ORIGINAL RESEARCH ARTICLE

Drug Saf 2010; 33 (1): 35-45
0114-5916/10/0001-0035/$49.95/0

Resolving a Double Standard for Risk Management of Thalidomide

An Evaluation of Two Different Risk Management Programmes in Japan

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Abstract

Background: Thalidomide, once withdrawn because of its teratogenicity, has now been re-launched worldwide. In Japan, thalidomide has been imported by individual doctors since around the year 2000. In October 2008, it was approved for the treatment of multiple myeloma (MM) by the Ministry of Health, Labour and Welfare (MHLW) on the condition that the manufacturer implemented a risk management programme termed the Thalidomide Education and Risk Management System (TERMS). It is likely that the imports of thalidomide will be used off-label to treat diseases other than MM. Thus, the MHLW is also planning to introduce a web-based registration system, referred to as the Safety Management System for Unapproved Drugs (SMUD), for thalidomide imported by individual doctors.

Objectives: To evaluate the difference between TERMS and SMUD and establish a way to resolve the 'double standard' for risk management of thalidomide treatment in Japan.

Methods: The fraction of patients with disorders other than MM was estimated by the volume of annual imports obtained from the MHLW and records of the imports for patients with MM, other oncological diseases (ODs) and non-ODs in 2007 through a major supplier covering 63% of the total imported thalidomide. The information for TERMS was obtained from web pages of the manufacturer and the MHLW. The components of TERMS were compared with those in SMUD.

Results: Provided that the distribution of the indication for thalidomide (MM) in 2007, estimated from the records of imports through the major supplier, is representative of the entire nation, it is estimated that on average 866 patients, including 851 (98.3%) with MM, are using thalidomide on any one day. However, if the major supplier's imports, which account for 63% of the total imports, are not representative of the nation as a whole, possibly only half of the patients treated with thalidomide in Japan have MM. This would be the case in a scenario where the remaining 37% of imports are exclusively used to treat disorders other than MM. TERMS consists of tools

for education and registration of patients, and has the potential for real-time intervention. SMUD is a system for registration of patients and exchange of safety information between health professionals, but has some mandatory components that encourage patient registration. TERMS and SMUD are different in nature, and they impose different criteria that doctors and patients should satisfy in order to use thalidomide. To eliminate this double standard, implementation of a single system would be desirable. However, improvement of SMUD may be the second best option by developing tools for patient education, enhancing the potential for real-time intervention and monitoring thalidomide usage by each patient.

Conclusions: On average, a total of about 1000 patients are estimated to be using thalidomide on any one day in Japan. It is likely that those patients are placed under one of two different risk management programmes. SMUD should be improved so that all patients are monitored in a way that results in a similar level of risk management.

Background

Thalidomide was used as a sedative between the late 1950s and the early 1960s when it was removed from the market because of its teratogenicity. In 1965, the effect of thalidomide on erythema nodosum leprosum was discovered.[1] Then in 1999, a marked effect of thalidomide on refractory multiple myeloma (MM) was reported,[2] which was subsequently confirmed by many other papers.[3-10] Some authors have interpreted these findings as suggesting that antiangiogenic and other effects of thalidomide are beneficial for a variety of malignant diseases.[11-17] However, thalidomide did not show significant effects in the treatment of most solid tumours,[18-25] although some researchers believe that it may be a promising treatment for specific types of solid tumours[26,27] or in the palliative care of cachexia due to terminal cancer.[28,29]

Individual Japanese doctors started importing thalidomide into Japan around the year 2000 in order to treat their patients. Facing a rapid increase in imports of thalidomide in the following 2–3 years,[30] the Japanese Society of Clinical Hematology (JSCH; currently reorganized as the Japanese Society of Hematology [JSH]) published 'guidelines for the appropriate use of thalidomide for MM'[31] in December 2004 to provide standards for the treatment of MM with this drug. From 2005 to 2008, the Ministry of Health, Labour and Welfare (MHLW) requested that a research group (including some of the present authors) develop a web-based system for patient registration and exchange of safety information between health professionals regarding imported thalidomide. Because the system may be expanded to cover drugs other than thalidomide imported by individual doctors, it was named the Safety Management System for Unapproved Drugs (SMUD).

In October 2008, the MHLW approved thalidomide for treating MM on the condition that the manufacturer (Fujimoto Pharmaceutical Corporation, Osaka, Japan) implemented a risk management programme designated the Thalidomide Education and Risk Management System (TERMS). In Japanese health insurance plans, the drug fee is not reimbursed for off-label use. Even after approval, imports of thalidomide are likely to remain for patients with disorders other than MM. To cover these latter patients with disorders other than MM, SMUD is to be operated by the non-profit organization, Drug Safety Research Unit Japan under a service contract with the MHLW sometime in late 2009.[32]

TERMS and SMUD are different in nature. TERMS is a system consisting of specifically

designed risk minimization tools for approved thalidomide, while SMUD is a system of patient registration for off-label use of imported thalidomide, but has some mandatory components that encourage patient registration. These two systems impose different standards, which doctors and patients should satisfy in order to use thalidomide. The redundancy or inconsistency caused by this 'double standard' may become troublesome in medical practice. In addition, imported thalidomide is, in general, cheaper than approved thalidomide, potentially leading to administrative confusion because some patients with MM may wish to use the imported thalidomide.

In this article, we estimate the number of patients who use thalidomide that are likely to be placed under the control of TERMS and those placed under SMUD following the introduction of these two systems. We also examine ways to resolve the double standard resulting from the co-existence of two different risk management systems.

Methods

Our study was not subject to evaluation by the ethics review board, as no individually identifiable data were used.

Estimation of the Number of Patients Treated with Thalidomide

The total annual imports of thalidomide into Japan in the fiscal years 2001–2007 (1 April 2000 to 31 March 2008) were obtained from the MHLW.[33] Only the data of annual imports (per fiscal year) were available from the MHLW. However, we obtained anonymized data of monthly thalidomide imports into Japan between October 2000 and December 2007 from a major supplier (RHC USA Corporation, Tokyo, Japan) that deals with procedures required by the administrative office when an individual doctor imports an off-license drug. Those data, so far unpublished, were provided to the authors courtesy of this supplier.

To ascertain the indication for thalidomide treatment, we collected the 'reason for drug use' given on the declaration sheet submitted to the administrative office for each purchase order[30] through this supplier. We assumed that thalidomide was used exclusively for this 'reason for drug use' even if one purchase order was sometimes issued for two or more patients at once. We divided the indications for treatment into three categories: 'MM', 'other oncological diseases (ODs)' and 'non-ODs'. The category 'other ODs' included renal cell carcinoma, hepatocellular carcinoma, non-small-cell lung cancer, colon cancer, prostate cancer, myelodysplastic syndrome and 'solid tumour'. The category of 'non-ODs' included Behçet's disease, graft-versus-host disease, Crohn's disease and leprosy. Monthly imports through the major supplier were plotted against calendar year to examine time trends of thalidomide imports. The prescribed daily dose (PDD) for MM was reported as 163 mg/day in a study conducted in Japan.[34] We calculated the PDD for 'other ODs' (134 mg/day) and 'non-ODs' (108 mg/day) from the data provided by the supplier. The average number of patients using thalidomide on any one day was obtained by dividing the average daily imports estimated for 2007 by the PDD for each indication. The possible range of the total number of patients and women of childbearing potential in the entire nation was calculated under several hypothetical scenarios for the indication of thalidomide. To estimate the latter, we used the proportion of females of childbearing potential in the US or 2.5% (1186/47 792) for MM, 5.3% (2048/38 597) for other ODs and 10.6% (1235/11 631) for non-ODs.[35]

Thalidomide Education and Risk Management System (TERMS)

The information for TERMS was obtained from the web pages of the manufacturer and the MHLW. We investigated questions given to each of three risk groups (males, females not of childbearing potential and females of childbearing potential) as well as frequency and timing for shipping of the questionnaire sent to patients, pharmacists and doctors for each risk group.

Safety Management System for Unapproved Drugs (SMUD)

The information for SMUD is available on the SMUD web pages.[32] We examined the differences between available tools for risk minimization between SMUD and TERMS.

Statistics

The annual national imports of thalidomide in 2002 were estimated as the sum of one-quarter of imports in the fiscal year 2001 (between April 2001 and March 2002) and three-quarters of imports in the fiscal year 2002; those for 2003–7 were also estimated in a similar fashion. The total number of patients and female patients of childbearing potential covered by TERMS and SMUD were estimated by assuming that all the patients with MM are covered by TERMS while other patients are covered by SMUD. Information on the distribution of indications for the use of imported thalidomide was available only for the data obtained from the major supplier. Therefore, for the different indications included, we estimated the possible range in the total number of patients and the number of female patients of childbearing potential using the method of sensitivity analysis under several scenarios for the distribution of thalidomide imported by suppliers other than the main one. The exact confidence limits of the fraction of all patients and of female patients of childbearing potential covered by TERMS and SMUD were estimated for each indication by the FREQ procedure in SAS 9.1 (SAS Institute, Cary, NC, USA).

Results

Thalidomide Imports and Estimated Number of Patients

National imports of thalidomide increased from 13 kg/year in 2001 to 33 kg/year in 2002, and became relatively stable at 48, 51, 53, 57 and 51 kg/year in 2003–7, respectively. Imports through the major supplier were 3.1 kg/year (24% of the national imports) in 2001, 17 kg/year (52%) in 2002, 36 kg/year (75%) in 2003, 37 kg/year (73%) in 2004, 36 kg/year (68%) in 2005, 32 kg/year (56%) in 2006 and 32 kg/year (63%) in 2007. In figure 1, the monthly imports of thalidomide through the major supplier are plotted against the calendar year during the period from October 2000 to December 2007. Thalidomide imports for all of the three indications increased from late 2001, although imports for 'other ODs' began to decrease from mid 2002. Since 2003, imports of thalidomide for treating MM became relatively stable, although a transitory increase took place prior to the price rise in May 2005.

Table I shows estimates of the total number of patients and female patients of childbearing potential for each treatment indication on any one day using the data during the year 2007. These numbers were based on the following assumptions:[1] distribution of the treatment indication for the entire nation is the same as for the major supplier (scenario A),[2] and thalidomide imported through other suppliers is used exclusively for one of three indication classes (scenarios B1 to B3). In any of these scenarios, the total number of patients using thalidomide on any one day in the nation is estimated to be around 1000. However, the number of female patients of childbearing potential varied between 26 and 69 in different scenarios. If we assume that only patients with MM are covered by TERMS and that the major supplier is representative of the entire nation (scenario A), then 26 (93%) of 28 potentially childbearing women may be covered by TERMS (table I). Using a hypothetical scenario in which thalidomide imported through other suppliers (19 kg in 2007) is used exclusively for either MM, 'other ODs' or 'non-ODs' (scenarios B1 to B3, respectively), then 26 (100%) of 26, 16 (44%) of 36 and 16 (23%) of 69 female patients of childbearing potential would be covered by TERMS, respectively (table I).

TERMS

The characteristics of TERMS and SMUD are summarized in table II. TERMS requires that each individual doctor, pharmacist, patient and specified wholesaler must receive and understand the safety information provided in the form of a

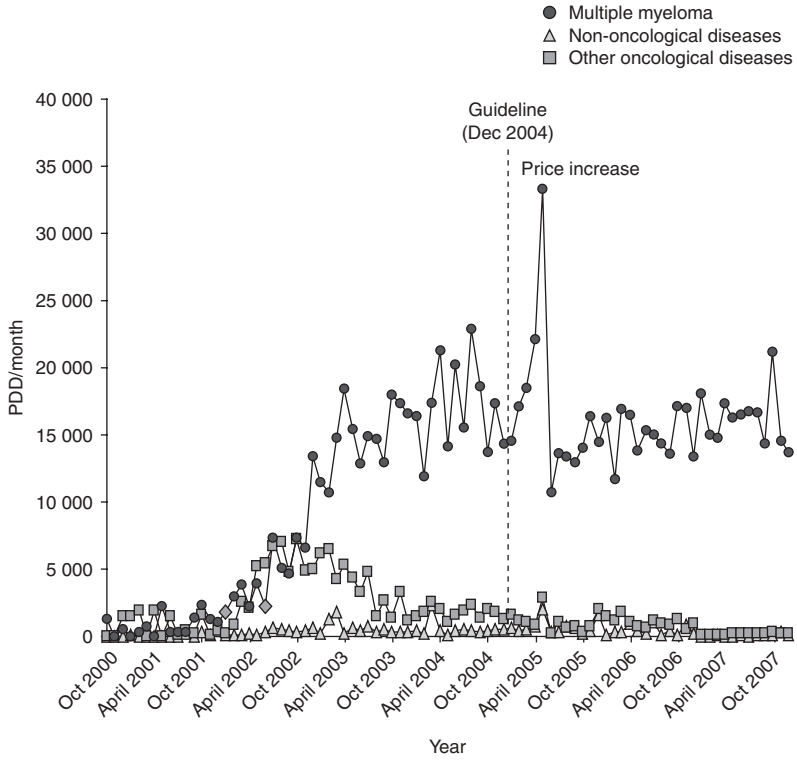

Fig. 1. Monthly thalidomide imports through the major supplier covering more than half of the total imports. The imports for three major indication classes are plotted. 'Guideline' indicates the 'guidelines on the appropriate use of thalidomide for multiple myeloma' issued by the Japanese Society of Clinical Hematology in December 2004. **PDD** = prescribed daily dose.

brochure or video tape supplied by the manufacturer, and that they must be registered at the 'TERMS centre' located at the manufacturer. Only doctors in one of about 500 teaching hospitals designated by the JSH with a certified haematology specialist can be registered to use thalidomide. For other hospitals, the use of thalidomide to treat MM may be allowed if doctors have support from a haematology specialist in another institution and are able to satisfy some additional conditions.

In TERMS, the patients are divided into three groups of males, females of childbearing potential and females not of childbearing potential. Figure 2 shows the procedures required at each patient visit to the hospital. Prior to the hospital visit, patients must complete a questionnaire, which is faxed to the TERMS centre. This procedure is followed by all patients irrespective of the risk group to which they belong, although the questions are somewhat different for the three risk groups (e.g. the result of a pregnancy test should be reported only for female patients of childbearing potential). In TERMS, thalidomide should be dispensed only within the hospital where it is prescribed. After each visit, a doctor and pharmacist must send a completed questionnaire to the TERMS centre by fax and receive a document sent from the centre by fax to authorize prescribing and dispensing the drug. In TERMS, the off-label use of thalidomide is allowed only within a clinical trial recognized by the institution.

SMUD

SMUD is a web-based system derived from components for risk management given in the

'guidelines on the appropriate use of thalidomide for MM' issued by the JSCH in December 2004. SMUD does not include the specific safety information document, although the safety information included in the JSCH guidelines is assumed to be used by patients, doctors and pharmacists. Each doctor and pharmacist should first be registered on the internet. The JSCH guideline stipulates that only sex, age, initials and diagnosis but no other personal information should be registered in order to protect the privacy of each patient. In SMUD, the doctor should answer several questions (questionnaire A, figure 3) on the internet before registering patient information. For each registered patient, a unique SMUD identification is automatically assigned. In contrast to TERMS, no survey is conducted during each patient visit, and therefore SMUD does not have the means for real-time intervention. However, the amount of thalidomide imported for each individual patient (e.g. one pack of 28×100 mg capsules) should be specified on the output list that is downloaded and presented to the administrative office (figure 3). The administrative office gives permission only when the total amount of imports given in the output list (e.g. three packs of 28×100 mg capsules; figure 3) is the same as that given in the purchase order. This may encourage patient registration, because the patient will not appear on the output list unless the doctor registers that specific patient in advance.

Table I. Estimates of thalidomide use for three major indication classes

Parameter	MM	Other ODs	Non-ODs	Total	Fraction [% (95% CI)] covered by the system	
					TERMS	SMUD
Imports through major supplier (kg)	31.9	0.3	0.1	32.3		
Estimates for the national imports						
Scenario A[a]						
imports (kg)	50.6	0.5	0.2	51.3		
no. of patients[b]	851	10	5	866	98.3 (97.2, 99.0)	1.7 (0.1, 2.8)
females of childbearing potential[c]	26	1	1	28	92.9 (76.5, 99.1)	7.1 (0.9, 23.5)
Scenario B1[d]						
imports (kg)	50.9	0.3	0.1	51.3		
no. of patients[b]	856	6	3	865	99.0 (98.0, 99.5)	1.0 (0.5, 2.0)
females of childbearing potential[c]	26	0	0	26	100 (86.8, 100)	0 (0, 13.2)
Scenario B2[e]						
imports (kg)	31.9	19.3	0.1	51.3		
no. of patients[b]	536	395	3	934	57.4 (54.1, 60.6)	42.6 (39.4, 45.9)
females of childbearing potential[c]	16	20	0	36	44.4 (27.9, 61.9)	55.6 (38.1, 72.1)
Scenario B3[f]						
imports (kg)	31.9	0.3	19.1	51.3		
no. of patients[b]	536	6	485	1027	52.2 (49.1, 55.3)	47.8 (44.7, 50.9)
females of childbearing potential[c]	16	0	53	69	23.2 (13.9, 34.9)	76.8 (65.1, 86.1)

a The major supplier is assumed to represent the entire nation.

b The estimates using the prescribed daily dose of 163 mg/day for MM, 134 mg/day for other ODs and 108 mg/day for non-ODs.

c The estimates assuming that the proportion of females of childbearing potential is 0.03 for MM, 0.05 for other ODs and 0.11 for non-ODs as reported by Uhl et al.[35]

d Thalidomide not covered by the major supplier is assumed to be used exclusively by patients with MM.

e Thalidomide not covered by the major supplier is assumed to be used exclusively by patients with other ODs.

f Thalidomide not covered by the major supplier is assumed to be used exclusively by patients with non-ODs.

MM = multiple myeloma; **ODs** = oncological diseases; **SMUD** = Safety Management System for Unapproved Drugs; **TERMS** = Thalidomide Education and Risk Management System.

Table II. Characteristics of Thalidomide Education and Risk Management System (TERMS) and Safety Management System for Unapproved Drugs (SMUD)

Parameter	TERMS	SMUD
Safety information	Eight brochures and one video for patients, doctors, pharmacists and wholesalers	No specific document is available The guidelines by the Japanese Society of Clinical Hematology, issued in December 2004, may be used
Registration		
means	Normal mail	Internet
subjects registered	Patient, doctor, pharmacist and wholesaler	Patient (sex, age, initials and diagnosis), doctor and pharmacist
Survey at each patient visit	Yes (figure 2)	No
Real-time intervention	Yes	No
Survey after treatment was terminated	Yes	Yes
Reports of adverse events	Reports are sent to the MHLW through the official spontaneous reporting system	Information is exchanged among health professionals. Some selected by the reporter and all reports of pregnancy are transferred to the MHLW
Other features	Strict performance-linked access system	Amount of imports for individual patients must be submitted to the administrative office to obtain the permission for imports for every purchase order

MHLW = Ministry of Health, Labour and Welfare.

During treatment, the doctor may report a serious adverse event or pregnancy via the internet. The reports of a serious adverse event or pregnancy sent from any doctor are posted on the web pages accessible by all SMUD users so that the information can be exchanged. Reports of serious adverse events selected by the reporter are transferred to the MHLW, but all the reports of pregnancy are automatically transferred to the MHLW. For a patient who no longer uses thalidomide, the doctor should complete questionnaire B (figure 3) concerning pregnancy and other safety issues during the treatment in order to remove the patient's identification from the output list.

Discussion

Ideally, tools for risk minimization should be pretested in order to not waste time and money. It is also recommended that if they cannot be pretested, tools with a proven track record of effectiveness may be employed.[36] TERMS was designed to incorporate all the elements of Systems for Thalidomide Education and Prescribing Safety (S.T.E.P.S.),[35,37] used without major problems for many years in the US. Although TERMS was pretested on a small scale, we believe that it still requires many refinements. For instance, exchange of as many as five documents (three questionnaires and two permissions) by fax (figure 2) for every patient visit is redundant and troublesome, and puts unnecessary strain on the hospital. It is also questionable whether such complicated procedures for low-risk patients (a male or female patient of no childbearing potential) are necessary. Another issue is that the number of teaching hospitals designated by the JSH is insufficient in rural areas. For instance, as of July 2009, no teaching hospital is available in the Okinawa prefecture, and only two are available in one of three other prefectures. The number of hospitals where thalidomide is allowed to be used for patients with MM will need to be increased in the future.

However, the more fundamental problem is that patients with disorders other than MM will not be readily covered by TERMS. This issue will be more challenging than other problems with the current version of TERMS because (i) the cost of

the official labelled drug is reimbursed in the healthcare plan in Japan, but this is not the case for off-label use; and (ii) at least formally, health services covered by health insurance should not be used at the same time as those not covered by insurance, though relaxation of this restriction is an issue that is currently being debated. Unless some new rules for these issues are stipulated, off-label use will remain the exception.

SMUD has been designed as a system for registration rather than as a self-contained system for risk minimization, although it does have some mandatory components (i.e. importing thalidomide is not permitted by the administrative office unless the total of imports of individual patients is the same as given in the purchase order). It is likely that thalidomide use for diseases other than MM is not covered by any system apart from SMUD, at least for the time being. Thalidomide use for indications other than MM appears to be declining, as estimated from the data provided by the major supplier (figure 1). Use for disorders other than MM may in fact be minimal, as in scenario A or B1 (table I). However, it is possible that scenario B2 or B3 (in particular B2) is closer to reality than scenario A or B1. This is because the country of origin and brand name of thalidomide provided by other suppliers are different from those provided by the main supplier. Although no accurate information is currently available, some groups of doctors importing thalidomide through one of the smaller suppliers are known to be prescribing the drug to treat patients with disorders other than MM (mainly solid tumours). Therefore, SMUD may have to cover one-half or more of female patients of childbearing potential in the nation (table I).

Compared with SMUD, TERMS may at least currently impose extremely restricted use of thalidomide to the extent that some patients might be deprived of the chance to benefit from it (table II). In contrast, restrictions imposed by the current SMUD are modest. However, adherence to TERMS will prevent the occurrence of untoward events more effectively than SMUD, which does not currently possess enough tools to achieve this end. For example, unlike TERMS, SMUD does not include specific education tools. The development of such education tools for patients, pharmacists and doctors is needed in the future

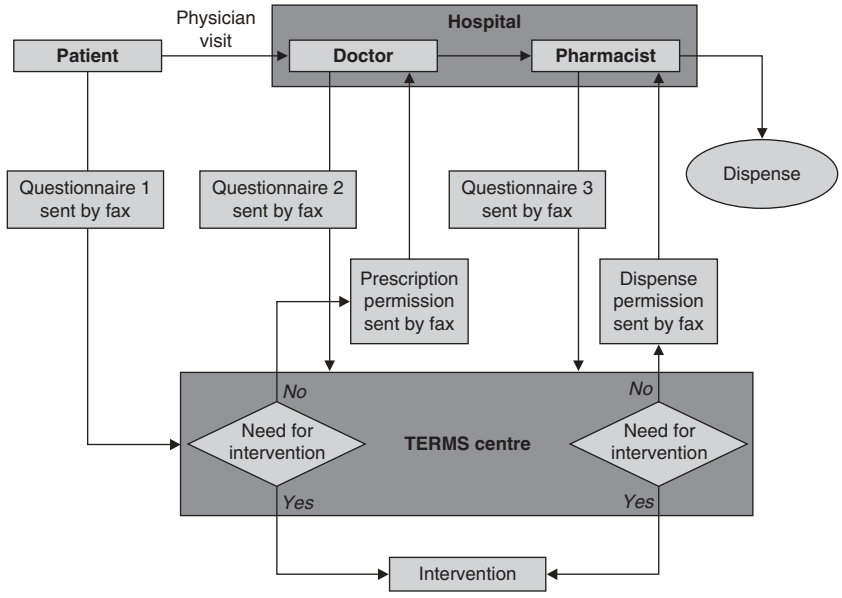

Fig. 2. Exchange of questionnaires and permissions required for each patient visit in the Thalidomide Education and Risk Management System (TERMS).

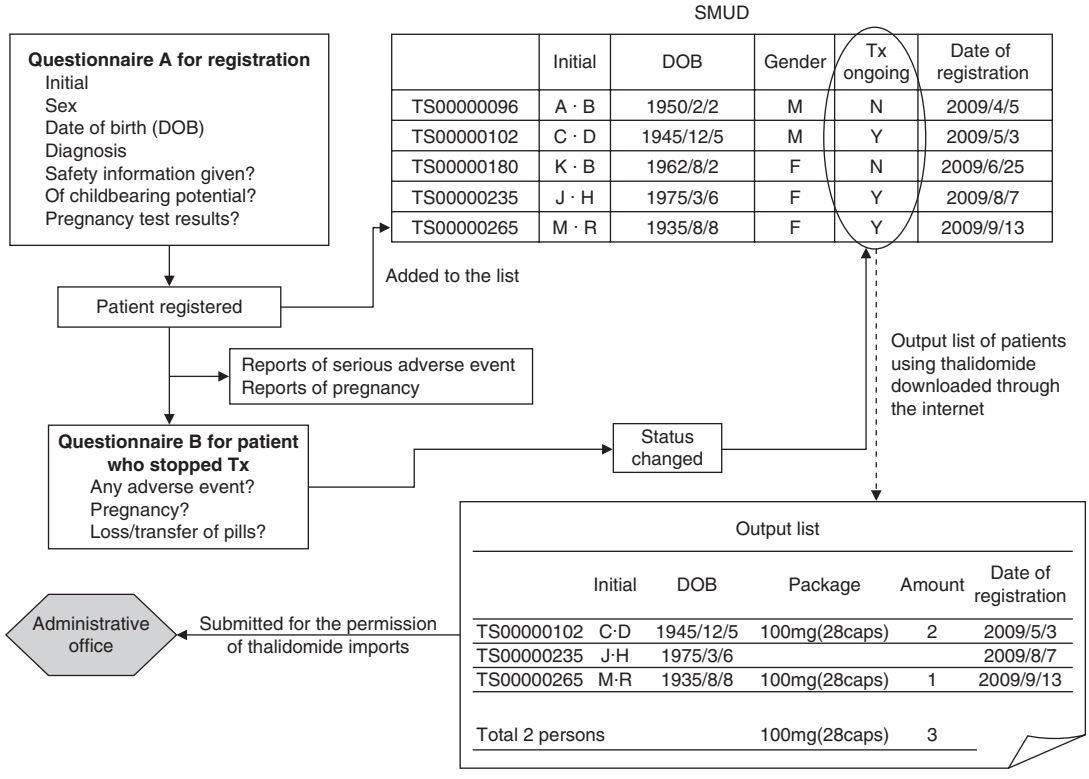

Fig. 3. Patient registration, reports on adverse events and pregnancy, and output list in the Safety Management System for Unapproved Drugs (SMUD). On the output list, only patients still under therapy are shown. The administrative office issues permission only when the amount of imports on the purchase order (not shown) is the same as the total amount given in the output list by a doctor. **Tx** = treatment.

and their use should be encouraged. Furthermore, some additional components (e.g. a tool using the telephone) should be included to enable real-time monitoring of pregnancy test results and other issues essential for risk minimization. Currently, only the initials, sex, date of birth and treatment indication are recorded, according to the JSCH guidelines.[31] However, to enable SMUD to facilitate real-time intervention, registration of full information with patient identification may be required. It is also desirable to establish a means of monitoring the number of tablets of thalidomide taken by each patient. For example, a periodic report from the pharmacist should be submitted on the amount of thalidomide dispensed to and actually used by each individual patient. This will enable any discrepancy between the total amount of thalidomide imported for a particular patient and the amount actually used by that patient to be recognized. Although insufficient information is available for a full estimation of costs, the cost of developing and running TERMS is likely to be much higher than such costs for SMUD, mainly because TERMS is a labour-intensive system.

Our study has limitations. For example, data on the fraction of patients with MM or other disorders, as well as data on monthly thalidomide imports into Japan, were available only from the major supplier. The prescribed daily doses for 'other ODs' and 'non-ODs' were calculated from the data from this supplier. It should also be noted that the fraction of female patients of childbearing potential with MM, 'other ODs' or 'non-ODs' are all derived from a study conducted in the US and published in 2006,[35] and may therefore not be directly applicable to the population of Japan in 2009. Furthermore, the number of

patients using thalidomide for MM, 'other ODs', and 'non-ODs' during 2007 were estimated by supposing that all of the imported thalidomide was actually used by the patients. This may therefore be an overestimate if some of the thalidomide imported is not actually taken by the patient. It is also possible that some doctors or patients may import thalidomide illegally without permission from the administrative office (e.g. in the traveller's luggage, or small international parcels that may slip through the official inspection process). If the amount of such illegal imports is not negligible, estimates of the number of patients may be too low in the current study.

In the US, prior to the introduction of iPLEDGE as a single risk-management programme for isotretinoin, several systems for risk management of this drug were developed. This was just after the implementation of 'System to Manage Accutane-Related Teratogenicity' (SMART) by Roche in 2002 when multiple generic manufacturers entered into the market. Although the multiple systems satisfied the same conditions as those for SMART, the situation was rated as being confusing.[38] Ideally, a single centralized system should manage all the patients treated with a drug requiring special risk management. Unfortunately, the regulation of generic drugs, healthcare systems and other issues may impede the implementation of a single centralized system. We believe that the sophistication of SMUD as a management tool should be augmented so that the problems associated with the double standard are mitigated until a single centralized system can be put into operation.

Conclusions

A total of around 1000 patients are using thalidomide on any one day for MM and other conditions in Japan. Although thalidomide was approved for use in Japan in October 2008, it is likely that imports of this drug for off-label use will remain steady. It may also take some months, or even years, before imports of thalidomide for MM completely stop when TERMS has been fully refined and accepted by all the hospitals in which patients with MM are treated by this drug. The available data do not allow reliable estimates for the number of female patients of childbearing potential using thalidomide. However, we believe this figure may range between 30 and 100 patients. The fraction of these female patients covered by TERMS may also be between around 20 and 100%. To bring all the patients treated with thalidomide under a single centralized system, several issues, including those associated with regulation of reimbursement in the healthcare system, need to be properly resolved. Until such a situation can be brought about, SMUD should be enhanced to accomplish a higher level of risk management. In this way, SMUD can work as a complementary system to TERMS.

Acknowledgements

The Drug Safety Research Unit Japan is a non-profit organization supported by the annual membership fee from individuals in addition to approximately 30 drug companies. Individual studies have been independently conducted under the contract with the Japanese Ministry of Health, Labour and Welfare, academic bodies such as the Japanese Society for Pharmacoepidemiology, and drug companies.

No specific sources of funding were used to assist in the preparation of this study. The authors have no conflicts of interest that are directly relevant to the content of this study.

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