ヒトゲノムの意味を理解する.
Discount Genome Information.
ゲノム情報の呪縛を断ち斬る.

Appreciate Genome Research.
ゲノム研究は「人を知る」ために欠かせない重要な研究だ.

最後に、私は人のゲノム研究は、人間を知るために重要な研究だと思っています。ゲノム情報ですべてが決まるという呪縛を断ち切ること、それと同時にゲノム研究は「人間を知る」ために欠かせない重要な研究だから支えていきましょうという態度を育てていくことが大事なのではないかと思っています。それは、私の体、私の情報、私の存在というのがこれまでの積み重ねに支えられている、と同時に今の社会、あるいは未来の社会を支えていくことを知り、実感し、自らもそれに加わる決意を育てていくことだと考えています。

わたくしの「からだ」の社会性

◎わたくしのからだの,
何がわたくしのもの？
◎わたくしのからだの,
何が私たちのもの？
◎わたくしのからだの,
何があなたたちと共有？
◎わたくしのからだの,
何があなたたちのもの？

ですから、「私の体の何が私のものであるか」ということから出発するのですが、「私の体の何が私達のものか」、「私の体の何があなた達と共有なのか」、そして私が死んだ後、あるいは私の知らないところであったとしても「私の体の何があなた達のもの」として役立つのか、あるいは役立てるためにあなた達は何をしてくれるのか、そういう問題があると思っています。いずれにしても、臨床の現場にゲノム研究の成果として遺伝子検査が入ってきたときに、それを受け入れて、臨床の場が荒れてしまうというのではなく、遺伝子検査の結果をふまえて目の前にいる患者さんを診るという、そういう医療になって欲しいと強く願っています。

ゲノム情報を活かすことのできる社会の構築、この生みの苦しみを越えて、ゲノム情報を活かした医療・医療政策、患者と医師、社会との関係の変化を支えるために何が必要であるのか。次の世代、次の世紀への私たちの責任の重さを思います。

言　語　解　説

1）**セカンドオピニオン**
（英 second opinion）医師から治療方針に関する説明を受けたことを、別の医師に相談すること。

2）OECD
（英 Organization for Economic Cooperation and Development の略）経済協力開発機構。OEEC の発展した機関。1961 年、OEEC 加盟諸国に、アメリカ、カナダが加わり、ヨーロッパと北米を結ぶ経済開発機構として発足。経済成長、発展途上国援助、世界貿易の拡大を目的とする。日本は 1964 年に加盟。

3）**相互作用**
物や現象が互いに作用し合い、また影響を及ぼし合うこと。交互作用。

4）FDA
（英 Food and Drug Administration の略）米国、食品医薬品局。

5）**ポストマーケティングサベランス**
（英 post marketing surveillance）市販後調査のことで、医薬品の場合、諸事情から認可後、一定期間後に副作用情報などを集め再評価を行うことがある。

6）**レギュレーション**
（英 regulation）法規制。

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www.nature.com/tpj

EELS (Ethical, Economic, Legal & Social) ARTICLE

Pharmacogenomics in Japan

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It is clear that in order for scientific advancement to become a reality, the exchange of views and information among people with different backgrounds is necessary. Thus, international cooperation is important for the global promotion of pharmacogenetics and pharmacogenomics. Unfortunately, information from Asia still seems to be insufficient, even in the globalized world of science and medicine. For this reason, we would like to provide an overview of pharmacogenomics in Japan.

INFRASTRUCTURE FOR PHARMACOGENOMICS LED BY THE GOVERNMENT

The Japanese government started the Millennium Project in April 2001 to focus on technological innovation concerning three subjects: computerization, an aging-society, and environmental issues. These points are expected to become more important and urgent to the Japanese economy as time progresses, hence any positive developments resulting from the project could brighten the outlook for the future. Research and analysis on the human genome was conducted as one of the projects. Data on 195 059 SNPs have been obtained, and to date, 84 557 of them have been analyzed for their allele frequency using samples from a general population of 752 Japanese. This includes around 6000 coding SNPs (cSNPs) for about 180 pharmacokinetic-related enzymes.[1] These data are expected to have a positive effect on pharmacogenomic research and clinical studies in the future.

In October 2002, the International Hap Map Project was started for haplotype mapping. Participating countries include the USA, UK, Japan, Canada, and China. A total of 200–400 blood samples from Mongolian, Caucasian, and Negro donors are to be collected for haplotype mapping over the next 3 years. Japan will bear one-quarter of the responsibility for analysis. The data will be published in 2004, and their clinical application to pharmacogenomics is expected.

The Personalized Medicine Project (Biobank Japan Project), aimed at optimizing drug therapy based on elucidating a patient's genetic constitution, was launched in June 2003. Participants in this project consist of eight medical institutes, 37 hospitals, two research institutes, and the new Biobank Japan. A total budget of 20 billion yen will be invested in this project by the government over a 5-year period, starting in 2003. The first order of business for the project will be to elucidate SNPs tied to drug efficacy as well as those related to the onset of adverse reactions and diseases. Over 40 such diseases will be studied, including cancer and diabetes. The research will be conducted using DNA and serum obtained from approximately 300 000 patients who have given their prior, informed consent for the project.

In order to promote sample collection, the placement of trained medical coordinators in the 37 hospitals involved is now under consideration. Security measures for the computer systems used are also being considered. These measures include fingerprint authorization as well as a system by which a computer will destroy itself if someone makes repeated, unsuccessful attempts to access restricted areas of the databases of the participating institutes.

Some experts say that the Personalized Medicine Project should be initiated only after nationwide discussion. At the same time, high expectations prevail because of the success of the Millennium Project. The promise held by the innovative analysis techniques and the ethical approach also have people excited about the project. However, concerns have been expressed over the paternalistic attitude many Japanese physicians still harbor. Some believe that because of this attitude, informed consent will not become a popular and widespread practice. In the wake of the various projects relating to the human genome and genes form the entire Japanese population, though, the health care environment in Japan is expected to eventually reform.

BIOETHICS

The Personal Information Protection Law was legislated in May 2003. It has been suggested that this law does not apply to fields of scientific research or matters concerning public health and hygiene. However, many feel that it is in these areas where the law is most necessary. At the express request of the Japan Medical Association (JMA), the Upper House Special Committee on Personal Information Protection stated in a subsidiary resolution that immediate consideration would be given to a separate law for fields such as health care. This consideration includes research, development, and application in fields where public cooperation is vital for the establishment of advanced technologies (such as gene therapy) and where a high level of protection

for personal information is sought by the public.

There are several ethical guidelines significant to the promotion of pharmacogenomics in Japan, including the following:

- Fundamental Principles of Research on The Human Genome (June/2000)
- Ethics Guidelines for Human Genome/gene Analysis Research (April/2001)
- Guidelines for Genetic Testing, by The Japan Society of Human Genetics, Council Committee of Ethics (August/2003)
- Ethical Guidelines for Performing Human Genetic Testing Contracted to the Japan Registered Clinical Laboratories Association (April/2001)

The second guideline is the most important among those listed, requiring compliance by all researchers in these fields. The basic policies are as follows: (1) respect for human dignity, (2) adequate prior explanation and consent by one's own free will (informed consent), (3) complete protection of personal information, (4) research conducted shall be useful to society and shall contribute to human intellectual advancement, health, and welfare, (5) priority shall be placed on the protection of individual human rights rather than social/scientific benefits, (6) assurance of study adequacy by preparation of and compliance with study protocols based on the guideline after their review and approval by an independent ethical review board, and (7) assurance of study legitimacy by third-party monitoring of study performance at each site and by publishing study results. In total, 153 research organizations, including universities, national and public institutions, hospitals, and businesses, have been registered as of October 2003. The terms 'human genome/gene analysis,' as used in the guideline, include analysis of germline mutation or polymorphism, but not that of somatic mutation, which includes cancer, gene expression analysis, or proteomics. Clinical studies and postmarketing surveillance are regulated by the Pharmaceutical Affairs Law and are thus excluded from the guideline.

PHARMACEUTICAL LAWS AND REGULATIONS

There are two notifications related to pharmacogenomics issued by the Ministry of Health, Labour, and Welfare. One is 'Clinical Pharmacokinetic Studies of Pharmaceuticals (June 1, 2001)' and the other is 'Methods of Drug Interaction Studies (June 4, 2001).' Both of them are concerned with genetic polymorphisms. The necessity for the accumulation of know-how on pharmacogenomic methods and the creation of an organization for this purpose is also described.

ESTABLISHMENT OF PHARMACOGENOMICS PLATFORMS BY INDUSTRY

Over the past few years, working groups of the Japan Health Sciences Foundation (JHSF) have conducted investigations on genomics and issued several reports. The JHSF then played the role of 'compass,' providing direction for the development of pharmacogenomics in Japan. A conference entitled 'Symposium on Genomic-based Medicine 2003' was held by the JHSF in April 2003.

In September 2000, 43 member companies of the Japan Pharmaceutical Manufacturers Association established the Pharma SNP Consortium to conduct pharmacokinetic research on Japanese gene polymorphism. Blood samples donated by 752 Japanese volunteers were used in a frequency analysis of 4272 SNPs from 202 genes associated with pharmacokinetics, including cytochrome *P*450 (CYP), transporter, and esterase. Function analysis of the gene products of some CYPs and transporters, along with their variants, were also conducted.[2] Some of these findings have already been published, and others will be published shortly. Cell lines were also established from the samples and deposited in the Health Science Research Resources Bank.

PHARMACOGENOMICS IN DRUG DEVELOPMENT

The report, 'Clinical Application of Pharmacogenomics,' published by the JHSF in April 2003, describes the current situation and issues concerning pharmacogenomics in Japan. It also lists the results of a questionnaire survey on clinical development using pharmacogenomics that was conducted in Japanese companies.[3] The questionnaire was mailed to its 91 associate members, and the 44 that were returned were used for analysis.

The present status of clinical development using pharmacogenomics in Japan is as follows: 16 companies are investigating or are scheduled to investigate the effect of genetic polymorphism clinically; four clinical studies on pharmacokinetics are underway, and six studies are planned for the next couple of years. Three clinical studies are underway on pharmacodynamics, and seven studies are planned. Five companies plan prospective studies for their marketed products. The reason why most other members are not planning such studies is that they have no appropriate candidates as yet. Seven companies have already established an organizing system for managing personal information, 15 have started considering such a system, and three were considering entrusting this to an outside company. Among the questionnaire items, questions concerning the current issues surrounding genotyping resulted in the following replies (from more than 50% of companies): 'to get an understanding of genotyping' and 'document preparation related to the informed consent,' these replies were followed by 'relationship with ethics guidelines,' 'acquisition of an agreement for the necessity of conducting genotyping in the company,' and 'acceptance of genotyping by Institutional Review Boards.' Many companies proposed education and the establishment of guidelines as measures to address such issues. Others suggested that the government should positively promote participation. What must be stressed is that the appropriate people should make an effort to protect genetic information and human rights suffi-

ciently, make the information public, and thereby obtain public acceptance. Others looked forward to sharing an understanding and cooperation in order to apply the data to pharmacogenomics. As it is unclear to what extent the medical environment and infrastructure are prepared for pharmacogenomics, there is a fear of uncertainty about the extent to which information or established diagnoses can be applied clinically. Thus, the government is required to prepare the infrastructure, while pharmaceutical companies positively promote clinical studies incorporating pharmacogenomics, since it is their mission to supply better drugs by making use of the latest scientific advances.

EXAMPLES OF PHARMACOGENOMICS

Immuohistochemistry and fluorescent *in situ* hybridization tests, used to select patients to whom trastuzumab should be administered, are covered by health insurance and have already been used in clinical practice.

Troglitazone, a drug for the treatment of type II diabetes, was forced to be withdrawn from the market in March 2000 due to liver toxicity. A total of 68 SNPs in 51 candidate genes from the blood samples of 110 patients were analyzed. The results indicated that SNPs in the metabolic enzymes, GSTT1 and GSTM1, might play a role in the development of this liver toxicity.[4]

A method for predicting the therapeutic effects of imatinib mesilate by gene expression in each subject has been developed.

Clinical trials to investigate the therapeutic effects of gefitinib based on changes in gene expression have been performed since 2001 and projects to identify SNPs related to acute lung injury have just started.

Projects to identify SNPs related to the effectiveness and adverse reactions of pioglitazone, an insulin-sensitizing agent, have begun. Any discovery should pave the way to tailor-made medicines as well as new drug development.

Omeprazole and lansoprazole, proton pump inhibitors, are metabolized mainly by CYP3A4 and CYP2C19. Genetic polymorphisms in CYP2C19 affect these pharmacokinetic profiles. The frequency of CYP2C19 as a poor metabolizer (PM) has been reported to range from 18 to 23% in Japan. PM or an extensive metabolizer (EM) in patients is determined on an individual basis, and their relationship with the efficacy and safety of the long-term administration of these products should be investigated via postmarketing surveillance.

Genetic polymorphisms in MxA and MBL affect responses to interferon in patients with hepatitis C. Development of a genetic test for them on the DNA chip is ongoing.

Genetic polymorphisms in the promoter region of UGT1A1 affect the severe toxicity of irinotecan. Development of a genetic test for them is ongoing.

The pharmacogenomic approach to drug research and development by Japanese companies is lagging compared to that of European and American companies, although it seems some clinical trials are being performed based on SNP data obtained in Japan. We strongly hope that the private sector in Japan will face the challenges of using pharmacogenomics in drug development. The understanding and support of clinical investigations is just getting underway. The institution of translational research centers may be necessary, and the importance of public acceptance cannot be underestimated. Research through reasonable and flexible use of the guidelines for genome research can be accomplished without compromising ethics. The incorporation and resolution of all these issues will allow us to make breakthrough advancements for a brighter, healthier future, both for Japan and worldwide.

DUALITY OF INTEREST

None declared.

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SPECIAL REPORT

Pharmacogenomics in Asia

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It is well known that genetic polymorphisms, such as SNPs, vary between races so that not only Western populations' pharmacogenetic/pharmacogenomic data but also data from Asians are viewed as vital to drug development and clinical practice. For this report, the current state of pharmacogenetic/pharmacogenomic-related activities in five Asian countries (China, Japan, the Republic of Korea, Singapore, and Taiwan) were researched and analyzed. The results show that there are multiple efforts underway in all of these countries, including the examination of guidelines, the implementation of projects to establish foundations for pharmacogenetics/pharmacogenomics, and several clinical trials, that have hardly been recognized up to now.

Introduction

It is well known that there are ethnic differences among genetic polymorphisms, such as SNPs. For example, of the 452 SNPs identified in cytochrome P450 (CYP) by the Pharma SNP Consortium, 244 could be considered unique to the Japanese [1]. Therefore, not only pharmacogenetic/pharmacogenomic (PGt/PGx) data from Western populations (Caucasian) but also from Asian populations should be viewed as vital to drug development and the clinical practice of medicine in the genomic era. For this report, the current situation of drug development incorporating PGt/PGx and programs aimed at establishing an infrastructure for PGT/PGx research in Asia will be discussed. The information presented was collected while interacting with experts in PGt/PGx from China, the Republic of Korea, Singapore, and Taiwan, as well as from published material [2].

Guidelines on pharmacogenetics/ pharmacogenomics

The US Food & Drug Administration (FDA) published the 'Draft Guidance for Industry on Pharmacogenomic Data Submissions' on November 3, 2003, to encourage the use of PGt/PGx in drug development [101]. Most pharmaceutical companies see this as a positive step.

In Japan

A draft proposal entitled 'Submitting clinical trials information in which pharmacogenomic approaches were used to the regulatory agency for making a guidance document for pharmacogenomic approaches on pharmaceutical developments' has also been issued by the Japanese Ministry of Health, Labor and Welfare (MHLW) on June 8, 2004 [102,103].

There have been two notifications related to PGt/PGx that have been issued by the MHLW. There are the 'Clinical Pharmacokinetic Studies of Pharmaceuticals' notification, which was released on June 1, 2001, and the 'Methods of Drug Interaction Studies', issued on June 4, 2001. Both notifications refer to genetic polymorphisms.

In Taiwan

The 'Guideline on Ethnic Factors in the Acceptability of Foreign Clinical Data' (2000) and relevant notifications were issued by the Department of Health (DoH) of Taiwan, which are related to PGt/PGx and are expected to encourage pharmaceutical companies to involve Asia in multinational clinical trials that incorporate genetic polymorphism analysis.

Although no specific guidelines or notifications referring specifically to PGt/PGx have been released in Asia to date, most institutions have begun the consideration of developing guidelines.

Guidelines on bioethics

When the General Conference of the United Nations Educational, Scientific and Cultural Organization (UNESCO) adopted the 'International Declaration on Human Genetic Data' in 2003, awareness surrounding bioethics issues seemed to be changing in most parts of the world in response to the rapid advances in human genome research [104]. The importance of bioethics is widely recognized in Asia, although social values and traditions are different between Asian and Western countries.

Keywords: China, Japan, pharmacogenetics, pharmacogenomics, Republic of Korea, Singapore, Taiwan

future medicine

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In China

At present, no bioethics-related law has been enacted; however, it has been reported that they will follow treaties made by the United Nations and UNESCO, in principle.

In Japan

There is one law and four ethical guidelines that are significant to the promotion of PGt/PGx: the 'Personal Information Protection Law' (May 23, 2003); the 'Fundamental Principles of Research on the Human Genome' (June 14, 2000); the 'Ethics Guidelines for Human Genome/Gene Analysis Research' (March 29, 2001); the 'Ethical Guidelines for Performing Human Genetic Testing, Contracted to the Japan Registered Clinical Laboratories Association' (April 10, 2001); and the 'Guidelines for Genetic Testing', issued by the Japan Society of Human Genetics, Council Committee of Ethics (August, 2003) [105,106]. Among the above guidelines, the 'Ethics Guidelines for Human Genome/Gene Analysis Research' has proven to be the most important. This guideline, which regulates human genome/gene analysis, requires compliance by researchers working in these fields. The key feature is the emphasis of transparency in order to promote scientific research. Needless to say, stressing ethics, such as informed consent, confidentiality and having a ethics committee, is essential. Clinical studies and postmarketing surveillance are regulated by the Pharmaceutical Affairs Law and are, as such, excluded from the guideline. This guideline is now under review, while the Personal Information Protection Law shall take effect as of April 1, 2005.

In the Republic of Korea

A 'Bioethics and Biosafety Law' was passed by the National Assembly in December 2003 after debates that lasted for more than 4 years. The law will become effective in January 2005, and a National Bioethics and Biosafety Review Committee will be established under direct control of the President. Furthermore, the 'Research Guideline for Functional Analysis of the Human Genome', which was published in June, 2002, contains autonomy, or the right to self-determination by the potential subjects, and the protection of the individual's genetic privacy, in addition to outlining the responsibilities of the Institutional Review Board.

In Singapore

There is the 'Ethical Guidelines for Gene Technology' for genetic testing guidance in clinical practice, which was issued by the National Medical Ethics Committee in February, 2001 [107].

In Taiwan

There are some general bioethics guidelines, such as the 'Guideline on the Collection and Use of Human Samples for Research Purposes'. However, there are no nationwide guidelines on bioethics concerning human genome/gene research or genetic testing at present. Therefore, comprehensive research guidelines for ethical issues related to human genome studies, including PGt/PGx, are currently under discussion at the DoH.

Promotional activities for pharmacogenetics/pharmacogenomics

Various activities, such as funding, examination of effective use, information provision and enlightenment, are performed country-by-country at the governmental and private-sector levels in order to promote PGt/PGx. These are described in further detail below.

In China

The Ministry of Health is funding disease genomics and Chinese PGx research work. In addition, the Chinese Pharmacology Society's Committee on Clinical Pharmacology is to consider the measures to be taken to make use of PGt/PGx [108].

The Chinese Human Genome Center is holding an international study meeting to promote PGt/PGx in conjunction with the Environmental and Occupational Health Sciences Institute (a joint institute of the Robert Wood Johnson Medical School and Rutgers University in the USA) [109,110].

Lastly, a Forum of Chinese Pharmacogenomics was held by the National Natural Science Foundation of China and the Bureau of Science and Technology to discuss the application of PGt/PGx to clinical practice.

In Japan

Three organisations have been active in promoting PGt/PGx: the MHLW, the Japan Health Sciences Foundation, and the Japan Pharmaceutical Manufacturers Association. The MHLW has held an internal study meeting with attendants from both the MHLW and the Pharmaceuticals and Medical Devices Agency to consider the measures that should be taken to make use of PGt/PGx. Working groups from the Japan Health Sciences Foundation has conducted

investigations on genomics, issued several reports, and organized a symposium to promote PGt/PGx, which was held in Tokyo in April, 2003 [111]. The Japan Pharmaceutical Manufacturers Association (JPMA) held a symposium to promote PGt/PGx properly on June, 2004, in Kyoto [112]. They are also drafting an independent guidance on clinical trials that incorporate PGt/PGx.

In the Republic of Korea

Several agencies and companies are involved in promoting PGt/PGx research in the Republic of Korea. The Ministry of Health and Welfare is funding the Korean Pharmacogenomics Research Network (KPRN), the disease genomics, pathogenic microbe genomics and proteomic research center [113]. The Korean Food & Drug Administration (KFDA) is preparing guidelines for the application of PGt/PGx for drug regulation [114], and the Ministry of Science and Technology is funding the National Research Laboratory for Pharmacogenomics and is further planning on funding research in toxicogenomics in non-clinical fields [115]. In addition, the Pharmacogenomics Research Study Group is arranging regular research seminars and symposia, and several international symposia have been held in the country, including:

- Yonsei Biomedical Symposium, Seoul (February, 2003)
- Pharmacogenomics: Impact on Clinical Trial, Seoul (October, 2003)
- Pharmacogenomics: A Step Toward Personalized Pharmacotherapy, Busan (February, 2004)

In Taiwan

The Center for Drug Evaluation is holding internal taskforce meetings to look into current PGt/PGx-related research projects and clinical trials, as well as evaluating methods to promote cooperation between the DoH, the Ethics, Legal and Social Implications (ELSI) Program, and the Center for Drug Evaluation in order to enact PGt/PGx-related regulations and laws [116].

Several symposia and workshops have also been hosted in Taiwan, including:

- Taipei Science and Technology Law Forum – Legal Reform in Response to the Bio-Tech Revolution in the 21st Century (August, 2002)
- Clinical Research Seminar Series – Pharmacogenomics and Population Pharmacokinetics by the Foundation of Medical Professionals Alliance in Taiwan (FMPAT), Taipei (December, 2002)
- Workshop on Biomedicine Research and Bioinformatics by GigiGenomics Co., Taipei (March, 2004)

Projects to establish a foundation for pharmacogenetics/pharmacogenomics

The research shows that many projects to establish a foundation for PGt/PGx are underway in Asia; many of which have hardly been recognized up to now.

In China

The Research Center for Medication in Minorities began in 1993 to apply PGt/PGx to clinical practice with an eye on ethnic differences for drug metabolism and the response in Chinese minorities. Many more projects, such as the Chinese Pharmacogenomics Research Project, the Project on the Relationship between Genomics and Severe Diseases, the Pharmacogenomics and Modernization of Chinese Herbs, and the Individualization of Drug Therapy for Patients with Hypertension, have taken place in China since 2001.

In Japan

Researchers in Japan have contributed to and are working on the International HapMap Project, the Project on Realization of a Medical Care System in Accordance with Genetic Information and the Pharma SNP Consortium [117]. Groups in China and Taiwan are also working on the International HapMap Project.

In the Republic of Korea

The KPRN and the National Research Laboratory for Pharmacogenomics were initiated in 2003 to apply PGt/PGx to clinical practice.

In Singapore

As Singapore is a pluralistic society, much PGt/PGx research focuses on the ethnic differences among Chinese, Caucasians, Indians, and Malays. Some research projects have been carried out at the National University Hospital and the National University of Singapore. The National University Hospital Pharmacogenetics Research Projects, the national DNA bank and the Singapore Tissue Network were also set up in 2002.

In Taiwan

The National Science Council and the DoH began the National Research Program for Genomic Medicine in 2002, and the PGt/PGx is set to be one of the major focuses in this program in the next 5 years, beginning in 2004. The Super

Highlights

- There are no specific guidelines or notifications on PGt/PGx in Asia to date; however, most countries have begun serious consideration of developing guidelines.
- The importance of bioethics is widely recognized in Asia and various types of ethical guidelines have been issued in each country.
- The 'Bioethics and Biosafety Law' was passed by the National Assembly in the Republic of Korea in December 2003 and will be effective in January 2005.
- Every country is educating people via various symposia and workshops.
- There are many projects working toward establishing a foundation for PGt/PGx in Asia.
- DNA banks have been established in most countries.
- Many clinical trials have already been conducted in every country.
- There are already some examples of practical use of PGt/PGx.

Control Genomic Database was also founded in 2002 to create a control pool that enables the comparison and contrasting of various local diseases, and more than 3000 blood samples have been collected, to date. In addition, the Pharmacogenomics Program at the Institute of Biomedical Sciences, Academia Sinica, and the Hepatitis B and C Pharmacogenomic Project are ongoing.

Recent developments in the pharmaceutical industry

In Japan

According to the results of a questionnaire survey given by the JPMA on experiences in clinical trials involving PGt/PGx, over 50 clinical trials have been performed by companies belonging to this organization. Although the majority of them concern metabolic enzymes, some concern drug reactions. At present, there are three examples of the use of PGx information on labels for prescribing information in Japan. They are trastuzumab, rituximab, and imatinib mesylate. Diagnostic kits are also under development.

In the Republic of Korea

Several bioventures are applying genotyping to clinical practice and multinational pharmaceutical companies are sponsoring several clinical trials, searching for any relationship between drug efficacy or adverse effects and specific genotypes.

In Singapore

A total of 20 clinical trials incorporating PGt/PGx, 10 of which are Phase I trials, 4 are Phase II trials and 6 are Phase III trials, were iniated by both industry (16) and hospitals or research institutes (4) from 2003 through to the first quarter of 2004, which account for approximately 15% of all trials.

In Taiwan

A number of multinational Phase III and post-marketing clinical trials, including blood sample collection for PGx analysis and the evaluation of pharmacokinetic-related genetic polymorphisms, have been started. A proprietary DNA-based diagnostic technology has already been developed using PGx approaches to determine which patients and carriers are susceptible to the conventional mono and combinational therapies involving interferon drugs for the treatment of hepatitis C.

Expert opinion

Which polymorphism people are interested in and from what studies advances have been made might depend on the frequencies of the polymorphism, the number of patients in the area, and the diseases each country is interested in. For example, the frequency of poor metabolizers of CYP2C19 in the Japanese population has been reported to lie in the range of 18–23%, while only 2.5–6% of Caucasians are poor metabolizers. In addition, the high incidence of stomach cancer in Japan presents a larger healthcare problem. Therefore, many reports exist on CYP2C19 for *Helicobacter pylori* eradication therapy in Japan. Although the polymorphisms that each researcher or country is interested in might be different, international cooperation is necessary to promote PGt/PGx globally.

Outlook

Regulatory agencies are getting ready to prepare PGx guidance documents in the USA, Europe, and Japan. It is necessary to respond to them in Asia so that people in every country can enjoy the benefit of medicine based on PGt/PGx. This paper shows that the pool of basic data and the building of the necessary infrastructure is beginning to be realized in PGx-based medicine in Asia. It is expected that all of the countries will make collaborative efforts toward global harmonization with each other.

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Utilisation of Foreign Clinical Data in Japanese New Drug Approval Review

On What Basis Did the Regulatory Agency Accept Them?

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Abstract

Objective: Foreign clinical evidence for efficacy and safety of new pharmaceutical drugs was utilised in decisions for marketing approval in Japan without specific regulatory guidelines until a new internationally harmonised guidance for bridging strategy was introduced in 1998. We examined how foreign clinical studies were used in recent marketing approval decisions and also how the new guidelines affected the trends of foreign data acceptance.

Methods: New drug applications (NDAs) approved between 1999 and 2003 with review reports issued by the regulatory authority available on the official website were scrutinised. Focusing on critical clinical trials including dose response studies in phase II and confirmatory studies in phase III, we classified the type of utilisation of foreign clinical data into several groups.

Results: Of the 171 NDAs approved during this period, 55 (32%) contained foreign studies as formally submitted data. Twenty NDAs (12%) were approved based on the bridging strategy. In 24 NDAs (14%) important foreign data were used as references, but not as formally submitted materials. NDAs that were given orphan drug status or priority review status were more likely to be submitted and approved on the basis of foreign clinical data. The number of bridging-based NDAs successfully approved increased from three in 2000 to ten in 2002, although confusion about the application of the new guidelines was observed after the guidelines' introduction.

Conclusions: While the traditional method of acceptance of foreign clinical data still persist, the bridging strategy is becoming a common and practical basis for the decision making of marketing approvals of new drugs in Japan.

Background

Irrespective of the diversities in regional regulatory requirements, the basic principles of new drug approval are the same worldwide: pharmaceutical products should be effective and safe for the population in each region for which the regulatory authority is responsible. In light of scientific efficiency *per se*, there is no doubt that the most convincing clinical evidence on a specific population should be obtained from studies that target the population of interest and that are conducted in the specific medical environment where the medications are actually prescribed.

Nevertheless, foreign clinical data have historically been utilised in new drug applications (NDAs) in many situations. While evidence on the similarities and differences in pharmacokinetic (PK) and pharmacodynamic (PD) profiles among different populations has been accumulating,[1,2] pharmaceutical firms now tend to compile a clinical data package for NDAs, making the most of such evidence. Because the need to make pharmaceutical research and development (R&D) activities more efficient and speedy is always pressing,[3] and competitive markets force the players to take the least costly approach to obtaining marketing approvals, duplication of clinical trials in different regions is not a preferable option for the industry. Even from the societal perspective in each region, duplication could lead to inefficient resource allocation in clinical R&D and delay the benefit from

new therapies, unless the information from such duplicated studies is really indispensable for critical decisions in marketing approval, as well as in daily medical practice.

The activities of the International Conference on Harmonisation (ICH) are a key regulatory response to the current concern.[4] The ICH, which consists of the regulators and the industries in the EU, the US and Japan, has issued more than 60 guidelines for pharmaceutical R&D and NDA since 1989. With respect to how to handle ethnic differences between the regions, the ICH-E5 guidelines for assessing ethnic factors in the acceptability of foreign clinical data, which were agreed upon in 1998 among the three regions, elucidate the scientific considerations when extrapolating foreign clinical data to a new region where an NDA is submitted.[5] In particular, foreign data extrapolation under the concept of the 'bridging study' is a bold but practical approach for both the regulators and the industries.

In Japan, where the major population (the east Asians) is apparently different from those in the US and EU, the regulatory attitudes toward the acceptability of foreign clinical data have been ambivalent. On one hand, the Ministry of Health, Labor and Welfare (MHLW) in a public notification in 1985, before the ICH-E5 guidelines' implementation, officially stated that it could accept any foreign clinical data as long as several conditions were met.[6,7] On the other hand, the MHLW required in the same notification that important studies, such as PK studies, population dose response studies in phase II and comparative studies (e.g. well controlled, randomised trials) in phase III should be performed in Japan. The focus of NDA review would inevitably be on those domestic studies, even if US/EU studies were submitted together. As a result, foreign clinical data that the applicants actually submitted to the MHLW as the components of a complete clinical data package were limited to non-pivotal studies, such as those for long-term efficacy/safety, special populations such as the elderly and those with renal dysfunction. The introduction of the ICH-E5 guidelines in 1998, however, allowed the applicants to consider the option to skip Japanese pivotal studies and submit US/EU trials of equivalent importance instead.

Aside from the rigid stance of the MHLW for official data acceptance, foreign study results have often been submitted as references, not as formal documents. There was no clear official rule for such reference purpose submissions. For orphan drugs and other drugs used in small numbers of patients, for example, it is sometimes the case that domestic studies are not practically feasible and there is no choice but to make use of foreign clinical data. In many of those cases, the MHLW seemed to have accepted evidence from abroad in relatively loose ways on a case-by-case basis. Considering the somewhat murky handling of foreign clinical data in the past, it is important to assess whether the objectives of the guidelines have actually yielded a substantially favourable payoff in the form of increasing foreign data utilisation.

The purpose of this research was to investigate quantitatively how foreign clinical trials in pivotal phases were utilised in recent Japanese new drug approvals. Foreign data utilisation based on the ICH-E5 guidelines was our primary interest, but we also delved into other types of foreign data utilisation (i.e. somewhat arbitrary utilisation for both formal and reference purposes) that occurred regardless of the implementation of the ICH-E5 guidelines.

Methods

NDAs approved by the MHLW between September 1999 and April 2003 were scrutinised to evaluate how foreign clinical data were utilised. NDA review reports prepared by the reviewers of the MHLW are available on the Internet (in Japanese).[8,9] The review reports for NDAs approved before September 1999 were not published by the MHLW. By the definition of the Pharmaceutical Affairs Law, NDAs include applications for new molecular entities, new combinations, new routes, new indications, new dosage forms or new regimens.

The total number of approvals between September 1999 and April 2003 was 178. For five of these, the reports were unavailable on the Internet. We excluded another two because they were about antiseptics for medical instruments and their clinical evaluation was significantly different. There were 171 NDAs approved with review reports that allowed us to assess how foreign clinical data were handled. Of these, 101 (59%) were NDAs for new molecular entities.

In Japan, the dichotomy between 'formal data' and 'reference data' is traditionally applied to classify the importance of submitted materials. 'Formal data' is an accurate translation of the Japanese. It refers to all the data used to support registration for the proposed use and commonly includes PK studies, PD studies, dose response studies in phase II, and the phase III studies essential for approval. Those data should be obtained and submitted in compliance with all the Japanese domestic regulations, and thus be subject to all the inspections by the regulatory authorities (e.g. Good Clinical Practice [GCP] inspections). On the other hand, 'reference data', which is also an accurate translation of the Japanese, refers to any supportive study results submitted by the applicants to help the reviewers to evaluate the efficacy and safety of the drugs. They are submitted for reference use and strict compliance with Japanese regulations is not necessarily required. Regarding the handling of foreign clinical data obtained in compliance with the US/EU GCP guidelines, the applicants have a choice between submission as formal data and submission

Table I. Utilisation of foreign clinical trials in new drug approval review in Japan

		A. No. of NDAs[a] (% of the total)	B. No. of NDAs already approved in the US or EU [B/A] (%)	C. No. of NDAs given orphan status [C/A] (%)	D. No. of NDAs given priority review status[b] [D/A] (%)
Formal use of foreign data					
I-1	Foreign studies were formally accepted under bridging strategy in line with E5 GL	20 (12)	20/20 (100)	2/20 (10)	6/20 (30)
I-2	Foreign studies were formally accepted, but not under bridging strategy	35 (21)	33/35 (94)	17/35 (49)	6/35 (17)
Reference use of foreign data					
II-1	Foreign studies were cited for reference use	21 (12)	19/21 (91)	6/21 (29)	2/21 (10)
II-2	Foreign studies were cited to show that the drug was standard therapy in the US or EU	3 (2)	3/3 (100)	0/3 (0)	0/3 (0)
III	Foreign studies were not utilised	92 (54)	50/92 (54)	11/92 (12)	0/92 (0)
Total		**171 (100)**	**125/171 (73)**	**36/171 (21)**	**14/171 (8)**

a NDAs approved between September 1999 and April 2003 and for which reviewers' reports were published on the web (n = 171).

b The numbers of priority NDAs include those of orphan NDAs (C).

E5 GL = International Conference on Harmonisation (ICH) E5 guidelines; **NDA** = new drug application.

as reference data, depending on their NDA strategy and the availability of Japanese data. Although the review should be supposedly done on the basis of formally submitted data, it seems from review reports that reference data submitted attracted considerable attention and sometimes played critical roles in approval decisions.

Focusing on the handling of the most important clinical trials (e.g. dose response studies in phase II, confirmatory randomised trials in phase III) in the data package, the pattern of foreign clinical data use was classified into five groups (table I). That is, important foreign clinical trials were: (i) accepted as formal data under the bridging strategy in line with the ICH-E5 guidelines; (ii) accepted as formal data, but not under the bridging strategy; (iii) used just as references, not as formal data; (iv) used to show that the application of a drug was considered to be historically established and accepted as a standard therapy worldwide (e.g. N-acetylcysteine for acetaminophen detoxification); and (v) not used. Examples of category (ii) included the cases in which foreign data were submitted as formal data in addition to Japanese formal data and also some exceptional cases of orphan drugs in which foreign data were the only clinical evidence. In such cases the similarity of PK/PD profiles between different populations was generally examined on a case-by-case basis, and not necessarily in line with the ICH-E5 guidelines. For NDAs submitted with an abbreviated or unusual data package (e.g. orphan drugs), we classified them according to the handling of trials that were most emphasised by the clinical reviewers in the reports.

Whether the bridging strategy based on the ICH-E5 guidelines was successfully accepted by the MHLW for each submission of NDA was judged based on the descriptions in the report.

Results

Foreign clinical studies played important roles in a significant number of approval decisions in the past 5 years, and the importance seems to be increasing (table I and table II).

Table II. Changes in the use of foreign clinical trials between 1999 and 2003

		Year of approval				
		1999[a]	2000 [no. (%)]	2001 [no. (%)]	2002 [no. (%)]	2003[b]
I	Formal use of foreign data (I-1 and I-2)	9	17 (26)	11 (29)	16 (40)	2
	{I-1. Accepted under bridging strategy}	{2}	{3 (5)}	{4 (11)}	{10 (25)}	{1}
II	Reference use of foreign data (II-1 and II-2)	0	5 (8)	10 (26)	7 (18)	2
III	Foreign data were not used (III)	9	44 (67)	17 (45)	17 (42)	5
Total		**18**	**66 (100)**	**38 (100)**	**40 (100)**	**9**

a NDAs approved after September 1999.

b NDAs approved as of April 2003.

NDA = new drug application.

Table III. New drug applications approved in Japan for which the bridging strategy was sought when submitted

Name of substance	Applicant	Indication	Date of approval	Review status	BS accepted by MHLW?	Comments
Sildenafil citrate	Pfizer	Erectile dysfunction	25 Jan 1999	Priority	Yes	
Donepezil hydrochloride	Eisai	Alzheimer's disease	8 Oct 1999		No → Yes	Additional dbt (vs placebo) was implemented after the submission
Zanamivir hydrate	GlaxoSmithKline	Influenza A/B	27 Dec 1999	Priority	No	Approved based on CPAC's decision
Eptacog alfa	Novo Nordisk	Haemophilia A/B	10 Mar 2000	Orphan	No	
Fexofenadine hydrochloride	Aventis	Allergic rhinitis	22 Sep 2000		No → Yes	Additional dbt (vs placebo) was implemented after the submission
Lansoprazole/clarithromycin/ amoxicillin	Consortium of 8 companies	*Helicobacter pylori*	22 Sep 2000	Priority	No	Supplementary indication
Olanzapine	Eli Lilly	Schizophrenia	22 Dec 2000		No	Foreign studies were reviewed as references
Anastrozole	AstraZeneca	Breast cancer	22 Dec 2000		Yes	
Oseltamivir phosphate	Roche	Influenza A/B	22 Dec 2000	Priority	Yes	
Alendronate sodium hydrate	Banyu/Teijin	Osteoporosis	20 Jun 2001		No → Yes	Additional dbt was implemented after the submission
Zolmitriptan	AstraZeneca	Migraine	20 Jun 2001		Yes	
Sumatriptan succinate	GlaxoSmithKline	Migraine	20 Jun 2001		Yes	
Insulin aspart	Novo Nordisk	Diabetes mellitus	2 Oct 2001		Yes	
Palivizumab	Abbott	Respiratory syncytial virus	17 Jan 2002	Priority	Yes	
Infliximab	Tanabe	Crohn's disease	17 Jan 2002	Orphan	Yes	
Sodium risedronate hydrate	Takeda/Ajinomoto	Osteoporosis	17 Jan 2002		Yes	
Goserelin acetate	AstraZeneca	Endometriosis	17 Jan 2002		Yes	Supplementary indication
Basiliximab	Ciba-Geigy	Acute organ rejection	17 Jan 2002	Orphan	Yes	
Oseltamivir phosphate	Roche	Influenza A/B	17 Jan 2002	Priority	Yes	Dry syrup for paediatric patients
Eletriptan hydrobromide	Pfizer	Migraine	11 Apr 2002		Yes	
Omeprazole/clarithromycin/ amoxicillin	Consortium of 7 companies	*H. pylori*	11 Apr 2002		Yes	
Gefitinib	AstraZeneca	Non-small cell lung cancer	5 Jul 2002	Priority	No	
Exemestane	Pharmacia	Breast cancer	5 Jul 2002		Yes	
Carvedilol	Daiichi	Heart failure	8 Oct 2002		No	Supplementary indication. Foreign studies were reviewed as references
Brinzolamide	Alcon Japan	Glaucoma	8 Oct 2002		Yes	
Leflunomide	Aventis	Rheumatoid arthritis	16 Apr 2003		Yes	

BS = bridging strategy; **dbt** = double-blind trial; **CPAC** = Central Pharmaceutical Affairs Council; **MHLW** = Ministry of Health, Labor and Welfare.

Types and Numbers of Foreign Data Utilisation

Table I illustrates in what way foreign clinical studies were utilised in each approval decision between 1999 and 2003. In 55 of 171 (32%) NDAs, foreign studies constituted a formal clinical data package; 20 NDAs (12%) were approved on the basis of successful bridging strategy (see table III for examples), and in 35 NDAs (21%) foreign data were formally accepted based on other justifications. Orphan drug status was granted prior to submission for 19 of 55 NDAs (35%), for which trials in Japan were not feasible mainly due to insufficient numbers of patients. NDAs given priority review status accounted for 22% (12/55), which was in clear contrast to the NDAs with no foreign studies (0/92). With respect to therapeutic categories, it is noteworthy that 12 out of 20 oncology NDAs were approved with foreign studies submitted as formal evidence; three NDAs were approved on the

basis of bridging strategy. For most of these 55 NDAs, marketing approvals were already in place in the US or EU at the time of the Japanese approval, with a few exceptions.

Foreign studies were also not utilised in such formal ways, but as references for reviewers. In 24 NDAs (14%) important foreign studies were presented in the review reports just as references (table I). There were three NDAs (2%) approved based on the recognition that the pharmaceuticals were standard therapies worldwide. Approvals with the same or similar indications were obtained in the US or EU for most of these NDAs (22/24 [92%]). Among the NDAs with foreign data submitted for reference use, 6 of 21 (29%) were orphan drugs. Priority review status was given to only two NDAs.

In about half of all the NDAs (92 NDAs [54%]), foreign studies were not utilised at all or, if presented, they were only used to outline the developmental situations in the US/EU, although 50 of these 92 NDAs (54%) had already been approved in the US or EU (table I).

Changes in Foreign Data Utilisation

Recent changes in the use of foreign clinical data since 1999 are shown in table II. It is difficult to infer the long-term trend because of our short observation timeframe, but these figures suggest that the utilisation of foreign clinical data is growing. The number of approvals based on the bridging strategy has increased steadily since the first success (sildenafil citrate for erectile dysfunction, table III) in 1999. The MHLW approved ten bridging-based NDAs in 2002, which accounted for 25 percent of all the NDA approvals of that year. In contrast, the proportion of approvals without foreign data decreased from 67% in 2000 to 42% in 2002.

Table III provides a list of those approved NDAs in which the applicants claimed at the first stage of submission that foreign data extrapolation was possible based on the bridging study. Many of them (20/26 [77%]) were approved in line with the applicants' claim, while for six NDAs the MHLW approved them based on different justifications and logic other than bridging. The unsuccessful examples, however, were mostly observed in the transition period (i.e. 1999 and 2000) just after the implementation of the ICH-E5 guidelines. For most of the NDAs in table III, the bridging studies were done as efficacy/safety studies in phases II and III. There were only a few NDAs, including basiliximab (orphan drug) in table III, for which bridging was established solely on the similarities in PK/PD profiles without conducting efficacy/safety studies in Japan.

Among the 26 NDAs in table III, seven NDAs were given priority review status. Three NDAs were for orphan drugs and, thus, were automatically given priority status.

Discussion

Two Aspects of Impact of the International Conference on Harmonisation (ICH)-E5 Guidelines

When evaluating the efficacy and safety of a drug by extrapolating foreign clinical data, sufficient attention should be paid to race and ethnic differences between two different regions.[2] A variety of genetic or intrinsic differences have been observed in important PK components, such as drug-metabolising enzymes (e.g. cytochrome P450s, N-acetyltransferases).[2,10] For example, the incidence of poor drug metabolisers varies to a great extent between populations. In addition to the PK characteristics, PD responses are likely to be different between the regions.[11] Environmental or extrinsic differences, as well as genetic or intrinsic differences play critical roles too. For example, surveys have shown that the average daily drug dose in Japan is generally lower than in the US and Europe.[11] This was allegedly associated not only with PK/PD disparities but also the historical preferences of Japanese physicians for applying a composite and somewhat subjective measure called 'usefulness', as well as efficacy and safety in clinical evaluation.[11]

Despite all these possible concerns in clinical evaluation, the MHLW was open to foreign clinical data even before the ICH-E5 guidelines.[7] However, formal use of foreign data did not occur substantially in most NDAs because the MHLW required that the critical studies be implemented in Japan and that foreign trials could be submitted only in addition to those studies.[6] From a historical perspective, this regulatory stance on new drug approval had its root in the implementation of the basic principle of 1967. The aim of the basic principle to introduce a scientific efficacy/safety evaluation system has been achieved; however, with all changes observed in the current pharmaceutical R&D environments, it is apparently time for the whole system to be substantially renovated.

The ICH-E5 guidelines have had a critical impact on Japanese clinical development activities in at least two respects. First of all, for the first time they provided a scientifically and internationally acceptable approach to asserting that data extrapolation is justified. Both the possible applicants and the MHLW benefited from the scientific contents and instructions of the guidelines. However, the real impact in Japan came from the fact that the guidelines forced the MHLW to accept foreign clinical data more than before. The nature of the ICH-E5 guidelines is

somewhat different from other ICH guidelines in that the ICH-E5 guidelines inevitably touch on the heart of regulatory principles, i.e. what to accept as evidence of efficacy and safety in NDAs. Although the guidelines clearly state that "this guidance (E5 guidelines) is not intended to alter the data requirements for registration in the new regions", it was of course impossible for the MHLW to keep the same regulatory stance as it did under the previous notification of 1985.[6] The MHLW issued a new notification at the same time as the guidelines' implementation and proclaimed that Japan would accept any type of foreign trial, including pivotal phase III comparative studies, as long as scientific and procedural requirements were satisfied.[12]

Acceptance of Foreign Data Under the ICH-E5 Bridging Strategy

It is apparent from table II and table III that the use of foreign data in NDA review has gained in importance since 1999. For the NDAs approved successfully based on the bridging strategy, confirmatory phase III trials in Japan were avoided or at least downsized, which lead to a reduction in development costs (e.g. direct and indirect costs associated with the time to application, opportunity costs for subjects and investigators accrued to the avoided trials) for not only the pharmaceutical firms but society as a whole. Regarding the improvement in efficiency in this context, table I suggests that there might be some room for further utilisation of foreign clinical data, since 54% of NDAs submitted were approved without substantial support from existing foreign clinical data. Although it might be difficult for some of these NDAs to use foreign data because of practical hurdles such as conflicts in licensing, the present regulatory environments indeed increase the numbers of R&D options for the industry and investigators in the long run.

The increasing successes of bridging approval (table III) seem to have been achieved in part by the intensive use of consultation services offered by the Organisation for Pharmaceutical Safety and Research (OPSR), as well as accumulated experience by both applicants and reviewers. In Japan, the OPSR (a quasi-governmental organisation) instead of the MHLW provided fee-based consultation services aimed at several steps of new drug development (e.g. end of phase II, before submission). The number of consultations on bridging strategies was 59 (40%) in 1998 and 98 (51%) in 1999, accounting for a significant share of the total consultations.[13] When the ICH-E5 guidelines were introduced in 1998, most attempts at bridging were implemented retrospectively with already existing clinical data on hand. The role of the OPSR was limited under such conditions because the OPSR was not a final decision maker in approval. In recent development programmes, however, the bridging strategy is applied prospectively, and regulatory advice can be available at a very early stage of development. There was a drastic change in the review agencies in April 2004, which could also improve the timing and quality of regulatory advice and decisions. In April 2004, the OPSR was merged with a review agency under the MHLW, the Pharmaceuticals and Medical Devices Evaluation Center, to form a new independent review agency, the Pharmaceuticals and Medical Devices Agency (PMDA). The PMDA is now responsible for scientific decisions in new drug development and registration from the pre-Investigational New Drug (IND) phases to the approval and postmarketing phases. It is thus likely that scientific and technical advice on successful bridging would be provided at an earlier stage and more consistently than before.

With respect to the clinical perspectives related to the applicability of foreign clinical data, however, there still remain many unsolved issues. For example, it is arguable whether foreign clinical data in psychiatry (e.g. schizophrenia, depression) could be extrapolated because of some observable variations in both intrinsic (e.g. severity of diseases) and extrinsic factors (e.g. daily medical practice).[14,15] It is a challenge for medical researchers, industry and the regulatory agencies to examine how far the guidelines can be applied while maintaining an appropriate level of scientific validity, and to accumulate evidence for their applicability.

Acceptance of Foreign Data Outside the Bridging Scheme

Another notable finding in the present survey is that Japan accepted a significant amount of foreign clinical data outside the strict bridging justification. In 21% of NDAs, foreign phase II or III studies were utilised in the formal data packages, and orphan drugs accounted for 49% (17/35). Both are shown in row I-2 of table I. Anti-HIV drugs developed in the US or EU were all designated as orphan drugs and accounted for a significant portion in row I-2 in table I. This reflects MHLW's historically flexible stance for accepting foreign data for orphan drugs.[7,16]

Foreign data were more readily accepted by the MHLW for anti-cancer drugs than for the other drug categories. Taking into account the specifics of oncology drugs, we came up with several reasons for this result. Many anti-cancer drugs were given orphan status, which, along with the flexibility of the MHLW, resulted in intensive utilisation of foreign trial data. Moreover, clinical development in oncology is typically different from other therapeutic fields. In most cases, NDAs are submitted after the completion of phase II trials, and phase III comparative trials are usually done after marketing approval. Also, there are historical

disputes over the appropriateness of traditional clinical evaluation in Japan.[17] All these backgrounds could enhance the use of foreign clinical studies in this field.

NDAs that contained foreign data formally were also much more likely to be those given priority review status (column D in table I). This is probably because most candidate drugs for priority review were those that already had excellent reputations in the US or EU and, therefore, the MHLW was inclined to give priority to them. We need to be careful about this causality relationship when interpreting these data.

Conclusions

Foreign clinical studies in the data packages of NDAs have played critical roles in recent approval decision making. They were identified as formally acceptable data in more than 30% of NDAs approved in Japan between September 1999 and April 2003. Their roles are becoming more important and expanded in response to the implementation of the ICH-E5 guidelines.

Finally, it is important to recognise that utilisation of foreign data itself is not the goal of the current policy changes. The true endpoints applied to evaluate the guidelines' implementation should be the accuracy and correctness of the decisions on both NDA submissions and approvals, overall societal costs saved in pharmaceutical R&D processes and the reduction of time to marketing approval. Further research is necessary to assess these aspects of the current internationalisation trends.

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Erratum

Vol. 18, No.1, 2004, Page 28: In the second paragraph of section 9, the fourth and fifth sentences should read 'For example, the cost per quality-adjusted life year (QALY) [a method of analysis chosen for such evaluation] of ß-interferon for multiple sclerosis (MS) ranges between 16 000 and 3 million euros (EUR) [2000/01 values]. The National Institute for Clinical Excellence in the UK previously used a cost per QALY of over EUR1 million as the basis of its decision in not recommending this class of product for MS patients.'

[Tsang L. The changing European regulatory landscape: present and future challenges to the development of biotechnological and emerging technology products. Int J Pharm Med 2004; 18 (1): 19-29]

臨床薬理 Jpn J Clin Pharmacol Ther 35(2) Mar 2004

〈抄録〉第24回 日本臨床薬理学会年会 2003年12月11～12日 横浜
シンポジウム13：ヘルスサービスシステムの中のファーマコジェネティクス

5．ファーマコジェネティクスとインセンティブ

津 谷 喜一郎*

【Scope is wide】

ファーマコジェネティクスは，医薬品の研究・開発から合理的使用まで，幅広い領域に関係する．2002年にThe Council for International Organizations of Medical Sciences (CIOMS, 国際医科学協議会) が設立したWorking Group for Pharmacogenetics and Pharmacoeconomicsが討議するtopicsは，開発から，教育・倫理・経済まで幅広いものである[1]．

この領域は，医療技術政策からみると，推進・評価・規制と，基礎研究・臨床研究・採用・普及標準化の2次元に整理できる[2]．また，市販前を「創薬」，市販後を「育薬」と呼ぶ流儀にならえば，「ゲノム創薬」から「ゲノム育薬」までと称することができる．

【Possible questions】

各playerにとってのインセンティブを意識しながら，いくつかのquestionの形で考えてみよう．

Q1：Pharmacogenetic (PGx) testを用いると臨床試験の症例数は減るのだろうか？

このquestionは，安全性ではどうか？ どのphaseについてか？ 市販後の臨床試験・臨床研究ではどうか？ 非臨床研究でゲノム情報を用いて開発された薬ではどうか？ などに分けられる．

Q2：effect sizeはどうなるか？

1990年代後半からのエビデンスに基づく医療 (evidence-base medicine: EBM) のなかで，effect sizeはnumber needed to treat (NNT) を用いて表すことも多い．PGx testを用いたうえで治療すると，NNTはどの程度小さくなるのであろうか？ ここでは，responderを見出すためのnumber needed to screen (NNS) と，薬物治療の反応率との双方からなる．いずれも確率的なものでありバラツキを考慮する必要がある．

Q3：結果にバイアスはないか？

PGx testを用いて，どの程度，正確 (accurate) な結果が得られるのであろうか？これには研究デザイン (study design) に関係する[3]，いくつかのタイプがある．(1) PGx testを行う群vs行わない群．PGx test +，すなわちresponderにのみ投薬．(2) 同じく2群で，PGx testを行った群で，extensive metabolizer (EM)，poor metabolizer (PM) に応じて最適の投与量，行わない群では従来の投与量を用いる．(3) 安全性をメインにして，同じく2群で，PGx testを行った群で，副作用が予想されるresponderには非投与．(4) 長期の効果を見ようとする場合，まず全員にPGx testを行い，responderを2群にわけ，投薬群と非投薬群で，数年後のアウトカムを比較する．(5) PGx testそのものの比較．PGx test AとPGx test Bの2群でそれぞれのresponderに投薬して比較する．

これらの研究デザインは，tree structureに書くと分かりやすく，各コスト情報を収集し臨床アウトカムを含めて解析すればpharmacoeconomics studyができる．ここで2群を構成する時，ランダム割付 (random allocation) を行えばエビデンスのgradeは高くなるが，その方法の受容性 (acceptability) は，有効性・安全性・コストに依存する．

2002年10月の大阪での第23回日本臨床薬理学会年会での発表を研究デザインで分類するとTableになる．前向き (prospective study) がほとんどないことが読み取れる．

研究デザインとは別に，臨床研究の質も問題になる．Quality control (QC) /quality assurance (QA) がここでも重要である．さらに，研究結果の如何によるpublication biasは，他の領域よりも重大な問題となりうる．臨床試験の登録制度が望ましい．

Q4：誰がPGx testのコストを払うべきか？

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Table　日本臨床薬理学会年会でのPGx study

2002年	study数
1. Case Report	0
2. PK Study	9
3. PK-PD Study	3
4. Cross-sectional Clinical Analysis	4
5. Cohort Study	0
6. Retrospective Clinical Study	0
7. Prospective Clinical trial	0
8. Pharmacoeconomics Assessment	0
9. Development of PGx diagnosis/test	0

税金か，公的保険か，個人か，また私的保険の場合もあり得，ヘルスサービスシステムの中で，混合診療の是非を含めた論議が必要である．PGx testは発病した患者のみならず，予防にも用いられる．日本の保険制度は原則的に予防給付はしないが，この議論も必要となろう．

Q5：何に対するコストか？

この領域では，便益（benefit）とともにコストも多様なものとなる[4]．直接コストは薬コストやPGx testコストだけではない．そこで得られた情報を管理するコストも必要である．一方ではPGx testによってコストは低減される．不必要や不適切な投薬が減る．副作用に伴うコストが減る．従来の“try and see”スタイルが変わり受診の回数が減る．また間接コストとしての労働生産性も考慮すべきである．

【Decision making】

エビデンスのgradeは，retrospective designで得られた情報をそのまま添付文書（labeling）に入れるか，あるいはprospective studyでconfirmすべきかという，行政当局の意思決定にも関わる．

より広く医療における意思決定には，古典的には，効果（effectiveness），効率（efficiency），公平（equity）の“3E”が知られているが，開発の視点も含めると「ダイナミズム」（dynamism）も必要になる．

高価な高度医療技術に伴うコストをコントロールするには2通りの方法がある．一つは強制的（coercitive）方法である．これには需要サイドの医師などに対するnegative listやpositive listによる使用制限，予算制，などが含まれる．また治療ガイドラインの作成も適正使用に加えてコスト抑制に貢献するかもしれない．供給サイドの医薬品企業に対しては開発の抑制である．

もう一つは，刺激的（incitative）方法である．コスト低減にインセンティブを与えるもので，医師などに対しては，限られた患者のみに処方したり，低価格の医薬品を用いることに対するインセンティブなどがある．

ゲノム創薬・育薬では，PGx testを用いた処方により，一般に対象となる患者の数は減ることが予想される．ここでは公的資金によるインセンティブが必要になると思われる．2002年9月−10月に，ヒューマンサイエンス振興財団（HS財団）の賛助会員企業91社に対し，全36問のアンケート調査が行われた．その中で「Non-responderへの無用な投薬が激減する場合，承認・上市にあたり，行政に求めるもの（インセンティブ）はどのようなものか」，「Non-responderの存在が明らかになったとき，non-responderを対象とした薬物の開発にあたり，行政に求めるものは何でしょうか」などが問われた[1]．多様な要素をもつこの領域に対処するレギュラトリーサイエンスの進展[5]が望まれる．

【参考文献】

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5）ファーマコジェネティクスとインセンティブ

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本日は，「ファーマコジェネティクスとインセンティブ」というタイトルでお話ししたいと思います。

CIOMS Working Group

2002年から，CIOMS Working Groupの“Pharmacogenetics and Pharmacoeconomics”が立ち上がりました（その後“Pharmacogenetics”と変化された）。略してCIOMS WG on PGx and PExと称しています。CIOMSはCouncil for International Organizations of Medical Sciencesの略で，通常，国際医科学協議会と訳されています。このWGには，私を含めて，通算5人の日本人メンバーがいます。WG全体で約30人です。準備会を含め，これまで，ジュネーブ，ロンドン，ボン，ワシントンDC，ワルシャワ，ウィンザーでの会議，またe-mailなどで議論したことをまとめ，2004年末までにCIOMS Reportを発行する予定です。

表1に示したのが，現時点（2003年12月）での各章のタイトル案です。まず用語集があり，(1)イントロ，(2)医薬品開発に対するインパクト，(3)医薬品開発におけるPGx，(4)行政的視点，(5)倫理，(6)コミュニケーションと教育,と続きます。このコミュニケーションの章では，研究者，臨床現場の人，行政，国民，患者のすべてが同じような言葉で話すことが大事であると議論されています。

表1　Topics of CIOMS WG on PGx and PEx (2002→)

- Terminology
1. Introduction/Problem Statement
2. Impact of Pharmacogenomics on Drug Development
3. Exploring Pharmacogenetics in Drug Discovery and Development
4. Regulatory Perspectives
5. Ethical Issues
6. Communication and Education
7. Genetic Data and Genetic Testing
8. Improvements in Existing Therapies
9. Abnormal Drug Response (I): Clinical, Social and Economic Burden
10. Abnormal Drug Response (II): Opportunities for Risk Reduction
11. Pharmacoeconomic issues in Pharmacogenetics
12. Database relating Pharmacogenetics
13. Pharmacogenetics: Unresolved Issues and Barriers to Progress
14. Progress reports regarding pharmacogenetics from Asia, European countries, Japan, USA, and other regions/countries

(7)遺伝データと遺伝子検査，(8)既存治療の改善と続き，(9)のADRでは，それによる経済的負担についても触れられます。先ほどの鎌滝先生の話にも，1998年のJAMAに出たADRのmeta-analysisの論文が引用されましたが，CIOMSはdrug safetyに関する活動を長年行ってきており，ADRによる社会的なコストが大変かかる，これをPGxを用いて減少させることができるのかということが，WGを立ち上げる1つのきっかけになっています。

そして，(11)薬剤経済学的，(12)データベースです。このデータベースには2通りの意味があり，1つは十数万とか数十万人の大きなバイオバンクとしてのデータベース，もう1つは，PGxを用いたどんな臨床研究や臨床試験がオンゴーイングであるかというデータベースです。

他に，(13)この領域においてどんな解決すべき問題があるか，(14)各国の報告です。

（最終版のCIOMS Reportは全12章にAnnexが9つという構成になりterminologyはAnnex6のEUの現状の部分に移った。またデータベースは多くの議論がなされたが章として入らなかった。）

医療技術政策の中のファーマコゲノミクス

上記(4)に行政的視点とあります。CIOMS WGの活動に対応する意味もあり，日本では本年2003年（平成15年）度から厚生労働科学研究費補助金・医薬品等医療技術リスク評価研究事業