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The impact of thalidomide use in birth defects in Brazil

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ABSTRACT

Although the thalidomide tragedy occurred more than 50 years ago, the medication is still being used worldwide for different reasons, and several aspects regarding its teratogenicity remain unsolved. Despite the strict regulation implemented, new cases of thalidomide embryopathy (TE) are still being registered in Brazil. Furthermore, the molecular processes that lead to malformations when the embryo is exposed to thalidomide have not yet been fully identified. In this article, we perform a critical analysis of thalidomide's history in Brazil, highlighting aspects of the occurrence of TE over the decades. Finally, we present the main perspectives and challenges for ongoing surveillance and prevention of TE in Brazil. The effective control of dispensing thalidomide, especially in areas where leprosy is endemic, is one of the most important and challenging points. Furthermore, the emergence of thalidomide analogues is fast approaching, and their availability would pose additional concerns. The understanding of the molecular mechanisms and targets of thalidomide in both experimental and human models is essential for generating new insights into teratogenic mechanisms, so that safer thalidomide analogues can be developed.

1. History of thalidomide

Thalidomide (α-N-phthalimido-glutarimide) was synthesized in 1954 in West Germany by the Chemie Grünenthal company, and was introduced to the German market in 1956 (Lenz, 1988) (Fig. 1). At the time, it was prescribed for the treatment of several conditions such as irritability, poor concentration, anxiety, insomnia, nausea, morning sickness, hyperthyroidism, and even infectious diseases (Lenz, 1988; Saldanha, 1994). Considered to be safe, it was available without medical prescription (Lenz, 1988; Saldanha, 1994). It quickly began to be manufactured and sold worldwide, under different trade names.

In 1959, an increasing number of newborns began to be reported with a phenotype called phocomelia (limb reduction defects of long bones, in which hands and feet varied between normal and rudimentary), frequently associated to malformations of inner organs. However, it was only at the end of 1961 that Lenz suggested a possible link between the sudden emergence of these congenital abnormalities and the use of thalidomide during pregnancy (Lenz and Knapp, 1962). At the same time, in Australia, McBride also observed a 20% increase in babies with phocomelia correlated with the use of the drug (McBride, 1961). Although the teratogeniciy of thalidomide had not yet been experimentally proven at that time, thalidomide was quickly withdrawn from the market in Germany and England, and later in several other countries (Saldanha, 1994). By August 1962, a large decline in births with limb malformations was observed (Shardein, 1993), but at least 10,000 affected children were already born worldwide (Oliveira et al., 1999; Matthews and McCoy, 2003).

Still in the 1960s, the therapeutic action of thalidomide on *erythema nodosum leprosum* (ENL) - an inflammatory complication of leprosy - was accidently discovered (Sheskin, 1965). Several studies since then have demonstrated its potential in the treatment of several other conditions — especially ENL and multiple myeloma (MM) — due to its anti-inflammatory, immunomodulatory, and anti-angiogenic properties (Sampaio et al., 1991; Rajkumar and Blood, 2006). Currently, thalidomide is used to treat a range of different conditions around the world, and analogues with better

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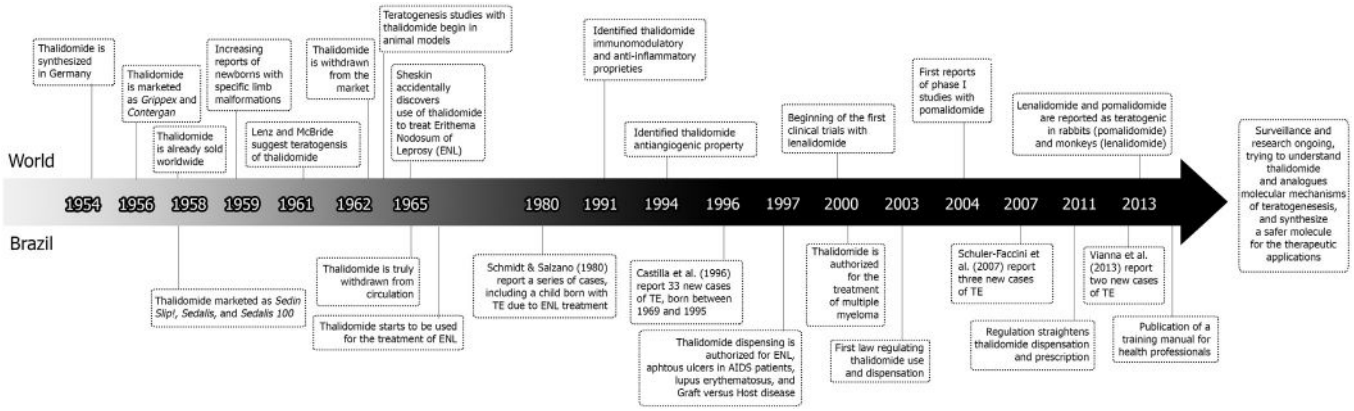

Fig. 1. Timeline of thalidomide history in Brazil and around the world.

therapeutic potential are available in many countries (Uhl et al., 2006; Kim and Scialli, 2011).

2. History of thalidomide in Brazil

Thalidomide was initially marketed in Brazil by 1958, and over the years it has had four different trade names: *Sedalis, Sedalis 100, Sedin*, and *Slip!* (Saldanha, 1994; Oliveira et al., 1999). All of them were prescribed as tranquilizers for sleeping disorders (Saldanha, 1994). In 1962, with the recognition of its teratogenicity, the licenses for medications containing thalidomide in its formulation were cancelled, but the act was only formally established in 1964. According to the Brazilian Association of People Affected by Thalidomide Syndrome (ABPST), thalidomide was only actually withdrawn from the market in 1965 (Associação Brasileira dos Portadores da Sindrome da Talidomida, 2016).

Paradoxically, still in the 1960s, thalidomide was authorized by the Ministry of Health of Brazil for the treatment of ENL (Oliveira et al., 1999). Therefore, the circulation of thalidomide has never ceased. Presently, thalidomide is not commercially branded in Brazil, but manufactured by just one governmental pharmaceutical facility. It cannot be marketed, being distributed directly from the Ministry of Health (Agência Nacional de Vigilância em Saúde, 2011).

3. Thalidomide embryopathy and regulation in Brazil

The number of thalidomide embryopathy (TE) cases registered in Brazil up until 1965 was around 300 people, although this may have been an underestimate. Some cases were difficult to be proven due to both the high incidence of self-medication and the time elapsed from consuming the drug until the diagnosis (Lenz, 1988; Saldanha, 1994; Oliveira et al., 1999). After the 1960s, non-governmental organizations (e.g., Movement for the Reintegration of People Affected by Leprosy), conducted active surveillance and reported new cases in different regions of Brazil. However, the only findings that were incorporated into the scientific literature were in the works of Gollop and Eigier (Gollop et al., 1987) and Castilla et al. (Castilla et al., 1996). Gollop and Eigier (Gollop et al., 1987) diagnosed, for the first time, a prenatal case of TE for a fetus whose mother was being treated for ENL, with daily doses of 100 mg taken up to the 35th day of gestation. In this case, the couple decided to interrupt the pregnancy, since the fetus had phocomelia in the four limbs (Gollop et al., 1987). Castilla et al. reported 34 cases of TE in South America between 1969 and 1995 (Castilla et al., 1996). Of these cases, 33 were from Brazil: one was born in 1969, six in the 1970s, twenty in the 1980s, and six in the 1990s. The occurrence was attributed to the high incidence of leprosy in Brazil and the poor control for this drug (Castilla et al., 1996). According to Brazilian registries, the prevalence of leprosy in Brazil is 1.27/10,000, but reaches up to 10.2/10,000 in endemic regions (Ministério da Saúde, 2014a), the second highest number of new cases in the world (Walker et al., 2015).

Therefore, the prescription of thalidomide for women of childbearing age had been banned throughout the country by July 1994 (Oliveira et al., 1999). Nonetheless, it was only in 2003 that the first Brazilian law for controlling the use of thalidomide was created (Agência Nacional de Vigilância em Saúde, 2003).

Despite the restrictions imposed on the use of thalidomide, in 2005 and 2006, three new cases were reported in different parts of the country. These cases were reported to the Teratogen Information Service (SIAT) in Porto Alegre (Schuler-Faccini et al., 2007). In two of the cases, thalidomide was prescribed to treat ENL, while for the other case it was to treat MM. In two of the cases, the mothers were not being treated with thalidomide but used it on their own through a close relative who had had it prescribed, a common habit in the Brazilian population (Schuler-Faccini et al., 2007).

4. Thalidomide embryopathy surveillance and strengthening of regulations

Considering that thalidomide was being used for several conditions, and the large distribution of the drug in Brazil - 5,889,210 pills between 2005 and 2010 - the highest number provided by a public health service in the world (Sales Luiz Vianna et al., 2015), and the emergence of new cases of TE (Vianna et al., 2013a), the need to establish a better surveillance system and to prevent new cases had become clear.

The first system implemented for TE surveillance was based on Brazilian hospitals that were part of the Latin American Collaborative Study of Congenital Malformations (ECLAMC) (Vianna et al., 2011). ECLAMC is a program for the clinical and epidemiological investigation of risk factors in the etiology of congenital anomalies in Latin American hospitals, and it uses a case-control methodological approach (Castilla and Orioli, 2004). The surveillance became proactive from 2007 onwards, when all babies born in hospitals that are part of ECLAMC began to be assessed directly for the TE phenotype. The sentinel phenotype, which is also known as thalidomide embryopathy phenotype (TEP), was established to describe newborns with pre-axial and bilateral intercalary limb reduction defects as well as complete amelia (Castilla et al., 1996; Yang et al., 1997). Two cases compatible with TEP were identified (but not confirmed) (Vianna et al., 2011). Some important

limitations were identified in this study, as low coverage: less than 5% of all births in Brazil occur in ECLAMC's, and these hospitals are located in areas of low prevalence leprosy.

Therefore, we performed a retrospective surveillance based on TEP through the Brazilian Live Births Database (SINASC), which compiles birth certificates from all the country with relevant information about demographics and details of the birth, including a description of any congenital anomaly (Sales Luiz Vianna et al., 2015) which later is classified according to the 10th Revision of the International Classification of Diseases (ICD-10). Besides retrospectively evaluating Brazilian births compatible with TEP, this study also compared data about the distribution of thalidomide pills and leprosy prevalence. As expected, thalidomide pills distribution, TEP and leprosy were found to overlap in several isolated regions of the country. One of them was the state of Maranhao, where three new cases of TE were reported (Vianna et al., 2013a). A direct correlation between the direct dispensing of thalidomide and the number of TEP cases was detected (Sales Luiz Vianna et al., 2015). After this, new regulations reinforced the control of dispensing and prescribing of thalidomide more rigid and efficient, as well as criminal liability for physicians and patients who do abide to it (Agência Nacional de Vigilância em Saúde, 2011).

5. Challenges and perspectives of thalidomide in Brazil

Brazil is the only country that has cases of TE after the 1960s reported which is correlated to the number of pills distributed in areas with high leprosy endemics. Additionally, a large number of pregnancies are unplanned and elective termination of gestation is not allowed in these cases. Therefore prevention of pregnancy during treatment with thalidomide is the most important approach. In 2013, after the last two cases were recognized (Vianna et al., 2013a), the Brazilian Ministry of Health published a guideline for health professionals, which aimed to educate primary care professionals about pregnancy prevention (Ministério da Saúde, 2014b). Educational programs and training courses were given in all Brazilian states and the information for patients' leaflet was reformulated.

Currently there is a growing concern in relation to thalidomide analogues. No analogues are yet available in Brazil; however, due to the superior efficiency in treating MM that has been observed in countries where they are used for use, the availability of these additional immunomodulatory drugs in Brazil in the near future is imminent. Furthermore, all of the analogues that are currently available have so far been shown to be teratogenic in at least one animal model (Christian et al., 2007; Mahony et al., 2013; D'Amato et al., 2013; Zeldis et al., 2013). Our group has already published a discussion regarding the concern about the possibility of new cases of TE if thalidomide analogues are allowed into Brazil (Vianna et al., 2014).

Obtaining a safe form of thalidomide is a common goal of both the scientific community and thalidomide users. Nonetheless, there are still important limitations for the synthesis of this molecule, which are specifically related to the action mechanism of the drug. Since the 1960s, the scientific community has been searching for the molecular mechanisms that trigger the malformations caused by thalidomide. Despite much knowledge has been generated in recent years, a single mechanism that covers all of the available evidence in both animal models (D'Amato et al., 1994; Hansen and Harris, 2004; Therapontos et al., 2009; Ito et al., 2010; Siamwala et al., 2012) and in humans (Vianna et al., 2013b) models is still a challenge (Vargesson, 2015).

The identification of thalidomide's action mechanism is also difficult by the TEP, characterized by multiple and nonspecific defects. Although some defects like phocomelia are characteristic, they are also observed in other genetic syndromes. Additionally, species-specific differences have been reported. More recently, new assessments in patients with TE born in the 1960s have revealed a wider spectrum of effects resulting from exposure to thalidomide, effects which were not identified at birth, in particular, psychiatric (Strömland et al., 1994; Imai et al., 2014; Kowalski et al., 2015) and cardiovascular (Kowalski et al., 2015) effects. To address these challenges, in 2014 the World Health Organization (WHO) held a meeting of experts in order to define criteria for diagnosis, and to update the action mechanisms of the thalidomide (World Health Organization, 2014).

Finally, the use of thalidomide (and possibly its analogues) is likely to increase in Brazil. This is not only because of its therapeutic efficacy, but also due to the low cost associated with the manufacturing of this drug in Brazil (Paumgartten and de Souza, 2013). Thus, pregnancy planning, public education, and continuous surveillance are essential. These strategies should proceed in parallel with experimental studies of animal models and people affected by TE, in order to obtain different evidence about the teratogenic mechanism of thalidomide. Obviously, these strategies are challenging with limited financial resources in a country of 200 million people with 3 million births a year. Regardless of this, the experiences reported here demonstrate the need for permanent action.

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