Translational Research: Precision Medicine, Personalized Medicine, Targeted Therapies: Marketing or Science?

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Abstract – Personalized medicine is based on: 1) improved clinical or non-clinical methods (including biomarkers) for a more discriminating and precise diagnosis of diseases; 2) targeted therapies of the choice or the best drug for each patient among those available; 3) dose adjustment methods to optimize the benefit-risk ratio of the drugs chosen; 4) biomarkers of efficacy, toxicity, treatment discontinuation, relapse, etc. Unfortunately, it is still too often a theoretical concept because of the lack of convenient diagnostic methods or treatments, particularly of drugs corresponding to each subtype of pathology, hence to each patient. Stratified medicine is a component of personalized medicine employing biomarkers and companion diagnostics to target the patients likely to present the best benefit-risk balance for a given active compound. The concept of targeted therapy, mostly used in cancer treatment, relies on the existence of a defined molecular target, involved or not in the pathological

† Articles, analyzes and proposals from the Giens workshops are those of the authors and do not prejudice the proposition of their parent organization.

process, and/or on the existence of a biomarker able to identify the target population, which should logically be small as compared to the population presenting the disease considered. Targeted therapies and biomarkers represent important stakes for the pharmaceutical industry, in terms of market access, of return on investment and of image among the prescribers. At the same time, they probably represent only the first generation of products resulting from the combination of clinical, pathophysiological and molecular research, *i.e.* of translational research.

Abbreviations: see end of article.

1. Introduction

The participants in the round table N°1 of the Giens meeting 2014 chose as objectives: to define personalized medicine, its avatars (stratified medicine and precision medicine) and its composing parts (targeted therapies, biomarkers and companion diagnostics); to evaluate the contribution of translational research to personalized medicine; to evaluate its status in current and future medicine; to clarify its modalities of registration, reimbursement, post-marketing benefit-risk and medico-economical evaluation; and to evaluate the scientific justifications and/or marketing motivations behind the claims for this label.

2. Definitions

Personalized medicine, following the commonly accepted definition taken over by the European Medicines Agency (EMA),[1] consists in "giving the right treatment to the right patient, each drug being given at the right dose and at the right time", to which can be added "and for the right duration". Following the Food and Drug Administration (FDA),[2] it is the "tailoring of medical treatment to the individual characteristics, needs, and preferences of a patient during all stages of care, including prevention, diagnosis, treatment, and follow-up".

Personalized medicine is often presented as "tailored" medicine, in contrast to a medicine that would be "ready to wear" or even "one size fits all". It concerns all stages of the medical act, from molecular diagnosis using biomarkers to detailed therapeutic modalities.

Stratified medicine, often abusively mistaken for personalized medicine, consists in identifying subgroups of patients in whom a "targeted" drug will have the best benefit-risk ratio (hence will be indicated), *i.e.* a particular case of the first step "the right drug to the right patient".

The wording "precision medicine" has been proposed to comply with the current line of thought in the USA, as a replacement to personalized medicine, owing to two contradictory reasons: one being that all good medicine is by definition personalized, and the other that a true personalized medicine is an illusion in the sense that the clinical situations where it is really possible to individualize the choice of the drug are extremely rare.[3] Indeed, the "targeted therapies" improve the benefit-risk ratio of only a part of the population

presenting the pathology, while the other patients can only receive "conventional" drugs. Following its proponents, precision medicine is based on molecular information which improves the diagnosis precision, hence the way patients are treated.[3] It therefore only deals, once again, with a population stratification in order to prescribe the drug correctly and in this respect, precision medicine can be considered as a synonym of stratified medicine, and not of personalized medicine that relies on very diverse modalities, beyond simple population stratification.

3. The right drug to the right patient

3.1. Translational research

To improve the benefit-risk ratio of existing drugs, it is necessary to delineate the diseases more precisely, *i.e.* to make nosology progress by evolving from a classification based on syndromes to a classification based on cellular or molecular biology. Such translational research, relying on genomic and genetic analysis of particular or extreme forms of the disease or deriving from basic research, also allows better understanding of the pathophysiological mechanisms that will be the basis of new therapeutic targets.

The biomarkers employed to select the patients likely to be responders, whether being genetic variants or abnormal, under- or over-expressed proteins, must then be integrated into the "environmental" factors category, pertaining to the patient (pathophysiological status), associated pathologies, concurrent treatments (drug-drug interactions), etc. Taking into account all these factors simultaneously will increasingly require the setting up of personal, comprehensive health databases.

If the drugs targeting these genes or proteins do not exist already, they can be new research objectives.

3.2. Targeted therapies

If the concept of a drug specific to a target linked with the pathology has been known and used for many years in many therapeutic fields (*e.g.*, hypertension, antibiotherapy…), the term "targeted therapy" is more recent and seems to be preferentially employed in cancer and chronic inflammatory diseases, where the