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DEBATE

Novel thalidomide analogues, “me too” drugs and the Brazilian law

Novos análogos da talidomida, medicamentos “me too” e a lei brasileira

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ABSTRACT

In Brazil, thalidomide has been used virtually without interruption since it was launched as a new and revolutionary sedative drug in 1956. After 1965, when its efficacy to treat erythema nodosum leprosum (ENL) was discovered, it was regarded as an essential drug because the prevalence of Hansen’s disease is high in the country. In the 1990s and thereafter myriad novel therapeutic uses for thalidomide (autoimmmune diseases, multiple myeloma, aphthous ulcers in AIDS, and others) have emerged owing to its immunomodulatory and antiangiogenic activities. Owing to a marked teratogenicity, however, the prescription and dispensing of thalidomide to patients is strictly controlled in Brazil and elsewhere. Notwithstanding the stringent regulations, a number of post-1965 cases of thalidomide embryopathy have occurred in Brazil. In 2003, a federal law (Law 10.651/2003) prohibited the sale and dispensing of thalidomide in commercial pharmacies. The law, however, made no provision for teratogenic drug analogues such as lenalidomide and pomalidomide, which have been cleared for marketing in the USA, Europe and other countries. Although they are much more expensive than thalidomide, the clinical superiority of novel analogues over thalidomide in multiple myeloma and other conditions remains unproven. Therefore, so far novel analogues can be considered as thalidomide “me too” drugs. This author strongly recommends that an amendment to the current law prohibiting the sale and dispensing of thalidomide in commercial pharmacies be extended to thalidomide analogues. Moreover, we consider that a demonstration of clinical superiority over thalidomide (through gold-standard comparative efficacy trials) should be an essential requirement for registration of any teratogenic analogue.

KEYWORDS: Lenalidomide; Pomalidomide; Cost Effectiveness; Multiple Myeloma; Teratogenic Drugs; Thalidomide Embryopathy

RESUMO

No Brasil, a talidomida tem sido usada praticamente sem interrupção desde o seu lançamento como novo e revolucionário medicamento sedativo em 1956. Depois de 1965, quando a sua eficácia para tratar o eritema nodoso (ENL) foi descoberta ela tem sido considerada como medicamento essencial porque a prevalência da hanseníase é alta no país. Nos anos 1990 e depois, surgiu uma diversidade de novos usos terapêuticos para a talidomida (doenças auto-imunes, mieloma múltiplo, ulcerações aftosas na AIDS, e outras) em virtude das suas atividades anti-inflammatórias e anti-angiogênicas. Por causa da teratogenicidade, a prescrição e dispensação da talidomida são rigorosamente controladas no Brasil e outros países. Em que pese o rigor da regulamentação, muitos casos de embriopatia pela talidomida ocorreram no Brasil após 1965. Em 2003, uma lei federal (Lei 10.651/2003) proibiu a venda e a dispensação de talidomida em farmácias comerciais. A lei, entretanto, não faz referência aos análogos teratogênicos tais como lenalidomida e pomalidomida cuja comercialização foi autorizada nos EUA, Europa e outros países. Embora sendo muito mais caros que a talidomida, a superioridade clínica dos novos análogos em relação à talidomida no mieloma múltiplo e outras doenças não foi demonstrada. Portanto, até agora os novos análogos podem ser considerados como medicamentos “me too”. Recomenda-se enfaticamente uma emenda à lei atual que estenda a proibição da venda e dispensação em farmácias comerciais aos análogos da talidomida. Deve-se exigir também a demonstração de superioridade clínica em comparação com a talidomida (por meio de ensaios clínicos comparativos de padrão ouro) para registro de qualquer análogo teratogênico.

PALAVRAS-CHAVE: Lenalidomida; Pomalidomida; Custo Efetividade; Mieloma Múltiplo; Medicamentos Teratogênicos; Embriopatia por Talidomida

Introduction

Thalidomide holds a unique position in the Brazilian drug regulatory framework. It is the only medicine that is regulated by a specific federal law (Law 10.651, 16 April, 2003)[1]. The law forbids the sale and/or dispensing of thalidomide in commercial pharmacies. It also states that thalidomide shall be distributed to public health units/hospitals and dispensed to patients through programs approved by the federal health authority (Ministry of Health)[1]. A copy of a physician's written order (on a special numbered prescription order form) must be retained by the public health unit or hospital pharmacy and sent to the local sanitary surveillance office. The Ministry of Health programs through which thalidomide can be distributed and dispensed are those for Hansen's disease, sexually transmitted diseases and AIDS (*i.e.*, aphthous ulcers in AIDS patients) and chronic degenerative diseases (*i.e.*, for lupus erythematosus and graft-versus-host disease)[1,2]. In addition, the law states that package labeling must warn that thalidomide is strictly prohibited for pregnant women and for women at risk of becoming pregnant. The package inserts must also provide detailed information about the drug and its proven teratogenic effects, and include a responsibility term that must be signed by prescribers and patients. To receive thalidomide, patients must present two documents at the public health unit or hospital pharmacy: a special prescription order and a signed responsibility term. Moreover, federal health programs must provide full information on the teratogenic risks of thalidomide, offer advice on pregnancy prevention methods, and give contraceptives to women of childbearing age under treatment for hanseniasis or any other disease for which the drug is indicated and prescribed[1]. Law 10.651/2003, however, made no provision for thalidomide analogues the first of which – lenalidomide – entered phase-III clinical trials at about the time the thalidomide law was enacted in Brazil[1]. Lenalidomide (brand name Revlimid™) was developed by a global biopharmaceutical company (Celgene Corporation, NJ) and first approved by the US FDA on 27 December 2005[3]. Approved therapeutic indications for Revlimid™ were the treatment of transfusion-dependent patients with myelodysplastic syndrome (with deletion 5q chromosomal abnormalities) (December 2005), treatment of multiple myeloma (in combination with dexamethasone) on 29 June 2006, and more recently (5 June 2013), treatment of relapsed or refractory mantle cell lymphoma[3]. On 8 February 2013, pomalidomide (brand name Pomalyst™), another thalidomide analogue developed by Celgene Corp., received FDA approval for the treatment of relapsed or refractory multiple myeloma[4]. Lenalidomide and pomalidomide (Figure 1) share with thalidomide both therapeutic (immunomodulatory) and teratogenic properties.

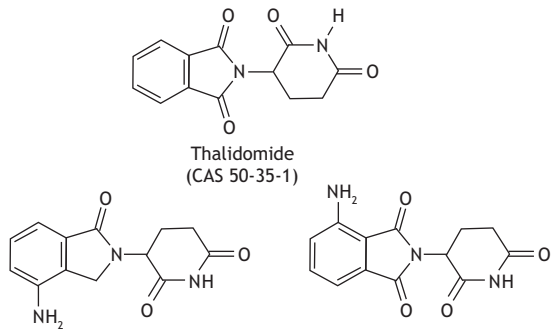

Figure 1. Novel thalidomide analogues lenalidomide and pomalidomide. The quest for safer (not teratogenic) and more effective thalidomide analogues has not been successful so far.

Thalidomide uses, misuses and current regulatory status

Thalidomide was developed by a German pharmaceutical company (*Chemie Grünenthal GmbH*, founded in 1946) and entered the market as a new and revolutionary sedative drug in the mid-1950s[5,6,7,8,9]. Compared to the sleeping pills and tranquilizing drugs available until then (*e.g.*, barbiturates and bromides), thalidomide seemed to be safe. *Chemie Grünenthal* toxicologists claimed that they "could not find a dose high enough to kill a rat", and most physicians believed that suicide attempts with overdoses of thalidomide, unlike those with barbiturates, would be doomed to failure[5,6,7,8,9]. Although a peripheral neuropathy was noted in patients treated with thalidomide, the manufacturer denied any causal relationship between the drug and this neurological condition and continued to claim that its product was safe[7]. In November 1961, however, Widukind Lenz, a pediatrician and medical geneticist, reported that an ongoing outbreak of birth defects (phocomelia, a pre-axial reduction of limbs, and amelia, or absence of limbs), seldom recorded before the mid-1950s, was due to thalidomide use during pregnancy[5,6]. The link between intake of thalidomide during gestation (first trimester) and congenital anomalies – noted by Lenz in Germany – was subsequently confirmed by McBride in Australia[10] and Smithells in the UK[11]. Within a few weeks of these first reports, thalidomide was withdrawn from the market in Germany and Great Britain. In Brazil, Belgium, Canada, Italy, Japan and a few other countries thalidomide continued to be sold for several months thereafter [5,6,8,9]. A suspicion about the neurological side-effects (peripheral neuropathy) delayed the approval of thalidomide in the USA, so that it had not been approved for marketing when the drug-induced epidemic of birth defects came to light. Thanks to Dr Frances Kelsey, a stubborn FDA official, the biggest pharmaceutical market in the world was spared a thalidomide disaster. Although not being sold in pharmacies, thalidomide caused a few cases of congenital anomalies in the USA due to the pre-approval distribution of free drug samples to physicians, a promotional practice intended to "seed the market"[5,6,7,8,9].

Babies with a thalidomide embryopathy phenotype that were born 9 or more months after the drug was banned in

Germany and the UK were considered by Lenz as "avoidable cases", many of which were from Brazil and Japan[5,6,7,8,9]. Thalidomide was banned worldwide in the mid-1960s, but its use was never completely discontinued in Brazil owing to an unexpected new therapeutic indication. In 1965, Jacob Sheskin, an Israeli doctor, prescribed thalidomide as a sedative for patients with hanseniasis and observed that it ameliorated symptoms of erythema nodosum leprosum (ENL), or Hansen's disease type-2 reaction[12]. Sheskin's serendipitous discovery that thalidomide was effective in the treatment of ENL (published as a series of cases) was further confirmed by several controlled clinical trials. As the prevalence of hanseniasis in Brazil is high, the health authorities have listed thalidomide as an essential drug.

New cases of thalidomide embryopathy in babies born after 1965 (*i.e.*, Lenz's "avoidable cases") remained virtually unnoticed until the mid-1990s. In 1994, two Brazilian non-governmental organizations (NGOs) — MORHAN (Movement for the Integration of People Affected by Hansen Disease) and ABPST (Association of People with Thalidomide Syndrome) — performed an active search and found 61 people born after 1965 with birth defects compatible with thalidomide embryopathy[13,14]. A further study by Castilla et al.[15] confirmed that at least 33 of these 61 (post-1965) cases of congenital anomalies were consistent with a diagnosis of thalidomide embryopathy.

At about that time (mid-1990s) a set of experimental and clinical studies shed new light on the anti-inflammatory (*e.g.* anti-TNFα) and antiangiogenic properties of thalidomide[16]. Between the late 1970s and early 2000, a series of clinical studies showed that thalidomide induced symptomatic remission of aphthous stomatitis[17,18,19,20], Behçet's disease[i] [21,22] and prurigo nodularis[23,24], and was beneficial in the treatment of graft-versus-host disease after transplantation[25], autoimmune diseases such as cutaneous and systemic lupus erythematosus[26,27,28], and certain conditions associated with HIV infection, such as aphthous ulcers and wasting syndrome[29,30,31]. A landmark in the emergence of thalidomide as a potentially useful drug in the treatment of some types of cancer[ii] was the demonstration that it possessed antiangiogenic activity.

A study by Robert D'Amato and coworkers, published in 1994, revealed that thalidomide was an inhibitor of angiogenesis in a rabbit cornea assay[32]. Solid tumors depend on the proliferation of new blood vessels to increase in size, and thus the malignant tissue produces substances that promote its vascularization[33]. Consequently, inhibition of angiogenesis was regarded as a promising pharmacological target for developing an entirely new class of effective anticancer agents[iii] [33]. Along this line, the next step was to test thalidomide in patients with relapsed and/or refractory multiple myeloma (MM)[iv] [34].

In an apparent reaction to an uncontrolled use of thalidomide entering the country illegally for a variety of new therapeutic indications, in 1998 the FDA approved the use of thalidomide for ENL, and some years later, in 2006, for patients newly diagnosed with MM[v] [39].

In Brazil, deep concerns raised by the uncovering of several post-1965 cases of thalidomide-compatible birth defects, and the emergence of new uses, prompted the Ministry of Health to prohibit the prescription of thalidomide to any woman of childbearing age (from menarche to menopause), except in very special circumstances and under strictly controlled conditions[41]. In 2002, the the Ministry of Health published clinical guidelines for the use of thalidomide in graft-versus-host disease, lupus erythematosus and MM[2]. As already mentioned, in 2003 the sale and dispensing of thalidomide in Brazil began to be regulated by a specific federal law[1]. No new case of thalidomide-compatible birth defects was recorded between 1997 and 2005[14]. Nonetheless, in 2005 a woman who took the drug for ENL gave birth to a male baby with thalidomide embryopathy, and in 2006 three additional cases were recorded: a female born to a woman who used thalidomide for ENL, and male twins born to a mentally disturbed 17-year-old girl who took pills prescribed for her mother, a patient with MM[42,43]. Moreover, a proactive surveillance found two babies with a thalidomide embryopathy phenotype born in 2007 — a male and a female. In both cases, however, the mothers denied any use of thalidomide[42,43]. As far as this author is aware, the most recent case of thalidomide embryopathy occurred in the state of Maranhão in 2010[vi] [44]. A patient with ENL, who had taken thalidomide during gestation, gave birth to a female baby with bilateral upper and lower limb reduction defects[44]. In 2011, a new regulation controlling the dispensing and prescription of thalidomide (introducing a more effective control on drug dispensing for off-label indications) was issued and put into effect by ANVISA, the health regulatory agency of Brazil[45] (Table 1, Figure 2).

i Behçet's disease or syndrome is a rare immune-mediated small-vessel systemic vasculitis, the symptoms of which include painful oral aphthous ulcers, genital ulcerations, cutaneous pustular lesions and uveitis.

ii As several antineoplastic drugs used in the mid-1960s were also teratogenic agents, some clinical researchers speculated that thalidomide, a potent human teratogen, might also possess antitumor properties. Still in the 1960s, thalidomide was trialed in patients with different types of cancer, but investigators found little or no evidence of an effective therapeutic response[35,36].

iii In 1971, Judah Folkman highlighted that solid tumors required neovascularization (angiogenesis) for growth and survival[33]. Since then, inhibition of new blood vessel growth has become a potential target for an effective anticancer therapy. Today, several drugs that inhibit angiogenesis are used in oncology to treat different types of tumors. Binding of signaling molecules (*e.g.*, vascular endothelial growth factor, VEGF) to the surface of endothelial cells is required for angiogenesis. Inhibition of angiogenesis can be achieved by using monoclonal antibodies (*e.g.*, bevacizumab) that specifically recognize and bind to VEGF, or by other drugs (*e.g.*, sorafenib and sunitinib) that block receptors on the surface of endothelial cells (or other proteins in the downstream signaling pathways)[37,38].

iv Multiple myeloma, also known as plasma cell myeloma, is an abnormal (malignant) proliferation of plasma cells that can affect the bones, the immune system, the kidneys and the red blood cell count.

v The incidence of Hansen's disease is very low in the USA. In 2007, 109 cases of Hansen's disease (most of which were imported) were reported to CDC-USA, whereas 249,009 cases occurred worldwide. Of all cases reported to the WHO in 2008, 77% were from Brazil, India and Indonesia[40]. The rarity of ENL in the USA explains why the FDA had no interest in approving thalidomide. FDA approval came three decades after Sheskin had reported that the drug was effective in treating type II reaction symptoms.

vi This case of birth defects — compatible with thalidomide use — was reported to the Ministry of Health (Department of Epidemiological Surveillance/ Hanseniasis Control Program, and the National Agency of Health Surveillance - ANVISA).

Table 1. Timeline of landmarks on thalidomide and analogue use and regulation

Year	Landmark event
1956	Chemie Grünenthal GmbH launched thalidomide as a new sedative drug.
1961	Widukind Lenz reported that the use of thalidomide by pregnant women was associated with the outbreak of phocomelia/amelia in Germany. Thalidomide was withdrawn from the market in Germany, UK and other countries.
1965	Jacob Sheskin reported that thalidomide ameliorates ENL painful symptoms.
1994	An NGO survey revealed a number of cases of birth defects compatible with thalidomide embryopathy among people born in Brazil after 1965. A study by Robert D'Amato et al. revealed that thalidomide inhibits angiogenesis.
1998	The US FDA approved thalidomide use in ENL.
1999	A clinical trial by Singhal et al. showed that thalidomide is active against advanced multiple myeloma.
2003	Brazil federal law forbade thalidomide sales and dispensing in commercial pharmacies and stated that it should be distributed and dispensed only through Ministry of health programs. A strict control on thalidomide prescription and dispensing is established.
2005	The US FDA first approved lenalidomide (Revlimid™) for myelodysplastic syndrome with deletion of 5q chromosomal abnormality. Despite the federal law, and strict control on the dispensing of thalidomide established by lower level regulation, new cases of babies born with thalidomide embryopathy continued in Brazil (2005-2010).
2006	The US FDA approved thalidomide use in relapsed and/or refractory MM. The US FDA (June 29) approved lenalidomide for use in combination with dexamethasone in patients with MM.
2010	The Brazilian health regulatory agency (ANVISA) denied approval for lenalidomide use in MM and myelodysplastic syndrome.
2011	New rules on thalidomide control, including those regarding the dispensing of thalidomide for off-label indications, were put into effect by ANVISA.
2012	After evaluating a request for reconsideration filed by the pharmaceutical company, ANVISA confirmed its previous decision (denial of approval) regarding lenalidomide registration.
2013	The US FDA approved pomalidomide (Pomalyst™) for relapsed and/or refractory MM.

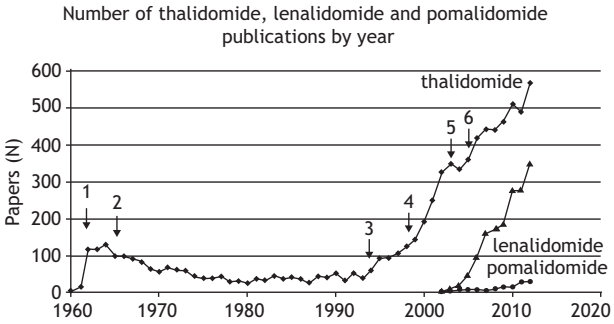

Figure 2. A search in the PubMed database (on July 15th, 2013) revealed that thalidomide (■) is one of the most studied drugs (7800 publications, 263 in 2013). Lenalidomide (▲) and pomalidomide (●) with 1845 (259 in 2013) and 143 (30 in 2013), publications, respectively, are far less studied. Landmark events indicated by arrows and numbers are as follows: 1 - 1961: teratogenic effects of thalidomide reported by Lenz; 2 - 1965: Sheskin reported that thalidomide ameliorated ENL symptoms; 3 - 1994: D'Amato et al demonstrated that thalidomide had antiangiogenic activity; 4 -1998: US FDA approved thalidomide for ENL; 5 - 2003: Thalidomide law was enacted in Brazil; 6 - 2005: US FDA approved thalidomide for myelodysplastic syndrome and 2006 thalidomide and lenalidomide were approved for multiple myeloma.

Innovative and "me too" drugs

A "me-too" drug[vii] is a drug that uses essentially the same therapeutic mechanism of action as an existing one, offering no significant additional benefit in terms of efficacy and/or safety (*i.e.*, they are not clinically superior). Many "me-too" drugs are chemically related to the prototype and hence are also structurally very similar to one or more drugs already on the market, with only minor differences[46,47]. In fact, "me-too" drugs largely duplicate the therapeutic action of drugs that are already available. As the R&D of pharmaceuticals is a lengthy process, a "me-too" drug may result from a parallel drug development (*i.e.*, despite being approved for marketing later, a "me-too" drug might have entered development long before the innovative drug began to be used in clinical practice). Nonetheless, in a number of cases "me-too" drugs are intentionally developed imitations of innovative medicines. The R&D process of a "me-too" drug is more predictable (or less risky) than that of an innovative medicine. At any rate, imitations are developed to compete with the pioneer drug and other existing medicines.

The deliberate development of "me-too" drugs has been questioned because these drugs do not bring additional benefits to patients[46,48]. Focusing on a market for "me-too"s, pharmaceutical companies use funds and resources that could otherwise be applied to the development of innovative medicines, many of which are desperately needed for a number of morbid conditions, including the neglected diseases. Along this line, Marcia Angell[48] and others proposed that a requisite for new drug approval by national regulatory agencies should be evidence not only of efficacy compared with placebo, but also of clinical superiority (efficacy and/or safety) to existing therapies. Such a proposal is controversial, and some authors have defended "me-too" drugs, arguing that non-innovative

vii "Me-too" drugs are sometimes also called "follow-on" drugs.

medicines enhance competition and stimulate the lowering of prices, which is ultimately beneficial to consumers.

One difficulty in imposing restrictions for launching a putative "me-too" on the market is that eventual differences between a structurally related drug and its prototype may appear only after they have been in large-scale use for some time. Drug effectiveness (clinical benefit under real conditions of use that differ from those of controlled trials) and certain aspects of drug safety are not fully disclosed by pre-marketing phase-III clinical trials. Post-marketing pharmacovigilance is required to detect very rare, albeit severe, adverse drug reactions and for estimating their incidences[viii] [49]. The antidiabetic drug troglitazone, for instance, was withdrawn from the market owing to an increased occurrence of idiosyncratic drug-induced liver injury (DILI). Furthermore, two other thiazolidinediones and putative "me-too" oral hypoglycemic drugs (pioglitazone and rosiglitazone) were considered as being negative compounds for DILI[ix] [52].

ANVISA's viewpoint on the registration of "me too" drugs states that: "... *it is difficult or even impossible to classify a (new) medicine as a "me too" drug on the occasion it is (first) registered because some of its attributes that would allow us to make this classification can only be (fully) assessed after the product is marketed and used in large scale*"[x] [53]. Owing to this fact, and also because "*current Brazilian laws do not support denying registration of new drugs based on such argument*", ANVISA does not necessarily reject applications for drugs that are apparently "me-too"s of medicines already on the market[53].

Another key problem with putative "me-too" drugs is that pharmaceutical companies, in an attempt to boost sales, do not adequately inform physicians and consumers about the degree of similarity of their products to existing drugs. On the contrary, companies generally claim that their ("me-too") products are in some way "better" than pioneer drugs, even when this statement is not supported by adequately designed and conducted comparative efficacy studies. Along this line, Angell[48] pointed out that many structurally related ("me-too") drugs are never tested at equivalent doses to show that there are significant differences in clinical outcomes for some patients. Thus, in most cases, companies' claims that *"patients respond differently to 'me-too' drugs is merely an untested – and self-serving – hypothesis"*[48].

Comparative efficacy and safety of thalidomide analogues versus thalidomide

A key problem regarding the safety of any thalidomide analogue is to find out whether it, too, has teratogenic properties. This question is not easily answered by routine preclinical studies because rodents are known to be refractory to thalidomide-induced teratogenicity, and rabbits — albeit more susceptible than rats — do not exhibit the same pattern of severe malformations as those found in primates[54,55,56]. A comparative developmental toxicity study of thalidomide and lenalidomide in rabbits showed that the former caused fetal structural anomalies (limb defects and others) in the absence of overt maternal toxicity, whereas the latter did not increase the incidence of malformations and produced other embryotoxic effects (prenatal growth retardation and embryo deaths) only at maternally toxic doses. These results were initially misinterpreted as an indication that lenalidomide would be less teratogenic than thalidomide. Moreover, authors stated in their conclusions that developmental toxicity studies on lenalidomide *versus* thalidomide would confirm that "... *structure–activity relationships may not predict maternal or developmental effects*"[54]. A further non-human primate study, however, revealed that lenalidomide given orally to monkeys (at non-maternally toxic doses) caused congenital anomalies (short limbs; bent digits, wrist and/or tail; supernumerary or absent digits) similar to those produced by thalidomide in the same study[xi] [55].

Thalidomide and lenalidomide are effective, both as single agents and in combination with other agents, when used to treat patients with relapsed and/or refractory MM. A combination of thalidomide, dexamethasone and cyclophosphamide has been used as a non-myelosuppressive induction regimen for MM patients eligible for autologous stem cell transplantation (ASCT), while combining melphalan (a nitrogen mustard alkylating agent), prednisone and thalidomide has become a treatment option for newly diagnosed MM patients ineligible for ASCT[60]. According to a recent review, ongoing trials continue to investigate novel thalidomide-based regimens to further optimize thalidomide use in the management of MM[60].

Although several clinical studies showed that lenalidomide (*e.g.*, lenalidomide plus dexamethasone) is effective in the treatment of MM[61], no randomized trial has compared the efficacy and safety of lenalidomide-based versus thalidomide-based

viii This is illustrated by idiosyncratic drug-induced liver injury (DILI). DILI is the most common single adverse drug reaction (ADR), which led to its withdrawal from the market[49]. Idiosyncratic DILI is a rare (10^{-3} to 10^{-4}) ADR that cannot be predicted by pre-clinical animal studies and is unlikely to be detected in typical phase-III clinical trials (involving 10^2 to 10^3 patients).

ix All three thiazolidinediones are oral hypoglycemic agents, agonists of PPAR-γ (peroxisome proliferator-activated receptor gamma) and possess anti-inflammatory properties. After a lengthy debate, rosiglitazone was removed from the market in many countries owing to post-marketing evidence that it increases the risk of myocardial infarct[50]. Recent post-marketing studies also provided evidence that pioglitazone and rosiglitazone enhanced the risk of bladder cancer in diabetic patients who used these drugs for one or more years[51].

x The viewpoint of the Brazilian agency of health surveillance, ANVISA, on "me too" drugs was, to some extent, based on its advisory technical committee on medicines (CATEME) report.

xi The mechanism of the teratogenic action of thalidomide and its remarkable species-specificity remained a complete mystery for nearly five decades. Recently, a study by Ito et al.[57,58] has started to decipher this enigma. Ito et al. identified cereblon (encoded by the CRBN gene) as a thalidomide-binding protein. Thalidomide binding to CRBN and inhibiting the associated ubiquitin ligase activity is the first step in a chain of events that leads to limb malformations in chicks, fish (fins), rabbits and primates but not in rats and mice. Along this line, recent studies have suggested that CRBN expression is required for anti-myeloma activity of lenalidomide, pomalidomide and thalidomide[59]. Therefore, it is possible that, mechanistically, teratogenicity and the antimyeloma activity of thalidomide analogues are two sides of the same coin.

regimens. A retrospective ("case-control") study by Gay et al.[64] compared the efficacy and toxicity of lenalidomide plus dexamethasone (len/dex) versus thalidomide plus dexamethasone (tha/dex) as initial therapy for newly diagnosed MM, and suggested that the former regimen would be somewhat more effective than the latter (thal/dex). Nonetheless, retrospective[xii] and non-randomized studies are notoriously weak in supporting general conclusions about the clinical superiority of one drug over another in the treatment of MM. Randomized and controlled prospective trials are still necessary to compare the efficacy and safety of these two therapeutic regimens.

Pomalidomide has also been shown to be effective in relapsed and/or refractory MM.

A variety of clinical studies have indicated that lenalidomide and pomalidomide, similarly to thalidomide, are immunomodulatory and antiangiogenic drugs that are not only effective in MM but also in myelodysplastic syndrome, lupus erythematosus, and several other morbid conditions. As far as this author is aware, however, no randomized clinical trial of thalidomide versus its novel analogues (lenalidomide or pomalidomide) for the aforementioned indications has so far been reported or is ongoing[61,62,63].

Thalidomide and lenalidomide are associated with side-effects such as neutropenia; thrombocytopenia; peripheral neuropathy; venous thromboembolism; syncope; bradycardia; skin reactions, including Stevens-Johnson syndrome; somnolence and dizziness[55,64]. Gay et al.'s non-randomized "case-control" study indicated that similar proportions of patients in thalidomide- and lenalidomide-regimen groups (MM treatment) experienced at least one grade 3 or 4 adverse event (AE) (57.5% *vs* 54.6%, *P*=0.568). Len/dex-treated patients experienced more hematologic AEs, mainly neutropenia (14.6% *vs* 0.6%, $P < 0.001$), while the most common AEs among tha/dex-patients were venous thromboembolism (15.3% *vs* 9.2%, $P = 0.058$) and peripheral neuropathy (10.4% *vs* 0.9%, $P < 0.001$[65]. An increased number of secondary primary malignancies have also been reported in several studies using lenalidomide maintenance[65].

In July 2010, ANVISA rejected a new drug application for lenalidomide use in MM and myelodysplastic syndromes[66]. On that occasion, the advisory technical committee on medicines ("CATEME") had recommended the agency not to approve lenalidomide for marketing, as no evidence (from sound comparative clinical trials) was presented to show that it was clinically superior to thalidomide-based regimens adopted in the treatment of MM and myelodysplastic syndrome[66]. The company filed a reconsideration request in July 2010, and in December 2012 ANVISA confirmed its previous decision to deny lenalidomide registration in the country[66].

In summary, so far unequivocal evidence is lacking to support any claim that thalidomide analogues are more effective than their prototype drug (thalidomide) for MM or any other clinical indication.

The cost of novel thalidomide analogues to the Brazilian Unified Health System

New drugs such as bortezomib (brand name Velcade™, the first proteasome inhibitor used in therapeutics) have become available for the treatment of MM and other chronic diseases, and concern has grown over the rising costs of treatments. The cost-effectiveness of MM treatment regimens, for instance, has been examined and compared by several recent studies. A study by Garrison et al.[67] addressed the problem of the cost-effectiveness of novel regimens for MM (transplant-ineligible patients), such as when melphalan (M) plus prednisone (P) is combined with bortezomib (VMP) and with thalidomide (MPT), both with lenalidomide maintenance (MPR-R) and without lenalidomide maintenance (MPR). The authors estimated lifetime costs (in US dollars) as high as $119,102, $142,452 and $248,358 with VMP, MPT and MPR-R, respectively. Ashraf Badros[69] also estimated that, owing to the high cost of lenalidomide tablets, treatment of MM with this thalidomide analogue would cost $163,381 (US dollars) per year for the average patient.

Although the cost-effectiveness of current treatment regimens for MM is still a matter of debate, thalidomide-based regimens seem to be much more cost-effective than those based on its novel analogue. In Brazil, where thalidomide is manufactured by a state-owned pharmaceutical industry (FUNED-MG), production costs are very low. The cost of a thalidomide tablet to the Brazilian Ministry of Health is approximately 0.20 (Brazilian) R$ (equivalent to about 0.08 USD), whereas in the USA - where it is manufactured by a private company — a similar tablet costs about 10.00 USD (equivalent to about R$ 24.4) *i.e.*, in the USA thalidomide is 122 times more expensive than in Brazil. For the Brazilian public health system (SUS), therefore, the difference between the costs of thalidomide- and lenalidomide-based treatment regimens for MM and other chronic diseases is tremendous.

Conclusion

As previously mentioned, the law (No. 10.651/2003) prohibits sales and imposes restrictions on the dispensing and distribution of thalidomide but makes no provision for its teratogenic analogues. Notwithstanding the fact that lenalidomide has recently received a denial approval decision, sooner or later ANVISA will approve the marketing of novel thalidomide analogues. If the thalidomide law remains unchanged, a worrying scenario can be foreseen. Current law does not prohibit the sale and dispensing of thalidomide (teratogenic) analogues in commercial pharmacies. Moreover, new product promotion by companies is likely to increase the frequency with which analogues are prescribed, regardless of their cost-effectiveness.

For the sake of coherent drug regulation, the current law must be amended so that restrictions on thalidomide sales, distribution and dispensing are extended to those analogues that are proven or suspected to be human teratogens. Additionally,

xii Gay et al.'s investigation[64] was a "case-control" designed study based on the Mayo Clinic's (USA) medical records.

a clause should be included stating that thalidomide analogues can only be registered in the country if gold-standard[xiii] comparative clinical trials demonstrate that they are clinically superior (in terms of efficacy and/or safety) to thalidomide-based (optimized) therapeutic regimens. The foregoing legal provision is needed to strengthen regulatory decisions that make exceptions to ANVISA's rule of not rejecting approvals for marketing based merely on the fact that the drugs are putative "me-too"s (*e.g.*, lenalidomide). It is of note that the "me-too" supporters' argument — that imitation medicines stimulate competition, thereby contributing to a reduction in drug prices — does not hold true for thalidomide and its analogues. In this particular case, the costs of treatment regimens are, in one way or another, covered predominantly by the public health system. It seems fair, therefore, that cost-effectiveness should be a requisite for the registration of novel thalidomide analogues.

In conclusion, restrictions imposed by current law on the sale and dispensing of thalidomide must be extended to its teratogenic analogues, otherwise a door is open to approve costly "me-too" drugs that are not clinically superior to their prototype medicine. Needless to say, the costs of expensive thalidomide "me-too" drugs are likely to be met predominantly, if not entirely, by the public health system.

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xiii A brief discussion of the advantages and disadvantages of study design options for assessing comparative efficacy is presented by Corinna Sorenson and colleagues[70].

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