INDO AMERICAN JOURNAL OF PHARMACEUTICAL RESEARCH

PERSONALIZED MEDICINE- A BOON FOR TREATING RHEUMATOID ARTHRITIS

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ARTICLE INFO

Article history
Received 06/08/2015
Available online
31/08/2015

Keywords
Rheumatoid Arthritis,
Genetic Variation,
Biomarkers,
Personalized Medicines.

ABSTRACT

Rheumatoid arthritis is a severe inflammatory disorder of unknown etiology. Synovial tissue is histologically examined which acts as evident for Rheumatoid arthritis disease diverseness. A genetic variation in human leukocyte antigen was considered to be the most threatening factor for treating rheumatoid arthritis. GREES(*Group for the respect of ethics and excellence in science*)- including members from industrial, academic and regulatory bodies held meeting and aimed for the development of a strategy for defining process essential for models prediction and tool generation for clinical practice in essential decision making for the Rheumatoid arthritis trials. The present report issued by GREES (*Group for the respect of ethics and excellence in science*)- focuses on designing of personalized medicines to achieve success in Rheumatoid arthritis treatment. Personalized medicine can be defined as a form of drug which involves the usage of information related to an individual's proteins, genetic material and environmental factors for the prevention, diagnosis and treatment of a particular disease. Personalized medicine can be improved by factors like adding biomarkers, studying genetic variation, drug metabolism, epigenetic variations and health factors. Certain biomarkers and genomics are helpful for efficient personalized therapy. Peripheral blood, readily available biosample can acts as an ideal biomarker. On the basis of targeted biomarker, drug trials are been carried. By the application of these aspects, affected tissue can be accessed. Targeted and non-targeted biomarkers help in discovering the novel pathways for the reliable usage of personalized medicines in the effective treatment of rheumatoid arthritis.

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*Please cite this article in press as **Ms. Humeera Rafeeq** et al. Personalized Medicine- A Boon For Treating Rheumatoid Arthritis. Indo American Journal of Pharm Research.2015:5(08).*

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INTRODUCTION

Rheumatoid Arthritis

Rheumatoid Arthritis is a severe inflammatory disorder of unknown etiology.[1] It is a self initiated immune disorder affecting the joints symmetrically, synovial membrane becomes hyperplastic, specified by puffiness and by the development of pannus. Immune responses leading to damage of cartilage (*1-3*) and bones results in impaired joint functioning, which is associated with the rapid evolvement of pathogenesis of Rheumatoid arthritis. Unsurprisingly, Rheumatoid arthritis shows heterogeneity with response to its treatment. Synovial tissue is histologically examined which acts as evident for Rheumatoid arthritis disease diverseness.[2] Rheumatoid arthritis allele is found in varying extend in various social groups (*races*), which may describe the variation of widespread presence of Rheumatoid arthritis in various communities and help in indicating the genetic diversification of Rheumatoid arthritis with response to physiological properties and parts of community or social group.[1]

Genetic Variation in Human Leukocyte Antigen acting as a threatening factor for rheumatoid arthritis treatment

A genetic variation in human leukocyte antigen was considered to be the most threatening factor for treating rheumatoid arthritis.[2] The next genetic risk in the progress of rheumatoid arthritis was discovered, it was due to a change in PTPN22 gene protein coding.[3] The similar sequencing of amino acid at positions 70-74 (*are affiliated with responses to Rheumatoid arthritis*) at certain HLA-DRB1 alleles, is commonly referred to as shared epitope (*SE*) alleles. Rheumatoid arthritis influencing shared epitope allele is present, which show the effect of dosage at this particular gene. Protective allele exhibits the property of the action of one gene dependent upon another for effective responses. Recently it has been reported that genetic variations of amino acids at the sequencing positions also plays an important part at 11 and 13 of HLA-DRβ chain. An antibody against the Fc portion of IgG referred as rheumatoid factor (RF) and autoantibodies (*ACPAs- Anti–citrullinated protein antibodies*) directed against peptides and proteins that are citrullinated has been observed in rheumatoid patients.[1] ACPA (*Anti–citrullinated protein antibodies*) positive contributes about 50% rheumatoid arthritis genetic component.[3] The combination of RF and IgG leads to the formation of immune complexes which influences the disease process. The extra articular manifestations are more commonly seen in males than that of in females. The occurrence of Rheumatoid factor and ACPAs (*Anti–citrullinated protein antibodies*) is also related with some determined DRB1 alleles. Extra-articular involvement is more likely in those who have Rheumatoid factor and/or are HLA-DR4 positive. Some antirheumatic drugs which are given for the modification of rheumatoid disease related with the human leukocyte antigen (*HLA*) allele shows drug influencing hypersensitivity responses in some patients.[1] Direct genotyping is done for human leukocyte antigen genes, which is expensive and inherition of variants is usually together, therefore the true disease triggering variant is masked. Thus the cost is reduced by indirectly genotyping the samples by a designed statistical technique referred as Imputation.[3] Grasping the character of human leukocyte antigen is the dominant factor in means of genetic variations which is applicable for the rheumatoid arthritis responsiveness which may help in studying the biological mechanism that leads to the diseased state, and helps in discovering the novel pathways for the reliable usage of personalized medicines.[1]

GREES (*Group for the respect of ethics and excellence in science*)- including members from industrial, academic and regulatory bodies held meeting and aimed for the development of a strategy for defining process essential for models prediction and tool generation for clinical practice in essential decision making for the Rheumatoid arthritis trials.[4] The present report issued by GREES (*Group for the respect of ethics and excellence in science*)- focuses on designing of personalized medicines to achieve success in Rheumatoid arthritis treatment.[5]

Personalized Medicine

Personalized medicine is the reshaping of a medical treatment towards particular characteristics of individual patients which does not exactly mean that the manufacturing of a drug is made for a particular patient, instead it involves the potential to classify the patients into various subpopulations which are uniquely vulnerable to a particular disease or responsiveness towards particular treatment.[6] Personalized medicine can also be defined as a form of drug which involves the usage of information related to an individual's proteins, genetic material and environmental factors for the prevention, diagnosis and treatment of a particular disease.[7] A key component for manufacturing personalized medicine is the Genomic medicine, which involves the knowledge usage of genomes and its derivatives like metabolites, proteins and RNA which leads for medical decision making. Personalized medicine is a rapid advancement in the scope of health care which is informed by analysis of each individual's genomic and other factors.[8] Along with the genomic information certain tools like family health history, assessment of health risk and predictive data will enable paradigms that will be able to identify patient's risk for decision making and guidance for clinical management, which forms a base for informed and perspective to patient's care.[6]

IMPROVEMENT OF PERSONALIZED MEDICINES

The 99% of the DNA constituents are same in all humans and the rest of the 1% results in human functional and structural variations. Adenine, Thymine, Guanine and Cytosine represented by four letters A, T, G and C are grouped up to form genes. These four codons create billions of codes which give up specific identities, which accounts for 1% in distinguishing humans. Genes not only account the physical traits but also the information regarding chemical nature of the body.[9]

Factors Improving the Personalized Medicines

Presently genetics is the current concern in novel aspects. Epigenetic variation may be the major concern in future.

1. Drug Interactions: it includes Enzyme competition and Target interactions.
2. Epigenetic Variations: Drug transport, Drug metabolism, Drug receptors and Drug targets. This includes analysis of germline genome and somatic genome of infectious agents (parasites and viruses) or cancerous tumours. Drug targeting development of particular endogenous proteins which are mutated variants is the very important and novel aspect for the personalized medicines. By screening with low molecular weighted compounds, the mutated target hits' can be identified, which have the ability to refold the originally incorrectly folded proteins caused due to inherited mutations.
3. Biomarkers: it includes Circulating biomarkers, proteins/peptides, DNA, miRNAs and Somatic mutations. They are able to predict drug response. For the treatment of different types of rheumatoid arthritis, the personalization importance is discussed, and anticitrullinated protein antibodies are highlighted as markers for treatment intensity.
4. Genetic Variations: it includes Drug metabolism, Drug targets and Drug transport.

In the treatment of diseases of central nervous system, human genomic variations are of great importance. The role played by different human leukocyte antigen gene with uncertainty towards adverse drug reactions after treating with few anti-epileptic agents.

5. Health Factors: it includes Pathophysiology, Age, BMI and Lifestyle.[10]

Advantages of Personalized Medicines-

Personalized Medicines have been advantageous in several ways:

- Patients are given more specific care.
- Side effects are reduced as the medicine prescribed is more effective.[11]
- On the basis of genetic make-up, an individual's risk can be identified by means of scientific advancements.[12]
- Except the identical twins the chemical nature is different for different people and has begun to be treated differently.. Each individual needs are fulfilled by meeting their demands in terms of medicinal engineering instead of a large community possessing positive reaction towards the treatment. Tests on specific genetic markers were proved to be effective in the treatment of breast and colon cancer in the department of Oncology.[13]
- Treatment with personalized medicine is cheaper because the disease is diagnosed early, the problem with several diagnosis test is reduced
- Time, failure rate and expenses of clinical trials are reduced.[11]
- It has the ability to predict the innovations over time in various technologies, resulting in health improvement.
- With the advancement in personalized medicine we will be able to study the heterogeneity within individuals and diseases.
- The major cause of the disease can be easily understood with further developments in personalized medicine.[7]

Future Scope of Personalized Medicines-

- In future drugs can be manufactured to a greater extend among particular subpopulations.[10]
- Grasping the character of human leukocyte antigen is the dominant factor in means of genetic variations which is applicable for the rheumatoid arthritis responsiveness which may help in studying the biological mechanisms that leads to the diseased state.[1]
- Certain biomarkers and genomics are helpful for efficient personalized therapy.
- Drug treatment is getting flexile as we are approaching an era of advancement of drugs targeting acquired mutations in somatic genomes.
- The increased usage of biomarkers and pharmacogenomics with the capability, will strengthen the drug treatment with efficacy in future, which is vastly increasing that will eventually elevate the health status of the population.[10]

APPLICATION OF THE CONCEPT OF PERSONALIZED MEDICINE TO RHEUMATOID ARTHRITIS

To provide the patient with better care, private and public sectors are looking forward for the usage of personalized medicine.[14] The concept of personalized medicine was first applied to treat breast cancer,[15] within the tumour tissue the molecular targets are identified, which is a must step for effective targeted treatment. At payers and regulatory levels, this practice is carried on. Drug trials are done on the basis of targeted biomarkers, Some of these conditions are applicable for Rheumatoid arthritis. [16]

Gene Expression as a Tool to Investigate Pathogenesis in Rheumatoid arthritis

Rheumatoid arthritis shows heterogeneity, indicated by comparing genetic characters between anti-citrullinated protein antibodies which are positive to diseases and ACPA (*anti-citrullinated protein antibodies*) which are negative. This resulted in two different pathogenic models possessing different rates of progress towards response to treatment. Apart from genetic advances for rheumatoid arthritis understanding, profiling of gene expression provides with effective data for its understanding as well. Variations in gene expression were analyzed by micro-array methods between osteoarthritis synovial tissues and rheumatoid arthritis showing differentiating diseases by various gene signatures. With the difference in gene expression in synovial tissue sample of rheumatoid arthritis, differences in early (*<1 yr*) and late (*>5yrs*) are observed with further progress in disease resulting in heterogeneity in rheumatoid arthritis. [17]

Gene Expression Signatures as Predictors of Treatment Response-

- Methotrexate: is the most common drug used for rheumatoid arthritis treatment. Its mechanism is not yet known
- Infliximab: for gene expression identification, it is the most studied drug, was first approved for rheumatoid arthritis biologically.
- Rituximab: About 40-50% patients were unresponsive to rituximab treatment, despite of B cells depletion in 100% of treated patients. It serological status posses no predictive value in drug outcome, until biomarkers were used for its validation.
- Anakinra: IL-1RA was treated for outcome in gene expression signature. Selected transcripts of infliximab and anakinra were observed, no overlapping was notes. It indicates that gene signature reflects specificity of drug rather than mechanism of pathophysiology.
- Tocilizumab: It acts against interleukin 6 receptor, it forms one among the antibodies panel for treating moderate to severe stages of rheumatoid arthritis disease.[17]

Peripheral blood, readily available biosample can acts as an ideal biomarker. [5] On the basis of targeted biomarker, drug trials are been carried. By the application of these aspects, affected tissue can be accessed.[16] These concepts can also be applied to osteoarthritis. [18]

CONCLUSION

Due to the high level of heterogeneity in rheumatoid arthritis, personalized medicine is of greater importance. Personalized medicines are developed by studying a person's genetic, genomic environmental factors. Personalized medicines can be improved by factors like adding biomarkers, studying genetic variation, drug metabolism, epigenetic variations and health factors. By means of personalized medicines a specific care is been given to the patient. Grasping the character of human leukocyte antigen helps in studying the biological mechanism that lead to the diseased state. Targeted and non-targeted biomarkers aid for better improvements in personalized medicines, helps in discovering the novel pathways for the reliable usage of personalized medicines in the effective treatment of rheumatoid arthritis.

REFERENCES

1 Hiroshi Furukawa et al., Human leukocyte antigen polymorphisms and personalized medicine for rheumatoid arthritis. Journal of Human Genetics, 2014; 9(2): e87792.

2 Glynn Dennis Jr et al., synovial phenotypes in rheumatoid arthritis correlate with response to biologic therapeutics: Arthritis Research and Therapy 2014, 16:R90.

3 James Bluett, Suzanne Verstappen, and Deborah Symmons. Landmark papers in RHEUMATOLOGY: Epidemiology and genetics. 1st ed, P.g 27. https://books.google.co.in/books?id=bwrHCQAAQBAJ&pg=PA1&lpg=PA1&dq=James+Bluett,+Suzanne+Verstappen,+and+Deborah+Symmons.+Landmark+papers+in+RHEUMATOLOGY:+Epidemiology+and+genetics.&source=bl&ots=Raf8kjB4Yc&sig=jjJkhIcGlfdM_2dgob8g72GEMoU&hl=en&sa=X&ved=0CB4Q6AEwAGoVChMIpbyw0YCpxwIVAkmOCh2rEgZz#v=onepage&q&f=false.

4 Smolen J S, Boers M, Abadie EC, et al. Updating the 2003 European regulatory requirements for registering disease-modifying drugs to be used in the treatment of rheumatoid arthritis. Rheumatology (Oxford) Volume 50, Issue 10 Pp. 1732-1736.

5 P Miossec et al., Biomarkers and Personalized Medicine in Rheumatoid Arthritis: Medscape Multispeciality. 2011;70(10):1713-1718.

6 Ginsburg GS, Willard HF. Genomic and personalized medicine: foundations and applications. Translational Research: 2009 Dec;154(6):277-87. doi: 10.1016/j.trsl.2009.09.005. Epub 2009 Oct 1.

7 National Cancer Institute. Personalized medicine. In: NCI Dictionary of Cancer Terms 2012. http://www.cancer.gov/dictionary?cdrid=561717 . [Accessed December 1, 2012].

8 W. Ken Redekop, Deirdre Mladsi. The Faces of Personalized Medicine: A Framework for Understanding Its Meaning and Scope. Value in Health: 09/2013; 16(6):S4-S9. DOI: 10.1016/j.jval.2013.06.005.

9 National Academy of Engineering: Engineering Better Medicines. http://www.engineeringchallenges.org/cms/8996/9129.aspx

10 M. Ingelman-Sundberg. Personalized medicine into the next generation. Journal of Internal Medicine, Volume 277, Issue 2 2015, 277; 152-154. doi: 101111/joim.12325 http://onlinelibrary.wiley.com/doi/10.1111/joim.12325/pdf.

11 The benefits of personalized medicine. The jackson laboratory. https://geneticheath.jax.org/personalized-medicine/what-is/benefits.html

12 Science Daily: Personalized Medicine http://www.sciencedaily.com/terms/personalized_medicine.htm

13 Engineering New Medicine, A CURRENT CHALLENGE: ENGINEERING BETTER MEDICINES http://www.pitt.edu/~kcc23/engineeringchallenge.html

14 Margaret A. Hamburg, M.D., and Francis S. Collins, The Path to Personalized Medicine N Engl J Med 2010; 363:301-304 July 22, 2010DOI: 10.1056/NEJMp1006304.

15 Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med 2005;353:1659-72.

16 Smith MD, Baeten D, Ulfgren AK et al. Standardisation of synovial tissue infiltrate analysis: how far we come. How much further do we need to go. 2005 Jun 23. doi: 10.1136/ard.2005.036905.

17 A N Burska et al., 2014. Gene expression analysis in RA: towards personalized medicine. The Pharmacogenomics Journal (2014) 14, 93-106; doi:10.1038/tpj.2013.48.

18 Kraus VB, Burnett B, Coindreau J, et al. Application of biomarkers in the development of drugs intended for the treatment of osteoarthritis. Osteoarth Cartil 2011;19:515-42. doi: 10.1016/j.joca.2010.08.019.

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