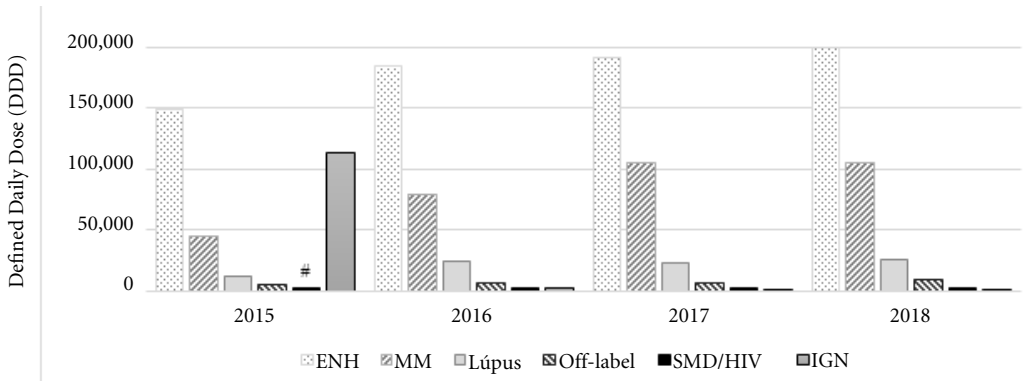

Figure 1. Dispensing of thalidomide (in DDD) for indication of medication in Minas Gerais, 2015-2018. #Corresponds to indications MDS/HIV/GVHD. IGN=Unknown Clinical Indication; DDD (100 mg) is calculated based on the main indication for the use of thalidomide (ENL).

Source: Minas Gerais Pharmaceutical Care Management System (SIGAF).

Prescriber's specialty

Information on medical specialty was not completed in 83.0% (n=24,229) of the dispensing records. Considering the completed records, thalidomide was prescribed by clinicians (61.5%), dermatologists (18.4%), and hematologists (10.3%). The rest (9.8%) were from 14 other medical specialties.

Discussion

The study evaluated the control structure of thalidomide in Brazil and its use in Minas Gerais. The increased indications for the use of thalidomide in the country and, to a lesser extent in the world, imposes the need for effective surveillance and control. The suspected cases of congenital malformations associated with its use, after 1965, elicits weaknesses in the control process[16-22].

Approximately 60% of the federative units' participation was secured in the diagnostic analysis of thalidomide control. The representativeness was lower in the Northern, Midwestern, and Northeastern regions, where leprosy detection rates were higher[24], which suggests inequalities in the thalidomide control and management infrastructure, and may reflect difficulties in monitoring use. Records of victims of the thalidomide syndrome of the third (2005-2010), fourth and fifth generations (after 2010) in Brazil[22], were concentrated in the Northeast region. The lack of response from some federative units in this region may be related to the lack of infrastructure or the fear of explaining possible weaknesses in the control process. In contrast, the Southeastern and Southern regions with the highest industrial and urban development (58.2% and 14.2% of the country's Gross Domestic Product, respectively) had 100% participation. It is assumed that these regions have an organizational structure that allows better management of processes, which may result in better control, but without reflecting the national reality.

The Ministry of Health is responsible for creating and maintaining the national register of thalidomide users, which must be carried out by the pharmaceutical care of the federative units[7]. Although most (6/8) of the secretariats report that the list of registered users is passed on to the Ministry of Health, data on the number and profile of users are not available in published official reports and cannot be accessed in the literature due to the scarcity of national studies on the use of that medicine.

The management and control approach seems to focus on the planning and distribution of thalidomide, considering the more frequent use of some means of control for this activity compared to dispensing. This shows that computerized systems to register drug dispensing are not yet a reality in Brazil[25]. Despite the availability

of Hórus as a pharmaceutical care management system in the country, its low use for managing distribution and, mainly, the dispensing of thalidomide, was observed. This system contains information on stock control, dispensing data, patient data, prescribers, and an indication of use[26]. However, many federative units seem to choose to develop and use their proprietary systems to manage their data.

National or proprietary computerized systems should be used, and there should be a flow of information for the construction of nationwide databases supporting pharmacovigilance actions, research, and health decision-making[25]. The Logistic Control System for Medicines (SICLOM) and the National System for the Management of Controlled Products (SNGPC) are examples of databases on drugs used to conduct studies of use and aid in monitoring the use of drugs in Brazil[27]. Thalidomide consumption records, containing user characteristics, such as gender and date of birth, can target pharmacovigilance to priority groups (e.g., patients with lupus, predominantly women of childbearing age, and older patients with MM at risk of developing neuropathy and thromboembolic events)[13] and facilitate research.

Thalidomide adverse events and technical complaints must be compulsorily notified to ANVISA by VigiMed[7]. Although a large part of the secretariats declared to report adverse events, a recent study showed underreporting of thalidomide adverse events to ANVISA (15 notifications in six years) compared to spontaneous reports to the manufacturer laboratory (n=23) and mainly to the records of adverse events (n=1,356) in medical records of patients with ENL within one year of treatment[15]. Notification forms should be accessible and straightforward, and professionals should be continuously trained to identify and report adverse events[28]. The flow of information with the generation of more reliable reports on adverse events is expected to improve with the replacement of Notivisa by VigiMed, used by the WHO collaborating center for international drug monitoring.

The program to control the use of thalidomide in the U.S., REMS®, was created and improved to avoid teratogenicity cases and is provenly effective[10-12]. RDC 11/2011 was established based on REMS® and showed similar control measures, such as limiting access to only registered pharmacies, prescribers, and eligible patients; instruction and counseling of patients; filling out informed consent; pregnancy tests; and warning labels about teratogenicity on the drug's packaging[7]. However, thalidomide control and use cannot be considered effective, due to the lack of consolidated user registry, adequate and fully functioning systems for dispensing, distributing, and reporting adverse events.

The control of the distribution of thalidomide in Minas Gerais is carried out exclusively by the pharmaceutical care management system, unlike dispensation. The highest distribution of thalidomide in the period (2011-2018) occurred in three of the four most populous municipalities in the state and with the highest number of leprosy cases. The reduction in distribution, mainly from 2011 to 2012 (25.5%), may reflect an improved use of the system, considering that it was initially implemented to manage resources and, subsequently, for effective control. Consequently, from 2012 to 2014, the distribution remained relatively constant. The reduced quantity distributed and dispensed in 2016 can be attributed to the drug's shortage in 2015, which was reflected in the following year. In 2017, an exacerbated growth was observed in the distribution, with no significant dispensation change compared to previous years. It can be inferred that the growth is due to the habit of increasing the stock after atypical situations of lack of medicines since the distribution and dispensation normalized in 2018.

The profile of thalidomide users corroborates the findings of other studies conducted in Brazil, showing a predominance of males, over 45 years of age and diagnosis of ENL[13,29]. The study identified a considerable percentage of dispensations for women of childbearing age, reinforcing the importance of strict dispensation control with pregnancy tests, guidance on contraception, and monitoring[7]. Besides users' characteristics, diagnosis completion in the databases provides relevant information about their profile, indicating patients in social vulnerability (with ENL[15]), predominantly older adults (undergoing MM), and women of childbearing age with lupus.

Educational approaches and pharmacovigilance are fundamental for preventing teratogenicity, as in the incident cases after 1965, attributed to the poor drug control[16-22,30]. Added to this is the low level of education of patients with ENL[29], increasing the risk of medication errors and adverse events due to difficulties in understanding the care needed for treatment. The use of appropriate language for patient guidance and monitoring are pharmacovigilance measures that can mitigate the risk of serious adverse events such as congenital malformations, thromboembolic events, and neuropathy.

The decrease in thalidomide dispensation (2015-2018) is in line with another study that showed a reduction in the number of prescriptions in 2011 compared to 2001[13]. The enactment of RDC 11/2011 and the approval of clinical protocols in 2011 may explain these results. In this study, the improvement in completing the pharmaceutical care management system's fields was the leading data quality influencer.

Although the increased dispensation was higher for MM, ENL continues to represent the main indication for thalidomide[13,31]. Leprosy is a compulsory notification disease in Brazil, second in the world concerning disease incidence (13%), second only to India (60%)[14]. In Minas Gerais, leprosy notification remained constant in the 2015-2018 period[24]. Comparatively, few epidemiological data are available for MM, a rare and incurable cancer that mainly affects older adults[32]. Therefore, it is a disease on the rise due to population aging. Thalidomide is the first-choice regimen for the treatment of MM in the SUS, its second main indication[13]. It is the second choice for the other indications, which are uncommon and have different dosing schedules, and justifies the slight increase in dispensations, such as for MDS (<1%) included in 2015.

The number of Brazilian thalidomide users is unknown, partly because only leprosy is a notifiable disease, the drug is the first choice for two of the six indications (ENL and MM), and unavailable official data.

The dispensation for off-label use of thalidomide is allowed by ANVISA in situations considered indispensable and as a last therapeutic alternative[7]. Increased off-label use was observed, although it still represents a small proportion compared to all dispensations, as previously noted[13]. This result should be represented with caution, since this increase may be due to the improved quality of completing diagnoses. On the other hand, this use is likely to be underreported due to requirements to justify exceptional use by the prescriber, which hampers control and advancing the construction of safety and efficacy clinical evidence. Studies point to the need for research on off-label use considering the pharmaceutical market, legal relationships, product safety and efficacy, and regulatory agencies' role to rationalize the decision-making process and improve control[33].

In dispensations, 83.0% (n=24,229) of the "Prescriber's Specialty" fields were not filled out. In the valid records, most of the registered medical specialties were found to conform with the clinical uses of thalidomide, as already reported in another study[13].

The qualitative evaluation showed that there is no standardized use of thalidomide control and management systems. The lack of response from the Midwest, North and Northeast regions limits our findings, but the survey presented by this study, combined with the late occurrence of cases of congenital malformation in Brazil[22], indicate essential weaknesses in the control of the drug in contrast to its widespread use in the country. Additional studies to this first diagnosis should be carried out to continuously assess the regional needs for thalidomide control and management systems.

Incomplete data on the use of thalidomide in Minas Gerais (quantitative loss of data from dispensation and information related to the disease, characteristics of users and prescribers) and the relatively short period available for analysis are limitations of this assessment. However, the changes observed in thalidomide dispensation are in line with the decreased use in ENL and increased use in MM[13]. The improved management system (e.g., reducing the proportion of unknown data) should contribute to future pharmacoepidemiological studies. The availability of secondary databases allows access to the information routinely collected for researching the use of medications to guide health decision-making.

Thalidomide surveillance is a significant public health challenge, despite all tragic history. Therefore, it is necessary to monitor the functioning of the existing structure to mitigate adverse events, especially teratogenicity, and improve care quality. The expanded off-label use of thalidomide shows that, while it has been the substance that caused one of the greatest disasters of the 20th century, it appears as a promising medicine in the 21st century[34], and reinforces the need for greater rigor in monitoring its use.

Collaborations

FT Campos: conception, planning, analysis, interpretation and writing of the work. RMM Santos: conception, planning, analysis, interpretation and writing of the work. JP Costa: analysis and interpretation of work results. CAM Pádua: conception, planning, analysis, interpretation and writing of the work.

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