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Intractable and rare diseases research in Asia

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Summary **Intractable and rare diseases are an important public health issue and a challenge to medical care. In recent years, much progress has been made in the United States (US), the European Union (EU), and some parts of Asia including Japan, South Korea, and Taiwan, involving specific legislation to encourage discovery and development of orphan drugs, patients' advocacy organizations to provide vast information on intractable and rare diseases and improve patients' access to healthcare, special research programs to strengthen basic and applied research on intractable and rare diseases, and so on. While China is also actively promoting regulation of intractable and rare diseases, but still lags far behind the US, EU, Japan, and other countries and regions with orphan drug legislation. Based on systematic analysis of the current status and future perspectives for intractable and rare diseases in Asia, we recommend that three important aspects of support from government, patients' advocacy organizations and rare disease registry networks, special research programs and global information exchange platform, should be given great attention in promoting the development of intractable and rare diseases research in Asian countries.**

Keywords: Orphan diseases, orphan drugs, legislation, regulation

1. Introduction

Rare diseases are rare and often debilitating or even life-threatening diseases or conditions with a prevalence of less than 0.65‰-1‰, as defined by the World Health Organization (WHO). Intractable diseases mainly refer to rare diseases that have resulted mostly from unidentifiable causes and/or lack of clearly established or curable treatments. Intractable and rare diseases are an important public health issue and a challenge to medical care. In recent years, much progress has been made especially in the United States (US) and the European Union (EU), involving specific legislation to encourage discovery and development of orphan drugs, patients' advocacy organizations to provide vast information on intractable and rare diseases and improve patients' access to healthcare, special research programs to strengthen basic and applied research on intractable and rare diseases, and so on. In Asia, Japan, South Korea, and Taiwan have established systematic economic and regulatory incentives to encourage development of drugs for intractable and rare diseases. China is also actively promoting regulation of intractable and rare diseases, but it has not been included in the national health system and special legislation on orphan drugs has not been established until now. We did a systematic analysis on current status and future perspectives for intractable and rare diseases in Asia (*1*), which showed that three important aspects should be given great attention in promoting development of intractable and rare diseases research in Asian countries (Figure 1).

2. The support from government

The first aspect is support from government. It should include not only specific legislation to encourage manufacturers to develop orphan drugs, but also a sound supply mechanism and reimbursement system to ensure access to orphan drugs for patients with intractable and rare diseases. In Western countries, specific legislation on orphan drugs was first established in the US in 1983, then Australia in 1997, and the EU in 1999. In Asian countries and

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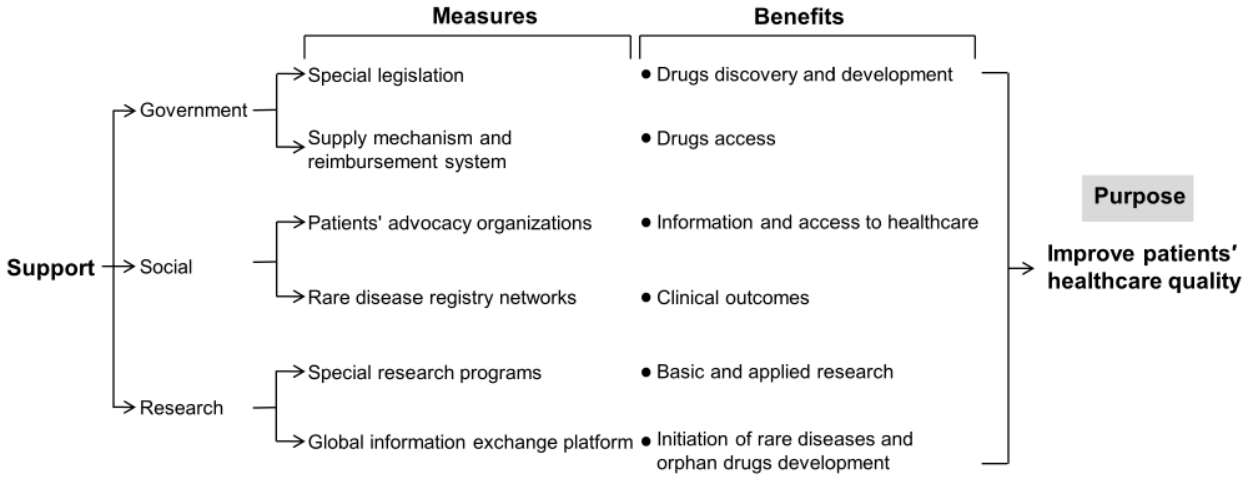

Figure 1. Three important supports in improving intractable and rare diseases in Asia.

regions, similar laws have also been established in Japan in 1993, Taiwan in 2000, and South Korea in 2003 (*2-4*). Incentives include financial subsidies, market exclusivity, tax credits, fee waivers, fast track approval, and protocol assistance, resulting in substantial improvements in treatment of patients with a range of intractable and rare diseases.

Furthermore, many measures for pricing and reimbursement have been taken to ensure access to orphan drugs for patients with intractable and rare diseases. For example, in Japan, the Japanese National Health Insurance (NHI) negotiates prices with pharmaceutical companies once a drug is approved for use, allowing a selling price of cost plus 10% for orphan drugs; 56 of 130 designated diseases in Japan are subject to reimbursement of medical expenses, with 30% of expenses paid by insurance companies and the rest paid by national and prefectures governments (*5*). In Taiwan, 77 approved orphan drugs and 40 special nutritional supplements can be imported, and the reimbursement cap is 70% of actual expenses but families that qualify for low-income status can receive reimbursement for up to 100% of drugs and nutritional supplements for patients (*6*). While China is actively preparing to regulate development of orphan drugs, but specific legislation on orphan drugs has not been established, current regulations only set forth general criteria to accelerate registration and approval of orphan drugs, detailed rules have not been implemented and incentives on orphan drugs imports have not been proposed until now. Moreover, although some regions, such as Shanghai and Shandong, have started to put out a trial use for reimbursement, the nationwide supply mechanism and reimbursement system have not been established, hampering access to orphan drugs for patients with intractable and rare diseases.

3. Social support

The second aspect is social support from patients' advocacy organizations and rare disease registry networks. It could provide quality information and a networking system to facilitate interaction among patients, clinicians, researchers, the pharmaceutical industry, and governmental bodies. Major patients' advocacy organizations in Western countries, such as the National Organization for Rare Disorders (NORD) in the US and the European Organization for Rare Diseases (EURORDIS) in Europe, can provide vast information on intractable and rare diseases and improve patients' access to healthcare. In Asia, many patients' advocacy organizations have also been established, such as the Japanese Intractable Disease Information Center (*http://www.nanbyou.or.jp*), the South Korean Organization for Rare Diseases (*http://www.kord.or.kr*), the Taiwan Foundation for Rare Disorders (TFRD) (*http://www.tfrd.org.tw*), the Hemophilia Home of China (HHC) (*http://www.xueyou.org/china*), and so on.

In recent years, progress has been made in dissemination of knowledge and information by established patients' advocacy organizations worldwide, but clinical studies on orphan drugs still encounter challenges due to the small size of the trial population and the fact that patients are often geographically dispersed. It is necessary to establish a global system for patient registration in order to promote epidemiological and basic research and improve the clinical outcome for patients with intractable and rare diseases (*7*). In Western countries, some web-based resources have been established, such as the Rare Diseases Clinical Research Network (RDCRN) in the US and the Orphanet in Europe, with the purpose of facilitating collaboration on clinical

outcomes as well as sharing advanced experience to minimize delays in access to orphan drugs for patients with intractable and rare diseases. In Asian countries, there are also many explorations on rare disease registry networks, for example, in China, a patients' advocacy organization of the China-Dolls Care and Support Association started voluntary registration in May 2010 and has registered 30 rare diseases with 3,000 cases, about 1,000 of which are osteogenesis imperfecta (*8*). Moreover, a comprehensive online database for registration of rare diseases cases has been created in 2012 *(http://www.chinards.com*), clinical data on around 50 types of rare diseases will be registered (*9*).

4. Support from special research

The third aspect is support from special research programs and the global information exchange platform. Special research programs strengthening basic and applied research on intractable and rare diseases would benefit patients with better diagnosis and more treatment choices. In Western countries, many special research centers or projects have been established to support research on rare diseases and development of orphan drugs, such as the Office of Rare Diseases Research (ORDR) in the US, and the Rare Disease Task Force (RDTF) in the EU. In Asian countries, the Specified Disease Treatment Research Program was established in Japan in 1972 with the support of the Ministry of Health, Labor, and Welfare, and 130 diseases have been the subject of special research programs and research grants from government sources expanded to 10 billion yen in 2010 (*10*). In South Korea, the Research Center for Rare Diseases (RCRD) was established in 2008 with the support of the Ministry of Family Affairs, Health and Welfare. The Center oversees 3 collaborative research projects, 9 single-center research projects, and 7 clinical research networks in order to provide a foundation for research on rare diseases and orphan drugs. While in China, research support comes mainly from the National Natural Science Foundation of China (NSFC). Data showed that 366 projects (involving 32 rare diseases) were funded by the NSFC from 1999 to 2007 with total funding of 89.358 million RMB and annual funding of about 10 million RMB, compared to just 1/10th of similar funding in the US (*11*).

Furthermore, the acquisition and diffusion of scientific knowledge and research results is the vital basis for identification of diseases, and most importantly, for research into new diagnostic and therapeutic procedures. So it is urgently needed to establish the global information exchange platform to promote information exchange among researchers active in the field of rare diseases and various difficult and complicated diseases research in the world. It is interestingly noted that there is a positive relationship between the number of published papers on a particular rare disease and the likelihood of initiation of rare diseases and orphan drugs development programs (*12*), but in contrast, few professional journals covering the topic of intractable and rare diseases have been established worldwide. In this context, the unique international professional journal in Asia − *Intractable & Rare Diseases Research* (*http://www.irdrjournal.com*), was launched in 2012, with the purpose of cultivating a global medical and drug information network on intractable and rare disease research, especially developing an Asian information exchange platform, to improve the quality of life for patients with intractable and rare diseases.

5. Conclusion

In conclusion, intractable and rare diseases are an important public health issue and a challenge to medical care. In recent years, much progress has been made in some parts of Asia, including Japan, South Korea, and Taiwan, in promoting the development of intractable and rare diseases research as well as improving the healthcare quality for patients with those diseases. China is also actively promoting the regulation of intractable and rare diseases, but still lags far behind the US, EU, Japan, and other countries and regions with orphan drug legislation. Three important aspects of the support from government, patients' advocacy organizations and rare disease registry networks, special research programs and global information exchange platform, should be given great attention in promoting the development of intractable and rare diseases research, especially for China and other countries in Asia.

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