Relationship among Translational Medicine, Evidence-Based Medicine and Precision Medicine
Review doi:10.11910/2227-6394.2016.04.01.03

Relationship among Translational Medicine, Evidence-Based Medicine and Precision Medicine

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ABSTRACT

Translational medicine is a new concept in international medical field. It integrates experimental research results and clinical guidance into the optimal implementation criteria for promoting the prediction, prevention and treatment of diseases. Based on people's higher demand for medicine and health, appearance of translational medicine changes the mode of medical research. Evidence-based medicine (EBM) refers to cautious and accurate application of the current best research evidence and combination of the clinician's professional skills and abundant clinical experience to consider the patients willing and value, consequently making the best diagnostic regimens for patients. Recently, some scholars have begun to question why the patients with the same diagnosis, course of disease and pathological condition have different efficacies and prognosis after treatment with the same drug. So far, an accurate answer cannot be given based on the research data of EBM to implement translational medicine. The concept of precision medicine is accepted gradually with the development of disease management model. In this study, practice and enlightenment of translational medicine, effect of EBM on translational medicine, EBM limitations as well as emergence and development trend of precision medicine were all reviewed in order to investigate the relationship among translational medicine, EBM and precision medicine.

Key words:
Translational medicine
Precision medicine
Evidence-based medicine
Evidence-based practice
Disease classification
Gene mutation

Introduction

Translational medicine, a new concept in international medical field in recent years, integrates experimental research results and clinical guidance into the optimal implementation criteria for promoting the prediction, prevention and treatment of diseases. Based on people's higher demand for medicine and health, appearance of translational medicine changes the mode of medical research. Evidence-based medicine (EBM) refers to cautious and accurate application of the current best research evidence and combination of the clinician's professional skills and abundant clinical experience to consider the patients willing and value, consequently making the best diagnostic regimens for patients. Evidence-based practice (EBP) establishes a clinical platform for integrating evidence and making them spread rapidly, which can promptly transform the research results into the diagnosis and treatment process of clinicians. It is the largest translational medicine to some extent. Hence, to carry out EBP is indispensible in realization of translational medicine [1].

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to implement translational medicine. The concept of precision medicine is accepted gradually with the development of disease management model. In this study, practice and enlightenment of translational medicine, effect of EBM on translational medicine, EBM limitations as well as emergence and development trend of precision medicine were all reviewed in order to investigate the relationship among translational medicine, EBM and precision medicine.

Translational Medicine

Concept of translational medicine

In 1992, doctor Choi proposed "Bench to Bedside" in *Science* for the first time [2]. In 1996, Geraghty published an article where "translational medicine" was proposed as a new term, namely translational medicine was the marriage between new discoveries in basic science and clinical practice [3]. It includes two aspects: bench to bedside and bedside to bench. The former refers to a process of experimental research results being applied clinically and transformed into medical products or treatment technology, while the latter refers to a process of providing thoughts for basic medicine and guiding experimental design via clinical observation. The core of translational medicine is to break the fixed barrier among basic medicine, clinical medicine and drug development and to connect basic researches with clinicians effectively for improving the medical level further.

Practice and enlightenment of translational medicine

Combination of translational medicine and EBM drives basic research results to transform into clinical application and enhances the transformation awareness of clinical scholars. The roadmap and standards of translational medicine are formulated with the help of Department of Drug Administration, but its effect is unsatisfactory. Randomized controlled trials of new drug registration are frequently conducted under the ivory-towered context, which often leads to the results out of clinical practice.

In the past few years, two drugs have been listed continuously in Europe and America. Zaltrap, a sort of drug that is used to treat colorectal cancer, can prolong the patients' survival time from 12.0 months to 13.5 months [4]. It has been approved by Department of Drug Administration and come into the market successfully. Its bid price comes up to 200 000 dollars every year. Ivacaftor, a mutation specific drug, has recently been approved by Food and Drug Administration (FDA) in January 2012 for patients carrying G551D mutation [5]. Hubert *et al*. [6] believed that ivacaftor could be applied to treat the patients with cystic fibrosis (CF) who had a class 3 mutation from the age of 6 years. It can effectively ameliorate the patients' respiratory function and infection, but its bid price reaches up to 370 000 dollars every year. Clinically, zaltrap is resisted while ivacaftor is very popular. The reason is that ivacaftor can accurately aim at the action mechanism of a subpopulation of patients with CF and open the translocator so as to perform the targeted therapy and benefit the patients. Therefore, successful practice of translational medicine should be assessed according to the capabilities of transformation products, including how many problems are resolved and how much value is brought to doctors and patients, rather than their authorization and application in clinic.

EBM

Effect of EBM on translational medicine

Originating from the 1980s, EBM can integrate best available research evidence with a practitioner's clinical expertise, while taking into consideration patient preferences and values for clinical decision-making [7]. Its global popularization promotes clinicians to surpass traditional empirical medicine and implements clinical practice based on the best research evidence, consequently moving towards science intuitively. EBP is a process that involves formulating clinical questions, searching for existing evidence, critically appraising the evidence, integrating the evidence with clinical expertise and patient preferences to derive the best treatment and care, and then evaluating the practice outcomes [8]. Its core is to emphasize on the use of quantitative research findings as the basis of clinical decision-making. To implement EBM must shorten the time of evidence to clinic [9]. Translational medicine begins to be carried out in order to make the research evidence apply in clinic as soon as possible. EBP shortens the time of evident to clinic and improves the quality of life of human beings. In addition, evidence-based proof has its own characteristics of translational medicine, including: (1) It comes from experiments on human body or population instead of basic research, closely associated with the clinic. (2) Studies on etiology, diagnosis, treatment and prognosis can provide different intensities and types of proofs according to different study designs. These grading proofs can be considered as clinical evidence to judge the efficacy of clinical diagnosis and treatment. (3) It emphasizes the best evidence

currently. New clinical research evidence can not only weed out the old, ineffective diagnostic trials and treatment methods, but also be replaced by newer and more accurate, effective, safe measures [10-11]. Thus it can be seen that EBP itself is enforced on the concept of translational medicine.

The limitations of EBM

EBM emphasizes the best available evidence and regards it as the major basis, so the accuracy of research evidence is very important. However, people gradually find that randomized controlled trials respected by EBM have a lot of limitations as time goes on. First of all, there are some problems in the diagnosis of many diseases. The disease of enrolled patients in trial group is essentially inconsistent, leading to inaccurate research results. Second, the current EBM ignores the reliability and accuracy of evidence itself, but excessively emphasizes the grading of research methodology, leading to fluctuated research foundation. And meanwhile, the difference of two drugs is compared in most randomized control trials, which is out of clinical practice [12]. Arbesman [13] proposes that the half-time period of all bioscience research results is 40 years. However, some established treatment guidelines is only 10 years according to EBM [14]. Melanoma is one of the translational cancer examples in clinic, including targeted therapy associated with specific biomarkers that impacted on the outcome of patients with melanoma. By analyzing the correlation of mutation status in primary tumor samples from 379 patients with myeloma with disease outcome, Andrulis *et al*. [15] provided evidence for the development of BRAF V600E mutation in the context of clonal evolution and described the prognostic and therapeutic relevance of this targetable mutation. According to treatment guidelines, doctors began to adopt the first-line agents, and then changed to the second-line agents if the first-line agents were ineffective or cause recurrence and so on, in which 3 cases were treated with the fourth-line agents. In 4-year follow-up period, it was found that the difference was statistically significant by comparison to the clinical efficacy, but all the patients were in the circulation of remission and recurrence. Gene study displayed that BRAF V600E mutation occurred in 7 cases in the process of treatment. This new gene mutation was consistent with 50% of melanoma. All of these patients conformed to the diagnostic criteria of multiple myeloma, but multiple myeloma was not the same disease. The efficacy must be different if the same regimen is applied. Hence, the precise identification of this underlying mutation is extremely essential, and knowing the translational implications can open a wide view of melanoma biology and therapy [16]. In additon, based on fuzzy diagnosis, it is very difficult to cure the disease according to the guiding principles of randomized controlled trials, and the patients are likely to be injured.

Precision medicine

Emergence of precision medicine

Before 21 century, the doctors assigned non-small cell lung cancer (NSCLC) into squamous cell carcinoma, adenocarcinoma and large cell carcinoma according to histopathology, but these cytological classifications were insignificant for pathological assessment, selection of therapeutic methods, efficacy evaluation and prognosis. The doctor could only select chemotherapy if somebody develops NSCLC. The efficacy was not only poor, but also serious adverse reactions could be caused. The patients' prognosis was poor and 5-year survival rate was less than 10%. At present, the same pathological tissue can not only reveal traditional histopathological types, but also provide some information of cancer driving factors and signaling transduction pathways, including KRAS, EGFR, protein kinase B, phosphatidylinositol kinase catalytic subunit A, BRAF, etc. Therefore, the patients can be divided into different subpopulations based on different driving factors so as to conduct accurate diagnosis [17]. Additionally, doctors can timely regulate therapeutic regimens according to the change of molecular markers, in order to make patients achieve clinical remission and avoid drug-induced adverse reactions. Kris *et al*. [18] found that the 5-year clinical remission rate of patients was more than 60% under the system of NSCLC with precision classification. Thus it can be seen that tumor classification based on driving factors has surpassed traditional diagnosis, and targeted therapy is implemented accurately according to this driving factor and signaling transduction pathway.

Inevitability toward precision medicine

Precision medicine refers to the tailoring of medical treatment to the individual characteristics of each patient. It does not literally mean the creation of drugs or medical devices that are unique to a patient, but rather the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease, in the biology and/or prognosis of those diseases they may develop, or in their response to a specific treatment [19]. Preventive or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side effects for those who will not. In 2011, *inevitability toward precision*

medicine was proposed in the article published by American Academy of Sciences, National Academy of Engineering, National Institutes of Health and National Research Council together [20]. Based on disease reclassification, accurate diagnosis, evaluation, prediction, treatment and prevention will be realized in a subpopulation of patients with the same etiology and common pathogenesis to assist these patients to recover fast, consequently realizing the maximum value for patients.

U.S. President Obama announced an ambitious plan called "precision medicine initiative" on Jan. 20, 2015, aiming to accelerate progress toward a new era of precision medicine, with a near-term focus on cancers and a longer-term aim to generate knowledge applicable to the whole range of health and disease [21-22]. It strengthens communal efforts to integrate patient-centric molecular, environmental, and clinical "big" data, and such efforts have already improved in the aspects of clinical management for diseases, including NSCLC [23], breast cancer [24], and hypertrophic cardiomyopathy [25]. To maintain this track record, it is necessary to cultivate practices that ensure reproducibility as large-scale heterogeneous datasets and databases proliferate. At present, the National Institutes of Health (NIH) has outlined initiatives to enhance reproducibility in preclinical research, both Science and Nature have featured recent editorials on reproducibility, and several authors have noted the issues of utilizing big data for public health, but few methods exist to ensure that big data resources motivated by precision medicine are being used reproducibly [26].Through analysis of 100 0000 male and female volunteers with different age stratifications and body conditions, its core is to study the effect of genetic variation on human health and disease occurrence to understand the mechanism of disease occurrence and develop corresponding drugs, in order to pave the way for precision medicine. To help speed the translation of modern science, FDA is working with the scientific community to make sure its oversight of genomic technology supports innovation, while ensuring that the public can be confident that the technology is safe and effective. Although the precision medicine initiative will probably yield its greatest benefits years down the road, there should be some significant near-term successes. Except for the results of cancer studies mentioned above, a large number of studies exposed to many kinds of therapies may provide early insights into pharmacogenomics-enabling the provision of the right drug at the right dose to the right patient [27]. The chances of identifying persons with rare loss-of-function mutations that protect against common diseases may point to attractive drug targets for a large population of patients, and observation on beneficial use of mobile health technologies may improve strategies for preventing and managing chronic diseases [28]. Thus it can be concluded that the full potential of precision medicine can be realized ultimately to give everyone the best chance at good health, with abundant resources, energy and sustained commitment of time, as well as ingenuity from the scientific, medical and patient communities.

Conclusion

The essence of precision medicine is to reclassify diseases according to molecular pathways and to realize precise prevention, diagnosis and treatment finally. Precision medicine surpasses translational medicine guided by product registration and sets a new goal for translational medicine. Precision medicine can be realized by long-term follow-up to patients, accurate records of clinical manifestations, therapeutic regimens and prognosis, extraction and preservation of biological samples as well as implementation of basic research, in which a repeated bench-to-bedside and bedside-to-bench cycle is run through. However, the power to drive this repeated cycle is a serious of EBM methodology and achievements.

To sum up, EBM means is required for realization of disease reclassification. Based on systemic biological ideas, individual information port is established and biological samples are combined in the formation of a large healthy data system. Precision medicine is the highest state of medical science, and translational medicine should aim at precision medicine. The process of realizing precision medicine needs combination of basic and clinical research, resultant force of government, community, family and enterprises as well as interdisciplinary cooperation of medicine, sociology, environmentology and modern information technology to promote research achievements to transform into clinical application. Therefore, EBM is a means of practicing translational medicine. Precision medicine is an orientation and goal of translational medicine, whereas translational medicine is the only way leading to realization of precision medicine.

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