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DEBATE

Thalidomide Analogs in Brazil: Concern About Teratogenesis

Análogos da Talidomida no Brasil: Preocupação com a Teratogênese

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ABSTRACT

It has been more than 50 years since thalidomide was withdrawn from the world market due to its teratogenic potential. However, its widespread use around the world resumed due to its immunomodulatory and anti-angiogenic properties. The drug established itself in new therapies, and interest continued with the emergence of more potent analogs, the most notable being lenalidomide and pomalidomide, which are not approved in Brazil. The question that arises after analog synthesis is: Do these drugs also have the same teratogenic potential? The answer to this question is based only on experimental studies because exposure to humans is not authorized and has not yet been described. Although thalidomide has been recognized as a powerful human teratogen for many years, its molecular mechanisms of teratogenesis remain to be fully explained. Efforts with animal models and human genetic studies have clarified some important pathways that are most likely involved in the teratogenic action of thalidomide. However, it has not yet been possible to identify the teratogenic domain of the molecule from the therapeutic ones. Moreover, there are species-specific differences that must be taken into consideration when teratogenicity is evaluated.

KEYWORDS: Thalidomide; Lenalidomide; Pomalidomide; Teratogenesis; Thalidomide Syndrome; INaGeMP

RESUMO

Faz mais de 50 anos que a talidomida foi retirada do mercado mundial devido ao seu potencial teratogênico. Entretanto, seu uso disseminado em todo o mundo foi retomado devido às suas propriedades imunomodulatórias e antiangiogênicas. A droga foi utilizada em novas terapias e o interesse continuou com a emergência de análogos mais potentes, os mais notáveis deles sendo a lenalidomida e a pomalidomida, que não estão aprovados no Brasil. A questão que surge após a síntese dos análogos é: Estas drogas também têm o mesmo potencial teratogênico? A resposta a esta pergunta baseia-se apenas em estudos experimentais, pois a exposição a humanos não está autorizada e ainda não foi reportada. Embora a talidomida tenha sido durante muitos anos reconhecida como um poderoso teratogêno humano, os mecanismos moleculares da teratogênese ainda não foram completamente explicados. Os esforços com modelos animais e estudos genéticos humanos para entender o efeito tóxico da droga esclareceram alguns importantes caminhos que estão muito provavelmente envolvidos na ação teratogênica. Entretanto, ainda não foi possível isolar o agente teratogênico das outras ações terapêuticas na talidomida e seus análogos. Além disso, há diferenças específicas da espécie que devem ser levadas em consideração quando a teratogenicidade é avaliada.

PALAVRAS-CHAVE: Talidomida; Lenalidomida; Pomalidomida; Teratogênese; Síndrome da Talidomida; INaGeMP



Thalidomide: A Controversial Drug

Thalidomide (α -[N-phthalimido]-glutarimide) was synthesized in 1954 in West Germany by the German company Chemie Grünenthal. The first trials revealed that it had a depressant effect on the central nervous system (CNS) and induced sleep; therefore, it was indicated primarily as a sedative agent^{1,2}. In 1956, thalidomide was introduced into the market as a sedative, as well as for several other indications, such as the treatment of irritability, poor concentration, anxiety, insomnia, nausea, hyperthyroidism, and infectious diseases^{2,3}.

After this, thalidomide quickly came to be manufactured and sold worldwide under more than 40 trade names and reached extraordinary levels of sales – about 15 tons in Germany in 1961⁴.

Toxicity studies in rodents had shown that thalidomide was a drug with a low risk of toxicity and few side effects⁵. The observed toxicity was so low that it was not possible to determine the lethal dose (LD₅₀) in animals. Additionally, suicide attempts with the drug were unsuccessful due to organic sequelae^{1,3}.

However, starting in 1959, there were a large number of reports of newborns with birth defects, initially in Germany². The clinical status of these children was mainly characterized by defects in the development of the long bones (in which hands and feet varied between normal and rudimentary) associated with other malformations⁶. It was only at the end of 1961, with an increasing number of cases, that Lenz suggested a possible correlation between birth defects and the use of thalidomide during pregnancy^{7,8}. In Australia, McBride also mentioned an increase in these birth defects and correlated it with the use of this drug⁹.

The suspension of the sale of thalidomide in Germany and England occurred in 1961, and subsequently in several other countries³. In August 1962, it was already possible to observe a significant decline in the number of limb malformations¹, thus confirming the causal relationship between thalidomide use during pregnancy and the increase in the prevalence of these malformations. Even so, thousands of children had already been born with such anomalies – the estimated number was 10,000 children born around the world, and the number of miscarriages as a result of using the drug is unknown^{10,11}.

In the same decade, thalidomide was already being used for the treatment of an inflammatory reaction from leprosy. In 1965, the Israeli dermatologist Jacob Sheskin prescribed thalidomide as a sedative and analgesic for six patients with erythema nodosum leprosum (ENL), an immune condition resulting from infection caused by *Mycobacterium leprae* and characterized by hot, painful, mobile skin lesions, either associated or unassociated with a systemic condition of fever, malaise, arthralgia, myalgia, and other symptoms^{12,13}. Besides being a great sedative, the clinical signs and symptoms were dramatically reduced within 48 hours. Thereafter, controlled placebo studies showed that thalidomide was responsible for the clinical improvement of the patients^{14,15}.

Undesirable Effects of Thalidomide

Due to the large amount of epidemiological data available in the 1960s, it was possible to determine the period of the gestation that is sensitive to the teratogenic action of thalidomide. The teratogenic window was established as being between the 34th and 50th day after the last menstrual period or 20 to 36 days after fertilization¹⁶. Within this period, it is also possible to make a correlation between the days of ingesting the drug and the observed malformations.

It is believed that between 10% and 50% of women who ingest thalidomide during this period of sensitivity have children affected by the embryopathy¹⁶, making this drug a potent teratogen for humans with small doses of thalidomide (between 50 and 100 mg) capable of producing typical defects¹.

Limb malformations are most frequently described among all the malformations produced by the teratogenic effects of thalidomide. The defects are bilateral but not necessarily symmetrical, and opposite limbs are affected unequally. It is possible to divide the limb defects into four groups^{1,6,16,17}:

- Phocomelia (short or rudimentary limbs) in all four limbs;
- Phocomelia or amelia (total absence) of upper limbs, with other defects in the lower limbs;
- Phocomelia or amelia in upper limbs, with normal lower limbs;
- Defects in predominant lower limbs (femoral hypoplasia or phocomelia of lower extremities), usually associated with curved upper limbs or other defects.

The lower and upper limbs have pre-axial and intercalary alterations, with the upper extremities usually affected by loss of fingers, and the lower extremities by polydactyly and syndactyly^{6,16}.

The limb defects also include aplasia of the thenar muscle, thumbs with three phalanges absent or hypoplastic, absence of phalanges, hypoplasia of the radius and ulna, and hypoplasia of shoulders and hips, among other malformations^{1,16}.

The limb defects may be associated with abnormalities in other organs, and virtually every organ of the body can be affected⁶. Malformations and/or hearing loss are very common, with microtia and anotia the most frequent^{16,17}. Ocular abnormalities such as coloboma, microphthalmia, and anophthalmia, are commonly found^{4,18}. The most common neurological abnormalities are deafness and facial paralysis; however, some studies have reported mental retardation in 6.6% of affected individuals⁴. Hemangioma in the midline of the face and lip and/or cleft palate is more frequent for victims of thalidomide than for the general population². Among the abnormalities in internal organs, abnormalities of the larynx, trachea, and lung lobulation are frequent¹⁶. Cardiac malformations, including ventricular septal defects, aortic coarctation, and tetralogy of Fallot, occur with considerable frequency, and are the leading cause of death⁶.



Estimates of the mortality rate among victims of thalidomide indicate rates of between 40% and 45%¹, with most of them due to heart, kidney, and gastrointestinal anomalies, which are less common among survivors due to their severities².

Resurgence and establishment of thalidomide

In the 1990s, the mechanism of action involved in improving ENL symptoms was mainly attributed to the degradation of high levels of tumor necrosis factor alpha (TNF- α)^{13,19}. In 1991, Sampaio et al. found that thalidomide was able to decrease the level of TNF- α released by monocytes and macrophages stimulated by endotoxin through the degradation of its in vitro messenger RNA (mRNA)^{19,20}.

Besides the immunomodulatory and anti-inflammatory effects, thalidomide also inhibits the development of new blood vessels²¹. Independent of activating interleukin (IL)-2 (which possesses anti-tumor activity) and decreasing IL-6 (a potent growth factor for malignant plasma cells)²², the angiogenetic inhibition mechanism for thalidomide appears to involve blocking growth factors²¹.

D'Amato et al.²¹ showed that intraperitoneal administration of thalidomide inhibits cornea neovascularization in rabbits and mice by blocking vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF)^{21,23} – the latter also occurs following oral administration. When the enantiomers of thalidomide are analyzed separately, the levogyrous configuration shows greater inhibition of angiogenesis compared to the other isoform, which may be an indication that the anti-angiogenic and teratogenic properties of the drug are strongly correlated²⁹.

The recognition of these anti-inflammatory, immunomodulatory, and anti-angiogenic properties has created opportunities for studies both with thalidomide and therapeutic targets in several clinical conditions that involve both TNF- α and angiogenesis-dependent factors. The result is that thalidomide is the first choice in many countries, including Brazil, for the treatment of ENL and multiple myeloma, and it is part of the treatment for several other conditions, such as lupus, graft-versus-host disease, and AIDS-related idiopathic ulcers^{4,10,24,25}.

Thalidomide Analogs

At the same time that thalidomide was restoring its place and approval for use on the world stage, there was interest in the synthesis of analogs with higher therapeutic potency and reduced side effects. These side effects, especially the teratogenicity and peripheral neuropathy, are the limiting factors of treatment.

The most well known thalidomide analogs are lenalidomide (CC-5013)²⁶ and pomalidomide (CC-4047)²⁷. These drugs were approved in the United States in 2006 and 2013, respectively, to treat multiple myeloma, and they have a subtle change in the phthalimido moiety of the original molecule. This subtle variation gives the analogs (at least for in vitro use) greater potency in inhibiting TNF- α and a

greater ability to co-stimulate T cells, as well as less detrimental side effects^{28,29}.

In Brazil, thalidomide is cheaply manufactured by the *Fundação Ezequiel Dias (FUNED*, a pharmaceutical arm of the government), which has proven to be very cost-effective. If analogs were to enter Brazil, they would not have the same cost-effectiveness due to the royalties³⁰.

Thus, a new class of drugs called immunomodulatory drugs (IMiDs) has arisen; for example, thalidomide, lenalidomide, and pomalidomide. The term “IMiDs” refers to the IMiD licensed by the Celgene Corporation (Summit, NJ) for the treatment of various inflammatory and neoplastic diseases. The IMiDs were originally defined by their ability to inhibit TNF- α and further stratified by their relative effects on other cytokines³².

IMiDs have several action mechanisms in common; for example, suppressing TNF- α , co-stimulation of T-cells, increased effector function of natural killer cells, VEGF expression, suppression of cyclooxygenase (COX-2) expression, etc^{29,31,32}. At the same time, they have different profiles for toxic effects; for example, constipation, peripheral neuropathy, neutropeny, thromboembolic events, and secondary malignancies^{26,27}.

Teratogenesis of Thalidomide Analogs

Studies assessing the teratogenicity of the analogs are still very limited in animals, and no human experience has been recorded. In 2007, Christian et al.³³ demonstrated that, in therapeutic doses, lenalidomide is not teratogenic in rabbits, which is one of the animal models for thalidomide teratogenicity. However, it was observed that at maternally toxic doses, lenalidomide produced developmental delays, low birth weight, and miscarriages, but no typical malformations were observed³³. This finding was not confirmed in primates, in which there was a malformation pattern consistent with thalidomide embryopathy²⁶.

The effects that are toxic to the embryo are also contradictory in the experiments with pomalidomide. In vitro and in vivo assays performed by Mahoni et al.³⁴ with zebrafish and chickens showed that lenalidomide, but not pomalidomide, was teratogenic. Besides this, the toxicity profile of pomalidomide was lower when compared with its counterparts, even in doses that achieved an anti-inflammatory response³⁴. However, data published by the manufacturer showed that pomalidomide is teratogenic in rats and rabbits, which includes limb and cardiac malformations compatible with thalidomide teratogenicity²⁷.

These discrepant results demonstrate the need for serial evaluation in different experimental models and at different doses to reach a consensus regarding the teratogenicity of thalidomide analogs. Because we are dealing with a molecule derived from a potent teratogen, its use during pregnancy and use by women of childbearing age is considered to be totally contraindicated without the use of two contraceptive methods.



Teratogenic Molecular Mechanisms of Thalidomide and its Analogs

The study of the teratogenic mechanisms of the IMiDs attempts to identify what the causes of the molecular teratogenesis are so that the moiety can be isolated and to obtain a safe medication. These targets remain to be identified, but many advances have been made in this area in recent decades, especially with thalidomide.

The hypotheses with greater scientific reliability are those tested in well-established animal models (rabbits, chickens, and zebrafish) and based on three main phenomena: the formation of reactive oxygen species (ROS), anti-angiogenic mechanisms, and binding to the cereblon protein (CRBN)^{21,35-42}.

Parman et al.³⁵ showed that thalidomide induces oxidation in the DNA of rabbit embryos exposed in utero to thalidomide, and that this is one of the indications that the formation of ROS and oxidative stress are involved in the process. In this study, oxidation did not occur in mouse embryos, which are resistant to thalidomide teratogenesis, and this could be one reason for the resistance and species-specific teratogenicity. In agreement with this is the hypothesis that ROS formation would reduce the capacity of the nuclear factor kappa beta (NF- κ B) – a redox-sensitive transcription factor and growth regulator of the limbs – to bind to the promoter of its target genes, thereby decreasing their expression. Examples of genes regulated by NF- κ B are fibroblast growth factor 10 (FGF10), msh homeobox 1 (MSX1), Twist, sonic hedgehog (SHH), and others that are essential for limb growth. Decreased expression of these genes causes a disturbance in the regulation of feedback with other genes; for example, suppression of FGF8 expression and overexpression of bone morphogenetic protein 4 (BMP4) compromises near-distal limb growth, which is expressed as phocomelia and amelia³⁶.

Other studies with animal models have also provided strong evidence supporting the anti-angiogenic role in the teratogenesis of thalidomide^{21,37,38}. Blood vessels are a primary target of thalidomide teratogenesis, and events such as the loss of FGF8 and FGF10 signaling are secondary to the effects on the affected vessels⁴².

Ito et al.⁴⁰ demonstrated that the CRBN protein interacts directly or indirectly with thalidomide and indirectly with the damage-specific DNA binding protein 1 (DDB1). Both are part of an E3 ubiquitin ligase complex together with the cullin 4A protein (CUL4A). They assert that the binding of thalidomide in CRBN would decrease the CRBN ubiquitination activity in the E3 ubiquitin ligase complex, and that the increase of the non-ubiquitinated substrates would cause an imbalance in the expression of some genes, such as FGF8, FGF10, and BMP4, etc.³⁹⁻⁴¹.

The fact that this protein is the primary target for binding to thalidomide has generated important developments regarding the action mechanisms of thalidomide and its analogs. For example, the loss of CRBN expression is associated with resistance to the multiple myeloma treatment during treatment with pomalidomide, and this has been evaluated as a possible biomarker response to treatment of multiple myeloma^{32,43}.

Human studies attempting to identify the teratogenic molecular mechanisms are based on genetic studies that seek to identify susceptibility factors in people affected by the syndrome. In a comparison of unaffected people with people who have thalidomide embryopathy, Vianna et al.⁴⁴ identified many more genetic variants related to the reduced enzyme expression of the endothelial nitric oxide synthase gene (eNOS or NOS3). In a published abstract, the same group identified the presence of rare variants in the gene region that encodes the binding moiety between thalidomide and CRBN⁴⁵. Although the results were not statistically significant, these rare variants should be studied further because they may be able to clarify individual response mechanisms for drug exposure.

In general, the findings in humans suggest that while not recognizing the real genetic contribution to the occurrence of thalidomide embryopathy, rare variants in the CRBN gene, as well as polymorphisms in NOS3, seem to have an important role and should be studied further. Additionally, other genes encoding proteins involved in oxidative stress, angiogenesis, and ubiquitin E3 ligase complex, may clarify other important issues, such as species-specific mechanisms, tissue specificity, and phenotypic differences.

Thalidomide Cases in Brazil Explain the Fear Surrounding the Introduction of an Analog

The first cases of malformations associated with the use of thalidomide-based drugs in Brazil were reported in 1960; however, cases were subsequently recorded for the year 1959. The official number in Brazil until 1965 is about 300 cases; however, some cases were difficult to prove due to the high incidence of self-medication and the time elapsed from drug ingestion until diagnosis^{2,3,11}.

Through 204 records from the Brazilian Association of Thalidomide Victims (ABVT), Schmidt and Salzano⁴⁶ evaluated 93 patients with thalidomide embryopathy who were born between 1959 and 1963. In this study, it was possible to establish epidemiological data, which revealed a greater concentration of births in the states of Rio Grande do Sul (RS), Minas Gerais (MG), and São Paulo (SP) and a greater number of births in 1962⁴⁶.

Despite the recognition of cases occurring from 1970 to 1990 by non-governmental organizations, such as the Movement for the Reintegration of People Affected by Leprosy (MORHAN) and the Brazilian Association of Thalidomide Syndrome Sufferers (ABPST), the only manifestations published in the scientific literature were from Gollop and Eigier⁴⁷ and Castilla et al.⁴⁸ Gollop and Eigier⁴⁷ prenatally diagnosed, for the first time, a case of thalidomide embryopathy in a fetus whose mother was in treatment for ENL with daily doses of 100 mg taken up to the 35th day of gestation. Pregnancy was interrupted by parental decision because the fetus showed phocomelia in all four limbs⁴⁷. Castilla et al.⁴⁸ reported 34 cases of thalidomide embryopathy in South America between 1969 and 1995, and of these, 33 cases were from Brazil – 1 was in 1969, 6 during the 1970s, 20 in the 1980s, and 6 in the 1990s. These cases occurred in nine Brazilian states, with the southeast re-



gion having the highest occurrence rate⁴⁸. The authors attributed the high incidence of a second generation of victims to the high prevalence of leprosy in Brazil, and also due to the drug's lax control measures.

Despite the restrictions imposed on thalidomide use after the international scandal, which involved Brazilian victims between 1970 and 1990, and the apparent control and monitoring of thalidomide embryopathy (mainly due to Law 10651/2003 which regulates the use of thalidomide)²⁵, in the years 2005 and 2006, new cases of thalidomide embryopathy have been reported. These cases come to the attention of the Teratogen Information Service (SIAT) of Porto Alegre in a totally random manner, without any notification or registration on the part of the competent health authorities or the inspection services related to the drug⁴⁹.

These three cases occurred in the states of Maranhão (MA), Rondônia (RO), and Rio Grande do Sul (RS). The recommendation to use thalidomide was for the treatment of ENL (two cases) and multiple myeloma (one case). In two cases, the mothers of the malformed babies were undergoing treatment with thalidomide, but they were using it at their own discretion through a close relative with a prescription – a very common habit in our population⁴⁹.

The emergence of these new cases suggests the need for surveillance to evaluate the real occurrence of new cases in Brazil. In 2011, a study was published that established a surveillance tool based on the typical congenital defects of this embryopathy – known as the thalidomide embryopathy phenotype (TEP). It identified two cases compatible with the syndrome. Although there was no proof of the medication being used by the mothers, the tool was shown to be sensitive and effective for its purpose. Besides this, TEP frequencies have been statistically higher in recent years, coinciding with the period of increased availability of thalidomide due to the expansion of its uses⁵⁰.

During this surveillance, two more cases of embryopathy were registered in 2010 in the interior of the state of Maranhão, where there is a high prevalence of leprosy. The discovery of the first case led to the identification of the second due to the typical characteristics of the syndrome¹⁷. From these notifications, new rules for the use and prescription of thalidomide came into force (Resolution RDC no. 11, March 2011) with more restrictive characteristics for the use and dispensation of the drug in Brazil⁵¹.

Conclusions

Even with stricter surveillance and regulations, the case history makes Brazil reticent to introduce a thalidomide analog. Using a new IMiD for restricted conditions is a possibility to be discussed; however, we agree with Paumgartten³⁰ that this should occur only in cases in which the clinical superiority is demonstrated by clinical trials. Besides this, the easy administration (orally) and the sharing of medications (a practice that is still quite common and which has been observed in the latest cases of the syndrome) cannot be overlooked in making this decision, because teratogenicity in humans for this class of drugs cannot be eliminated.

Thus, the caution of waiting for larger and improved experiences with the use of a new drug can be considered to be a watershed – the case of thalidomide in the United States reinforces this idea. In dealing with thalidomide in Brazil, this caution is enhanced due to the history marked by the precarious surveillance and continuous recording of cases of thalidomide embryopathy.

Thalidomide analogs are used outside Brazil primarily for cancer treatment. With the approval of an analog, there will probably be efforts to test these molecules under other conditions, particularly in ENL, which is still very common in Brazil. Thus, one would not be able to guarantee that this medication is totally out of the teratogenic range and that the first in utero exposure of second-generation IMiDs would occur in Brazil.

The notion that thalidomide analogs are, from a clinical point of view, generally more potent than the parent compound, can be seen as a simplified way to understand and explain the action mechanisms and the biological function of the IMiDs, especially in relation to the teratogenicity in animals compared with humans. The study of the molecular targets of thalidomide and its analogs, both for their therapeutic action and ability to induce malformations, should help to understand this intriguing phenomenon of teratogenesis and assist in the development of safer compounds.

Meanwhile, because the drug has so many features that can benefit people with various debilitating conditions, it is necessary to implement new prevention approaches that seek to effectively control the drug and ensure its safe and rational use.

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