—Regular Articles—

Analysis of Information Submitted by Clinical Trial Sponsors regarding the Safety of Investigational Drugs

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(Received October 8, 2003; Accepted December 25, 2003)

During performance of clinical trials in medical institutions, information regarding the safety of investigational drugs is submitted by trial sponsors according to guidelines for good clinical practice. In the present study, reports of clinical trials conducted at the University of Tokyo Hospital were examined, focusing on the safety information provided to the Institutional Review Board (IRB). Two hundred two reports (52 protocols) of safety information were submitted to the IRB by clinical trial sponsors between April 2000 and March 2001, of which 185 contained a total of 3021 cases of adverse events. Of those, 194 reports were judged by clinical investigators/physicians not to be associated with any significant problems and the trials were continued. For 157 of those 194 reports, it was considered unnecessary to inform the test subjects of the report contents, including the adverse events. The decision of whether or not the test subjects should be informed of such contents tended to depend on the causal relationship between the adverse events and drug intake, as well as the predictability of the adverse events. For 8 of those 194 reports, the IRB recommended that the clinical investigators/ physicians provide information to the test subjects and/or submit detailed information on the status of these subjects to the IRB. From these results, we suggest that establishment of a system to unify and evaluate drug safety information is necessary to provide safe and efficient clinical trials.

Key words——investigational drugs; safety information; clinical trials; IRB

INTRODUCTION

During performance of clinical trials in medical institutions, information regarding the safety of investigational drugs is submitted by the trial sponsors according to guidelines for good clinical practice. Investigators/physicians working at the University of Tokyo Hospital are required to submit their opinion in addition to relevant safety information to the Institutional Review Board (IRB). Based on the submitted materials, continuation of the clinical trials of the corresponding investigational drugs is discussed and determined by the IRB.

In the present study, reports of clinical trials conducted at the University of Tokyo Hospital were examined, focusing on the safety information provided for the examined drugs to the IRB. We also analyzed the correspondence submitted by the investigators along with the final judgment by the IRB regarding continuation/discontinuation of the respective study. Based on the information obtained, the current status and problems associated with the management of safety information regarding investigational drugs are discussed.

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METHODS

Contents of the Safety Information Provided to the IRB All cases considered by the IRB regarding new safety information offered by the sponsors of clinical trials in fiscal year 2000 (April 1, 2000 to March 31, 2001) were reviewed. For the protocol used for the investigational drugs, the report contents were classified as either an adverse event report or other. Further, the difference in number of reports of adverse events was compared between those associated with foreign developed investigational drugs and those associated with domestic development. We investigated the reported adverse events of each case and classified them based on the kind of information source, which included foreign and domestic post-marketing data, foreign and domestic clinical trial data, and published reports.

Correspondence of investigators regarding safety information and decision by the IRB We examined the contents of comments by the investigators/physicians attached to each report and determined whether they had informed the subjects who were receiving administration of the investigational drugs regarding the content of the respective report. The decision of the IRB regarding the continuation of clinical trials based upon the submitted reports was also examined.

RESULTS

Contents of Safety Information Examined by the IRB During the survey period, 202 reports (52 protocols) concerning safety information were submitted to the IRB by the sponsors of clinical trials, of which 185 (91.6%) contained a total of 3021 cases of adverse events, with each report containing from 1 to 120 cases (Fig. 1). The average number of adverse events per protocol was 69 for drugs with foreign development and 4 for those with domestic development (Fig. 2). Foreign post-marketing data, foreign clinical trial data, domestic post-marketing data, domestic clinical trial data, and published reports accounted for 80.6, 13.8, 2.6, 2.6, and 0.4%, respectively, of the sources of information (Table 1).

Correspondence of investigators regarding safety information and decisions by the IRB The opinions of the investigators/doctors included in the 202 reports on safety information are shown in Fig. 3. One hundred ninety four (96.0%) of these reports were judged by the investigators/physicians not to be associated with any significant problems and the trials were continued. For 157 of those 194 reports, it was considered unnecessary to inform the test subjects of the contents, including the adverse events. Seven (3.5%) reports led to an alteration of the testing protocol and/or consent explanatory documents (Table 2).

Further investigation revealed that "an unknown or weak causal relationship between adverse events and drug intake", "known events with drugs that were described in the consent explanatory docu-

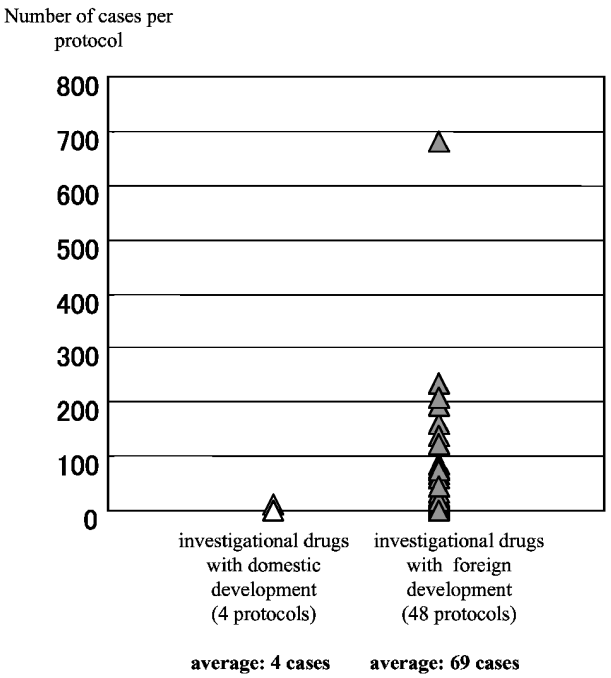

Fig. 2. Number of Cases of Adverse Events per Protocol

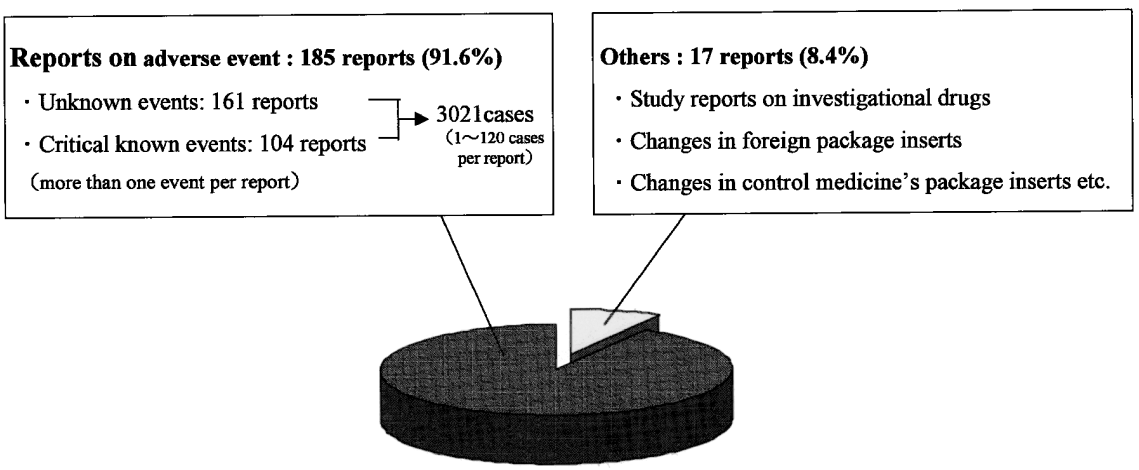

Fig. 1. Contents of Safety Information Examined by the IRB
Two hundred and two reports for 52 protocols were analyzed.

ments'', and ''insufficient information regarding the adverse event'' were most often listed as reasons by the investigators/physicians for not informing the test subjects of the respective report contents, while ''unknown severe adverse events or unknown adverse events whose causal relationship with drugs cannot be denied'', ''unknown adverse events related with drugs'', and ''known, but severe adverse events related with drugs'' were most often given as reasons for informing. In addition, reasons given for alterations of protocol and/or consent explanatory documents included ''changes in foreign package inserts'' and ''appearance of reports of severe adverse events regarding the corresponding investigational drug''.

Among the 202 reports examined in the present study, continuation of clinical studies was approved by the IRB for 194 (96.0%), whereas conditioned approval was given for the remaining 8 (4.0%). As for those given conditioned approval, the IRB recommended that the investigators/doctors provide information regarding the drugs to the test subjects and submit detailed information on the status of the subjects (Fig. 4).

Table 1. Sources of Information on 3021 Cases of Adverse Events

Source of information	Number of cases	(%)
Foreign post-marketing data	2436	80.6%
Foreign clinical trial data	416	13.8%
Domestic post-marketing data	78	2.6%
Domestic clinical trial data	79	2.6%
Published reports	12	0.4%
Total	3021	100.0%

Table 2-1. Reasons Investigators Considered it Unnecessary to Inform the Test Subjects of Safety Information

Contents	Number of matters
Unknown or weak causal relationship	63
Known events	62
Insufficient information	48
No influence on occurrence frequency of adverse events	26
Difference in target disease	17
Others	7

One hundred and fifty seven reports were analyzed, some containing more than one reason.

Table 2-2. Reasons the Investigator Considered it Necessary to Inform the Test Subjects of Safety Information

Contents	Number of matters
Unknown severe adverse events or unknown adverse events whose causal relationship cannot be denied	14
Unknown events	10
Known, but severe adverse events	5
Known event influencing the patient's life	5
Others	3

Thirty seven reports were analyzed, some containing more than one reason.

Table 2-3. Reasons that Led to an Alteration of the Testing Protocol and/or Consent Explanatory Documents

Contents	Number of matters
Changes of foreign package inserts	4
Report of severe adverse reactions on investigational drugs	2
Changes of control medicine's package inserts	1

Seven reports were analyzed.

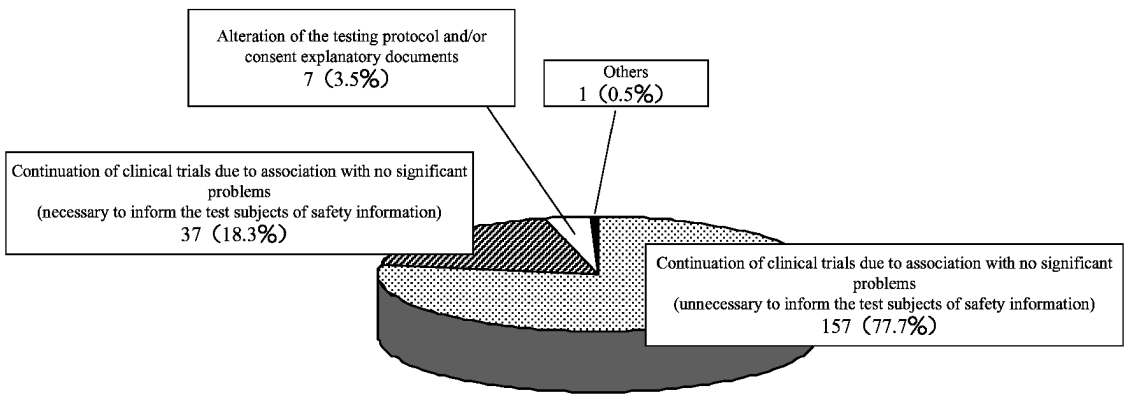

Fig. 3. Opinions of Investigators/Doctors on Safety Information (n=202)

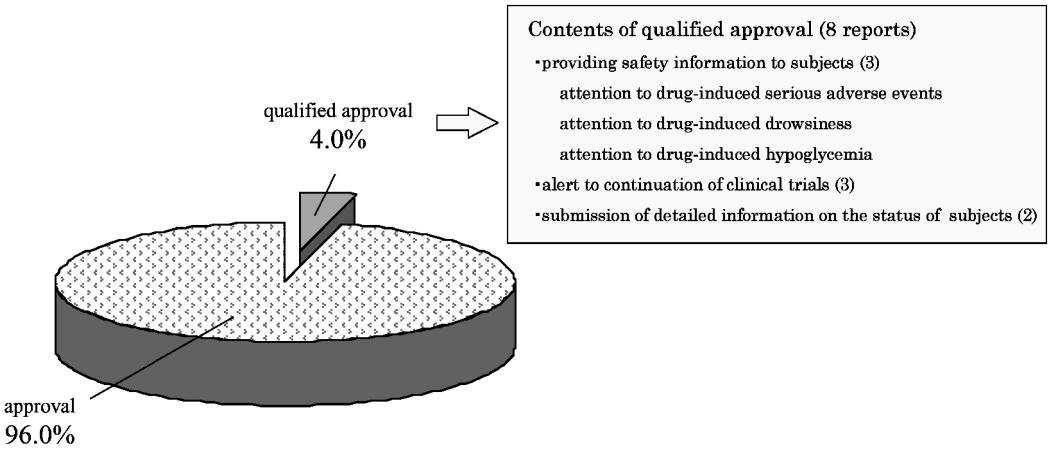

Fig. 4. Final Decisions of IRB on the Continuation of 202 Clinical Trials
IRB examined 202 safety information reports and considered the investigator's opinion.

DISCUSSION

The method of safety information management regarding investigational drugs in clinical trials is determined by good clinical practice, as safety information is one of the most important factors for test subjects to determine their entry into or continuation of the trial. Safety information is also important for the IRB of each medical institution to discuss the continuation of clinical trials. However, the methods used by trial sponsors to report such information and medical institutions to manage these data have not been unified in Japan. For this reason, medical institutions have been attempting to determine how to point out problems associated with safety information of drugs, as well as manage such information, provide the appropriate information to test subjects, and judge whether or not the clinical trials should be continued based upon the submission of safety information.[1—6)]

Two hundred two reports regarding drug safety information were provided by clinical trial sponsors from April 2000 to March 2001, most of which included cases of adverse events that amounted to a total of 3021. The number of cases in each report ranged from 1 to 120. Further, the number of case reports for drugs with foreign development was 69, while there were 4 case reports for those with domestic development. Ninety percent or more of the sources of safety information had foreign origin, resulting from the fact that our hospital accepts many clinical studies of drugs that have been developed in foreign countries. In addition, since some of the drugs with foreign origin have already been used in clinical practice in foreign countries, many pieces of safety information are available in foreign countries. The same situation has been reported by other Japanese institutes performing the clinical trials. Studies in Kanazawa University Hospital revealed that 82.4% of 1907 case reports on safety information submitted between April 1999 and November 2000 originated from foreign countries.[2)] In addition, in the International Medical Center of Japan, the survey of 140 case reports on safety information submitted between April 2000 and March 2001 revealed that 71, 8, 9 and 11% originated from foreign post-marketing data, foreign clinical trial data, domestic post-marketing data and domestic clinical trial data, respectively.[6)]

The investigators/physicians determined that most of the problems regarding safety information were not serious enough to consider discontinuation of clinical trials. However, approximately 20% of the submitted safety information was communicated to test subjects, of which a portion was associated with alterations in the consent explanatory documents. The final determination of whether or not the test subjects should be informed of such information tended to depend on the causal relationship between the adverse events and drug intake, as well as the predictability of adverse events. The important role of the IRB to perform safe clinical trials was suggested from the finding that for 4% of the reports the IRB recommended that the test subjects be informed of reported contents and the investigators/physicians reconsider the continuation of the clinical trials.

The results of the present study revealed that many pieces of safety information were submitted to our hospital, however, there is no unified system available in Japan to effectively manage such information. Without such system, it is difficult for the IRB to review all safety information in detail during the limited term and consequently, it is possible that test subjects can receive only limited pieces of safety information. In addition, it is possible that the IRBs in each institution may make a different judgement for the same safety information. In order to establish a high quality and uniform review system for the evaluation of investigational drugs, it is considered necessary to construct a system that uniformly manages and evaluates reports submitted to each medical institution, and/or to prepare national guidelines for such uniform evaluation.

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